Heavy Snoring Is a Risk Factor for Case Fatality and Poor Short-Term Prognosis after a First Acute Myocardial Infarction

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Study Objectives: Sleep disordered breathing has been associated with an increased risk for developing coronary heart disease. Data on the effects of sleep disordered breathing on case fatality and prognosis of a myocardial infarction are sparse. The present study aimed to investigate a possible relationship of snoring and case fatality and mortality after an acute myocardial infarction.

Design, Settings, Patients, and Measurements: In this study, we enrolled 1660 first acute myocardial infarction cases and examined the effects of self- or relative-reported heavy snoring on case fatality and prognosis. The average follow-up time was 8 years, SD = 262 days.

Results: There was a variation in the association between snoring and mortality with time, with a strong association in the first 28 days after infarction but not later during the follow-up. Occasional and regular heavy snorers, when compared to those never having heavy snoring, had a 2.04 (95% confidence interval, 1.50 to 2.79) and 3.30 (95% confidence interval, 2.37 to 4.58) hazard ratio for mortality within the first 28 days after controlling for age, gender, obesity, history of diabetes and hypertension, physical activity, smoking, and education, respectively. There was no association between snoring and new myocardial infarction, stroke, or hospitalization for heart failure during the follow-up.

Conclusions: Heavy snoring is associated with case fatality and short-term mortality in patients with a first acute myocardial infarction.

Keywords: Acute myocardial infarction, prognosis, case fatality, sleep disordered breathing, snoring

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SNORING AND SLEEP DISORDERED BREATHING HAVE BEEN ASSOCIATED WITH AN INCREASED RISK FOR MORTALITY AND CORONARY HEART DISEASE[1-8] AND an accelerated atherosclerosis progression.[9] Obstructive sleep apnea syndrome, characterized by repetitive collapse of the upper airway during sleep, is the most plausible mechanism linking snoring to unfavorable outcomes. Heavy snoring is almost always present in obstructive sleep apnea, constituting its most important sign.[10-13]

Apart from being a risk factor for coronary heart disease in initially healthy populations, there are several potential routes by which sleep disordered breathing may affect the outcome of an acute myocardial infarction. Oxygen desaturation, sympathetic activation, and pressor surges are the immediate consequences of the apnea episodes.[14,15] Moreover, sleep disordered breathing has been implicated in the development of insulin resistance,[16] dyslipidemia,[17] increased systemic inflammation,[18,19] hypercoagulability,[20] and impaired endothelial function[15,21]; and these factors may also influence the prognosis of an acute myocardial infarction. Only a few small studies have investigated the effect of sleep disordered breathing on survival directly after an acute myocardial infarction, and they provided inconclusive results.[22-24] Moreover, to date, we are unaware of studies that have assessed the importance of sleep disordered breathing on case fatality in acute myocardial infarction. Therefore, we investigated the relationship between heavy snoring and case fatality and prognosis of a first acute myocardial infarction in a large cohort.

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METHODS

Subjects and Design

We followed individuals enrolled as acute myocardial infarction cases in the Stockholm Heart Epidemiology Program (SHEEP), a population-based case-control study of incident acute myocardial infarction.[25] The study base comprised all Swedish citizens living in the Stockholm County, 45 to 70 years of age, free of previous clinically diagnosed acute myocardial infarction. Male cases were identified during a 2-year period (1992-93) and female cases during 3 years (1992-94). Cases were identified through a special organization at the 10 emergency hospitals in the region. Criteria for acute myocardial infarction included (i) certain symptoms according to case history information, (ii) specified changes in blood levels of the enzymes CK and LD, (iii) specified ECG changes, and (iv) autopsy findings. Later comparison with a population-based incidence register indicated close to complete ascertainment of all first acute myocardial infarctions.[26]

A questionnaire was administered in the in-hospital period or for some cases shortly after it. If a patient died before the questionnaire could be answered or the general condition of the patient could not allow it the answers were obtained from rela-

