Effects of acetazolamide on sleep disordered breathing in pulmonary vascular disease: a randomised controlled trial

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Shareable abstract (@ERSpublications)
Acetazolamide 250 mg twice daily for 5 weeks is safe and significantly reduces nocturnal hypoxaemia to clinically relevant levels and improves obstructive sleep apnoea in pulmonary vascular disease https://bit.ly/3X0cRqc

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Abstract

Background Patients with pulmonary vascular disease (PVD) often suffer from nocturnal hypoxaemia, but also from sleep apnoea. Short-term use of acetazolamide increases ventilation due to metabolic acidosis and also reduces loop gain. We investigated whether prolonged use of acetazolamide improves sleep disordered breathing in PVD.

Methods In a randomised controlled crossover trial, patients with PVD were randomly assigned to acetazolamide 250 mg and placebo twice daily for 5 weeks. Patients underwent respiratory polygraphy at baseline and at the end of each intervention phase. Outcomes of interest were the effect of acetazolamide on mean nocturnal oxygen saturation (S_{pO_2}), time with oxygen saturation <90% ($t_{<90}$), apnoea–hypopnoea index (AHI) and sleep apnoea severity.

Results In 20 patients with PVD (55% women, nine with pulmonary arterial hypertension, 11 with distal chronic thromboembolic pulmonary hypertension; mean±SD nocturnal S_{pO_2} 88.8±3.5%, obstructive AHI 12.6±12.3 events·h^{-1}), 5 weeks of acetazolamide resulted in a significant improvement in nocturnal oxygenation compared to placebo (mean nocturnal S_{pO_2} +2.3% (95% CI 1.3–3.3%); p<0.001 and $t_{<90}$ −18.8% (95% CI −29.6– −8.0%); p=0.001). Acetazolamide increased the proportion of patients with mean nocturnal S_{pO_2} ⩾90% from 45% to 85%. The percentage of patients with AHI >5 events·h^{-1} was reduced from 75% to 60% and with AHI >15 events·h^{-1} from 30% to 15%. Two patients discontinued the study because of mild side-effects.

Conclusions Acetazolamide given for 5 weeks reduces nocturnal hypoxaemia in PVD to a clinically relevant level and reduces the proportion of patients with obstructive sleep apnoea.

Introduction

Pulmonary vascular diseases (PVDs), especially pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH), lead to hypoxaemic respiratory insufficiency and increased respiratory drive, which is perceived as dyspnoea. The hypoxaemia results from low cardiac output, increasing ventilation/perfusion (V'/Q') mismatch, worsened diffusion capacity and possibly an increase in right-to-left shunts. Hypoxaemia continues to increase at night with an increase in V'/Q' mismatch in the supine position, physiologically decreasing chemosensitivity and minute ventilation, and a decrease in the increased awake hypoxaemic ventilatory drive, and further decreasing cardiac output during sleep [1–3]. Lower nocturnal percutaneous oxygen saturation (S_{pO_2}) is also associated with higher mortality in PAH [4]. In addition to sleep-related hypoxaemia, other forms of sleep-related breathing disorders, especially central sleep apnoea (CSA) with periodic breathing, but also obstructive sleep apnoea (OSA), are common in PVD [1, 5–10]. The type of sleep disordered breathing (SDB) depends on the form and severity of pulmonary hypertension and concomitant diseases. However, the pathophysiological

consequences of PVD primarily favour hypoxaemia and CSA with periodic breathing. The decreased cardiac output and thus prolonged circulatory time of chemical stimuli, ventricular uncoupling, changes in respiratory drive, hypoxaemia- and hypocapnia-induced changes in loop gain [11], hypervolaemia, and decreased upper airway muscle control contribute to instability in breathing and sleep apnoea in PVD. Right ventricular dysfunction and ventricular uncoupling may delay the chemoreflex response and promote unstable breathing by altering loop gain [12]. In addition, nocturnal hypoxaemia may further adversely affect pulmonary haemodynamics. Nocturnal oxygen supplementation leads to an improvement in sleep-associated hypoxaemia and also CSA with periodic breathing [6, 13]. Why is it important to improve SDB in PVD? Sleep apnoea and nocturnal hypoxaemia and particularly intrathoracic pressure changes in OSA can worsen haemodynamics and promote cardiac arrhythmias, aggravate dyspnoea, and impair sleep quality and quality of life [10, 14]. In addition, hypoxaemia has been associated with worse prognosis in patients with PVD [4, 10, 15]. We have previously shown that nocturnal oxygen therapy and short-term acetazolamide administration improve nocturnal hypoxaemia and SDB [13, 16]. However, supplemental oxygen therapy may not be tolerated by every patient and may not be feasible in all circumstances, making acetazolamide tablets an attractive alternative.

