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Relationship between sleep apnoea and mortality in patients with ischaemic heart failure

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ABSTRACT

Objective: To determine whether the influence of sleep apnoea (SA) on the risk of death differs in patients with ischaemic and in those with non-ischaemic heart failure (HF).

Design: Prospective observational study.

Patients: Consecutive patients with HF with left ventricular ejection fraction $\leq 45\%$ newly referred to the HF clinic between 1 September 1997 and 1 December 2004.

Main outcome measures: Patients underwent sleep studies and were divided into those with moderate to severe SA (apnoea–hypopnoea index ≥ 15 /h of sleep) and those with mild to no SA (apnoea–hypopnoea index < 15 /h of sleep). They were followed up for a mean of 32 months to determine all-cause mortality rate.

Results: Of 193 patients, 34 (18%) died. In the ischaemic group, mortality risk adjusted for confounding factors was significantly higher in those with SA than in those without it (18.9 vs 4.6 deaths/100 patient-years, hazards ratio (HR) = 3.03, 95% CI 1.04 to 8.84, $p = 0.043$). In contrast, in the non-ischaemic HF group, there was no difference in adjusted mortality risk between those with, and those without, SA (3.9 vs 4.0 deaths/100 patient-years, $p = 0.929$).

Conclusions: In patients with HF, the presence of SA is independently associated with an increased risk of death in those with ischaemic, but not in those with non-ischaemic, aetiology. These findings suggest that patients with ischaemic cardiomyopathy are more susceptible to the adverse haemodynamic, autonomic and inflammatory consequences of SA than are those with non-ischaemic cardiomyopathy.

Despite their similar clinical presentations, heart failure (HF) due to ischaemic or non-ischaemic causes differs with respect to pathophysiology, response to treatment and prognosis.^{1–5} HF due to ischaemic aetiology has a poorer prognosis than HF due to non-ischaemic aetiology.⁵ It is therefore important to determine what conditions contribute to these different clinical courses. One such condition may be coexisting sleep apnoea (SA).

There are two types of SA, central and obstructive (CSA and OSA, respectively), which have in common repetitive apnoeas and hypopnoeas accompanied by intermittent hypoxia–reoxygenation, and recurrent arousals, which cause increased sympathetic nervous system activity and blood pressure, parasympathetic withdrawal and elaboration of reactive oxygen species and inflammatory mediators.^{6,7} In addition, unlike CSA, OSA also causes large negative intrathoracic pressure swings owing to generation of ineffectual inspiratory

efforts against the occluded upper airway that cause increases in left ventricular after load.^{6,7} Taken together, such effects could promote the progression of HF through direct effects on the myocardium, including myocyte hypertrophy, necrosis and fibrosis, or indirectly through effects on coronary arterial endothelium, such as progression of atherosclerosis or provocation of myocardial ischaemia through an imbalance between cardiac oxygen supply and demand. Indeed, it has been reported that both CSA and OSA are independent risk factors for mortality in HF.^{8–11} However, it has not been established whether such mortality risk differs according to the aetiology of HF. The latter adverse effects related to the coronary arterial endothelium and provocation of myocardial ischaemia might be particularly relevant to patients with established coronary atherosclerosis. Indeed, in patients with coronary artery disease, SA is an independent prognostic factor for recurrent cardiovascular events and mortality.^{12,13} Therefore, patients with HF with pre-existing coronary artery disease may be more prone to the adverse consequences of SA than patients with HF with non-ischaemic cardiomyopathy. We therefore hypothesised that since patients with ischaemic HF may be more susceptible to the adverse consequences of SA than those with non-ischaemic HF, SA would be more likely to contribute to mortality risk in the former than in the latter.

