Obstructive sleep apnoea and the progression of thoracic aortic aneurysm: a prospective cohort study

Thomas Gaisl[1,2], Protazy Rejmer[1], Maurice Roeder[1], Patrick Baumgartner[1], Noriane A. Sievi[1], Sandra Siegfried[3], Simon F. Stämpfli[4], Robert Thurnheer[5], John R. Stradling[6], Felix C. Tanner[7] and Malcolm Kohler[1]

Affiliations: [1]Dept of Pulmonology, University Hospital Zurich, Zurich, Switzerland. [2]Dept of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA. [3]Dept of Biostatistics, Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland. [4]Dept of Cardiology, Lucerne Cantonal Hospital, Lucerne, Switzerland. [5]Pulmonary Division, Münsterlingen Cantonal Hospital, Münsterlingen, Switzerland. [6]National Institute for Health Research Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust and University of Oxford, Oxford, UK. [7]Dept of Cardiology, University Hospital Zurich, Zurich, Switzerland.

Correspondence: Malcolm Kohler, Dept of Pulmonology, University Hospital Zurich, Raemistrasse 100, 8091 Zurich, Switzerland. E-mail: malcolm.kohler@usz.ch

@ERSpublications
Obstructive sleep apnoea may be an independent risk factor for faster thoracic aortic aneurysm expansion and thus potentially contributes to life-threatening complications in aortic disease
https://bit.ly/35Qp4kO

Cite this article as: Gaisl T, Rejmer P, Roeder M, *et al*. Obstructive sleep apnoea and the progression of thoracic aortic aneurysm: a prospective cohort study. *Eur Respir J* 2021; 57: 2003322 [https://doi.org/10.1183/13993003.03322-2020].

ABSTRACT

Background: Obstructive sleep apnoea (OSA) is associated with an increased prevalence of aortic aneurysms and it has also been suggested that severe OSA furthers aneurysm expansion in the abdomen. We evaluated whether OSA is a risk factor for the progression of ascending thoracic aortic aneurysm (TAA).

Methods: Patients with TAA underwent yearly standardised echocardiographic measurements of the ascending aorta over 3 years and two level III sleep studies. The primary outcome was the expansion rate of TAA in relation to the apnoea–hypopnoea index (AHI). Secondary outcomes included surveillance for aortic events (composite end-points of rupture/dissection, elective surgery or death).

Results: Between July 2014 and March 2020, 230 patients (median age 70 years, 83.5% male) participated in the cohort. At baseline, 34.8% of patients had AHI ⩾15 events·h^{-1}. There was no association between TAA diameter and AHI at baseline. After 3 years, mean±SD expansion rates were 0.55±1.25 mm at the aortic sinus and 0.60±1.12 mm at the ascending aorta. In the regression analysis, after controlling for baseline diameter and cardiovascular risk factors, there was strong evidence for a positive association of TAA expansion with AHI (aortic sinus estimate 0.025 mm, 95% CI 0.009–0.040 mm; p<0.001 and ascending aorta estimate 0.026 mm, 95% CI 0.011–0.041 mm; p=0.001). 20 participants (8%) experienced an aortic event; however, there was no association with OSA severity.

Conclusion: OSA may be a modest but independent risk factor for faster TAA expansion and thus potentially contributes to life-threatening complications in aortic disease.

This article has an editorial commentary: https://doi.org/10.1183/13993003.04440-2020

This article has supplementary material available from erj.ersjournals.com

This study is registered at ClinicalTrials.gov with identifier number NCT02204774. Data availability: The dataset for this study is available from the corresponding author upon reasonable request.

Received: 30 Aug 2020 | Accepted: 26 Oct 2020

Introduction

A thoracic aortic aneurysm (TAA) is a confined dilation of all three layers of the thoracic aorta. TAAs have a prevalence of approximately 0.3% in Western countries and they are more common among the male sex [1]. Although clinically silent, a TAA may result in sudden life-threatening complications such as thrombosis, dissection and rupture [2]. TAA management includes controlling for currently known risk factors, serial imaging to monitor progression and surgical intervention [2]. The majority of TAAs involve the ascending aorta; their aetiology is mostly degenerative and associated with the general risk factors for atherosclerosis [3]. However, these factors, alone, are poor predictors of the incidence and subsequent growth rate of TAAs, and the underlying mechanisms that contribute to TAAs are poorly understood [4]. A combination of mechanical and biological factors is thought to contribute to vessel degeneration, but longitudinal clinical studies on this subject are scarce. Therefore, the investigation of modifiable factors influencing the growth rate of TAAs is of major interest.

Obstructive sleep apnoea (OSA) is a common sleep-related breathing disorder, induced by complete or partial obstruction of the upper airway, resulting in nightly apnoeas and hypopnoeas [5]. Over 20% of males and 10% of females in Western countries are affected by some degree of asymptomatic OSA [6, 7]. Population studies have reported that severe OSA may be associated with the development of atherosclerosis [8, 9]. In addition to being a systemic pro-atherosclerotic factor, OSA is also thought to impact the vessels within the thorax through various mechanical processes occurring during apnoeas (*e.g.* chronic hypertension, passive stretching of the aorta and intermittent hypoxia [10]), therefore establishing OSA as a candidate risk factor for TAA. Meta-analyses of randomised controlled trials have shown that OSA is highly treatable, since most common therapies (*e.g.* continuous positive airway pressure (CPAP) therapy) effectively counteract the adverse effects of the disorder, notably arterial hypertension and apnoeas [11].