Acetazolamide increases minute ventilation and the apnoea threshold and lowers the plant gain component of loop gain [17], and thus has the potential to improve both CSA and to a lesser extent OSA [18]. Acetazolamide may also improve haemodynamics by improving oxygenation, thereby indirectly reducing SDB. Data on the effect of acetazolamide on SDB in PVD are scarce and lacking to date on prolonged use [13].

We hypothesised that 250 mg acetazolamide twice daily for 5 weeks would increase mean nocturnal oxygen saturation (S_{pO_2}) and decrease the apnoea–hypopnoea index (AHI) in patients with PAH or CTEPH. The aim of the study was to determine whether acetazolamide can improve SDB in PVD without causing relevant side-effects.

Methods

Study design

In a double-blind, placebo-controlled, randomised crossover study, patients with PAH (World Health Organization (WHO) Group 1) or peripheral CTEPH (WHO Group 4) were assigned to 5 weeks of treatment with acetazolamide (250 mg twice daily) or placebo [19]. Patients underwent ambulatory respiratory polygraphy at baseline and at the end of both intervention phases. Both participants and investigators were blinded to allocation. The study was approved by the local ethics committee (KEK-ZH-2016-00089) and registered at ClinicalTrials.gov (NCT02755298). The study was conducted in compliance with all ethical standards for drug trials and in accordance with the Declaration of Helsinki.

Study population

Adult patients (aged 20–80 years) treated at the Swiss Reference Centre for Pulmonary Hypertension of the University Hospital Zurich (Zurich, Switzerland) with pre-capillary pulmonary hypertension classified as either PAH or CTEPH were eligible to participate. The patients had pre-capillary pulmonary hypertension with mean pulmonary arterial pressure (mPAP) >25 mmHg, pulmonary arterial wedge pressure <15 mmHg and pulmonary vascular resistance (PVR) >3 WU according to the guidelines at the time [20]. Patients had to be in stable condition and on the same medication regime for the 4 weeks prior to inclusion in the study. Patients were excluded if they were pregnant, had left heart disease, or had more than a mild obstructive or restrictive ventilatory disorder on pulmonary function tests.

Interventions, randomisation and blinding

Patients were allocated to receive 250 mg acetazolamide twice daily for 5 weeks and an identical looking placebo (Kantonsapotheke Universitätsspital Zürich, Zurich, Switzerland) for 5 weeks, each in random order. To avoid a carry-over effect, the sequences were performed at least 2 weeks apart. Patients were allocated to a treatment sequence in balanced blocks of four using a computer-generated list.

Outcomes

The main outcome of interest was the effect of acetazolamide on mean nocturnal S_{pO_2}. Other outcomes of interest were the effect of acetazolamide on time with oxygen saturation <90% ($t_{<90}$), AHI, sleep apnoea severity group based on AHI, oxygen desaturation index (ODI), nocturnal heart rate and subjective daytime sleepiness as assessed by the Epworth Sleepiness Scale (ESS). In addition, the association between the effect of acetazolamide on mean nocturnal S_{pO_2} and baseline characteristics was analysed. The relationship between changes in nocturnal hypoxaemia and daytime arterial blood gases was also investigated.

Assessments

At baseline and at the end of each intervention phase, a level 3 sleep study was conducted at home, using a nasal pressure prong, respiratory inductance plethysmography, finger pulse oximetry and an accelerometer (Alice Night One; Philips Respironics, Murrysville, PA, USA). Measurements included airflow, snoring, respiratory effort, oxygen saturation, pulse rate and body position. The sleep studies were scored by a single investigator who was blinded to treatment assignment, according to the most recent American Academy of Sleep Medicine scoring criteria [21]. Apnoea was defined as ⩾90% reduction in airflow for at least 10 s and hypopnoea was defined as a reduction of airflow of ⩾30% in comparison to the preceding baseline lasting for ⩾10 s in association with a ⩾3% drop in oxygen saturation. Central apnoea was differentiated from obstructive apnoea by the absence of respiratory effort, and central hypopnoea was differentiated from obstructive hypopnoea by the absence of obstructive pattern of inspiratory flow limitation (flattening) and snoring during the event. Periodic breathing was scored when at least three continuous cycles of waxing and waning of ventilation were present with periods of hyperventilation separated by central apnoeas or hypopnoeas [21]. The indices (*e.g.* AHI) were calculated per hour of monitoring. The morning after the sleep study, patients had an arterial blood gas analysis.