PATIENTS AND METHODS

Subjects

We enrolled consecutive patients with HF newly referred to the Heart Failure Clinic of the Mount Sinai Hospital in Toronto between 1 September 1997 and 1 December 2004 who met the following inclusion criteria: (a) men and women of at least 18 years of age; (b) HF due to ischaemic or non-ischaemic dilated cardiomyopathy for at least 6 months; (c) left ventricular systolic dysfunction (left ventricular ejection fraction (LVEF) $\leq 45\%$ at rest by radionuclide angiography or echocardiography performed within 3 months before polysomnography); (d) New York Heart Association (NYHA) class II–IV after optimisation of medical treatment and (e) stable clinical status with optimal medical treatment for ≥ 1 month before entry. Exclusion criteria were (a) unstable angina, myocardial infarction or cardiac surgery within the previous 3 months; (b) pregnancy and (c) prior history of SA. Subjects underwent overnight polysomnography irrespective of the presence or absence of symptoms of SA. The investigation was

Figure 1 Progress of the cohort through the study. CPAP, continuous positive airway pressure; HF, heart failure; M-NSA, mild or no sleep apnoea; OSA, obstructive sleep apnoea; PSG, polysomnography; SA, sleep apnoea.

approved by the local research ethics board and all subjects provided written informed consent before entry.

Baseline assessment

Before undergoing polysomnography, demographic data, medical history and drug use were obtained from patients' clinic records. To assess the degree of subjective daytime sleepiness, the Epworth Sleepiness Scale¹⁴ was administered to the participants by a polysomnographic technologist. Atrial fibrillation was defined by its presence on the electrocardiographic recording during polysomnography. HF was considered to be of ischaemic aetiology based on a history of documented myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, or at least 75% narrowing of at least one of the three major coronary arteries at angiography, whereas HF was considered to be of non-ischaemic aetiology in the absence of the above evidence of ischaemic heart disease or a negative radionuclide or echocardiographic stress test.

Polysomnography

Overnight polysomnography was performed using standard techniques and criteria for scoring sleep stages and arousals.¹⁵ Thoracoabdominal motion and tidal volume were determined using calibrated respiratory inductance plethysmography (Respirace, Ambulatory Monitoring, White Plains, New York, USA) and arterial oxygen saturation (SaO₂) was monitored by oximetry. Apnoeas and hypopnoeas were scored according to established criteria for our laboratory.¹⁵ The apnoea-hypopnoea index (AHI) was quantified as the frequency of apnoeas and hypopnoeas for each hour of sleep. Patients were divided into those with mild or no sleep apnoea (M-NSA) with an AHI <15, and those with moderate to severe SA with an AHI ≥15. The latter group was subclassified into either CSA, in which >50% of apnoeas and hypopnoeas were central, or OSA, in which ≥50% were obstructive. An AHI cut-off point of 15/h was selected to conform to that used in our previous studies.^{8 16} Treated OSA was defined as initiation of continuous positive airway pressure (CPAP) treatment, followed by documentation at a routine assessment in the sleep disorders clinic 3 months later of continued use at that time.⁸ Patients were considered to have untreated OSA if they did not start CPAP or if they started CPAP but abandoned treatment before this 3-month follow-up assessment. Patients with treated OSA (ie, those who started CPAP and continued to use it at the 3-month follow-up visit)

were excluded from this analysis because in a previous study we showed that such compliance is associated with a strong tendency to reduced mortality.⁸ With respect to patients with CSA, we showed in the CANPAP trial,¹⁶ that use of CPAP to treat CSA had no effect on overall mortality in patients with HF. Therefore, in this study, patients with CSA who received CPAP treatment were not excluded from the prospective analysis. Technicians who were blinded to the patients' baseline clinical characteristics analysed the sleep studies.

Outcomes

The study outcome was the cumulative rate of death from any cause from the date of the diagnostic sleep study until 1 January 2005. Follow-up data, including the date of death, were obtained from a telephone interview with the patient or their family conducted by trained personnel, review of the patient's hospital or HF clinic record, or personal communication with the patient's doctor.

