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Effect of Oxygen and Acetazolamide on Nocturnal Cardiac Conduction, Repolarization, and Arrhythmias in Precapillary Pulmonary Hypertension and Sleep-Disturbed Breathing

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BACKGROUND: Sleep-disturbed breathing (SDB) is common in patients with precapillary pulmonary hypertension (PH). Nocturnal oxygen therapy (NOT) and acetazolamide improve SDB in patients with PH, and NOT improves exercise capacity. We investigated the effect of NOT and acetazolamide on nocturnal cardiac conduction, repolarization, and arrhythmias in patients with PH and SDB.

METHODS: In a randomized, placebo-controlled, double-blind, crossover trial, 23 patients with arterial (n = 16) or chronic thromboembolic PH (n = 7) and SDB defined as a mean nocturnal oxygen saturation $< 90\%$ or dips ($> 3\%$) > 10/h with daytime $Pao_2 \geq 7.3$ kPa were studied. Participants received NOT (3 L/min), acetazolamide tablets (2×250 mg), and sham-NOT/placebo each during 1 week separated by a 1-week washout period. Three-lead ECG was recorded during overnight polysomnography at the end of each treatment period. Repolarization indices were averaged over three cardiac cycles at late evening and at early morning, and nocturnal arrhythmias were counted.

RESULTS: NOT was associated with a lower overnight (68 ± 10 beats/min vs 72 ± 9 beats/min, $P = .010$) and early morning heart rate compared with placebo. At late evening, the heart rate-adjusted PQ time was increased under acetazolamide compared with placebo (mean difference, 10 milliseconds; 95% CI, 0-20 milliseconds; $P = .042$). In the morning under NOT, the heart rate-adjusted QT (QTc) interval was decreased compared with placebo (mean difference, -25 milliseconds; 95% CI, -45 to -6 milliseconds; $P = .007$), and the interval between the peak and the end of the T wave on the ECG was shorter compared with acetazolamide (mean difference, -11 milliseconds; 95% CI, -21 to -1 milliseconds; $P = .028$). Arrhythmias were rare and similar with all treatments.

CONCLUSIONS: In patients with PH with SDB, NOT reduces nocturnal heart rate and QTc in the morning, thus, favorably modifying prognostic markers.

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ABBREVIATIONS: 6MWD = 6-min walk distance; AF = atrial fibrillation; bpm = beats/min; CTEPH = chronic thromboembolic pulmonary hypertension; NOT = nocturnal oxygen therapy; PAC = premature atrial contraction; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; PQc = heart rate-adjusted value of PQ; QTc = heart rate-corrected value of QT; RV = right ventricle; SDB = sleep-disturbed breathing; Spo_2 = oxygen saturation; TpTe = interval between the peak and the end of the T wave on ECG; TpTec = heart rate-corrected value of the interval between the peak and the end of the T wave on ECG; WHO = World Health Organization

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Sleep-disturbed breathing (SDB) is highly prevalent in patients with pulmonary arterial and chronic thromboembolic pulmonary hypertension (CTEPH), with more than one-third suffering from periodic breathing and more than two-thirds from sustained nocturnal hypoxemia.[1-3] SDB is relevant because it impairs quality of life.[2] Oxygen deprivation in pulmonary vascular cells during SDB further triggers pulmonary vasoconstriction with increase in pulmonary vascular resistance maintaining a vicious cycle.[3,4] Remodeling of the right ventricle (RV) in response to increased afterload together with hypoxemia and consecutive myocardial ischemia may affect myocardial autonomic activity, lead to conduction and repolarization abnormalities, and represent an arrhythmogenic substrate.[5-7] Cardiac arrhythmias are important influencing factors to morbidity and mortality in patients with pulmonary hypertension (PH) and result in clinical deterioration and compromised cardiac function.[6]

We have shown that SDB in precapillary PH is significantly ameliorated with nocturnal oxygen therapy (NOT) or the ventilatory-stimulant drug acetazolamide and that NOT improves the 6-min walk distance (6MWD), symptoms, and hemodynamics during daytime.[1,8-11] In the present study, we evaluated the hypothesis that NOT and acetazolamide would improve cardiac conduction, repolarization, and arrhythmias in patients with PH and SDB.