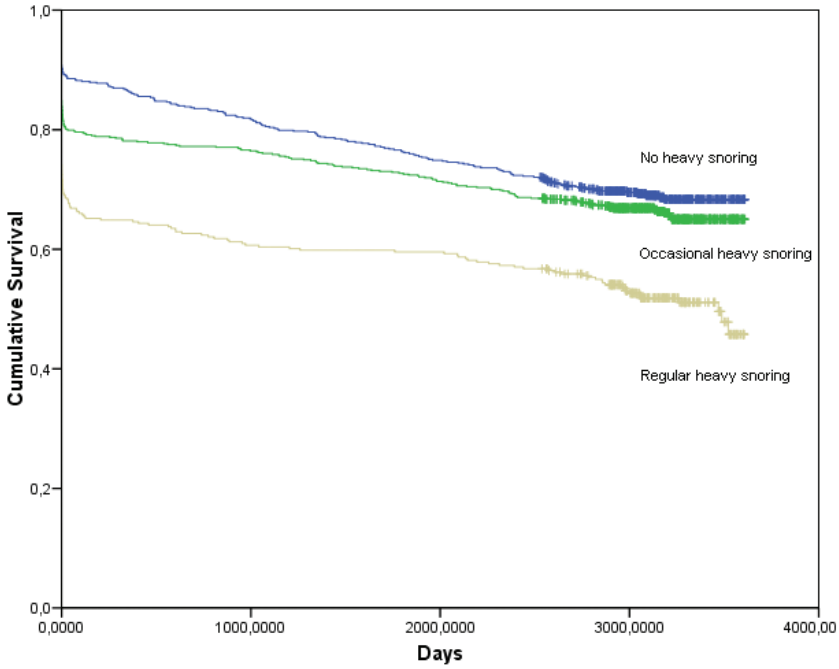

Figure 1—Cumulative survival according to snoring frequency.

tives. The relatives were chosen in the following priority order: husband/wife, children 18+ years of age, brothers or sisters if <80 years of age, parents if <80 years of age. More than half of the relatives were cohabiting partners.

Snoring

Frequency of heavy snoring was asked as (i) never, (ii) some occasions per year, (iii) some occasions per month, (iv) some occasions per week, (v) every day. For the subsequent analyses we categorized the patients as reporting no heavy snoring (the original first group), occasional heavy snorers (the second, third, and fourth original group) and regular heavy snorers (daily heavy snoring).

Covariates

Diabetes

Subjects were classified as diabetics if they had a history of diabetes or had treatment for diabetes.

Hypertension

Hypertension was defined as being on antihypertensive drug therapy, for the reason of hypertension, when included in the study; or a history of regular antihypertensive drug therapy during the last 5 years (or a part of that time).

Obesity

Patients with a BMI value >30 kg/m^2 were classified as being obese.

Physical Inactivity

Patients who reported inactive leisure time, including occasional walks, during the last 5-10 years were categorized as physically inactive.

Smoking

Subjects who had never smoked regularly (i.e., for at least 1 year) were considered as never-smokers. Subjects, who smoked when included into the study, or had stopped smoking within the last 2 years, were classified as smokers. Subjects, who had stopped smoking for more than 2 years before inclusion, were classified as ex-smokers.

Socioeconomic Position

As a measure of socioeconomic position we classified educational attainment as mandatory school only vs. high school, college, or university.

We used the *Killip classification* system to evaluate the left ventricular function.[27]

Pharmacological treatment was collected through the questionnaires, for most cases administered during the in-hospital period or shortly afterwards. The patients were asked to report on current use of pharmacological drugs, all brand names and these were later assigned generic codes. Returned questionnaires were checked for missing data and if necessary a supplementary telephone interview was performed.