Statistical analysis

Comparisons between the two groups were performed by the Student *t* test for continuous variables that were normally distributed, and by Mann-Whitney *U* test for variables that were not normally distributed. A χ^2 or Fisher's exact test was used to compare nominally scaled variables. Cumulative probabilities of event curves were estimated with the Kaplan-Meier method. To compare rates of death from any cause between patients with and without SA within the ischaemic and non-ischaemic HF groups, and to control for potential confounding related to differences in baseline characteristics, conventional Cox proportional hazards models were used. On multivariate analysis, variables were included if they conferred at least a 10% change in the hazard ratio (HR) for death when added to the model.¹⁷ Independent variables were introduced into the model one at a time and included age, sex, body mass index, NYHA class, LVEF, ischaemic aetiology, atrial fibrillation, a history of hypertension, hyperlipidaemia, diabetes, drugs and polysomnographic variables. Relationships were summarised as HR with 95% confidence interval (CI). The best cut-off value for AHI predicting risk of mortality was generated with receiver operating characteristic (ROC) curves, and was identified as the value that minimised the expression $((1 - \text{sensitivity})^2 + (1 - \text{specificity})^2)$. Data are presented as mean (SD) or frequencies. A two-tailed *p* value of <0.05 was considered significant. All analyses were performed using SPSS 13.0.1.

Table 1 Baseline characteristics of the patients

Characteristics	Ischaemic			Non-ischaemic		
	M-NSA (n = 40)	SA (n = 39)	p Value	M-NSA (n = 73)	SA (n = 41)	p Value
Age (years)	59 (10)	63 (10)	0.077	50 (15)	56 (10)	0.037
Male (%)	85	90	0.532	55	85	<0.001
BMI (kg/m ²)	30.0 (6.2)	27.2 (3.9)	0.130	29.0 (4.9)	30.6 (6.1)	0.133
LVEF (%)	24.5 (10.6)	23.9 (9.6)	0.797	26.1 (10.2)	23.0 (9.3)	0.107
NYHA class, III+IV (%)	43	74	0.004	44	40	0.882
Atrial fibrillation (%)	5	13	0.227	6	20	0.019
History hypertension (%)	45	49	0.745	29	46	0.060
History diabetes (%)	28	46	0.088	18	22	0.595
ESS	7.0 (4.3)	7.5 (4.3)	0.628	7.3 (3.7)	7.4 (3.2)	0.903
Drugs						
β blockers (%)	78	74	0.748	77	78	0.872
ACEi ± ARB (%)	95	92	0.629	93	88	0.337
Total sleep time (min)	277.5 (81.4)	305.4 (67.7)	0.102	323.3 (70.8)	282.9 (14.0)	0.009
Total AHI (n/h of sleep)	8.7 (3.6)	32.3 (14.6)	<0.001	5.9 (3.8)	34.9 (14.9)	<0.001
Obstructive AHI (n/h of sleep)	6.4 (4.5)	13.7 (14.0)	0.002	4.5 (3.8)	18.9 (16.0)	<0.001
Central AHI (n/h of sleep)	2.3 (2.8)	18.6 (16.9)	<0.001	1.4 (2.4)	16.0 (17.4)	<0.001
% Central events	NA	55.1 (38.5)		NA	44.5 (38.0)	
% Minimum Sao ₂	86.8 (8.9)	84.0 (6.5)	0.122	87.5 (6.6)	83.3 (9.5)	0.006

Value are expressed as mean (SD), unless otherwise indicated.

ACEi, angiotensin-converting enzyme inhibitor; AHI, apnoea-hypopnoea index; ARB, angiotensin receptor blockers; BMI, body mass index; ESS, Epworth Sleepiness Scale; LVEF, left ventricular ejection fraction; M-NSA, mild or no sleep apnoea; NYHA, New York Heart Association; SA, sleep apnoea; Sao₂, arterial oxyhaemoglobin saturation.

