Composition of nocturnal hypoxaemic burden and its prognostic value for cardiovascular mortality in older community-dwelling men

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Received 14 May 2018; revised 17 August 2018; editorial decision 5 October 2018; accepted 22 November 2018; online publish-ahead-of-print 22 December 2018

Aims

To investigate the composition of nocturnal hypoxaemic burden and its prognostic value for cardiovascular (CV) mortality in community-dwelling older men.

Methods and results

We analysed overnight oximetry data from polysomnograms obtained in 2840 men from the Outcomes of Sleep Disorders in Older Men (MrOS Sleep) study (ClinicalTrials.gov Identifier: NCT00070681) to determine the number of acute episodic desaturations per hour (oxygen desaturation index, ODI) and time spent below 90% oxygen saturation (T90) attributed to acute desaturations (T90desaturation) and to non-specific drifts in oxygen saturation (T90non-specific), respectively, and their relationship with CV mortality. After 8.8 ± 2.7 years follow-up, 185 men (6.5%) died from CV disease. T90 [hazard ratio (HR) 1.21, $P < 0.001$], but not ODI (HR 1.13, $P = 0.06$), was significantly associated with CV death in univariate analysis. T90 remained significant when adjusting for potential confounders (HR 1.16, $P = 0.004$). Men with T90 > 12 min were at an elevated risk of CV mortality (HR 1.59; $P = 0.006$). Approximately 20.7 (5.7–48.5) percent of the variation in T90 could be attributed to non-specific drifts in oxygen saturation. T90desaturation and T90non-specific were individually associated with CV death but combining both variables did not improve the prediction.

Conclusion

In community-dwelling older men, T90 is an independent predictor of CV mortality. T90 is not only a consequence of frank desaturations, but also reflects non-specific drifts in oxygen saturation, both contributing towards the association with CV death. Whether T90 can be used as a risk marker in the clinical setting and whether its reduction may constitute a treatment target warrants further study.

Keywords

Hypoxaemia • Cardiovascular • Sleep • Oximetry • Death • Mortality

Introduction

Nocturnal hypoxaemic burden—the cumulative exposure to hypoxaemia experienced overnight—may contribute to the pathophysiology of cardiovascular (CV) disease and CV death by increasing the production of reactive oxygen species, vascular inflammation,

autonomic imbalance, activation of the sympathetic nervous system, and elevating blood pressure.^{1–6}

In overnight sleep studies, nocturnal hypoxaemic burden is usually quantified using finger pulse oximetry by counting the number of episodic oxygen desaturations per hour of sleep (oxygen desaturation index; ODI) or measuring the time spent below 90% oxygen

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saturation (T90).⁷ Punjabi et al.⁸ showed that prevalent CV disease was related to the extent of hypopnoea associated oxygen desaturation during sleep. More recently, T90 was found to be an independent predictor of all-cause mortality in stable chronic heart failure patients⁹ and was associated with an increased incidence of fatal stroke in community-dwelling older men.¹⁰ These and other studies suggest that nocturnal hypoxaemia may be a key variable damaging the heart and CV system.^{9,11–14}

Although widely considered the consequence of short acute episodic oxygen desaturations elicited by obstructive and/or central apnoeas and hypopnoeas prevalent in patients with sleep-disordered breathing, non-specific transient drifts of oxygen saturation during night, even in subjects without sleep-disordered breathing, might contribute to nocturnal hypoxaemic burden. The role of the composition of nocturnal hypoxaemic burden with respect to acute episodic desaturations–resaturation events and/or non-specific transient drift of oxygen saturation for predicting CV outcomes is unclear as tools for its automated quantification and detailed characterization are not readily available.^{15,16}

The aim of this study was to characterize the composition of nocturnal hypoxaemic burden and its prognostic role for CV mortality in an elderly male population. Using a novel custom-made computer algorithm that distinguishes T90 due to well-defined desaturations (T90desaturation) from those caused by non-specific drifts in oxygen saturation and incomplete resaturation (T90non-specific), we determined their prognostic value for CV mortality in older community-dwelling men participating in the Outcomes of Sleep Disorders in Older Men (MrOS Sleep) study (ClinicalTrials.gov Identifier: NCT00070681), a sub-study of the ongoing prospective Osteoporotic Fractures in Men study (MrOS).