A clinical association between TAA and OSA was initially documented in patients with Marfan syndrome, among whom the severity of OSA independently affected aortic diameter and adversely influenced aortic event-free survival rate [12–14]. A cross-sectional study in a non-Marfan population confirmed a higher prevalence of OSA in patients with TAA when compared with patients with normal aortic dimensions, suggesting that OSA may contribute to aneurysm expansion [5]. Finally, longitudinal data suggested that severe OSA may contribute to faster aneurysm expansion in the abdomen, but similar data on TAA are currently lacking [15].

With the aim of addressing this knowledge gap, we conducted a prospective cohort study in patients with TAA with the primary objective of investigating the association between OSA and yearly TAA progression. The secondary objective of the study was to analyse the association between OSA and the need for aortic surgery, or death from presumed or proven aortic rupture/dissection.

Methods

Study design and participants

This prospective study investigated a cohort of 230 TAA patients with baseline measurements (anthropometrics, respiratory polygraphy, echocardiography and 7-day ambulatory blood pressure) and a 3-year follow-up which consisted of yearly echocardiographs (*i.e.* four visits altogether). The primary outcome was the aneurysm expansion rate over a period of 3 years and its relationship with OSA (reflected by the apnoea–hypopnoea index (AHI)). Secondary outcomes included a composite end-point of surgery (or fulfilling the criteria for one) or elective endovascular repair because of rapid progression of TAA (usually >10 mm·year^{-1} and/or an aneurysm diameter >50–60 mm), or death from proven or presumed aortic rupture/dissection. From July 2014 onward, patients with TAA were identified from three databases in Switzerland (figure 1) according to the following inclusion criteria: 1) a history of TAA according to at least one echocardiography report and 2) age ⩾18 years. For this study, TAA was predefined as an aortic diameter exceeding the sex-specific cut-offs at the level of the sinus of Valsalva (*i.e.* ⩾39 mm for females and ⩾44 mm for males) or the ascending aorta (*i.e.* ⩾42 mm for females and ⩾46 mm for males) [16]. Exclusion criteria included 1) current treatment with CPAP therapy for OSA at baseline, 2) a history of central sleep apnoea, 3) a history of morphine/opioid medication, or heroin or alcohol addiction, 4) a documented moderate or severe aortic regurgitation, 5) a documented moderate or severe aortic stenosis and 6) pregnancy. All subjects were invited by mail to take part and the study was approved by the Cantonal Ethics Committee Zurich, Switzerland (KEK-ZH-Nr. 2014-0035). All participants provided written informed consent prior to participation. The cohort was registered *a priori* (ClinicalTrials.gov identifier NCT02204774) and *post hoc* analyses are highlighted.

Respiratory polygraphy

All patients underwent a full level III respiratory polygraphy (ApneaLink Air; ResMed, San Diego, CA, USA) during the habitual sleep time at their homes. The setup and scoring was performed according to

