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ORIGINAL PAPER

Impact of sleep-disordered breathing and efficacy of positive airway pressure on mortality in patients with chronic heart failure and sleep-disordered breathing: a meta-analysis

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Abstract
Backgrounds To conduct a meta-analysis to investigate whether sleep-disordered breathing (SDB) is an independent risk factor for mortality and whether positive airway pressure (PAP) decreases mortality in patients with chronic heart failure (HF). The impact of SDB and the effects of PAP on mortality in patients with chronic HF remain unclear.
Methods We searched the MEDLINE, EMBASE, and Cochrane databases. Clinical trials that addressed mortality and the effect of PAP on mortality in chronic HF patients with SDB were included in this meta-analysis.
Results Eleven studies (1,944 participants in total) that addressed mortality in chronic HF patients with SDB were included in this study. Patients with SDB showed a significantly increased mortality risk compared to those without SDB [risk ratio (RR) 1.66 (1.19–2.31)]. In subanalyses, a significant increase in risk of mortality was observed for central sleep apnea versus no-SDB [RR 1.48 (1.15–1.91)], whereas no significant increase in risk was observed for obstructive sleep apnea versus no-SDB. Five randomized controlled studies (395 participants) that assessed the effect of PAP in chronic HF patients with SDB were analyzed. Adaptive servo-ventilation (ASV) significantly reduced all-cause mortality in chronic HF patients with SDB [RR 0.13 (0.02–0.95)], whereas continuous PAP did not significantly reduce all-cause mortality [RR 0.71 (0.32–1.57)].
Conclusions The prevalence of SDB in patients with chronic HF is associated with worse survival, and ASV reduces all-cause mortality in patients with chronic HF concomitant with SDB.

Keywords Sleep-disordered breathing · Sleep apnea · Heart failure · Mortality · Positive airway pressure · Prognosis

Introduction

Sleep-disordered breathing (SDB), including central sleep apnea (CSA) and obstructive sleep apnea (OSA), is highly prevalent in patients with chronic heart failure (HF) [1, 2]. A recent study focused on the development of chronic HF caused by SDB [3]. However, the general impact of SDB on mortality in chronic HF patients is questionable. SDB is usually treated with positive airway pressure (PAP) therapies such as continuous PAP (CPAP), bi-level PAP, and adaptive servo-ventilation (ASV), which have been reported to improve hypopnea, apnea, cardiac function, and hemodynamic status [4–7]. These therapies are expected to improve the prognosis of chronic HF patients with SDB. However, the effect of PAP on mortality in chronic HF with SDB remains unclear.

Therefore, this study focused on two distinct meta-analyses. First, to analyze mortality in chronic HF patients with SDB, we assessed changes in the mortality rate in chronic HF patients with SDB who did not receive PAP therapy. Second, to analyze the efficacy of PAP, we determined the effect of PAP on mortality in chronic HF patients with SDB.

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Methods

MEDLINE, EMBASE, and the Cochrane Collaboration databases were queried to identify articles that investigated (1) the prognosis of chronic HF patients with SDB who did not receive PAP therapy (an analysis of mortality in chronic HF patients with SDB) and (2) the effect of PAP on prognosis in chronic HF patients with SDB (an analysis of the efficacy of PAP).