RESULTS

Characteristics of the subjects

Of the 242 patients meeting eligibility criteria, 218 (90%) agreed to have a sleep study. Of 218 patients enrolled, 88 (40%) had ischaemic HF and 130 (60%) had non-ischaemic HF. Of those with ischaemic HF, 100% underwent coronary angiography, whereas of those with non-ischaemic HF, 126 (97%) underwent coronary angiography. Of the four patients with non-ischaemic HF who did not have coronary angiography, all had negative stress tests. SA was found in 53% (OSA in 25% and CSA in 28%) of those with ischaemic HF and in 41% (OSA in 26% and CSA in 15%) of those with non-ischaemic HF. Compared with the non-ischaemic group, the ischaemic group had a significantly higher prevalence of CSA (28% vs 15%, $p = 0.020$), were older (60.9 (9.8) vs 52.0 (13.2), $p < 0.001$), had a high proportion of men (88% vs 70%, $p = 0.002$), a lower body mass index (28.3 (5.2) vs 29.9 (5.4), $p = 0.033$) and a higher proportion in NYHA class III and IV (57% vs 39%, $p = 0.009$).

Patients were followed up prospectively for mean and maximum durations of 32.0 months and 87.8 months, respectively. Complete follow-up data were obtained in 95%. Figure 1 shows that, 11 patients were lost to follow-up and 14 patients whose OSA was treated with CPAP were excluded from further analysis. Thus, a total of 193 patients, 79 with ischaemic and 114 with non-ischaemic HF were included in the final analysis.

Of these 193 patients, 144 (75%) were men and 49 (25%) were women. Their ages ranged from 18 to 84 years (mean (SD) 55.9 (12.8) years), and their mean (SD) body mass index was 29.0 (5.4) kg/m². Patients in NYHA classes III and IV comprised 48% of the population. Mean (SD) LVEF was 24.7 (10.0)%. At the baseline assessment, 77% of patients were taking β blockers, 92% angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARB), 79% diuretics (thiazide and loop) and 21% spironolactone.

Table 1 shows characteristics of the patients. In the ischaemic group, patients with SA had a significantly higher NYHA class than those with M-NSA. In the non-ischaemic group, patients

with SA were significantly older and were more likely to be men and to have atrial fibrillation than those with M-NSA. There were no differences in types or dosages of β blockers between those with ischaemic and those with non-ischaemic HF. There was also no significant difference in the dose of furosemide between patients with and without SA in either the ischaemic or non-ischaemic HF group (data not shown). Only 6 (3.1%) patients had a cardioverter-defibrillator implanted, and there was no significant difference in the implantation rate between patients with non-ischaemic and ischaemic HF (1.7% vs 5.1%, $p = 0.193$). Table 1 shows polysomnographic characteristics of the patients. By definition, patients in the SA group had a higher AHI than the M-NSA group, and they had more frequent movement arousals.

Outcomes

During the follow-up period, 34 (18%) deaths occurred. In the ischaemic group, 22 (28%) died, whereas in the non-ischaemic group, only 12 (11%) died ($p = 0.007$). For all subjects in the ischaemic and non-ischaemic groups, the unadjusted mortality rate was higher in those with SA than in those with M-NSA (unadjusted HR = 2.39, 95% CI 1.20 to 4.73, $p = 0.013$). However, after adjusting for other risk factors such as age and NYHA class, using multivariate Cox analysis, the risk of death associated with SA was only of borderline significance (adjusted HR = 1.86, 95% CI 0.93 to 3.71, $p = 0.079$).