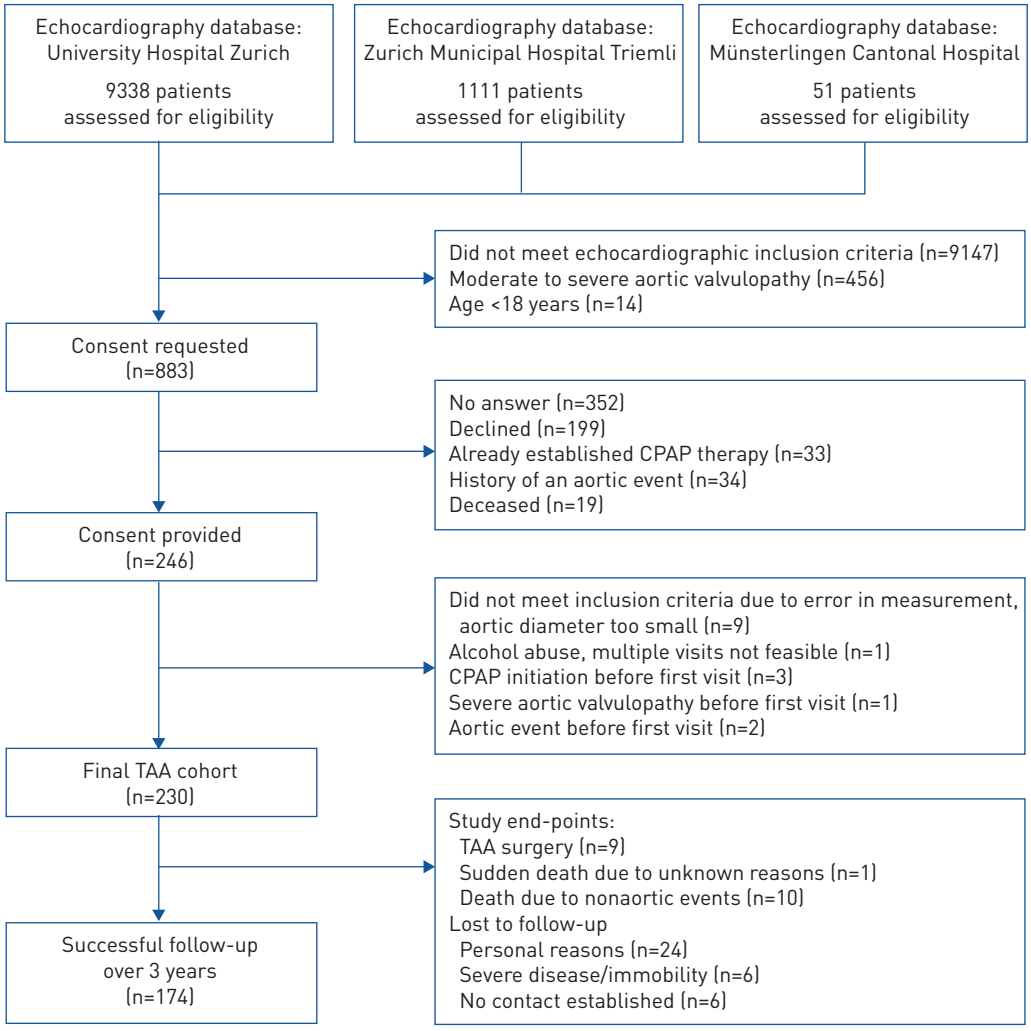

FIGURE 1 Study flowchart. CPAP: continuous positive airway pressure; TAA: thoracic aortic aneurysm.

the guidelines of the American Academy of Sleep Medicine recommendations from 2007 (version A) [17]. Two blinded investigators reviewed all raw data manually and the sleep study was repeated in case of artefacts or <4 h recording time (28 cases).

Echocardiography

All echocardiographic studies were performed with a 3.5-MHz transducer on a cardiovascular ultrasound system (Vivid E9 with XDclear; GE Healthcare, Little Chalfont, UK). According to a standardised approach, all measurements for this study were performed in the left parasternal long axis window using two-dimensional, guided M-mode, documenting the end-systolic diameter of the aortic sinus (defined as the largest diameter of the sinus of Valsalva) and the ascending aorta (at the level of the right pulmonary artery). Every measurement was performed three times and the data were averaged by the mean. According to the recommendations of the American Society of Echocardiography, the "leading edge-to-leading edge" technique was applied [18]. The limitations of the ultrasound technology did not allow for the inclusion of TAA at the descending aorta. Since investigators were blind to the preceding measurements, in some cases (approximately 24%) a negative growth rate (*i.e.* <0 mm) was calculated. For statistical analysis, the average of the three annual expansion rates for each patient was calculated.

Statistical analysis

Sample size calculation required 230 participants, assuming a 60% prevalence of OSA (defined as AHI $\geqslant$5 events·h^{-1}) [15] and a dropout rate of 10% per year, in order to detect a difference in TAA expansion of 1 mm (SD 0.647, α=0.05, β=0.9 and assuming more than 126 complete cases). The cut-off value of 1 mm was chosen as this is considered the minimal clinically important difference at the individual level.

Descriptive statistics of baseline patient characteristics are presented as mean with standard deviation or median (interquartile range (IQR)) for continuous measurements and as number (percentage of total) for categorical measurements. For the primary outcome, a least-squares linear regression analysis was fitted with predefined cardiovascular confounding variables. Estimates of the regression analysis are reported with 95% confidence intervals and a two-sided p-value of <0.05 was considered statistically significant for all reported tests. Statistical analysis was performed with Stata version 15 (StataCorp, College Station, TX, USA) and R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). Data and quality monitoring was conducted by a third party (RMC Consult, Grenzach-Wyhlen, Germany).

Results

Study profile and participant characteristics

Figure 1 shows the study flowchart. Between July 2014 and March 2020, all patients completed the study. The baseline characteristics are shown in tables 1 and 2 (and supplementary tables E1 and E2). None of the patients were diagnosed with a syndromic connective tissue disorder (*e.g.* Marfan, Ehlers–Danlos or Loeys–Dietz syndromes) or a major vascular inflammatory disorder (*e.g.* Takayasu/giant cell arteritis). Of the final TAA cohort (n=230), 20 patients reached an end-point during the study period, 36 patients were lost to follow-up and 174 patients completed the fourth annual visit. Complete annual expansion rate data were available for 160 patients. In 14 cases, data points for the primary outcome for a maximum of one visit were missing due to technical difficulties. Mean±SD follow-up interval over 3 years was 369±54 days. The patients spent a median (IQR) of 1099 (943–1117) days within the cohort. There was no association between TAA baseline diameter and severity of OSA at baseline (r=0.25, p=0.82 for aortic sinus and r=0.21, p=0.81 for ascending aorta).