Methods

Study population

Osteoporotic Fractures in Men study was designed to describe the epidemiology of osteoporosis and fractures in older men, including the identification of risk factors for fracture and bone loss. Between March 2000 and April 2002, 5994 community-dwelling men aged 65 years and older were enrolled.¹⁷ Participants were recruited from six U.S. centres. Participants considered for enrolment in MrOS had to be able to walk without the assistance of another person and not have a bilateral hip replacement.¹⁸

A total of 3135 men from the MrOS cohort were recruited for participation in the MrOS Sleep study. All men provided written informed consent, and the study was approved by the Institutional Review Board at each site. The men were screened for use of mechanical devices during sleep including pressure mask for sleep apnoea, mouthpiece for snoring or sleep apnoea or oxygen therapy. In general, those who reported nightly use of any of these devices were excluded from the MrOS Sleep study. However, 17 men who reported any use of one of these devices but could forego use during the night of the sleep study were included. The 3135 men completed an exam conducted between December 2003 and March 2005 that included a clinic visit and overnight in-home polysomnography (PSG). Of these men, 2911 (92.9%) had technically adequate PSG.

Follow-up

Participants were surveyed for potential incident CV disease or clinically relevant arrhythmia events by postcard and/or phone contact every 4 months with >99% response rate (see [Supplementary material online](#)). For both non-fatal and fatal CV events, all documents were adjudicated by a board-certified cardiologist using a pre-specified adjudication protocol developed using methods that had been successfully employed at the co-ordinating centre for both prior randomized trials and epidemiological studies of CV disease.

Overnight polysomnography

Unattended PSG was performed over one night at the participant's residence using the Sleep Monitoring System (Safiro, Compumedics, Inc., Charlotte, NC, USA) as described in the [Supplementary material online](#). Sleep-disordered breathing severity was assessed by the apnoea hypopnoea index (AHI) (no: $0 \leq \text{AHI} < 5$; mild: $5 \leq \text{AHI} < 15$; moderate-to-severe: $\text{AHI} \geq 15$). Apnoeas were defined as a complete or almost complete cessation of airflow, lasting >10s, and usually associated with desaturation or an arousal, and hypopnoeas were defined as a reduction in airflow <70% of a 'baseline' level, associated with a >3% desaturation or arousal.

Quantification and characterization of nocturnal hypoxaemic burden

Nocturnal hypoxaemic burden was defined as total sleep time spent at oxygen saturation levels below 90% (T90). To further characterize the composition of nocturnal hypoxaemic burden, we quantified the component of T90 associated with acute oxygen desaturation events accompanied by resaturation (T90desaturation) vs. T90 associated with non-specific drifts in oxygen saturation or incomplete resaturation (T90non-specific). Acute desaturations were defined as episodic, monotonic drops in oxygen saturation by at least 4% from any prior level that were followed by a resaturation to at least two-thirds of oxygen saturation level observed prior to desaturation within a period of 150s starting from the onset of desaturation (see [Supplementary material online](#) for technical details).

The requirement of a resaturation after a scored desaturation event is not implemented in the current American Academy of Sleep Medicine (AASM) scoring rules,¹⁹ but allows the discrimination between distinct episodic desaturation events and non-specific drifts of oxygen saturation as well as the determination of the onset and end of the desaturation event. *Figure 1* shows representative oximetry traces of T90 due to low oxygen saturation and acute episodic desaturations, respectively. In addition to T90, we calculated the ODI as a count of desaturations of at least 4% per hour of sleep.