Figure 2 shows the Kaplan-Meier plots of the time to death. In the ischaemic group, the mortality rate was significantly higher in those with SA than in those with M-NSA (5-year mortality rate of 57% or 18.9 deaths/100 patient-years vs a 5-year mortality rate of 21% or 4.6 deaths/100 patient-years: unadjusted HR = 3.81, 95% CI 1.47 to 9.84, $p = 0.006$). In contrast, in the non-ischaemic group, the mortality rate did not differ between those with SA and those with M-NSA (5-year mortality rate of 13% or 3.9 deaths/100 patient-years vs 14% or 4.0 deaths/100 patient-years: unadjusted HR = 0.99, 95% CI 0.30 to 3.30, $p = 0.987$). The death rate in the ischaemic HF

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Figure 2 Kaplan-Meier survival curves of death from any cause in patients with (A) ischaemic heart failure (HF) and (B) non-ischaemic HF. In the ischaemic group, mortality was significantly higher in patients with sleep apnoea (SA; $p = 0.006$). After adjusting for confounding factors, SA remained a significant independent risk factor for death (HR = 3.03, $p = 0.043$) (A). In contrast, in the non-ischaemic group, there was no difference in mortality between the two groups (unadjusted $p = 0.987$) (B). HR, hazard ratio; M-NSA, mild or no sleep apnoea; SA, sleep apnoea.

group with M-NSA was similar to that in the patients with non-ischaemic HF with SA or with M-NSA (4.6 vs 4.0 deaths/100 patient-years, $p = 0.679$).

Table 2 shows the causes of death. SA was associated with a higher cardiovascular death rate in patients with ischaemic, but not in those with non-ischaemic HF (8% vs 31%, $p = 0.007$, and 7% vs 7%, $p = 0.988$, respectively). Similarly, SA was associated with an increased risk of sudden death in the ischaemic, but not in the non-ischaemic group ($p = 0.019$ and $p = 0.490$, respectively). In addition, when SA was divided into predominantly OSA or CSA, the association between either of them and mortality was the same as for the entire SA group. In the ischaemic group, both OSA and CSA were associated with a similar increased risk of death (unadjusted HRs of 4.06, 95% CI 1.36 to 12.13, $p = 0.012$, and 3.62, 95% CI 1.27 to 10.34, $p = 0.016$, respectively). Moreover, the pattern of excess mortality due to sudden death in the ischaemic group with SA was similar in the CSA and OSA subgroups: there were four sudden deaths in each. In contrast, in the non-ischaemic group, there was no increased risk of death associated with the presence of OSA or CSA (unadjusted HRs of 0.79, 95% CI 0.17 to 3.72, $p = 0.762$, and 1.34, 95% CI 0.28 to 6.44, $p = 0.714$, respectively). Among the patients with CSA in this study, there was no significant difference in mortality between the CPAP-treated and untreated groups (40% vs 21%, $p = 0.213$).

After adjusting for confounding factors that included age, NYHA class, and a history of diabetes, SA remained a significant independent risk for death in the ischaemic group (adjusted HR = 3.03, 95% CI 1.04 to 8.84, $p = 0.043$). However, in the non-ischaemic group, after adjusting for confounding factors that included age, LVEF, NYHA class, and atrial fibrillation, SA was not a significant independent risk for death (adjusted HR = 0.94, 95% CI 0.26 to 3.47, $p = 0.929$).

In addition, for patients with ischaemic HF, ROC analysis showed that the best AHI cut-off value to predict mortality was ≥ 16 per hour of sleep (mean (SD) area under the curve 0.71 (0.04), sensitivity 72.7, and specificity 64.9).

DISCUSSION

The most important finding of this prospective cohort study was that SA was associated with an increased mortality risk in patients with ischaemic, but not in those with non-ischaemic, HF. This increased mortality risk in the ischaemic patients was independent of other known risk factors (adjusted HR = 3.03). However, among patients with ischaemic HF without SA, the mortality rate did not differ from that of all patients with non-ischaemic HF. Thus, the excess mortality in patients with ischaemic HF versus non-ischaemic HF could be attributed, at least in part, to SA. In addition, this increased risk of death in the ischaemic patients with SA was due to a higher risk for cardiovascular deaths, and, in particular, for sudden death compared with those without SA. Another interesting finding was that the AHI threshold value that best predicted increased