TABLE 1 Patient characteristics of the final thoracic aortic aneurysm cohort

Patients	230
Anthropometrics	
Age years	69.7 (60.6–74.7)
Male	192 (83.5)
BMI $kg \cdot m^{-2}$	26.3 (24.4–29.4)
Height cm	178 (170–182)
Weight kg	83.6 (75.5–92.0)
BSA m^2	2.0 (1.9–2.1)
Neck circumference cm	40.5 (38.0–42.5)
Blood pressure data mmHg	
Office (average of three)	
Systolic	129.2 (119.3–144.3)
Diastolic	81.5 (74.9–89.3)
Home (7-day average)	
Systolic	124.5 (116–133.9)
Diastolic	75.2 (70.0–81.6)
Comorbidities	
Smoking	
Active smoker	30 (13.0)
Ex-smoker	107 (46.5)
Never-smoker	93 (40.4)
History of hypertension	178 (77.4)
History of diabetes mellitus type 2	18 (7.8)
HbA1c %	5.7±0.7
History of dyslipidaemia	135 (58.7)
Cholesterol $mmol \cdot L^{-1}$	4.6±1.2
Triglycerides $mmol \cdot L^{-1}$	1.6±0.8
HDL $mmol \cdot L^{-1}$	1.4±0.5
LDL $mmol \cdot L^{-1}$	2.6±1.1
History of stroke	33 (14.3)
History of coronary artery disease	53 (23.0)
History of atrial fibrillation	53 (23.0)
Family history of aortic aneurysms	22 (9.6)
Abdominal aortic aneurysm	10 (4.3)
Bicuspid aortic valve	14 (6.1)

Data are presented as n, median (interquartile range), n (%) or mean±SD. BSA: body surface area; BMI: body mass index; Hb: haemoglobin; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

TABLE 2 Baseline characteristics of the primary outcome in patients with thoracic aortic aneurysm

Patients	230
OSA data	
AHI events·h^{-1}	9.7 (3.7–20.8)
⩾5	147 (63.9)
⩾15	80 (34.8)
⩾30	32 (13.9)
OSA syndrome[#]	29 (12.6)
ODI events·h^{-1}	9.4 (4.0–20.9)
Absolute time with S_{pO_2} <90% min	57 (8–178)
Relative time with S_{pO_2} <90% % of recording time	13 (3–43)
ESS score	6.3±3.8
Aortic dimension mm	
Male (n=192)	
Aortic sinus (end-systole)	45 (43–47)
Ascending aorta (end-systole)	44 (40–47)
Female (n=38)	
Aortic sinus (end-systole)	39 (37–40)
Ascending aorta (end-systole)	43 (42–45)

Data are presented as n, median (interquartile range) or n (%). OSA: obstructive sleep apnoea; AHI: apnoea–hypopnoea index; ODI: oxygen desaturation index; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry; ESS: Epworth Sleepiness Scale. [#]: defined as AHI ⩾5 events·h^{-1} and ESS score ⩾11.

Primary outcome

At baseline, 34.8% of patients had AHI ⩾15 events·h^{-1} and the prevalence of OSA syndrome (defined as AHI ⩾5 events·h^{-1} and Epworth Sleepiness Scale score ⩾11) was 12.6% (table 2). Mean±SD expansion rates over 3 years were 0.55±1.25 mm at the aortic sinus and 0.60±1.12 mm at the ascending aorta (supplementary figure E1). TAA expansion rates were larger in higher AHI categories (p_{trend}<0.001 for aortic sinus and ascending aorta) (figure 2 and supplementary table E5). In the regression analysis, controlled for baseline diameter, cardiovascular risk factors and blood pressure, there was strong evidence for a positive association of TAA expansion with baseline diameter (table 3 and supplementary table E4) and AHI (p=0.001 for both the aortic sinus and ascending aorta). A separate model with the oxygen desaturation index (ODI) yielded similar results (supplementary table E4). Alternative markers for OSA severity (*e.g.* time with arterial oxygen saturation measured by pulse oximetry (S_{pO_2}) <90%) are reported in supplementary table E4. Expansion rates at the aortic sinus were higher for males when compared with females (0.809 mm, 95% CI 0.163–1.456 mm; p=0.02); however, there was no statistically significant difference at the ascending aorta (0.289 mm, 95% CI −0.285–0.863 mm; p=0.320). Sensitivity analysis suggested that the results were not sensitive to multiple imputation (n=14 cases of incomplete data) or when an intention-to-treat analysis (n=230) was implemented.

Secondary outcome

During follow-up, 20 patients experienced a predefined end-point: nine patients underwent elective TAA surgery, 10 patients died due to causes unrelated to their TAA and one patient died due to unknown reasons (sudden death, no autopsy; last measurements: 39 mm (aortic sinus) and 35 mm (ascending aorta)). No patients experienced a TAA rupture and/or emergency surgery for TAA. The patients who underwent elective TAA surgery (n=9) did not differ significantly from the rest of the cohort (n=212) in terms of their OSA severity (median (IQR) surgery AHI 13.6 (1.6–44.5) events·h^{-1} *versus* rest AHI 9.8 (3.8–20.6) events·h^{-1}; p=0.16); however, their TAA expansion rates were significantly higher (mean (IQR) surgery expansion 0.14 (0.06–0.40) mm·year^{-1} *versus* rest expansion 0.63 (0.03–0.67) mm·year^{-1}; p<0.001).