Other measures

All participants completed a questionnaire at the time of the sleep visit, which included questions about medical history, specifically history of physician diagnosis of diabetes, chronic obstructive pulmonary disease (COPD), asthma, hypertension, and CV disease [coronary artery disease (CAD), myocardial infarction (MI), stroke, and heart failure (HF)]. Participants were also asked about their smoking status, alcohol use, and physical activity [Physical Activity Scale for the Elderly (PASE)]. Height and weight were used to calculate body mass index (BMI). Thyroid function was assessed from serum samples as described previously.²⁰

Figure 1 Examples of pulse oximetry traces (SaO_2) derived from overnight polysomnography. (A) Low baseline oxygen saturation, but not acute desaturation events determine T90. (B) Distinct desaturations, but not baseline saturation—indicated by the blue arrows—determine T90.

Statistical analysis

Variables of nocturnal hypoxaemic burden (T90desaturation, T90non-specific, and ODI) were divided into quartiles for Kaplan–Meier curve survival analysis and log-rank testing. Anthropometric data, lifestyle metrics, and medical history were compared using dichotomized variables and student's *t*-test and χ^2 test, respectively. Cox proportional hazard models were constructed for continuous variables normalized to standard deviation and dichotomized variables. The proportionality of hazard ratio (HR) was tested using cumulative sums of martingale residuals. Adjustments were performed for those variables in Table 1 that differed significantly between dichotomized groups in any of the comparisons. Correlations were assessed using Spearman's rank coefficient. IBM SPSS Statistics 24 was used for statistical analysis. All data are available via the MrOS Online website (<http://mrosdata.sfcc-cpmc.net>).

Results

Participant characteristics

Characteristics of the MrOS Sleep cohort are summarized in Table 1. At the baseline visit, participants were aged 76.3 ± 5.5 years and their BMI was $27.2 \pm 3.7 \text{ kg/m}^2$; 49.3% of men were overweight and 20.3% obese. Approximately 60% of men were former or current (2.0%) smokers and 65.4% reported weekly alcohol consumption. Nearly 50% of men reported a history of hypertension, 13.2% had diabetes, 17.2% had a history of CAD/MI, and 5.9% had HF. Histories of asthma and COPD were reported by 7.8% and 5.3% of participants, respectively. Prevalence of liver disease (2.2%), kidney disease (1.1%), and stroke (3.8%) were low. The average AHI obtained from overnight PSG was 20.2 ± 12.9 .

Composition of nocturnal hypoxaemic burden

The distribution of T90 across the study cohort is shown in Figure 2A. In 513 study participants (18.1%), oxygen saturation was at no time-point below 90%. Acute episodic desaturations below 90% (T90desaturation) occurred in 2266 participants (79.8%). In 1965 (69.2%) participants, saturation below 90% due to non-specific drifts of oxygen saturation and incomplete resaturation not related to acute episodic desaturations (T90non-specific) occurred. In those men who spent time below 90% oxygen saturation, 20.7 (5.7–48.5)

% that time could be attributed to T90non-specific. Correlation coefficients between T90 and T90non-specific and T90desaturation, respectively, were $\rho = 0.911$, $P < 0.001$ and $\rho = 0.966$, $P < 0.001$. The correlation coefficient between T90non-specific and T90desaturation was $\rho = 0.828$, $P < 0.001$.

Correlations between ODI and T90 ($\rho = 0.664$, $P < 0.001$), T90desaturation ($\rho = 0.749$, $P < 0.001$) and T90non-specific ($\rho = 0.494$, $P < 0.001$) are shown in Figure 2B. T90 varied widely across men with no, mild and moderate-to-severe sleep-disordered breathing (Figure 2C).

Cardiovascular mortality

Outcome data on CV mortality were available for 2840 men. During the follow-up period of 10.2 (7.9–10.7) years [median (interquartile range)], 185 men (6.5%) died from CV disease. The median follow-up time of men who died from CV disease was 4.4 (2.5–7.0) years. There were 104 confirmed CAD deaths, 36 cerebrovascular deaths, 22 HF deaths, 5 peripheral vascular disease deaths, and 5 arrhythmic deaths.