Materials and Methods

Design and Setting

The data for this study were collected as part of a randomized, double-blind, sham/placebo-controlled three-period crossover trial in patients with PH and SDB.[8] The study compared effects of (1) nocturnal supplemental oxygen by nasal cannula (3 L/min, NOT) and placebo tablets, (2) acetazolamide tablets (2 × 250 mg) and sham NOT (room air by nasal cannula with a flow rate of 3 L/min), with (3) sham NOT and placebo tablets (Fig 1). Subsequently, these treatment combinations are termed NOT, acetazolamide, and placebo. Each treatment was applied for 1 week in the patient's home; the last night patients spent at hospital for sleep studies. During washout of 1 week, patients did not receive study treatment. The trial was performed from December 2010 to August 2012. This study was conducted in accordance with the amended Declaration of Helsinki. The study was approved by the cantonal ethical review board of Zurich (KEK-ZH-NR: 2010-0129) and registered at ClinicalTrials.gov: NTC-01427192.

Patients, Randomization, and Blinding

Consecutive patients aged 20 to 80 years diagnosed with pulmonary arterial hypertension (PAH) (World Health Organization [WHO] group 1) or inoperable CTEPH (WHO group 4)[12] were eligible for enrollment upon written informed consent. All patients were diagnosed according to current guidelines and had undergone right-sided heart catheterization at the time of initial evaluation.[13] Patients were considered for inclusion if they were in a stable condition on the same medication for > 4 weeks. Eligible patients had SDB defined as either a mean nocturnal oxygen saturation (Spo_2) < 90% or an oxygen desaturation index (> 3% dips) > 10/h during ambulatory nocturnal pulse oximetry. Patients with Pao_2 < 7.3 kPa during daytime, predominantly OSA, more than mild lung disease ($FEV_1 \leq 60\%$), or concomitant left ventricular disease were excluded.

NOT (or sham-NOT) was delivered via a nasal cannula at a flow rate of 3 L/min by an oxygen concentrator (Respironics EverFlo; Koninklijke Philips N.V.). The sham concentrators were prepared by modifying the similar concentrators to provide room air. Acetazolamide (Diamox; Vifor Pharma) was administered at a dose of 2 × 250 mg/d with breakfast and dinner. Identical-looking capsules containing acetazolamide or placebo were prepared by the cantonal pharmacy of Zurich and packed in containers labeled with a code that was broken only after data analysis. Allocation to one of the six study sequences was performed by an independent pharmacist, assuring a balanced block design. Patients and investigators participating in evaluation of outcomes were blinded to the treatment.

ECG Measurements and Potassium

Three-lead ECG recordings were obtained during the last night of each treatment period (Alice 5; Koninklijke Philips N.V.).[2,14] ECG measurements were performed manually on a computer screen (Alice Sleepware; Koninklijke Philips N.V.) by a trained reviewer blinded to treatments. Supraventricular and ventricular arrhythmias were counted. Premature atrial contractions (PACs), paroxysmal tachycardia, flutter, and fibrillation were scored. Paroxysmal atrial fibrillation (AF) was specified as an event lasting > 30 s. AFs lasting < 30 s were defined as atrial bursts. Supraventricular disturbances included sinus bradycardia (< 40/min) and tachycardia (> 100/min). Ventricular disturbances included premature contractions, tachycardia, flutter, and fibrillation. In addition to computing ECG-derived variables over the entire night, we averaged conduction and repolarization parameters over three cardiac cycles 10 min after lights off (late evening) when the treatment (NOT, acetazolamide tablet evening dose) was after a short time on therapeutic dose, and 10 min before lights on (early morning) when the treatment was effective for several hours. These measurements included: RR interval corresponding to the distance between two consecutive R spikes, P-wave duration, PQ interval, and QRS duration. RR was used to calculate heart rate. A prolonged QRS complex was defined as ≥ 120 milliseconds.[15] The indexes of cardiac repolarization were determined as follows: QT interval, defined as time from the earliest onset of the QRS complex to the end of T wave.[16] The end of T wave was fixed as an intersection between a line tangent to the descending arm of T wave and the isoelectric line.[17] The interval between the peak and the end of the T wave on ECG (TpTe) corresponds to the time from the point of largest amplitude of T-wave deflection to the end of T wave.[17,18] For heart rate-adjusted PQ (PQc), the Soliman and Rautaharju method was used.[19] Bazett's formula was used to obtain heart rate-corrected values of QT (QTc) and TpTe (TpTec).[20] TpTe/QT was calculated as a measure of dispersion of repolarization.[18] Potassium analysis was retrieved from a radial artery blood sample taken in the morning (ABL90 Flex blood gas analyzer; Radiometer Medical ApS).

Data Analysis and Statistics

Comparisons between treatments (NOT, acetazolamide, and placebo) were calculated using Wilcoxon matched-pairs test and Fisher exact test. Data are presented as number (%), medians (quartiles), and mean difference (95% CI). A P value < .05 was considered statistically significant. All statistical analyses were performed using SPSS (IBM).

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