Quality assessment

Absolute and relative intra-observer variability (supplementary table E6) indicated a normal distribution of the ultrasound measurement error, and the intraclass correlation coefficients for the aortic sinus (0.982, 95% CI 0.980–0.984) and ascending aorta (0.987, 95% CI 0.985–0.989) indicated excellent reliability (supplementary tables E7 and E8). Finally, there was no evidence of a significant association between the three observers and annual TAA expansion rate (supplementary table E9).

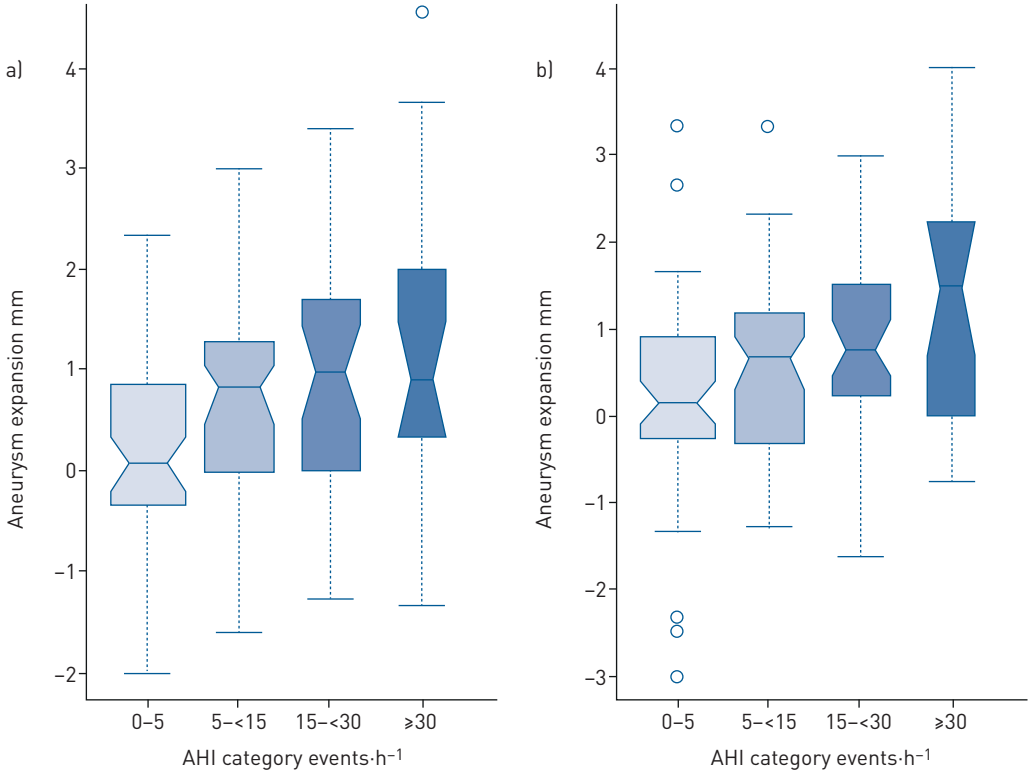

FIGURE 2 Thoracic aortic aneurysm expansion rates by apnoea–hypopnoea index (AHI) categories of complete cases (n=160): a) aortic sinus and b) ascending aorta. p_{trend}<0.001 for aortic sinus and ascending aorta. Boxes indicate median and interquartile range (size of the box represents the relative n of the category), and whiskers indicate minimum–maximum; outliers are indicated by circles.

Post hoc *analysis*

As a result of the baseline measurements, 25% (n=57) of patients received their results and decided to undergo further sleep laboratory testing (which was not part of the study; no randomisation involved). Ultimately, 11% (n=25) of the cohort patients initiated CPAP therapy during the follow-up. Of those 25 patients, 11 patients discontinued CPAP therapy after a median (IQR) of 3 (1–5) months and 14 patients stayed on CPAP for the rest of the study (⩾3 years). In a *post hoc* analysis, median (IQR) expansion rates for these 14 patients on CPAP were 0.21 (−0.10–0.50) mm·year^{-1} at the aortic sinus and

TABLE 3 Least-squares linear regression based on aortic size at the end of the study as the primary outcome in a complete-case analysis[#], controlled for baseline diameter and predefined cardiovascular confounders