For the analysis of mortality in chronic HF patients with SDB, we searched the databases for the following keywords: "heart failure", "congestive heart failure", "HF", "CHF", "sleep-disordered breathing", "apnea", "hypopnea", "sleep apnea", "obstructive sleep apnea", "OSA", "OSAS", "OSAHS", "SAHS", "central sleep apnea", "CSA", "CSAHS", "CAHS", "Cheyne-Stokes respiration", "Cheyne-Stokes", "Cheyne-Stokes", "mortality", "death", "prognosis", "prognostic", "outcomes", "outcome", and "predictor." For the analysis of PAP efficacy, the abovementioned keywords were used in addition to the following keywords: "adaptive servo ventilation", "adaptive ventilation", "servoventilation", "servo-ventilation", "CPAP", "bi-level positive airway pressure", "pressure", "ventilation", "PAP", "ASV", "CPAP", "BiPAP", "BPAP", "therapy", and "treatment." The search was limited to the English language articles and to the human studies published between January 1980 and March 2014. Reference lists of the selected articles were reviewed for other potentially relevant citations. In addition, the authors of the selected studies were contacted to obtain further information, if needed. The titles and abstracts of all citations were reviewed to identify potentially relevant studies. Abstracts were selected by two investigators (S.N. and A.K.) after a discussion. Regarding the analysis of mortality in chronic HF patients with SDB, we selected studies that included (1) patients with chronic HF who were screened for SDB, (2) at least 20 study participants, and (3) a control group of patients without SDB. Regarding the PAP efficacy analysis, we selected randomized controlled studies that included (1) a patient population with chronic HF and SDB, (2) patients in whom treatment was planned with or without PAP for SDB, and (3) at least 20 study participants. Reviews, editorials, animal studies, case reports, and conference abstracts were excluded from both analyses. After the full articles were retrieved, studies were further excluded if there was an overlap in the study population between studies, in which case the study with the larger sample size was included.

Trial information from the selected articles, including baseline clinical characteristics of the study population and outcome measures, were extracted using a prepared standardized extraction database. The quality of the mortality analyses in chronic HF patients with SDB was assessed with the Newcastle-Ottawa Scale (NOS) (Supplementary Table 1), and the quality of the PAP efficacy analyses was assessed with the Cochrane Risk of Bias Assessment (Supplementary Table 2). Absolute numbers were recalculated when percentages were reported. These steps were performed independently by two investigators (S.N., A.K.). The primary endpoint of both analyses was all-cause mortality.

The data collected from all studies were collated to estimate the pooled impact of the prevalence of SDB versus no-SDB and the impact (risk ratio, RR) of PAP efficacy. The calculations were based on a random effects model. When no event occurred in a group, a continuity correction was used to allow for the calculation of an RR. Heterogeneity among trials was quantified with Higgins' and Thompson's I^2. I^2 can be interpreted as the percentage of variability resulting from heterogeneity between studies rather than from sampling error. An $I^2 < 50$ % was considered to indicate at least moderate heterogeneity. All results are presented as point estimates, and the corresponding 95 % confidence intervals (CIs) are indicated in parentheses. To assess the effect of individual studies on the summary estimate of effect, we performed an influence analysis using a jackknife procedure; pooled estimates were recalculated by omitting one study at a time. A meta-regression analysis was performed based on the trial data. Potential publication bias was assessed with Egger's test and represented graphically by using Begg funnel plots of the natural log of the RR versus its standard error. All analyses were performed with Review Manager version 5.2 (The Cochrane Collaboration, Copenhagen, Denmark) and STATA version 13 (Statacorp, Texas, United States).

Results

An analysis of the mortality in HF patients with SDB

We screened the title or the abstract of 869 potentially eligible articles (Fig. 1). Of these, 858 articles were excluded because they were either not relevant or duplicates. Finally, 11 trials were included in this study after a full-text analysis, thus enrolling 1,944 patients (1,399 in the SDB group and 545 in the no-SDB group) in this meta-analysis [3, 8–19]. Table 1 summarizes the characteristics of the included studies. Patients with SDB showed significantly increased all-cause mortality and cardiac-cause mortality compared to patients without SDB [RR 1.66 (1.19–2.31); RR 1.79 (1.21–2.86), respectively] (Fig. 2). In sub-analyses, a significant increase in risk for all-cause mortality was observed with CSA versus the no-SDB controls [RR 1.48 (1.15–1.91), Fig. 2], whereas the risk was not significantly increased for OSA versus no-SDB