Univariate survival analysis

The Kaplan–Meier curves of T90 quartiles illustrate significantly elevated CV mortality rates in participants whose T90 was in the highest quartile (12.1–339.9 min), vs. those in the lower three quartiles, in whom mortality was comparable (at 10 years: 8.8% vs. 5.6%, for upper and lowest three quartiles, respectively; $P = 0.02$) (Figure 3). Participants in the highest quartile were more likely to be obese, less physically active, former smokers, to have HF, a history of hypertension, COPD, and less likely to consume alcohol compared with those in lower quartiles (Table 1).

The distribution of desaturation-related hypoxaemia quartiles (T90desaturation) shows a similar pattern in their Kaplan–Meier curves, where the highest quartile (8.7–276.0 min) was associated with a CV mortality at 10 years of 8.9% vs. 5.6% for the other three quartiles ($P = 0.01$) (Figure 3). Participants in the highest quartile consumed less alcohol, had a higher BMI, were more likely to have diabetes, HF, hypertension, COPD, and sleep apnoea (Table 1).

Kaplan–Meier curves of T90non-specific quartiles (Figure 3) show increased CV mortality (at 10 years: 9.2% vs. 5.5%, $P = 0.01$) in participants whose T90non-specific was in the highest quartile

Table 1 Study cohort characteristics

Variables	All	T90 ≤ 12 min (Q 1–3)	T90 > 12 min (Q 4)	P-value	T90non-specific ≤ 3 min (Q 1–3)	T90non-specific > 3 min (Q 4)	P-value	T90desaturation ≤ 9 min (Q 1–3)	T90desaturation > 9 min (Q 4)	P-value
	n = 2840	n = 2132	n = 708		n = 2111	n = 729		n = 2168	n = 672	
Anthropometric data										
Age (years)	76.3 ± 5.5	76.2 ± 5.5	76.6 ± 5.4	0.07	76.1 ± 5.4	76.8 ± 5.59	0.001	76.2 ± 5.5	76.6 ± 5.4	0.08
Ethnicity/race										
White	2584 (91%)	1929 (90.5%)	655 (92.5%)	0.24	1907 (90.3%)	677 (92.9%)	0.10	1966 (90.7%)	618 (92.0%)	0.54
African American	96 (3.4%)	76 (3.6%)	20 (2.8%)		76 (3.6%)	20 (2.7%)		76 (3.5%)	20 (3.0%)	
Asian	84 (3.0%)	70 (3.3%)	14 (2.0%)		71 (3.4%)	13 (1.8%)		69 (3.2%)	15 (2.2%)	