Follow-up

The centralized health care system in Sweden provides virtually complete follow-up information for all patients by

Table 1—Characteristics of the Study Participants According their Snoring Frequency

	No heavy snoring	Occasional heavy snoring	Regular heavy snoring	P value
N	637	667	356	
	Mean (SD)	Mean (SD)	Mean (SD)	
Age (y)	60.5 (7.2)	59.5 (7.1)	59.7 (6.8)	0.03
Peak CK (ng/mL)	26.7 (26.5)	27.8 (26.4)	30.8 (28.0)	0.22
	N (%)	N (%)	N (%)	
Male sex	387 (60.8)	479 (71.8)	284 (79.8)	<0.001
Hypertension	237 (37.6)	263 (40.2)	145 (42.2)	0.36
Obesity (BMI >30 kg/m^2)	96 (15.2)	120 (18.3)	90 (26.1)	<0.001
Physical inactivity	316 (50.2)	327 (49.6)	190 (53.5)	0.46
Living in a partnership	414 (65.0)	533 (80.2)	268 (75.3)	<0.001
Cigarette smoking				
Nonsmokers	170 (26.8)	152 (22.8)	71 (19.9)	
Previous smokers	152 (23.9)	185 (27.7)	90 (25.3)	
Current smokers	313 (49.3)	330 (49.5)	195 (54.8)	0.08
High School/College or University	198 (31.5)	206 (31.0)	98 (28.1)	0.51
History of diabetes mellitus	92 (14.5)	98 (17.7)	65 (18.4)	0.22
Q wave infarction	287 (54.8)	296 (60.3)	148 (62.5)	0.08
Killip classification				
1	317 (65.9)	325 (72.5)	154 (69.1)	
2	133 (27.7)	96 (21.4)	53 (23.8)	
3	26 (5.4)	20 (4.5)	10 (4.5)	
4	5 (1.0)	7 (1.6)	6 (2.7)	0.21
Regular medication use				
Beta-blockers	427 (67.0)	411 (61.6)	195 (54.8)	0.80
Aspirin	405 (63.6)	386 (57.9)	182 (51.1)	0.24
Ca antagonist	39 (6.1)	53 (8.0)	30 (8.4)	0.33
Diuretics	171 (26.8)	143 (21.4)	72 (20.2)	0.29
Digitalis	26 (4.1)	10 (1.5)	11 (3.1)	0.04
ACE inhibitors	69 (10.8)	57 (7.7)	36 (10.1)	0.36

BMI = body mass index

matching their unique ten digit person identification numbers to health care registers. The average follow-up, from the acute myocardial infarction, was 8 years, SD = 262 days. All-cause and cardiac mortality was used as a primary end-point as provided by the National Cause-of-death Register. Patients were also followed for non-fatal acute myocardial infarction using the Swedish Myocardial Infarction Register.[28] Information on hospitalization for heart failure (ICD-9 and 10 codes were 428 and I50, respectively) and stroke (431, 434, I64, I63, I61) was derived from the Swedish Hospital Discharge Register.[29-31]

For approximately half of the deceased cases we had information on the exact time of death within the day. Death during sleeping hours was defined as death occurred between midnight and 06:00.

Statistics

Two-sided one-way ANOVA test and chi square test were used to test differences between the snoring groups in the mean values of continuous measures and prevalences, respectively. Cox proportional hazard models were used to examine the association between heavy snoring and the adverse outcomes. The group of patients with no heavy snoring was the reference category in these models. Proportionality of hazards was investigated visually by log-log curves and by formal tests for interaction with time. Due to the clear evidence for non-proportionality hazard ratios were calculated for total and cardiac mortality separately for the first 28 days and for the rest of the follow-up period. Statistical analyses were performed using SAS 9 for Windows.

RESULTS

Table 1 presents the characteristics of the three snoring categories among the 1660 patients included to the study. Those reporting no heavy snoring were somewhat older than snorers. Prevalence of male sex and obesity increased with increasing frequency of heavy snoring.