Statistics

A per-protocol analysis of patients with sleep studies (good quality, >3 h) in both sequences was performed for this study on physiological measures. Data are expressed as mean with standard deviation unless otherwise indicated (primary outcome normally distributed). To analyse the treatment effect of acetazolamide compared with placebo, a linear mixed model was fitted to the data using the intervention (acetazolamide *versus* placebo), period and intervention×period interaction as fixed effects and the subject as a random intercept, thus controlling for carry-over (interaction between treatment and period) and period effects according to standards for crossover studies. Tests were conducted to determine whether the intervention×period interaction could be removed from the model. Model assumptions were tested by visual inspection of homogeneity and normality of residuals and random effects. The association between the effect of acetazolamide on nocturnal S_{pO_2} and oxygenation during the day was evaluated by Pearson's correlation. Linear regression models were used to test the association of the treatment effect of acetazolamide on mean nocturnal S_{pO_2} (main outcome) with patient characteristics, haemodynamics and baseline nocturnal S_{pO_2}. Statistical significance was assumed at $p<0.05$. An *a priori* sample size estimation

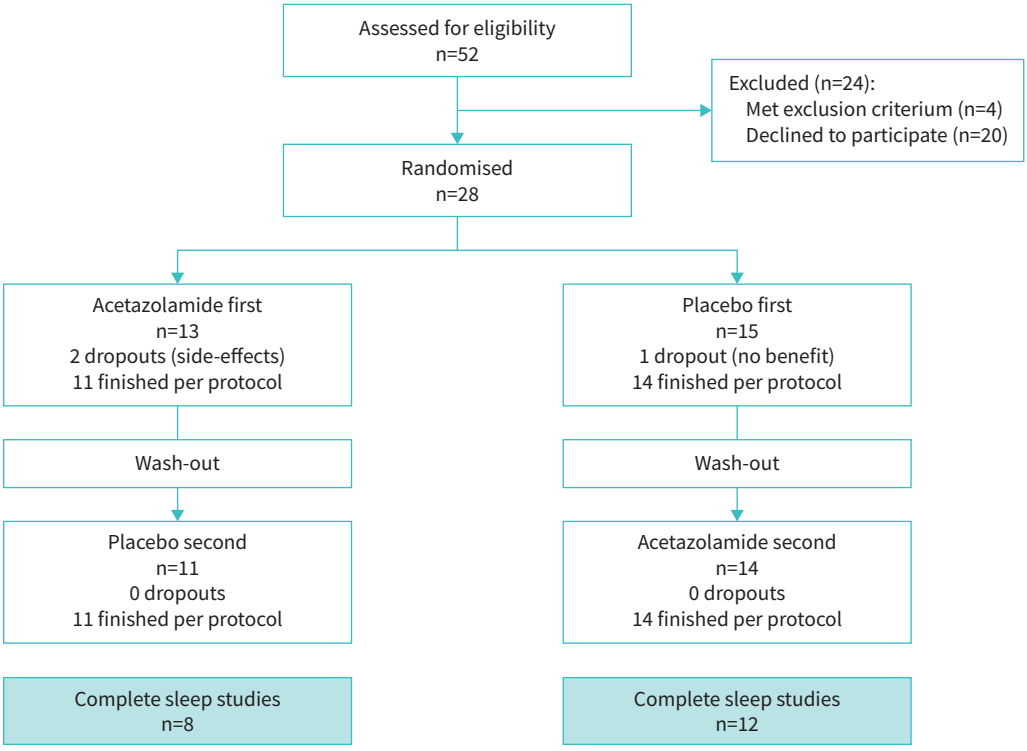

FIGURE 1 Patient flow and availability of sleep studies.

for the main outcome of this analysis (secondary outcome in the protocol) indicated that a total of 18 patients had to be included into this crossover study to detect an acetazolamide-induced difference in mean nocturnal S_{pO_2} with a power of 80% at a two-sided 0.05 significance level, if the true difference between acetazolamide and placebo is 3% with a standard deviation of 3% [13]. More subjects were included, as sample size estimation for 6-min walk distance (6MWD) reported elsewhere [19] was based on the assumption of a minimal important difference in the 6MWD of 20 m between interventions with a detection power of 80%.

Data are reported in accordance with the CONSORT statement for randomised controlled trials (RCTs) [22, 23]. Stata version 15.1 (StataCorp, College Station, TX, USA) was used for statistical analysis.