Other	76 (2.7%)	57 (2.7%)	19 (2.7%)		57 (2.7%)	19 (2.6%)		57 (2.6%)	19 (2.8%)	
Bodyweight										
BMI (kg/m ²)	27.1 ± 3.7	26.5 ± 3.4	29.1 ± 4.07	<0.001	26.5 ± 3.4	28.9 ± 4.1	<0.001	26.6 ± 3.5	29.1 ± 4.1	<0.001
Overweight	1400 (49.3%)	1050 (49.3%)	350 (49.4%)		1037 (49.2%)	363 (49.8%)		1070 (49.4%)	330 (49.2%)	
Obese	576 (20.3%)	315 (14.8%)	261 (36.9%)		321 (15.2%)	255 (35.0%)		329 (15.2%)	247 (36.8%)	
Lifestyle										
PASE score	1460 ± 71.5	148.5 ± 71.2	138.6 ± 71.8	0.001	148.7 ± 71.9	138.4 ± 69.6	0.001	147.5 ± 71.1	141.3 ± 72.7	0.05
Smoking										
Never	1124 (39.6%)	876 (41.1%)	248 (35.0%)	0.014	883 (41.8%)	241 (33.1%)	<0.001	878 (40.5%)	246 (36.6%)	0.08
Past	1657 (58.4%)	1214 (57.0%)	443 (62.6%)		1190 (56.4%)	467 (64.1%)		1241 (57.3%)	416 (61.9%)	
Current	57 (2.0%)	40 (1.9%)	17 (2.4%)		37 (1.8%)	20 (2.7%)		47 (2.2%)	10 (1.5%)	
Alcohol consumption	1848 (65.4%)	1421 (67.0%)	427 (60.7%)	0.002	1409 (67.1%)	439 (60.6%)	0.002	1439 (66.7%)	409 (61.2%)	0.01
Medical history										
Diabetes	376 (13.2%)	267 (12.5%)	109 (15.4%)	0.05	266 (12.6%)	110 (15.1%)	0.08	268 (12.4%)	108 (16.1%)	0.01
CAD/MI	489 (17.2%)	352 (16.5%)	137 (19.4%)	0.08	353 (16.7%)	136 (18.7%)	0.23	358 (16.5%)	131 (19.5%)	0.07
HF	167 (5.9%)	110 (5.2%)	57 (8.1%)	0.006	113 (5.4%)	54 (7.4%)	0.04	109 (5.0%)	58 (8.6%)	0.001
Hypertension	1404 (49.5%)	1009 (47.3%)	395 (55.8%)	<0.001	1010 (47.8%)	394 (54.1%)	0.004	1025 (47.3%)	379 (56.4%)	<0.001
Stroke	107 (3.8%)	81 (3.8%)	26 (3.7%)	1.0	82 (3.9%)	25 (3.4%)	0.6	87 (4.0%)	20 (3.0%)	0.2
Asthma	222 (7.8%)	167 (7.8%)	55 (7.8%)	0.9	161 (7.6%)	61 (8.4%)	0.5	174 (8.0%)	48 (7.1%)	0.5
COPD	150 (5.3%)	87 (4.1%)	63 (8.9%)	<0.001	81 (3.8%)	69 (9.5%)	<0.001	98 (4.5%)	52 (7.7%)	0.002
AHI	20.2 ± 12.9	17.8 ± 11.2	27.2 ± 15.2	<0.001	18.5 ± 11.8	25.0 ± 14.7	<0.001	17.5 ± 11.0	28.8 ± 15.0	<0.001
Thyroid function										
Low	236 (8.3%)	176 (8.3%)	60 (8.5%)	0.9	183 (8.7%)	53 (7.3%)	0.3	180 (8.3%)	56 (8.3%)	0.8
Normal	2564 (90.3%)	1925 (90.3%)	639 (90.3%)		1897 (89.9%)	667 (91.6%)		1956 (90.3%)	608 (90.5%)	