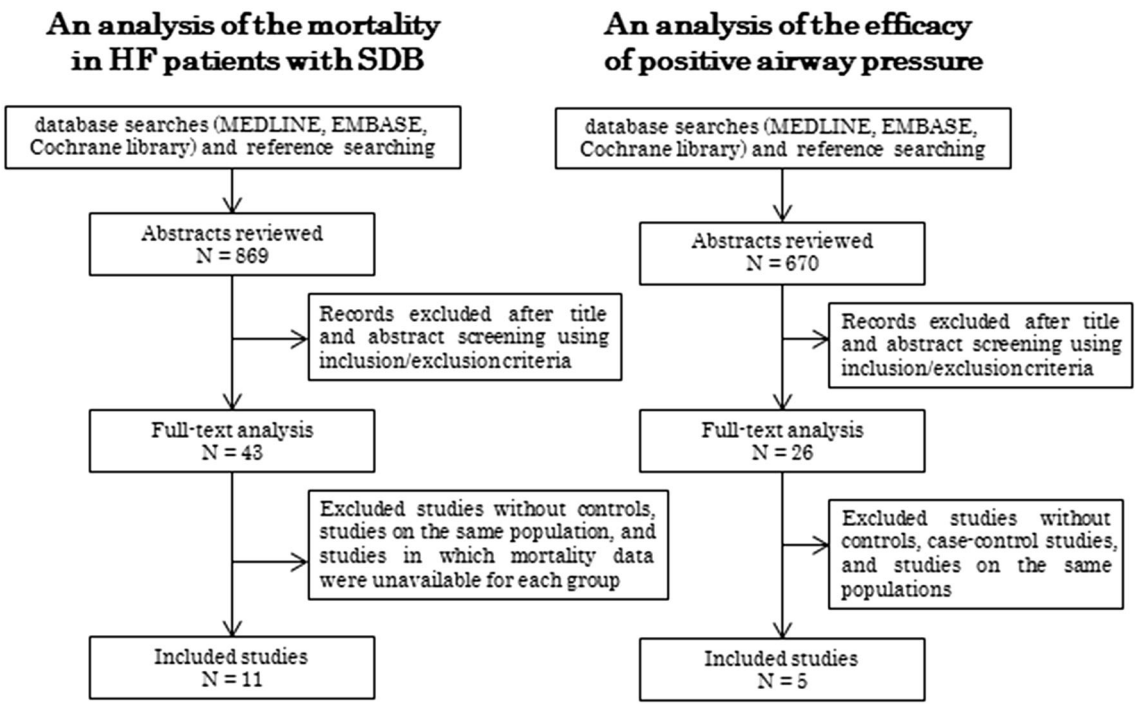

Fig. 1 Flow chart depicting the selection of studies included in this meta-analysis

[RR 1.09 (0.83–1.42), $P = 0.6$, Fig. 2]. A subgroup analysis was performed for all-cause mortality according to other baseline characteristics (Fig. 3). The effect sizes were greater in trials that recorded a mean apnea–hypopnea index of ≥30/hour in the SDB arm ($P = 0.01$) and a mean follow-up duration of ≥3 years for all patients ($P = 0.002$).

A univariate meta-regression analysis for all-cause death outcomes favored a higher apnea–hypopnea index in the SDB arm ($P = 0.4$), and a longer follow-up duration for trials ($P = 0.5$), although neither was statistically significant (Supplementary Figure 1). In the univariate meta-regression analyses of other variables, no significant associations were found between all-cause mortality and age, gender, ischemic heart disease, body mass index, left ventricular ejection fraction, use of beta blockers, use of angiotensin-converting enzyme inhibitors (ACE-I), or use of angiotensin receptor blockers (ARB) at baseline.