Results

Patient population

Of 28 patients randomised to one of the sequences, 25 completed the study. Two dropouts occurred during the acetazolamide phase due to side-effects and one dropout occurred during the placebo phase due to lack of hoped-for subjective benefit [19]. Another three lacked sleep studies of sufficient length (good quality, >3 h)

TABLE 1 Patient characteristics

Patients	20
Age, years	60.9±15.9
Female:male	11:9
BMI, kg·m^{-2}	26.3±5.0
mPAP, mmHg	34.4±9.1
PAWP, mmHg	11.1±2.0
CI, L·min^{-1}·m^{-2}	2.7±0.5
PVR, WU	4.6±2.0
NYHA Functional Class	2±0.9
6MWD, m	573±84
Pulmonary hypertension drugs#	1.8±0.3
ERA	14
PDE5i/riociguat	8
Prostanoid	1
Combination therapy	6
P_{aO_2}, kPa	10.1±1.6
S_{aO_2}, %	94.1±6.2
pH	7.44±0.03
P_{aCO_2}, kPa	4.6±0.5
Bicarbonate, mmol·L^{-1}	24.3±1.4
Base excess, mmol·L^{-1}	−0.6±1.8
Baseline AHI >5 events·h^{-1}	11 (55)
Mean nocturnal S_{pO_2}, %	88.8±3.5
$t_{<90}$, %	48.8±38.1
$t_{<85}$, %	16.7±27.4
$t_{<80}$, %	3.3±6.6
ODI (>3%), events·h^{-1}	13.5±11.6
AHI, events·h^{-1}	12.6±12.3
Central AHI, events·h^{-1}	0.6±0.6
Supine AHI, events·h^{-1}	35.0±21.8
Mean nocturnal heart rate, beats·min^{-1}	67.2±9.3
ESS score	5.4±3.6
FVC, % pred	95±15
FEV_1, % pred	90±14
D_{LCO}, % pred	69±12

Data are presented as n, mean±SD or n (%). BMI: body mass index; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; CI: cardiac index; PVR: pulmonary vascular resistance; NYHA: New York Heart Association; 6MWD: 6-min walk distance; ERA: endothelin receptor antagonist; PDE5i: phosphodiesterase-5 inhibitor; P_{aO_2}: arterial partial pressure of oxygen; S_{aO_2}: arterial oxygen saturation; P_{aCO_2}: arterial partial pressure of carbon dioxide; AHI: apnoea–hypopnoea index; S_{pO_2}: oxygen saturation measured by pulse oximetry; $t_{<90/85/80}$: time spent with nocturnal S_{pO_2} <90/85/80%; ODI: oxygen desaturation index; ESS: Epworth Sleepiness Scale; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; D_{LCO}: (single-breath) diffusing capacity of the lung for carbon monoxide. #: specific pulmonary vasodilators.

under either acetazolamide (n=3) or placebo (n=2). Thus, 20 patients with a complete dataset could be included in the per-protocol analysis (figure 1).

The 20 patients (55% women; mean±SD age 60.9±15.9 years) with PAH (n=9) or distal CTEPH (n=11) who could be included in the study had mean±SD mPAP 34.4±9.1 mmHg and PVR 4.6±2.0 WU under optimal medical and supportive therapy. They had mean±SD nocturnal S_{pO_2} 88.8±3.5% and $t_{<90}$ 48.8±38.1% before randomisation. 70% of patients had OSA based on obstructive AHI >5 events·h^{-1} (30% AHI <5 events·h^{-1}, 65% AHI 5–30 events·h^{-1}, 5% AHI >30 events·h^{-1}), particularly positional OSA, but usually not severe OSA. None had CSA with periodic breathing. Patient characteristics at the time of study inclusion are listed in table 1.

Effect of 5 weeks of acetazolamide 250 mg twice daily on nocturnal S_{pO_2} and sleep apnoea

Compared with placebo, acetazolamide 250 mg twice daily significantly increased mean nocturnal S_{pO_2} by +2.3% (95% CI 1.3–3.3%) (p<0.001) and significantly decreased $t_{<90}$ by −18.8% (95% CI −29.6– −8.0%) (p=0.001) (table 2 and figure 2). Acetazolamide increased the proportion of patients with mean nocturnal S_{pO_2} ⩾90% from 40% to 85% (Chi-squared 8.6, p=0.003). Compared with placebo, acetazolamide also reduced the slightly increased ODI and AHI (table 2). In this PVD population with OSA in 70% at baseline, the percentage of patients with AHI >5 events·h^{-1} was reduced from 75% to 60% (Chi-squared 5.1, p=0.024) and with AHI >15 events·h^{-1} from 30% to 15% (Chi-squared 6.5, p=0.011) on acetazolamide compared to placebo (figure 3). Under acetazolamide, the mean nocturnal heart rate was significantly lower (table 2). Acetazolamide use had no effect on ESS score compared with placebo, which was already low at baseline.

Association of baseline characteristics with effect of acetazolamide on nocturnal S_{pO_2}

The effect of acetazolamide on mean nocturnal S_{pO_2} (change between baseline nocturnal S_{pO_2} and nocturnal S_{pO_2} on acetazolamide) was not associated with age, sex, body mass index, pulmonary hypertension group or haemodynamic parameters, but was negatively associated with baseline nocturnal S_{pO_2}. That is, the lower the mean nocturnal S_{pO_2} initially, the greater the increase in nocturnal S_{pO_2} under acetazolamide.