AHI, apnoea hypopnoea index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; HF, heart failure; MI, myocardial infarction; Q, Quartile.

Figure 2 (A) Histogram of total sleep time spent below 90% oxygen saturation (T90), T90 attributed to desaturations (T90desaturation), and to non-specific drifts of oxygen saturation (T90non-specific) across the study cohort. The inset displays a zoomed-in view for T90 ≥ 100 min. (B) Relationship between T90 indices and oxygen desaturation index (ODI). (C) Box plots of T90 quartiles in men with no, mild and moderate-to-severe sleep-disordered breathing as determined by the apnoea hypopnoea index (AHI).

(3.1–332.2 min). These men were more likely to be white, marginally older, had a higher BMI, less physically active, were more likely to be smokers, to have a history of hypertension, HF, COPD, sleep apnoea and less likely to consume alcohol (Table 1).

The distribution of ODI was not associated with CV mortality in the Kaplan–Meier analysis ($P = 0.5$).

To establish whether combinations of different T90desaturation and T90non-specific intensities affect CV mortality, we created joint scores of dichotomized T90desaturation and T90non-specific data and investigated Kaplan–Meier curves (Figure 4). CV mortality was the highest for those participants who fell in the highest T90desaturation and T90non-specific quartiles.

Cox-proportional hazard analysis

None of the models violated the assumption of proportionality of hazards. Unadjusted Cox-proportional hazard analysis shows significant associations with CV mortality and all variables of nocturnal hypoxaemic burden, except ODI (Table 2). After adjusting for race, age, weight status, PASE score, smoking, alcohol consumption, diabetes, hypertension, HF, COPD and AHI, T90 remained a significant predictor of CV mortality for the continuous and dichotomized variable, respectively ($HR = 1.16$; $P = 0.004$, $HR = 1.59$; $P = 0.006$). T90desaturation was significant in the adjusted regression model

(continuous: $HR = 1.011$, $P < 0.001$, dichotomized: $HR = 1.61$; $P = 0.007$). T90non-specific dichotomized on the highest quartile (>3 min) was also predictive in the adjusted model ($HR = 1.46$; $P = 0.022$). Dichotomizing data based on whether participants are in the highest T90desaturation quartile as well as the highest T90non-specific quartile (Figure 4) did not yield a better prediction in the adjusted Cox model ($HR = 1.56$; $P = 0.016$).

To assess whether the relationship between T90, T90 desaturation, or T90non-specific and CV mortality was modified by the presence of sleep-disordered breathing as defined by $AHI \geq 15$, we additionally adjusted for interaction terms in the Cox model. Neither of the T90 variables displayed a significant interaction with the dichotomized AHI (data not shown).

Discussion

This study is the first to investigate the composition of nocturnal hypoxaemic burden and its prognostic value for CV mortality. In a large cohort of older community-dwelling men, nocturnal hypoxaemic burden determined by T90 was significantly and independently associated with CV mortality. We systematically characterized the composition of oximetry derived nocturnal hypoxaemic burden by a

Figure 3 Survival analysis of nocturnal hypoxaemic burden metrics. (A) oxygen desaturation index (ODI), (B) time spend below 90% oxygen saturation (T90); (C) T90 attributed to non-specific drifts of oxygen saturation (T90non-specific); (D) T90 attributed to acute desaturations (T90desaturation). Graphs show Kaplan–Meier curves for quartiles (Q) and log-rank test results.

novel automated computer algorithm, demonstrating that nocturnal hypoxaemic burden in elderly men does not only constitute well-defined desaturation–resaturation patterns (T90desaturation), but is also partly determined by non-specific drifts of saturation below 90% and incomplete resaturations (T90non-specific). The association with CV mortality was significant for both components of T90. Entering the combined score of high T90desaturation and T90non-specific into a Cox regression model did not yield a higher HR as compared with either component individually, possibly due to the high correlation between T90desaturation and T90non-specific in the MrOS cohort.

The prognostic value of T90 does not depend on the presence or severity of sleep-disordered breathing as measured by the AHI. Even in the absence of an elevated AHI, high desaturation-related nocturnal hypoxaemic burden may expose elderly men to increased CV mortality. Additionally, in participants with sleep-disordered breathing, non-specific drifts in oxygen saturation and incomplete saturations possibly reflect the fusion of subsequent desaturations with insufficient time between events to resaturate and sagging oxygen saturation levels. Comorbidities such as HF, which were more prevalent in patients with more severe sleep-disordered breathing, may

contribute to non-specific drifts and heterogeneous desaturation patterns by different mechanisms including prolonged circulation time and fluid shift.^{2,21}

In accordance with observations of patients with HF, the ODI was not independently associated with CV mortality in this study.⁹ While the ODI is considered a measure of intermittent hypoxaemia due to repetitive desaturation–resaturation episodes, it does not provide information on the actual depth or duration of desaturations and hypoxic episodes. Accordingly, T90 is only moderately associated with AHI or ODI, suggesting that nocturnal hypoxaemic burden is not adequately captured by frequency-based metrics that use a single minimum oxygen nadir to identify events, potentially limiting their use as a predictive marker.^{13,14}

Characterization of T90 as proposed here might also have therapeutic implications. Current treatment strategies for nocturnal hypoxaemia include positive airway pressure, mainly targeting nocturnal apnoeas and hypopnoeas and accompanied desaturations, where the titration of the treatment is primarily guided by the reduction in the number of apnoeas/hypopnoea events or desaturations during night. However, positive airway pressure guided by the AHI may not necessarily translate into improved survival.^{15,22} Despite the need to