	Aortic sinus		Ascending aorta	
	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
Intercept	1.544 (−2.211–5.299)	0.42	−0.255 (−3.687–3.177)	0.89
Baseline diameter mm	0.973 (0.922–1.025)	<0.001*	0.984 (0.942–1.026)	<0.001*
AHI events·h^{-1}	0.025 (0.009–0.040)	0.002*	0.026 (0.011–0.041)	0.001*
Age years	0.001 (−0.021–0.021)	0.99	0.002 (−0.019–0.022)	0.86
Male (reference level: female)	0.735 (0.024–1.447)	0.04*	0.204 (−0.436–0.844)	0.53
BSA m^2	−0.632 (−2.313–1.048)	0.46	0.372 (−1.246–1.990)	0.65
Number of antihypertensives (0–5)	0.038 (−0.139–0.214)	0.68	0.004 (−0.168–0.175)	0.97
BMI kg·m^{-2}	0.006 (−0.057–0.069)	0.85	−0.005 (−0.065–0.056)	0.88
History of dyslipidaemia (yes/no)	0.071 (−0.099–0.241)	0.41	0.068 (−0.097–0.232)	0.42
Active smoker (yes/no)	−0.182 (−0.788–0.424)	0.55	−0.005 (−0.589–0.579)	0.99

AHI: apnoea–hypopnoea index; BSA: body surface area; BMI: body mass index. #: n=160. *: p<0.05.

0.51 (0.00–1.31) mm·year^{-1} at the ascending aorta. There was no evidence for a statistically significant difference in median expansion rates when this group (n=14) was compared with the non-CPAP group (n=146). The main outcome did not differ when the regression analysis was restricted to the non-CPAP group (supplementary table E4).

Discussion

TAAs can have life-threatening complications, and the mechanisms underlying their prevalence and expansion are still poorly understood. In this study, an association between OSA severity (*i.e.* AHI) and TAA expansion rate was confirmed, making it highly relevant as it opens research avenues into possible strategies to identify populations at risk and to slow down TAA progression. Our results are similar to those previously reported for patients with abdominal aortic aneurysms, although the average TAA expansion rate was significantly smaller than that of abdominal aortic aneurysms [10]. Interestingly, in the *post hoc* analysis, TAA expansion rates were even smaller (but not statistically significant) for patients who initiated and sustained CPAP therapy at the beginning of the trial. This is in line with a previous publication which suggested that, in patients with TAA, sustained and effective CPAP therapy may counteract the adverse effects of OSA on aneurysm expansion [19]. Although this was an observation for which no experimental data were presented, this finding underlines the potential role of OSA in the pathogenesis of TAA.

Our regression analysis (table 3) showed strong evidence for the dominant role of baseline diameter on the subsequent expansion rate, which is in accordance with Laplace's law and a well-known fact in the literature on TAA [2]. In our model, >80% of the variability in the follow-up measurements of the aortic sinus and ascending aorta were explainable by the baseline diameter value alone. Considering the submillimetre confidence interval for expansion rates in our model, the proposed clinical impact of OSA severity on TAA expansion remains relatively small during the 3-year period of this study. Nevertheless, OSA is a common chronic disorder that often requires lifelong therapy and cardiovascular consequences may accumulate over decades. In the bigger picture, the pathophysiology of TAA remains undoubtedly multifactorial and OSA may represent only one of the few potentially modifiable risk factors underlying aortic disease.

In a 3-year follow-up echocardiography study of a demographically similar cohort, mean±SD expansion rates of 0.82±1.10 mm·year^{-1} for the aortic sinus and 0.75±1.10 mm·year^{-1} for the ascending aorta were reported [20]. However, in contrast to our cohort, the aforementioned study did not use a sex-specific definition of TAA and thus overall aortic dimensions were higher. Furthermore, considering the inherent limitations of ultrasound technology use (inter- and intra-observer variability), our measurements are in line with the current literature, albeit below the previously reported average [20].

Patients in our cohort experienced an above average rate of "aortic events", with an extrapolated event rate of 1.30 per 100 patient-years, whereas the aforementioned cohort reported 0.88 events per 100 patient-years (also mostly TAA surgery) [20]. As most of the aortic events in our cohort were related to elective TAA surgery (at least 90%), rather than emergencies, we attribute this to highly successful implementation of primary prevention in the current cohort. A family history of TAA was reported in 9.6% of our patients, suggesting a genetic component (*e.g. ACTA2* mutation) in the pathogenesis, which is also recognised in the literature [2]. Furthermore, 4.3% of our TAA patients were diagnosed with a concurring abdominal aneurysm, which supports the hypothesis that systemic factors contribute to aneurysm formation at different sites. The latter finding is also in line with a previously reported estimate of the number of patients who experience both a thoracic and an abdominal aneurysm (4%) [21].

The underlying mechanisms through which OSA might contribute to aortic disease are currently not well understood [10]. It is also not clear whether OSA pathophysiology affects thoracic and abdominal aneurysms differently [10]. Recent literature suggests that untreated OSA may contribute to TAA progression *via* three main mechanisms. First, chronic hypertension and vascular dysfunction, resulting from underlying neurohumoral changes induced by OSA [22], are known risk factors for the pathogenesis of TAA [2]. Indeed, the prevalence of arterial hypertension in our cohort was disproportionately high (77.4%) (table 1). Nevertheless, it is worth noting that the small group within our cohort who initiated and sustained CPAP therapy during the study (n=14) reported lower office blood pressure compared with the rest of the cohort. However, this difference was not statistically significant as the small sample size may have played a role (mean±SD systolic 121.8±10.4 *versus* 125.0±11.9 mmHg; p=0.329 and diastolic 75.0±7.3 *versus* 76.5±9.2 mmHg; p=0.401). While we did not measure nocturnal blood pressure, it is worth noting that arterial blood pressure in OSA patients is particularly elevated during sleep and nocturnal nondipping patterns (diminished night-time blood pressure reductions), as well as larger intermittent rises in blood pressure, are especially prominent [23]. Thus, office blood pressure is likely to underestimate the true effects of both OSA and CPAP.