TABLE 2 Effect of acetazolamide on nocturnal oxygen saturation (measured by pulse oximetry (S_{pO_2})) and sleep disordered breathing

	Baseline (n=20)	Placebo (n=20)	Placebo–baseline difference (95% CI), p-value	Acetazolamide (n=20)	Acetazolamide–baseline difference (95% CI), p-value	Between-group difference (95% CI), p-value
Mean nocturnal S_{pO_2}, %	88.8±3.5	89.3±3.5	0.5 (−1.7–2.7) p=0.651	91.6±2.9	2.8 (0.8–4.8) p=0.009*	2.3 (1.3–3.3) p<0.001*
$t_{<90}$, %	48.8±38.1	41.6±32.4	−7.2 (−29.8–15.4) p=0.524	22.8±31.4	−26.0 (−48.3– −3.6) p=0.024*	−18.8 (−29.6– −8.0) p=0.001*
$t_{<85}$, %	16.7±27.4	15.4±26.5	−1.2 (−18.5–16.2) p=0.886	4.6±12.5	−12.1 (−25.7–1.5) p=0.081	−10.8 (−22.4–0.8) p=0.066
$t_{<80}$, %	3.3±6.6	3.7±3.9	0.4 (−4.8–5.5) p=0.892	0.1±0.5	−3.2 (−6.2– −0.2) p=0.039*	−3.5 (−7.5–0.5) p=0.081
ODI (>3%), events·h^{-1}	13.5±11.6	12.2±8.3	−1.3 (−7.7–5.2) p=0.689	7.6±5.6	−5.9 (−11.8– −0.1) p=0.048*	−4.6 (−6.7– −2.5) p<0.001*
AHI, events·h^{-1}	12.6±12.3	11.0±8.6	−1.6 (−8.3–5.2) p=0.620	7.6±6.4	−5.0 (−11.2–1.3) p=0.118	−3.4 (−5.5– −1.3) p=0.002
Supine AHI, events·h^{-1}	35.0±21.8	20.5±14.8	−15.2 (−27.8–2.6) p=0.023	16.1±7.8	−18.2 (−31.6–4.7) p=0.013	−3.7 (−12.1–4.7) p=357
Mean nocturnal heart rate, beats·min^{-1}	67.2±9.3	67.8±8.7	0.6 (−5.1–6.4) p=0.833	64.2±6.7	−3.0 (−8.2–2.1) p=0.248	−3.6 (−6.2– −1.0) p=0.007*
Sleep study analysis time, h:min	07:03±0:08	06:12±0:08	p=0.154	06:24±0:07	p=0.081	p=0.731
ESS score	6.2±3.7	6.5±4.1	0.2 (−0.6–0.9) p=0.673	6.9±3.4	1.0 (−0.1–1.9) p=0.037	0.7 (−0.6–1.9) p=0.248

Data are presented as mean±SD, unless otherwise stated. $t_{<90/85/80}$: time spent with nocturnal S_{pO_2}<90/85/80%; ODI: oxygen desaturation index; AHI: apnoea–hypopnoea index; ESS: Epworth Sleepiness Scale. The apnoeas and hypopnoeas were primarily obstructive. All patients with elevated AHI had obstructive sleep apnoea and no patient had central sleep apnoea with periodic breathing. Time spent in supine position was overall <20%. Differences including 95% confidence intervals and p-values were calculated with t-tests (within-group change) and linear mixed models (treatment effect). *: p<0.05.