optimize positive airway pressure adherence and lower the AHI, which may have been insufficient in recent intervention outcome studies,^{23,24} the reduction in nocturnal hypoxaemic burden itself may constitute a treatment target to reduce CV mortality. In addition to positive airway pressure, nocturnal low-dose oxygen supplementation might also reduce T90.²⁵ Men in the highest quartile of T90 were more likely to be obese, smokers, and to have HF as well as COPD. The cohort study design does not allow cause-effect relationships between hypoxaemic burden and CV mortality to be determined with certainty. Smoking-related lung disease, obesity, and HF, when

severe, cause sustained drifts below 90% saturation particularly in deep non-REM sleep and REM sleep, due to a variety of mechanisms such as increased loading and decreased functional efficiency of respiratory muscles, obstructive snoring, and pulmonary congestion.^{1,2} However, these disorders also increase CV risk through other non-hypoxia mechanisms. Therefore, to assess the independent impact of our exposure variables on CV mortality, we co-varied the Cox models for smoking, obesity, COPD, and HF.

Interventions to reduce nocturnal hypoxaemic burden might involve lifestyle interventions such as weight loss and aggressive risk factor management.²⁶ Additionally, screening for concomitant conditions beyond sleep-disordered breathing and obesity might help to identify a possible treatment target to reduce nocturnal hypoxaemic burden in patients with a high T90non-specific.

Nocturnal hypoxaemic burden might provide a helpful risk marker, which can be easily obtained by low-cost overnight oximetry. In this study, older men with T90 >12 min were at an elevated risk of CV mortality. Interestingly, this threshold is lower than the one reported in a cohort of patients with HF, where T90 >22 min was proposed as the cut-off for increased all-cause mortality.⁹ When using 20 min as a cut-off in the current study, the adjusted HR was somewhat lower [1.38 (0.96–2.003); *P* = 0.07] suggesting that the actual adverse effects of hypoxaemia in individual patient populations might depend on pre-existing conditions such as heart failure or concomitant risk factors.

Limitations

Our observations are based on predominantly white elderly men and cannot be extrapolated to other populations. The age at baseline was quite high (76 ± 6 years), which may have introduced a 'survivor' bias. In keeping with the original enrolment criteria of the MrOS sleep study, we did not exclude 15 men, who reported treatment with mechanical devices during sleep within the 3 months preceding overnight PSG. Given that use of treatment was likely intermittent (i.e. individuals did not use treatment during testing) and the small percentage of sample reporting this (0.5%), any impact of including these individuals is likely negligible.

Figure 4 Kaplan–Meier survival analysis of participants based on combined scores of time spend below 90% oxygen saturation (T90) attributed to non-specific drifts of oxygen saturation (T90non-specific) and T90 attributed to well-defined acute desaturations (T90desaturation). The arrows indicate high (Quartile 4) vs. low (Quartile 1–3) as defined by dichotomization (see Methods section for details).

Table 2 Association of nocturnal hypoxaemic burden with cardiovascular mortality in participants of the MrOS Sleep Cohort with by Cox regression

Variables	Univariate analysis		Multivariable analysis ^a	
	HR (95% CI)	P-value	HR (95% CI)	P-value
ODI (per SD)	1.13 (0.99–1.29)	0.062	1.16 (0.97–1.38)	0.097
T90 (per SD)	1.21 (1.10–1.33)	0.001	1.16 (1.05–1.28)	0.004
T90 (>12 min; Q4)	1.68 (1.24–2.27)	0.001	1.59 (1.14–2.22)	0.006
T90non-specific (per SD)	1.13 (1.03–1.24)	0.01	1.09 (0.98–1.20)	0.116
T90non-specific (>3 min; Q4)	1.74 (1.29–2.35)	<0.001	1.46 (1.06–2.02)	0.022
T90desaturation (per SD)	1.23 (1.13–1.34)	<0.001	1.21 (1.11–1.32)	<0.001
T90desaturation (>9 min; Q4)	1.65 (1.21–2.24)	0.001	1.61 (1.14–2.27)	0.007
T90non-specific (Q4) plus T90desaturation (Q4)	1.78 (1.28–2.48)	0.001	1.56 (1.08–2.23)	0.016

CI, confidence interval; HR, hazard ratio; SD, standard deviation.