The second mechanism through which OSA may contribute to TAA progression involves passive stretching of the aorta during sleep, which subjects the vessels to additional negative shear stress, resulting in fibrinolytic imbalance in the short term and degeneration in the long term [10]. An invasive study utilising an aortic catheter detected significant negative intrathoracic pressure swings (approximately −13 to −19 mmHg) during apnoeas, which can last up to 1 min and were repeated many times per hour, depending on disease severity [24]. As a result, pathological negative pressure surges during apnoeas (as the patient continues to inhale against an obstructed airway) are forwarded to the walls of the aorta, promoting dilation. The fact that in our cohort obstructive apnoeas were the most common type of apnoea (68%), followed by mixed (16%) and central (16%) apnoeas, underlines the significance of this mechanism.

Finally, the literature suggests that intermittent hypoxia (desaturations of 5–30% during apnoeas) and subsequent oxidative stress with arousal-induced sympathetic activation results in short-term bursts of vasoconstriction and blood pressure surges of approximately 10–80 mmHg, adding mechanical shear stress from within the vessel [10, 25]. Since these blood pressure surges can be blunted by oxygen administration [26], it is thought that hypoxaemia influences the autonomous nervous system *via* chemoreceptors [10]. The potential role of short-term intermittent hypoxia is supported by the fact that the ODI also significantly predicted TAA expansion rates, while long-term indices (*e.g.* time with S_{pO_2} <90%) were not associated with TAA expansion in this cohort (supplementary table E4).

Limitations

While OSA was repeatedly assessed during our follow-up, we utilised level III respiratory polygraphy and not the gold standard of in-hospital polysomnography. While a randomised trial has proven that level III devices are noninferior to polysomnography in the clinical setting for OSA, we might have missed or misclassified cases of mixed or central sleep apnoea to a small extent [27]. Furthermore, we did not collect genetic data in order to estimate the genetic predisposition and our cohort might be nonrepresentative of patients with TAA as a whole, since no syndromic connective tissue disorders or major vascular inflammations (*e.g.* aortitis) were included. As TAA is a lifelong disease, our follow-up of only 3 years may also be regarded as too short and thus underestimate aneurysm expansion. Sustained CPAP initiation among the TAA cohort might also have introduced a bias towards the null hypothesis (*i.e.* underestimation of the true association). Finally, the design of this cohort study does not allow establishing any causal relationships between OSA, CPAP treatment and TAA.

Conclusions

Besides already known risk factors for TAA expansion (*e.g.* baseline diameter, genetic predispositions, *etc.*), OSA may be a modest underlying factor contributing to aortic disease. Although the clinical impact over a period of 3 years may seem small, the cardiovascular consequences of untreated OSA usually accumulate over decades. Since OSA is effectively treatable, and sustained CPAP therapy might alleviate the adverse effects of OSA on TAA expansion, further trials establishing a causal link are required.

Author contributions: T. Gaisl, P. Rejmer, S. Siegfried and M. Kohler had full access to all of the data. Study concept and design: J.R. Stradling and M. Kohler. Acquisition, analysis or interpretation of data: T. Gaisl, P. Rejmer, M. Roeder, P. Baumgartner, N.A. Sievi and S.F. Stämpfli. Drafting of the manuscript: T. Gaisl. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: T. Gaisl and S. Siegfried. Administrative, technical or material support: T. Gaisl, S.F. Stämpfli, R. Thurnheer, F.C. Tanner and M. Kohler. Study supervision and funding: M. Kohler.

Conflict of interest: T. Gaisl reports personal fees from Bayer AG (consulting), outside the submitted work. P. Rejmer has nothing to disclose. M. Roeder has nothing to disclose. P. Baumgartner has nothing to disclose. N.A. Sievi has nothing to disclose. S. Siegfried has nothing to disclose. S.F. Stämpfli reports personal fees for consultancy from Amgen, AstraZeneca, Bayer, Novartis and Pfizer, outside the submitted work. R. Thurnheer has nothing to disclose. J.R. Stradling reports personal fees for consultancy from Bayer AG and ResMed, outside the submitted work. F.C. Tanner has nothing to disclose. M. Kohler reports personal fees for consultancy from Bayer AG, AstraZeneca, Novartis, GSK, Boehringer Ingelheim and Mundipharma, outside the submitted work, and is founder and owner of the "Deep Breath Initiative" a company that provides services in the field of exhaled breath analysis.

Support statement: This work was supported by the Universität Zürich. Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 Kalsch H, Lehmann N, Mohlenkamp S, *et al.* Body-surface adjusted aortic reference diameters for improved identification of patients with thoracic aortic aneurysms: results from the population-based Heinz Nixdorf Recall study. *Int J Cardiol* 2013; 163: 72–78.
2 Isselbacher EM. Thoracic and abdominal aortic aneurysms. *Circulation* 2005; 111: 816–828.