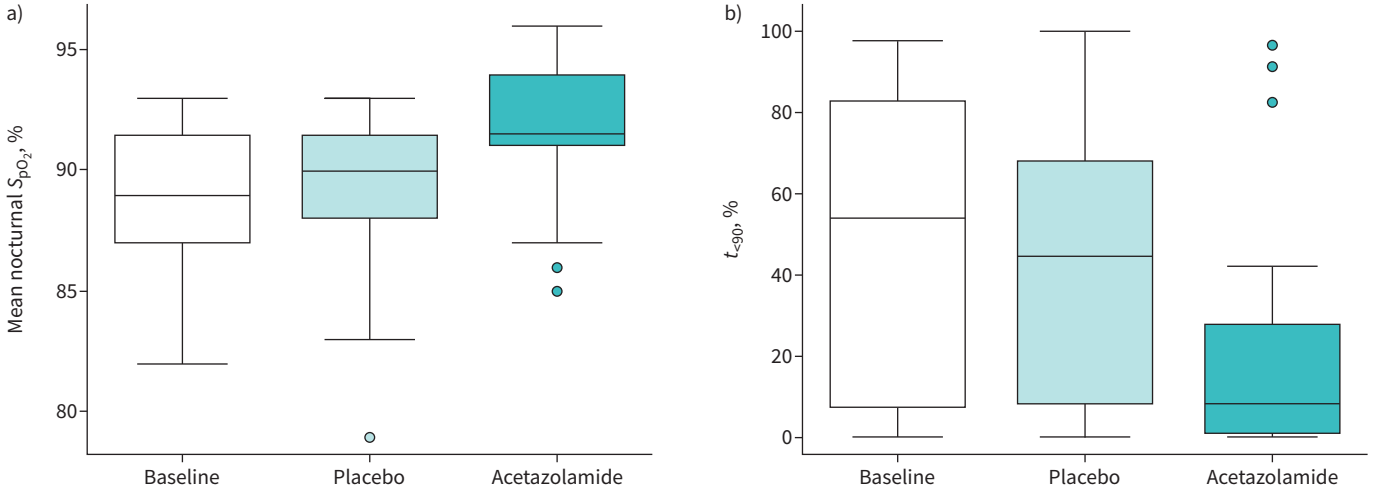

FIGURE 2 Box-and-whisker plots showing median (interquartile range) of a) mean nocturnal oxygen saturation (measured by pulse oximetry (S_{pO_2})) and b) time during the sleep study with oxygen saturation <90% ($t_{<90}$) at baseline prior to randomisation, on placebo and on acetazolamide.

Effect of 5 weeks of acetazolamide 250 mg twice daily on daytime arterial blood gas parameters and its association with its effect on nocturnal S_{pO_2}

Five weeks of acetazolamide 2×250 mg·day^{-1} resulted in a significant reduction in bicarbonate concentration and pH from morning arterial blood gas analysis, and a significant decrease in P_{aCO_2} accompanied by a significant increase in arterial partial pressure of oxygen (P_{aO_2}) and arterial oxygen saturation (S_{aO_2}) of roughly 2 kPa and 2%, respectively (table 3). The increase in nocturnal S_{pO_2} was strongly positively associated with the increase in daytime P_{aO_2} (r=0.75, p<0.001) and S_{aO_2} (r=0.75, p<0.001) in response to intake of acetazolamide.

Discussion

In this randomised, placebo-controlled crossover study of the effect of acetazolamide 250 mg twice daily for 5 weeks on nocturnal hypoxaemia and SDB in patients with PVD and pre-existing nocturnal hypoxaemia (mean nocturnal S_{pO_2} 88.8%, $t_{<90}$ 49%) and mild OSA (AHI 13 events·h^{-1}; AHI >5 events·h^{-1} in 70%), a significant improvement in nocturnal S_{pO_2} (+2.3%) and a significant reduction in $t_{<90}$ (−18.8%), ODI (−4.6 events·h^{-1}) and nocturnal heart rate (−3.6 beats·min^{-1}) were demonstrated, in addition to an improvement in daytime oxygenation (S_{aO_2} +1.7%, P_{aO_2} +1.9 kPa). The proportion of patients with mean nocturnal S_{pO_2} ⩾90% nearly doubled from 45% to 85%.

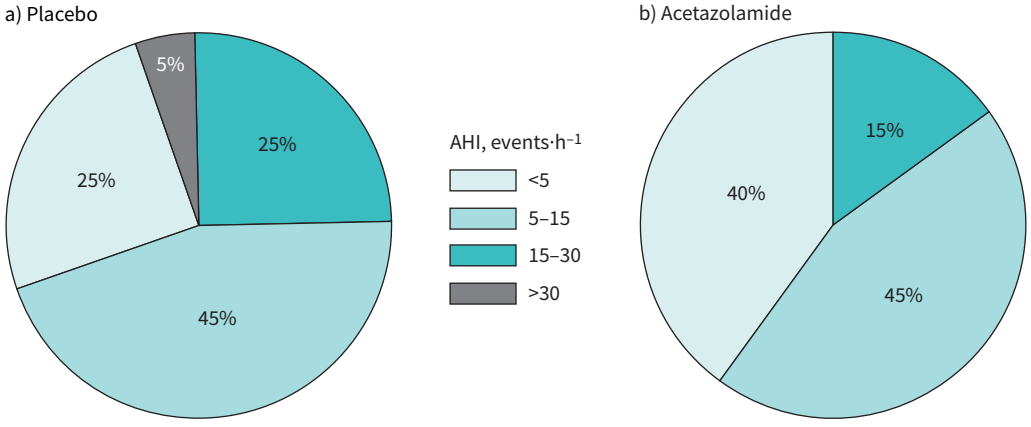

FIGURE 3 Pie charts of the distribution of apnoea–hypopnoea index (AHI) groups on a) placebo and b) acetazolamide. On placebo, 25% had AHI <5 events·h^{-1} and 70% had AHI <15 events·h^{-1}; on acetazolamide, 40% had AHI <5 events·h^{-1} and 85% had AHI <15 events·h^{-1}.