^aAdjusted for age, race, BMI (categorical), PASE score, smoking status, alcohol consumption, diabetes, heart failure, hypertension, chronic obstructive pulmonary disease, AHI, total sleep time.

In elderly men, 12 or more minutes of sleep spent at oxygen saturation below 90% (T90), which cannot be explained by episodic desaturations alone, increases the risk of heart-related death by 59%.

Take home figure In community-dwelling older men, T90 is an independent predictor of CV mortality.

While we adjusted for multiple potential confounders, including diabetes, HF, COPD, and AHI, we cannot exclude the possibility that unmeasured confounders influenced the study findings. However, given that the sample was recruited from the community, it is unlikely that there was an appreciable number of individuals with severe cardiopulmonary disorders not identified in our analyses.

The composition and the characteristics of nocturnal hypoxaemic burden in cohorts comprising primarily of patients with obstructive sleep apnoea, central sleep apnoea, or HF may differ significantly. Given the sigmoidal shape of the oxy-haemoglobin dissociation curve, oximetry determined desaturations to describe nocturnal hypoxaemic burden critically depend on the baseline oxygen saturation in the individual patient. There is no widely accepted consensus on the precise definition of what constitutes an oxygen desaturation event. Previous studies mostly used a desaturation criterion of $\geq 4\%$, but others used a threshold of $\geq 3\%$.^{7,18} The definition chosen in this study applies rather stringent criteria, including resaturation, aiming to discriminate between well-defined episodic desaturation-resaturation events and non-specific drifts of oxygen saturation and may greatly affect the duration of T90 attributed to episodic desaturations vs. non-specific drifts. Fully automated oximetry data processing ensured objective assessment and reproducible results. While

hypoxaemic burden due to intermittent desaturation/reoxygenation episodes captured by T90desaturation was shown to result in oxidative stress, autonomic nervous system activation and ischaemia-reperfusion injury, thereby increasing CV mortality,^{1,2,16} the sequela of more sustained hypoxaemic burden captured by T90non-specific are less well understood. Future mechanistic and preclinical studies are needed to explore CV responses to different components of T90.

Conclusions

In community-dwelling older men, nocturnal hypoxaemic burden quantified by T90 derived from overnight oximetry is an independent predictor of CV mortality. Older men with T90 >12 min are at an elevated risk of CV mortality. T90 is not merely the consequence of brief well-defined episodic desaturations, but also reflects non-specific drifts of oxygen saturation, especially in older men, who have morbidities such as severe sleep apnoea, COPD, and/or HF. Both components of T90 contributed towards the association with CV death. Whether T90 derived from simple overnight oximetry is an effective risk marker in the clinical setting, and whether its reduction

constitutes a treatment target warrants further prospective studies and randomized trials.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Funding

This study was supported through a grant from the Australian Research Council [DP0663345]. The MrOS Study is supported by National Institutes of Health funding. The following institutes provide support: The National Institute on Aging, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Center for Advancing Translational Sciences, and National Institutes of Health Roadmap for Medical Research [U01-AG027810, U01-AG042124, U01-AG042139, U01-AG042140, U01-AG042143, U01-AG042145, U01-AG042168, U01-AR066160, UL1-TR000128]. The National Heart, Lung, and Blood Institute provides funding for the MrOS Sleep ancillary study [R01-HL071194, R01-HL070848, R01-HL070847, R01-HL070842, R01-HL070841, R01-HL070837, R01-HL070838, R01-HL070839] and the National Sleep Research Resource [R24-HL114473]. S.R. was supported in part by National Institutes of Health [R35-HL135818]. P.S. and R.D.M. were supported by Practitioner Fellowships from the National Health and Medical Research Council of Australia.

Conflict of interest: P.S. reports having served on the advisory board of Biosense-Webster, Medtronic, Abbott, Boston Scientific, CathRx. D.L. reports having served on the advisory board of LivaNova, Medtronic, ResMed. R.D.M. reports receiving research funding from Philips Respironics, ResMed, Fisher&Paykel. All other authors did not declare any potential conflict of interest.

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