Follow-up time among individuals who did not sustain clinical events ranged from 6.9-9.9 years. Table 2 shows the unadjusted proportions of participants who died during follow-up, sustained nonfatal acute myocardial infarction, or were hospitalized for heart failure or stroke. Figure 1 presents cumulative survival according to snoring frequency. Regular heavy snorers had the highest total and cardiac mortality, followed by occasional heavy snorers. There was a variation in the association between snoring and mortality with time, with a strong association in the first 28 days after infarction but not later during the follow-up. Table 3 presents the un- and multiadjusted hazard ratios for adverse outcomes among the three groups. Due to miss-

Table 2—Adverse Outcomes During the Follow-Up Among SHEEP Patients According their Snoring Frequency

	No heavy snoring	Occasional heavy snoring	Regular heavy snoring
N	637	667	356
All-cause death (whole follow up)	197 (30.9)	226 (33.9)	173 (48.6)
Cardiac death (whole follow up)	132 (20.7)	175 (26.2)	137 (38.5)
Cardiac death (short-term, 28 days)	64 (10.1)	120 (18.0)	105 (29.5)
New AMI (whole follow up)	135 (21.2)	130 (19.5)	63 (17.7)
Stroke (whole follow up)	55 (8.6)	49 (7.4)	28 (7.9)
HF (whole follow up)	161 (25.3)	138 (20.7)	68 (19.1)

AMI = acute myocardial infarction, HF = heart failure

ing values among the potential confounding factors only 1622 patients were included in the multivariable models. Short-term total and cardiac mortality increased with increasing frequency of heavy snoring in the unadjusted, age- and sex-adjusted and multiadjusted models. The corresponding hazard ratios for total and cardiac mortality for the rest of the follow up were weak and statistically not significant, as were hazard ratios for non-fatal acute myocardial infarction, stroke or heart failure.

Analyses restricted to those who were living in a partnership revealed an essentially similar association between snoring and mortality than for the whole group. The multiadjusted hazard ratios for short term total and cardiac mortality were 1.95 (1.35-2.82), 3.04 (2.05-4.52), and 2.00 (1.36-2.95) and 3.23 (2.13-4.90) when occasional and regular heavy snorers were compared to those not reporting heavy snoring, respectively.

The predictive value of snoring was again essentially similar to that of the whole group when only those were included in the analyses whose snoring information came from themselves or the partners, i.e., not other relatives. The multiadjusted hazard ratios for short term total and cardiac mortality were 2.28 (1.53-3.38), 3.54 (2.32-5.39), and 2.39 (1.57-3.65) and 3.85 (2.47-6.02) when occasional and regular heavy snorers were compared to those not reporting heavy snoring, respectively.

For 235 patients, all survived the first 28 days, information both on self-reported and a cohabiting partner reported snoring was available. The specificity and sensitivity of the information derived from partners compared to the information from the patients themselves were 84.4% (69.9%-93.0%) and 94.4% (80.0%-99.0%), respectively. Replacement of self-reported snoring to cohabiting partner reported snoring in the statistical models for these 235 patients provided virtually the same results.

Among patients not reporting heavy snoring, 4.5% of the cardiac deaths occurred during sleeping hours, in contrast to the 8.0% and 10.2% among occasional and regular heavy snorers, respectively. When compared to non-snorers, hazard ratios for cardiac death during sleeping hours were 2.63 (1.00-6.89) and 5.23 (1.94-14.10) among occasional and regular heavy snorers, respectively.

Hypertension may be on a possible causal pathway of sleep disordered breathing—cardiac mortality and adjusting for hypertension could lead to an overadjustment. However, when we removed hypertension from our multiadjusted models there was only a slight change in relative risks. The hazard ratios for short-term total mortality were 2.04 (1.50-2.77) and 3.41 (2.47-4.70), and for short-term cardiac mortality were 2.05 (1.48-2.84) and 3.63 (2.59-5.08) when occasional and regular heavy snorers were compared to those not reporting heavy snoring in these new models, respectively.

DISCUSSION

We found that over 60% of the acute myocardial infarction patients reported occasional or regular heavy snoring. Heavy snoring, especially if regular, was associated with a markedly increased case fatality and short-term mortality, but it had no association with longer-term mortality, non-fatal acute myocardial infarction, stroke, or heart failure. Snorers also died more often during the night.