An analysis of the efficacy of positive airway pressure

We screened the title or the abstract of 670 potentially eligible publications (Fig. 1). Of these, 665 articles were excluded because they were either not relevant or duplicates. Finally, five trials were included after a full-text analysis, thus enrolling 395 patients (196 in the PAP therapy group and 199 in the control group) in this study [4, 7, 18, 20, 21]. Table 2 summarizes the characteristics of the included studies. Different types of PAP were applied in the included studies: ASV was used in three trials, and CPAP was used in two trials. ASV therapy significantly reduced all-cause mortality in chronic HF patients with SDB [RR 0.13 (0.02–0.95), Fig. 2], whereas CPAP therapy did not significantly reduce all-cause mortality [RR 0.71 (0.32–1.57), Fig. 2]. In the sub-analysis, ASV therapy significantly reduced all-cause mortality in HF patients with CSA [RR 0.13 (0.02–0.95), Fig. 2], whereas ASV therapy did not significantly reduce all-cause mortality in chronic HF patients with OSA [RR 0.14 (0.01–2.58), Fig. 2]. Univariate meta-regression analyses did not reveal significant associations between mortality and age, male gender, body mass index, ischemic cardiomyopathy, apnea–hypopnea index, use of diuretics, use of ACE-I or ARB, use of beta blockers, or left ventricular ejection fraction at baseline. Furthermore, no significant associations were found between the changes in left ventricular ejection fraction and mortality after therapy in the PAP therapy arm [Coef. −0.781 (−6.250 to 4.687), $P = 0.3$]. In addition, no significant association was found between changes in the apnea–hypopnea index and reduced mortality after therapy in the PAP therapy arm [Coef. 0.059 (−0.080 to 0.199), $P = 0.3$].

In an analysis of mortality in chronic HF patients with SDB, a sensitivity analysis using the jackknife procedure omitting one study at a time showed consistent estimates for an increased relative risk in patients with SDB. None of

Table 1 Summary of the characteristics of the included studies in the analysis of mortality in chronic heart failure patients with sleep-disordered breathing

Study	Year	Sample size	Study design	Average duration of follow-up (months)	Mean age (years)	Male (%)	Heart failure inclusion criteria	Sleep-disordered breathing group criteria
Hanly (12)	1996	22	Prospective cohort	44	64	NA	New York Heart Association functional class 3–4 Left ventricular ejection fraction <35 %	Central sleep apnea
Sin (18)	2000	35	Prospective cohort	NA	59	87	New York Heart Association functional class 2–3 Left ventricular ejection fraction ≤45 %	Central sleep apnea and Apnea–hypopnea index ≥15
Roebuck (17)	2004	78	Prospective cohort	52	53	82	New York Heart association functional class 2–4 Left ventricular ejection fraction ≤55 %	Apnea–hypopnea index ≥5
Corra (8)	2006	133	Prospective cohort	39	58	94	Left ventricular ejection fraction ≤40 %	Apnea–hypopnea index ≤30
Yumino (19)	2009	193	Prospective cohort	32	56	75	New York Heart Association functional class 2–4 Left ventricular ejection fraction ≤45 %	Apnea–hypopnea index ≥15
Luo (16)	2010	128	Prospective cohort	35	55	20	New York Heart Association functional class 2–4 Left ventricular ejection fraction ≤45 %	Apnea–hypopnea index ≥5
Hagenah (11)	2010	35	Prospective cohort	38	62	84	New York Heart Association functional class 2–3 Left ventricular ejection fraction ≤35 %	Central sleep apnea and Apnea–hypopnea index >10
Bakker (9, 10)	2011	46	Prospective cohort	75	60	78	Left ventricular ejection fraction ≤45 %	Apnea–hypopnea index >10
Javaheri (13)	2011	314	Population-based retrospective analysis	24	67	56	Not available	Not available
Jilek (14)	2011	182	Prospective cohort	49	62	86	Left ventricular ejection fraction ≤50 %	AHI ≥22.5
Khayat (15)	2012	304	Prospective cohort	6	58	68	Left ventricular ejection fraction ≤45 %	AHI ≥15

the studies influenced the overall results toward statistical non-significance (Supplementary Figure 2). In both analyses, the funnel plots of both studies were rather symmetrical (Supplementary Figure 3). Formal testing did not indicate a relevant small study effect or publication bias (Egger's test, $P = 0.8$, and rank correlation test, $P = 0.4$ in the analysis of mortality in HF patients with SDB; Egger's test, $P = 0.1$, and rank correlation test, $P = 1.0$ in the analysis of the efficacy of PAP).

Discussion

This meta-analysis confirms that the presence of SDB in conjunction with chronic HF is associated with worse survival. Furthermore, this meta-analysis showed that ASV therapy significantly reduced all-cause mortality in chronic HF patients with CSA, but not OSA; whereas CPAP therapy did not significantly reduce all-cause mortality in HF patients with SDB. In addition, the sub-analysis indicated that the presence of CSA in chronic HF increases mortality, whereas the presence of OSA was not associated with worse survival; this result, however, did not show statistical significance.