TABLE 3 Effect of acetazolamide on arterial blood gas parameters

	Baseline (n=18)	Placebo (n=18)	Placebo–baseline difference (95% CI), p-value	Acetazolamide (n=19)	Acetazolamide–baseline difference (95% CI), p-value	Between-group difference (95% CI), p-value
P_{aO_2}, kPa	10.1±1.6	9.7±1.7	−0.4 (−1.4–0.8) p=516	11.4±1.8	1.3 (0.2–2.5) p=0.022*	1.9 (1.2–2.6) p<0.001*
S_{aO_2}, %	95.5±1.9	94.9±2.7	−0.6 (−2.2–1.0) p=455	96.7±1.9	1.2 (−0.1–2.4) p=0.070	1.7 (0.6–2.8) p=0.003*
pH	7.44±0.03	7.45±0.03	0 (−0.02–0.03) p=0.715	7.37±0.03	−0.07 (−0.09– −0.05) p<0.001*	−0.07 (−0.10– −0.05) p<0.001*
P_{aCO_2}, kPa	4.6±0.5	4.5±0.6	−0.1 (−0.5–0.2) p=0.467	3.9±0.5	−0.7 (−1.1– −0.4) p<0.001*	−0.7 (−0.9– −0.5) p<0.001*
Bicarbonate, mmol·L^{-1}	24.3±1.4	23.9±2.0	−0.5 (−1.7–0.8) p=0.446	18.7±1.5	−5.6 (−6.6– −4.6) p<0.001*	−5.7 (−9.9– −1.5) p<0.009*
Base excess, mmol·L^{-1}	−0.6±1.8	−1.3±2.8	−0.7 (−2.3–0.9) p=0.376	−8.4±2.3	−7.9 (−9.2– −6.5) p<0.001*	−7.8 (−9.3– −6.4) p<0.001*

Data are presented as mean±SD, unless otherwise stated. P_{aO_2}: arterial partial pressure of oxygen: S_{aO_2}: arterial oxygen saturation; P_{aCO_2}: arterial partial pressure of carbon dioxide. Differences including 95% confidence intervals and p-values were calculated with t-tests (within-group change) and linear mixed models (treatment effect). *: p<0.05.

We have previously shown in a group of patients with pre-capillary pulmonary hypertension and either nocturnal hypoxaemia with nocturnal S_{pO_2} <90% or sleep apnoea with AHI >10 events·h^{-1} that 1 week of acetazolamide improves mean nocturnal S_{pO_2} by a median of 3% and reduces periodic breathing and central and total AHI [13]. As shown previously, acetazolamide increases daytime ventilation by inducing metabolic acidosis, resulting in increases in daytime P_{aO_2} and nocturnal S_{pO_2}. However, additional stimulation of respiratory drive in patients with increased neural respiratory drive could further exacerbate the perception of dyspnoea. This is the first RCT on acetazolamide in patients with PVD over an extended period of time, and we showed that acetazolamide was generally well tolerated with no severe adverse effects (details reported separately) [19]. However, 7% of patients discontinued acetazolamide due to mild side-effects [19].

In contrast to the use of nocturnal oxygen, the use of acetazolamide also leads to a sustained improvement in oxygen saturation during the day. Of course, the increase in dyspnoea as a possible side-effect of acetazolamide and the absence of an effect on the 6-min walk test [19] as a parameter of exercise performance in patients with PVD should argue against its long-term daytime use. However, from the available data, it can be hypothesised that a treatment strategy with acetazolamide administered in the evening before bedtime but not in the morning to avoid the side-effects of stimulated ventilation during the day is worth investigating. Because nocturnal oxygen and 24-h oxygen supplementation improve nocturnal hypoxaemia and exercise capacity, and the latter also improves New York Heart Association Functional Class and quality of life in PVD, oxygen should currently be preferred over acetazolamide until more evidence is available [13, 24]. Supplemental oxygen is particularly beneficial for patients with low diffusing capacity of the lung for carbon monoxide [25]. It is considered important to maintain P_{aO_2} >8 kPa to avoid hypoxaemic pulmonary vasoconstriction and thus a further increase in PVR, although it is not clear whether patients with PVD respond to hypoxaemia in the same way as patients without PVD [26].