Several population-based prospective studies found that snoring[1-4,7,8] or obstructive sleep apnea syndrome as recorded by polysomnography[5] is associated with an increased risk for mortality and development of coronary heart disease. Sleep disordered breathing also seems to predict poor prognosis in established coronary heart disease. Mooe et al.[6] investigated over 400 patients with disabling angina pectoris and verified coronary artery disease. Sleep disordered breathing as detected by polysomnography was associated with a worse long-term prognosis and had an independent association with cerebrovascular events. In a smaller sample, Milleron et al.[32] found that untreated obstructive sleep apnea was associated with adverse outcomes in patients with a significant coronary stenosis (≥70%). In another small study, Hagenah et al.[33] failed to provide evidence for increased mortality associated with obstructive sleep apnea among patients with an established coronary artery disease.

Only a few studies have directly examined the effects of sleep disordered breathing on an acute coronary event, and the results are conflicting. Peker et al.[24] examined 62 patients surviving an acute myocardial infarction or unstable angina in a stable phase and found that untreated obstructive sleep apnea was a predictor of cardiovascular mortality. In another study, snoring was not associated with recurrent events in 283 women who survived acute myocardial infarction or unstable angina and were also examined in a stable metabolic state.[22] Marin et al.[23] could not detect a statistically significant difference in mortality within 30 days between 55 patients having a sleep apnea during the early phase of an acute myocardial infarction and those who had not (n = 196). It ought to be underscored, however, that in contrast to our study, these earlier studies included small numbers of patients; thus the statistical power limited the conclusion could be drawn. Moreover, to date, we are unaware of studies that assessed the importance of heavy snoring or sleep disordered

Table 3—Hazard Ratios for Adverse Outcomes with 95% Confidence Intervals

Outcomes	Unadjusted HR (95% CI)	P for trend	Multiadjusted HR (95% CI)*	P for trend
Total mortality within 28 days				
no heavy snoring	1.00		1.00	
occasional heavy snoring	1.87 (1.40 - 2.49)		2.04 (1.50 - 2.79)	
regular heavy snoring	3.19 (2.37 - 4.29)	<0.001	3.30 (2.37 - 4.58)	<0.001
Total mortality beyond 28 days				
no heavy snoring	1.00		1.00	
occasional heavy snoring	0.75 (0.57 - 0.97)		0.80 (0.61 - 1.05)	
regular heavy snoring	1.12 (0.82 - 1.51)	0.98	1.12 (0.81 - 1.54)	0.89
Cardiac mortality within 28 days				
no heavy snoring	1.00		1.00	
occasional heavy snoring	1.86 (1.38 - 2.52)		2.08 (1.49 - 2.90)	
regular heavy snoring	3.29 (2.41 - 4.50)	<0.001	3.52 (2.49 - 4.98)	<0.001
Cardiac mortality beyond 28 days				
no heavy snoring	1.00		1.00	
occasional heavy snoring	0.82 (0.58 - 1.17)		0.87 (0.61 - 1.26)	
regular heavy snoring	1.09 (0.72 - 1.66)	0.97	1.01 (0.64 - 1.59)	0.86
New AMI (whole follow-up)				
no heavy snoring	1.00		1.00	
occasional heavy snoring	1.01 (0.79 - 1.28)		1.00 (0.78 - 1.28)	
regular heavy snoring	1.11 (0.82 - 1.50)	0.55	0.99 (0.72 - 1.36)	0.95
Stroke (whole follow-up)				
no heavy snoring	1.00		1.00	
occasional heavy snoring	0.89 (0.60 - 1.30)		0.94 (0.63 - 1.41)	
regular heavy snoring	1.17 (0.74 - 1.84)	0.68	1.21 (0.75 - 1.95)	0.55
Heart failure (whole follow-up)				
no heavy snoring	1.00		1.00	
occasional heavy snoring	0.86 (0.69 - 1.08)		0.92 (0.73 - 1.16)	
regular heavy snoring	0.97 (0.73 - 1.29)	0.59	1.02 (0.76 - 1.37)	0.91

AMI = acute myocardial infarction
*Multiadjustment includes age, gender, obesity, history of diabetes and hypertension, physical inactivity, smoking, and education

breathing on case fatality in acute myocardial infarction.