In patients with chronic HF, SDB potentially increases cardiac death by certain mechanisms. CSA and OSA coexist in patients with chronic HF, but the harmful effects of CSA and OSA differ considerably. With respect to OSA, the production of exaggerated negative intrathoracic pressure by inspiratory efforts against the occluded pharynx immediately increases transmural pressure, which is the pressure inside the LV minus the pressure outside the LV, contributing to increased LV wall stress (i.e., afterload) as well as increased aortic wall stress [22]. It not only increases venous return to the right ventricle (i.e., preload), but hypoxic pulmonary vasoconstriction caused by OSA also increases the right ventricular afterload. Consequent right ventricular distension and leftward septal displacement during the diastole phase impair LV filling. The combination of increased LV afterload and diminished LV preload during obstructive apnea reduces stroke volume and cardiac output. Increased LV transmural pressure also raises myocardial oxygen demand, and apnea-related hypoxia increases sympathetic nerve traffic [23, 24]. Negative tracheal pressure also causes shortening of the right atrial refractory period and increased susceptibility to atrial fibrillation, mainly by enhanced vagal activation [25]. Together, these mechanisms can precipitate myocardial ischemia, fatal arrhythmia, aortic dissection, and worsening HF [26–28]. Therefore, negative intrathoracic pressure could increase death caused by cardiovascular events. Another direct mechanism by which long-standing OSA might induce left ventricular systolic dysfunction is by raising blood pressure. Hypertension is the most common risk factor for ventricular hypertrophy and failure [29]. In this meta-analysis, the presence of OSA was likely associated with worse survival, and ASV tended to decrease mortality in patients with OSA and chronic HF, although these results did not reach statistical significance. This result may be attributed to the smaller sample size (not enough statistical power) in the subgroup analysis with wider CIs. On the other hand, it remains unknown whether CSA is an epiphenomenon in the setting of chronic HF or whether it may lead to an increased risk or progression of chronic HF. Severe CSA is associated with impaired cardiac autonomic control and increased cardiac arrhythmias [30]. CSA both increases muscular sympathetic nerve activity and decreases oxygen saturation in patients with chronic HF [31]. In patients with chronic HF and coexisting sleep apnea, the convergence of the independent excitatory influences of chronic HF and sleep apnea on the central sympathetic neurons results in higher sympathetic nerve activity in the muscles during wakefulness [32]. This additional stimulus to the central sympathetic outflow may accelerate the progression of chronic HF. Consequently, activation of the nervous system and hypoxia could increase death caused by arrhythmia, ischemia, and the progression of chronic HF. These mechanisms provide the basis for the results obtained in this study. Regarding alternative treatments for chronic HF patients with SDB, optimizing treatment of the underlying HF is of foremost importance. In patients with OSA, behavioral modification is the basic therapy, including weight reduction, exercising, changing the sleep position, and abstaining from alcohol. Oral appliances and upper airway surgery are alternative therapies. In patients with CSA, cardiac resynchronization therapy should be considered in indicated patients, because some small, non-randomized controlled trials have shown improvement in CSA with its use [33, 34].

PAP has been reported to reduce the severity of SDB, improve exercise capacity, and improve cardiac function [4–6, 35]. In recent decades, although considerable progress has been made in the treatment of severe HF, such as medications, cardiac resynchronization therapy, and transplantation, the effect of PAP therapy on hard outcomes has less evidence to support it than the abovementioned HF therapies. A meta-analysis by Sharma et al. [36] demonstrated that ASV was more effective than continuous or bi-level pressure ventilation, oxygen therapy, or no treatment in HF patients with SDB. Our results indicate that the clinical superiority of ASV over CPAP may be relevant to mortality. Therefore, further studies are warranted to assess whether ASV is better than CPAP with respect to mortality and clinical parameters in chronic HF patients with SDB.