A recent meta-analysis studying the effect of different doses of acetazolamide on SDB and arterial blood gas parameters in patients with OSA (13 studies) or different types of CSA (15 studies; including high-altitude periodic breathing, Cheyne–Stokes breathing in heart failure or opioid-induced CSA) compared with an inactive control showed a significant effect of acetazolamide (36–1000 mg·day^{-1}) on mean nocturnal S_{pO_2} (+3.5% (95% CI 2.3–4.8%)) and a trend towards lower $t_{<90}$ and a lower ODI. Acetazolamide significantly lowered the central AHI (−9.5 (95% CI −14.0– −4.9) events·h^{-1}) but not the obstructive AHI (−7.5 (95% CI −16.9–1.8) events·h^{-1}) [18]. In this meta-analysis, acetazolamide also lowered daytime blood pressure but, interestingly, not heart rate. As expected based on its mechanism of action, acetazolamide decreased pH (−0.06 (95 CI −0.07– −0.04)), bicarbonate (−5.1 (95% CI −6.2– −3.9) mmol·L^{-1}) and P_{aCO_2} (−4.0 (95% CI −5.2– −2.8) mmHg (−0.5 (95% CI −0.7– −0.4) kPa)) and increased P_{aO_2} (+10.3 (95% CI 7.6–13.0) mmHg (+1.4 (95% CI 1.0–1.7) kPa)) due to increased ventilation [18]. Like patients with CSA associated with high loop gain, patients with PVD already have an increased ventilatory drive. The effects of acetazolamide in this meta-analysis in sleep

apnoea are comparable to the effects of 5 weeks of acetazolamide on arterial blood gases and metabolic parameters in our patients with PVD (table 3).

Acetazolamide not only resulted in significant improvement in mean nocturnal S_{pO_2} and decrease in $t_{<90}$, but also in a decrease in initial slightly elevated AHI and ODI. Interestingly, all PVD patients with an elevated baseline AHI (70% with AHI >5 events·h^{-1}) had OSA rather than CSA. The number with at least moderate OSA based on AHI >15 events·h^{-1} was halved from 30% to 15% and the percentage with normal AHI <5 events·h^{-1} was increased from 25% to 40%. While increased loop gain predominantly plays a role in CSA in PVD and heart failure, in a proportion of OSA patients, in addition to an anatomically narrow upper airway prone to collapse, high loop gain contributes to unstable breathing [27]. Loop gain is usually higher in the supine position and most of our patients had supine position-dependent OSA. It is possible that increased loop gain explains why our patients with PVD had a relatively high prevalence of OSA and why this improved with acetazolamide. However, in a recent RCT, low loop gain was a predictor of acetazolamide efficacy in OSA [28]. In addition, increased loop gain in the supine position may occur in patients with CSA/Cheyne–Stokes respiration, but not necessarily in OSA [29]. A high loop gain would be a pathophysiological basis, which is why patients with PVD may not only have more frequent CSA, but also why OSA would be favoured in PVD. In case of fluid retention due to heart failure, rostral fluid shift to the lungs and upper airway may also predispose patients with PVD to both CSA and OSA. However, the weight of the patients did not change significantly in this study and the medication (including any diuretics) of the stable patients with PVD was not changed during the study.

A limitation of this study is the use of respiratory polygraphies instead of polysomnographies, so that the distribution of sleep stages cannot be assessed. However, these are unlikely to be important for the primary outcome of the study, mean nocturnal S_{pO_2}. Another limitation is the relatively small number of patients and that the sample size of the study was calculated for a different outcome (6MWD [19]). A strength of this study is its design as a double-blind randomised controlled crossover trial, which allows comparisons not only at the group level but also at the individual level. In a randomised crossover trial, each subject serves as his or her own control and is randomly assigned to the intervention in a different order. In addition, compared with a conventional randomised controlled parallel-group trial, fewer participants are required to achieve the same power, which is advantageous when studying patients with rare and potentially heterogenous diseases such as PVD. Such a study design is appropriate when investigating a treatment with a short-term effect where no carry-over effect is expected, as demonstrated in our study.

The lower pH (between-group difference between acetazolamide and placebo −0.07 (95% CI −0.10–−0.05)) can theoretically lead to a certain distortion of the S_{pO_2} due to the different oxygen binding curves at different pHs, as the oxygen binding curve is shifted to the right. At a non-acidic pH, the treatment effect of acetazolamide on S_{pO_2} would be even greater. However, this is negligible due to the small rightward shift.

Conclusions

Acetazolamide results in a significant and clinically relevant increase in mean nocturnal S_{pO_2} and a reduction $t_{<90}$ in patients with PVD. In these patients with PAH (WHO Group 1) or distal CTEPH (WHO Group 4), acetazolamide not only improves nocturnal hypoxaemia but also reduces the severity of commonly observed OSA and leads to an improvement in daytime S_{aO_2}.

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Data availability: The data that support the findings of this study are not openly available but are available from the corresponding author upon reasonable request.

This study is registered at ClinicalTrials.gov with identifier number NCT02755298.

Ethics statement: The study was approved by the local ethics committee (KEK-ZH-2016-00089).

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