Why heavy snoring was strongly related to short-term mortality, especially during the night, and not to long-term outcomes is not completely clear, but it falls in line with some previous findings. Patients seems to be especially vulnerable for consequences of apnea, i.e. nocturnal reduction in coronary blood flow, reduction in blood supply, sympathetic activation, and pressor surges during the unstable period shortly after an acute myocardial infarction.[34] Hypoxemia and sympathetic activation in sleep disordered breathing predispose to potentially fatal cardiac arrhythmias, such as heart block[35] and ventricular arrhythmias.[36] Doherty et al.[37] found in a long-term follow up study of sleep disordered breathing patients that untreated obstructive sleep apnea is not as much related to the incidence but rather to the severity of cardiovascular disease and to sudden deaths especially in nocturnal or early morning hours. Experimental data also support that sleep disordered breathing might have deleterious effects on the acute phase of an acute myocardial infarction. In an animal model of sleep disordered breathing, Joyeux-Faure et al.[38] demonstrated that chronic intermittent hypoxia increased the sensitivity of the heart to infarction. The infarct sizes were considerably higher among rats treated with intermittent hypoxia prior to an ischemia-reperfusion protocol than rats without such pretreatment. Seppälä et al.[39] interviewed cohabiting partners of cases of sudden death. Snorers died more often during sleeping, and the autopsy records showed that cardiovascular causes of death were more prevalent among snorers when compared to non-snorers. Gami et al.[40] found that people with obstructive sleep apnea had a peak in sudden death from cardiac causes during the sleeping hours, which contrasts strikingly with the nadir of sudden death from cardiac causes during this period in people without obstructive sleep apnea and in the general population. The severity of obstructive sleep apnea also correlated with the risk of nocturnal sudden death from cardiac causes.

Obstructive sleep apnea is a treatable disorder. Recent studies suggest that nasal continuous airway pressure (CPAP) treatment does not only effectively reduce blood pressure and sleepiness, and improve quality of life but it also decreases risk for cardiovascular events in patients with sleep disordered breathing.[32,34,37,41,42] Our results on the short-term mortality raise the possibility that CPAP treatment can be considered during the acute phase of an acute myocardial infarction in habitual and even in occasional heavy snorers. Studies are warranted for evaluating the potential benefit of CPAP treatment in the acute phase of an acute myocardial infarction.

Limitations

As in many previous investigations, we did not objectively assess sleep disordered breathing but relied on self- and/or relative-reported heavy snoring. Self-reported habitual snoring

was found to be a reliable sleep disordered breathing screening method, and severity of apnea increases with increased snoring[10,11,43,44]; however, in contrast to polysomnographic recordings, it does not allow direct quantitative assessment of apnea or to investigate the possible mechanisms.

In our study, for some cases, especially for those patients who died before the administration of questionnaires or were in poor general condition, snoring was reported by relatives. If the relatives tend to report more snoring than the patients themselves, then this non-differential misclassification could potentially inflate the relative risk estimates for snoring. However, our secondary analyses did not provide support for a major misclassification. Results were largely the same when we restricted our analysis to patients living in a partnership or when we deleted those cases from our analyses whose snoring was not self-reported or was not provided by a cohabiting partner. We also found high specificity and sensitivity between self- and cohabiting partner reported snoring among those having both sources of information. Moreover, when we replaced self-reported snoring to cohabiting partner reported snoring in our models for these patients, we got virtually the same results. The increased prevalence of death during sleeping hours among heavy snorers provides a further argument against a major misclassification.

Our study, like all similar studies, was inherently observational. As with any observational study, unevenly distributed characteristics associated with snoring and acute myocardial infarction prognosis could over- or underestimate the true effects. Though, we adjusted for several potential confounders in our multivariate analyses, we cannot exclude the possibility of uncontrolled confounding. However, any remaining confounder able to influence our results considerably would need to be strongly associated with both snoring and prognosis of acute myocardial infarction and generally unrelated to the factors included in our models, i.e., age, gender, obesity, history of diabetes and hypertension, physical activity, smoking, and education.

Conclusion

The majority of acute myocardial infarction patients were occasional or habitual heavy snorers in this study and heavy snoring was associated with an increased risk for case fatality and short-term mortality. Snoring subjects with acute myocardial infarction more often died during the night.

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