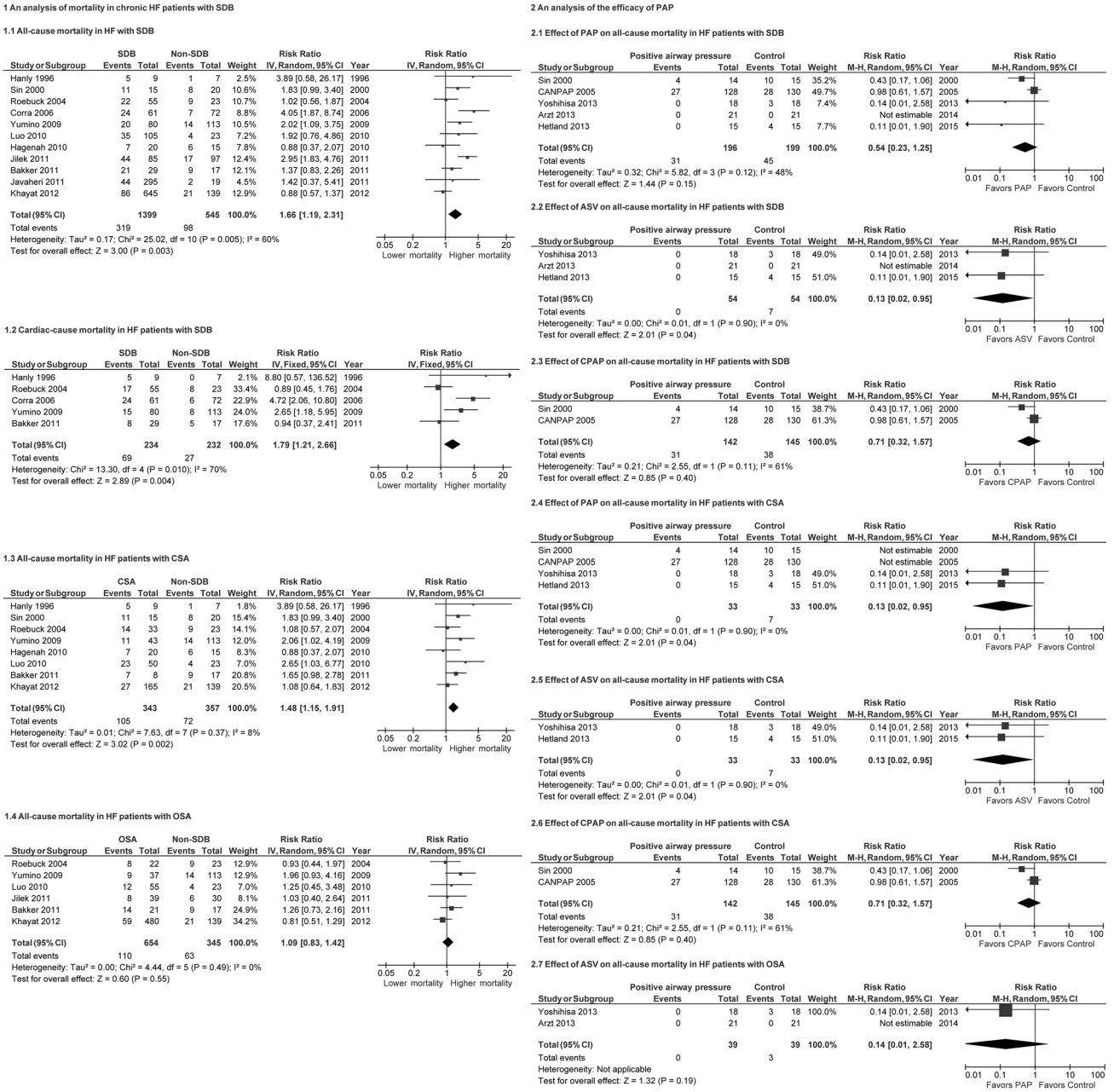

Fig. 2 Forest plots from the analysis. *Markers* represent point estimates of risk ratios; the *marker size* indicates the study weight in the random-effect meta-analysis. *Horizontal bars* indicate 95 % confidence intervals. *HF* heart failure, *SDB* sleep-disordered breathing, *CSA* central sleep apnea, *OSA* obstructive sleep apnea, *CI* confidence interval, *IV* inverse variance, *M–H*, Mantel–Haenszel, *PAP* positive airway pressure, *ASV* adaptive servo-ventilation, *CPAP* continuous positive airway pressure, *RCT* randomized controlled trial