Table 2 Causes of death

Cause	Ischaemic			Non-ischaemic		
	M-NSA (n = 40)	SA (n = 39)	p Value	M-NSA (n = 73)	SA (n = 41)	p Value
Total deaths (n)	6	16	0.006	8	4	0.987
Cardiovascular, n	3	12	0.007	5	3	0.988
Sudden death, n (%)	0 (0)	8 (50)	0.019	1 (13)	1 (25)	0.490
Progressive HF, n (%)	2 (33)	3 (19)	0.473	3 (38)	1 (25)	0.778
Other cardiac, n (%)	1 (17)	1 (6)	0.457	1 (13)	1 (25)	0.490
Non-cardiac, n (%)	2 (33)	1 (6)	0.100	2 (25)	0 (0)	0.301
Unknown, n (%)	1 (17)	3 (19)	0.910	1 (13)	1 (25)	0.584

HF, heart failure; M-NSA, mild or no sleep apnoea; SA, sleep apnoea.

risk of mortality in patients with ischaemic HF was ≥ 16 per hour of sleep.

The main clinical significance of SA in HF appears to be its potential to increase the risk of death. However, there remains some controversy on this point. For OSA, only two studies have examined this topic: one study found increased mortality associated with OSA,⁸ whereas the other did not.¹⁸ In the latter smaller study, all patients were recruited from a heart transplantation waiting list. Since transplantation is a random event that would influence survival independently of the severity of cardiac disease, the results are difficult to interpret. Neither of these studies examined mortality based on ischaemic or non-ischaemic HF aetiology. For CSA, whereas some studies found an increased risk related to CSA,^{9–11} others did not.^{18–19} Careful reading of these previous studies shows that in those involving higher proportions of patients with ischaemic HF (64–100%) the presence of CSA was associated with increased mortality risk,^{9–11} whereas in studies involving lower proportions of patients with ischaemic HF (11–53%), the presence of CSA was not associated with increased mortality.^{18–19} Our study sheds light on the reasons for these differences by demonstrating that SA, including both CSA and OSA, is associated with higher mortality risk in patients with ischaemic, but not in those with non-ischaemic HF.

One possible explanation for this finding was that among patients with ischaemic HF, those with SA had a worse New York Heart Association (NYHA) class than those with M-NSA, whereas this was not the case among the non-ischaemic patients. However, even after adjusting for differences in NYHA class and other potential confounders, SA remained a significant predictor of mortality risk among patients with ischaemic HF. Conversely, even though non-ischaemic patients with SA were older, were more often male and had a higher prevalence of atrial fibrillation (all known to increase risk of death in HF) than those with M-NSA, SA was not associated with increased risk of mortality. Thus, these data suggest a second possible explanation for the increased mortality risk associated with SA in patients with ischaemic, but not in those with non-ischaemic HF; increased susceptibility, in the former, to the adverse pathophysiological effects of SA.

Both CSA and OSA cause recurrent hypoxia and arousals from sleep, which increase sympathetic nervous system activity, reduce cardiac parasympathetic activity, and cause repetitive surges in heart rate, blood pressure and left ventricular after load.^{6–7, 20} There is also growing evidence that intermittent hypoxia mimicking the effects of SA can stimulate production of reactive oxygen species, vascular endothelial growth factors, inflammatory mediators and stimulate development of atherosclerosis.^{6–21} Downstream, these factors promote trophic stimulation of the myocardium, vascular endothelial dysfunction, increased platelet aggregability and blood coagulability, and may also contribute to the development and progression of atherosclerosis.⁶ The mechanical loading of the myocardium can also increase myocardial oxygen demand in the face of a reduced supply, causing a reduction in cardiac output in those with ischaemic heart disease.^{22–23} These autonomic and mechanical stresses could also increase the potential for malignant cardiac arrhythmias, and sudden death, especially in those with ischaemic HF. Recent reports showed that ventricular arrhythmias are more common in patients with HF and SA, whether CSA or OSA, than in those without it.^{24–25} In this study, the incidence of sudden death was significantly greater in the ischaemic patients with SA than in the those without SA, and

this is probably owing primarily to malignant cardiac arrhythmias (table 2).