3 Johnston KW, Rutherford RB, Tilson MD, *et al.* Suggested standards for reporting on arterial aneurysms. Subcommittee on Reporting Standards for Arterial Aneurysms, Ad Hoc Committee on Reporting Standards, Society for Vascular Surgery and North American Chapter, International Society for Cardiovascular Surgery. *J Vasc Surg* 1991; 13: 452–458.
4 Reed D, Reed C, Stemmermann G, *et al.* Are aortic aneurysms caused by atherosclerosis? *Circulation* 1992; 85: 205–211.
5 Gaisl T, Baumgartner P, Rejmer P, *et al.* Prevalence of obstructive sleep apnea in patients with thoracic aortic aneurysm: a prospective, parallel cohort study. *Respiration* 2020; 99: 19–27.
6 Heinzer R, Vat S, Marques-Vidal P, *et al.* Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med* 2015; 3: 310–318.
7 Young T, Palta M, Dempsey J, *et al.* The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993; 328: 1230–1235.
8 Marin JM, Carrizo SJ, Vicente E, *et al.* Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005; 365: 1046–1053.
9 Peppard PE, Young T, Palta M, *et al.* Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000; 342: 1378–1384.
10 Gaisl T, Bratton DJ, Kohler M. The impact of obstructive sleep apnoea on the aorta. *Eur Respir J* 2015; 46: 532–544.
11 Bratton DJ, Gaisl T, Wons AM, *et al.* CPAP vs mandibular advancement devices and blood pressure in patients with obstructive sleep apnea: a systematic review and meta-analysis. *JAMA* 2015; 314: 2280–2293.
12 Cistulli PA, Sullivan CE. Sleep apnea in Marfan's syndrome. Increased upper airway collapsibility during sleep. *Chest* 1995; 108: 631–635.
13 Kohler M, Blair E, Risby P, *et al.* The prevalence of obstructive sleep apnoea and its association with aortic dilatation in Marfan's syndrome. *Thorax* 2009; 64: 162–166.
14 Kohler M, Pitcher A, Blair E, *et al.* The impact of obstructive sleep apnea on aortic disease in Marfan's syndrome. *Respiration* 2013; 86: 39–44.
15 Mason RH, Ruegg G, Perkins J, *et al.* Obstructive sleep apnea in patients with abdominal aortic aneurysms: highly prevalent and associated with aneurysm expansion. *Am J Respir Crit Care Med* 2011; 183: 668–674.
16 Campens L, Demulier L, De Groote K, *et al.* Reference values for echocardiographic assessment of the diameter of the aortic root and ascending aorta spanning all age categories. *Am J Cardiol* 2014; 114: 914–920.
17 Iber C, Ancoli-Israel S, Chesson AL, *et al.* The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. 1st Edn. Westchester, American Academy of Sleep Medicine, 2007.
18 Lang RM, Bierig M, Devereux RB, *et al.* Recommendations for chamber quantification. *Eur J Echocardiogr* 2006; 7: 79–108.
19 Cistulli PA, Wilcox I, Jeremy R, *et al.* Aortic root dilatation in Marfan's syndrome: a contribution from obstructive sleep apnea? *Chest* 1997; 111: 1763–1766.
20 La Canna G, Ficarra E, Tsagalau E, *et al.* Progression rate of ascending aortic dilation in patients with normally functioning bicuspid and tricuspid aortic valves. *Am J Cardiol* 2006; 98: 249–253.
21 Agricola E, Slavich M, Tufaro V, *et al.* Prevalence of thoracic ascending aortic aneurysm in adult patients with known abdominal aortic aneurysm: an echocardiographic study. *Int J Cardiol* 2013; 168: 3147–3148.
22 Thiel S, Haile SR, Peitzsch M, *et al.* Endocrine responses during CPAP withdrawal in obstructive sleep apnoea: data from two randomised controlled trials. *Thorax* 2019; 74: 1102–1105.
23 Kario K. Obstructive sleep apnea syndrome and hypertension: ambulatory blood pressure. *Hypertens Res* 2009; 32: 428–432.
24 Clarenbach CF, Camen G, Sievi NA, *et al.* Effect of simulated obstructive hypopnea and apnea on thoracic aortic wall transmural pressures. *J Appl Physiol* 2013; 115: 613–617.
25 Garpestad E, Parker JA, Katayama H, *et al.* Decrease in ventricular stroke volume at apnea termination is independent of oxygen desaturation. *J Appl Physiol* 1994; 77: 1602–1608.
26 Leuenberger U, Jacob E, Sweer L, *et al.* Surges of muscle sympathetic nerve activity during obstructive apnea are linked to hypoxemia. *J Appl Physiol* 1995; 79: 581–588.
27 Corral J, Sanchez-Quiroga MA, Carmona-Bernal C, *et al.* Conventional polysomnography is not necessary for the management of most patients with suspected obstructive sleep apnea. Noninferiority, randomized controlled trial. *Am J Respir Crit Care Med* 2017; 196: 1181–1190.