The results of this meta-analysis provide an encouraging rationale for large-size, randomized, controlled trials such as SERVE-HF [37] (a multinational, multicenter, randomized parallel trial designed to evaluate the effect of ASV in optimal medical management compared with medical management alone in 1,200 patients with CHF and CSA) to evaluate hard endpoints in chronic HF patients with SDB.

Limitations

We acknowledge the following limitations of this analysis. First, each of the included studies had their own specific and general limitations. All included studies differed with respect to study design, patient characteristics, follow-up duration, therapy regimen, ventilator type, ventilator start time, and included sleep apnea

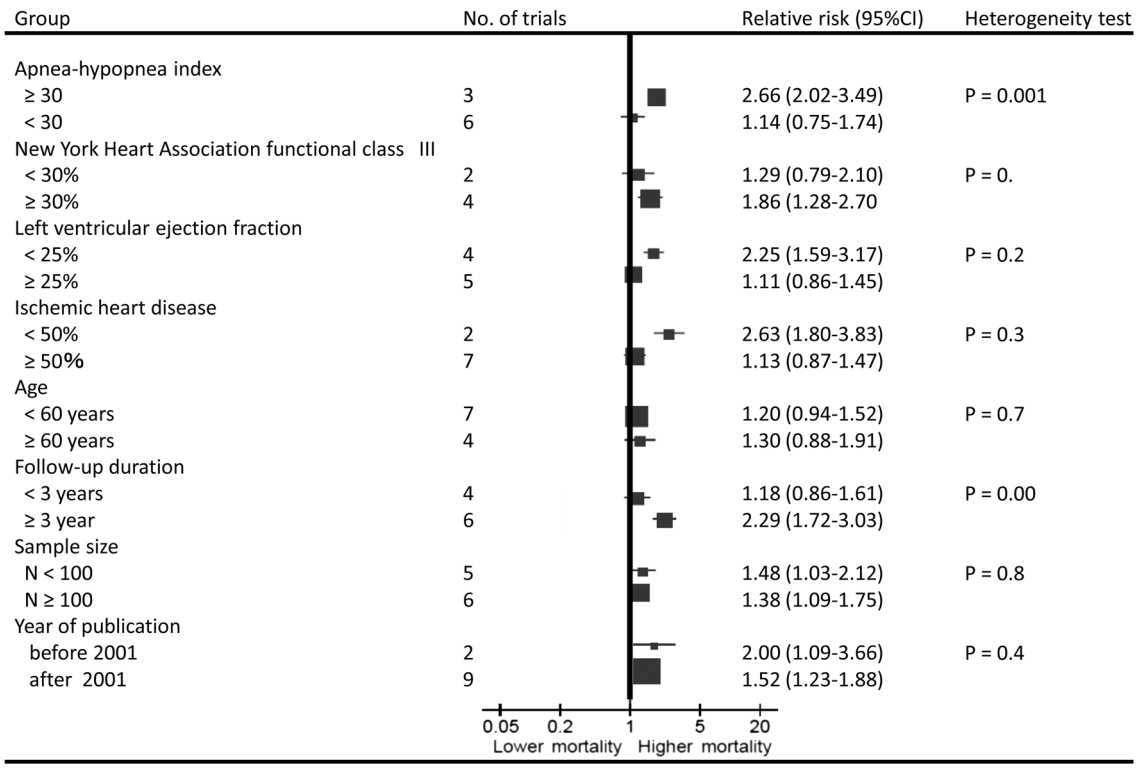

Fig. 3 A subgroup analysis of mortality in chronic heart failure patients with sleep-disordered breathing