In contrast to patients with ischaemic HF, in patients with non-ischaemic HF the mortality rate was no higher in those with SA than in those with M-NSA. One possible explanation is that if repetitive apnoea-related surges in sympathetic nervous system activity cause intermittent inotropic stimulation of the heart during sleep, this stimulus may have different influences based on the aetiology of HF. In fact, previous studies showed that whereas temporary or intermittent infusion of inotropic agents conferred a survival benefit in patients with non-ischaemic HF, it conferred an adverse effect on survival in those with ischaemic HF.^{2–8} These data support the concept that the myocardial stimulatory effect of apnoea-related sympathetic activation may have more adverse effects on prognosis in patients with ischaemic than in those with non-ischaemic HF.

We found that the AHI with optimal sensitivity and specificity to predict mortality was ≥ 16 per hour of sleep, a finding in accordance with previous studies from our centre. For example, we reported that among patients with HF, those with untreated OSA whose AHI was ≥ 15 had a higher mortality rate than patients with HF with an AHI < 15 .⁸ Compared with patients with HF with an AHI < 15 , those with CSA and an AHI ≥ 15 had reduced heart transplant-free survival.¹¹ Treatment of such patients by CPAP improved LVEF and 6 min walking distance, and lowered norepinephrine levels.^{16–26} In addition, in a post hoc analysis of the multicentre CANPAP trial, among the 57% of patients in whom CPAP suppressed the AHI to < 15 , heart transplant-free survival was significantly greater than in the control group who did not receive CPAP.²⁷ Thus our finding in this study that the AHI threshold that best predicts risk of death was ≥ 16 is in keeping with those previous studies. Although Lanfranchi *et al* found that in 54 patients with HF an AHI > 30 was a predictor of mortality,²⁸ compared with this study, they examined fewer patients, excluded those with OSA, used cardiorespiratory monitoring without determination of sleep stages instead of full polysomnography, and did not perform ROC analysis, and so did not determine a non-arbitrary AHI cut-off point for mortality risk.

Our observations are subject to some limitations. First, although we controlled for most traditional factors that have been associated with risk of mortality in previous studies, we cannot exclude the possibility that unmeasured factors may explain some of our findings. Second, this study involved patients seen in a specialised tertiary HF clinic of an academic hospital and mortality rate in this study was lower than reported in several recent observational studies of community-based HF populations. This is probably because, compared with subjects in other studies, our subjects were much younger (mean age 55.9 years compared with > 70 years), had a higher prevalence of non-ischaemic HF (60% compared with $< 50\%$) and a greater proportion were receiving ACEi and β blockers.^{29–30} Third, separate multivariate analyses of the OSA and CSA groups were attempted but failed to generate a workable model because of the small number of patients and events involved. However, univariate analysis demonstrated a similar increased risk of death associated with both OSA and CSA. Finally, we cannot be certain that SA severity did not change over time. However, in previous randomised trials involving patients with HF with CSA or OSA, no change in SA severity was seen in the control groups.^{15–16, 26}

In conclusion, our results suggest that the presence of SA, whether obstructive or central, increases mortality risk in patients with ischaemic, but not those with non-ischaemic,

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HF. It is well established that patients with ischaemic HF have higher mortality than those with non-ischaemic HF.⁵ Our data suggest that some of this excess mortality in patients with ischaemic HF may be attributable to SA. Therefore, treatment of SA seems more likely to have beneficial effects in patients with HF with ischaemic than in those with non-ischaemic aetiology. Randomised trials with stratified analysis of patients with ischaemic and non-ischaemic HF will be needed to test this hypothesis.

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