thresholds (Table 1). Although the sensitivity analysis showed that there was no statistically significant difference, there is a possibility that these differences may have influenced the results of the present meta-analysis. We excluded patients treated with PAP in each study as much as possible, but some patients in two of the included studies were treated with CPAP during the follow-up periods [15, 17]. In the sensitivity analysis omitting these two studies from the included studies, it was observed that their inclusion did not influence the overall results [RR (SDB versus no-SDB) 2.00 (1.45–2.75), $P < 0.001$; RR (CSA versus no-SDB) 1.75 (1.3.0–2.36), $P < 0.001$; RR (OSA versus no-SDB) 1.36 (0.94–1.97), $P = 0.1$]. SDB may simply represent a marker that is associated with worse survival. However, the magnitude of SDB in each study was different, and the control groups in three of the studies selected for the analysis of mortality in CHF patients with SDB had mild or moderate SDB [9, 15, 19]. Nevertheless, the overall result was significantly consistent if these three studies were omitted. Another drawback is that some studies were small; the smallest study included only 22 patients. The decision to include smaller studies was necessary to maximize the utilization of all available data on this important topic. A sensitivity analysis confirmed that there were no heterogeneities between the small studies and the other studies. In two studies, the absolute numbers of events were back-calculated from percentages, which were based on Kaplan–Meier event estimates. This method can be erroneous, especially if significant numbers of patients were lost to follow-up. It was not possible to verify these data with the corresponding authors of the original articles. The risk of bias assessment suggested that several studies had poor methodological qualities, allowing for potential bias and confounding. Secular trends in chronic HF therapy have been occurring over the past decade (for example, cardiac resynchronization therapy and increased use of implantable defibrillators); these newer therapies may affect SDB itself, and particularly CSA and its outcomes. Thus, the results could be different if the meta-analysis was carried out using studies that implemented the current treatments. In the present analysis, the association between the severity of sleep apnea and the efficacy of ASV on mortality in patients with CSA could not be analyzed because very few trials were included. Further studies should evaluate the association between sleep apnea severity and the effect of ASV on mortality. We fully understand that our results are clearly limited to the populations studied. Despite these limitations, we view our findings as an important addition to the literature because they provide a compelling rationale for further

Table 2 Summary of the characteristics of the included studies in the analysis of positive airway pressure efficacy

Study	Year	Study design	Intervention	Control Type	Average duration of follow-up	Mean age (years)	Male (%)	Heart failure inclusion criteria	Sleep-disordered breathing inclusion criteria
Sin (18)	2000	Randomized	Continuous positive airway pressure CPAP	No treatment	NA	57.9	100	New York Heart association functional class 2–4 Left ventricular ejection fraction ≤45 %	Central sleep apnea and Apnea–hypopnea index ≥15/h
CANPAP (4)	2005	Randomized	Continuous positive airway pressure	No treatment	24 months	63.4	96.5	New York Heart Association functional class 2–4 Left ventricular ejection fraction <40 %	Central sleep apnea and Apnea–hypopnea index ≥15/h
Yoshihisa (7)	2013	Randomized	Adaptive servo-ventilation	No treatment	18 months	64.3	80.6	New York Heart association functional class 2–4 Left ventricular ejection fraction >50 %	Sleep-disordered breathing and Apnea–hypopnea index ≥15/h
Arzt (20)	2013	Randomized	Adaptive servo-ventilation	No treatment	3 months	64.5	91.5	New York Heart Association functional class 2–3 Left ventricular ejection fraction ≤40 %	Sleep-disordered breathing and Apnea–hypopnea index ≥20/h
Hetland (21)	2013	Randomized	Adaptive servo-ventilation	No treatment	Not available	70.5	93.3	New York Heart Association functional class 3–4 Left ventricular ejection fraction ≤40 %	Central sleep apnea and Cheyne-Stokes breathing for >25 % of sleeping time

research and represent the best available evidence until more data are available.

Conclusion

The results of this meta-analysis show that the prevalence of SDB in patients with chronic HF is associated with worse survival, and that ASV reduces all-cause mortality in patients with chronic HF concomitant with SDB.

Conflict of interest None.

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