Theophylline Therapy for Cheyne-Stokes Respiration During Sleep in a 41-Year-Old Man With Refractory Arterial Hypertension

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We report a case of a 41-year-old man who was noted to have position-dependent Cheyne-Stokes respiration with central sleep apnea (CSA) during sleep. The patient had multiple cardiovascular risk factors and target organ damages, including a history of two myocardial infarctions, transient ischemic attack, and chronic kidney disease. His hypertension was refractory to a number of antihypertensive medicines, however, a complete elimination of sleep-disordered breathing with oral theophylline treatment was paralleled by a significant BP fall with a subsequent need for reduction of antihypertensive drugs. Following these surprising observations we decided to withdraw theophylline from treatment (in-clinic). Theophylline discontinuation resulted in a gradual increase in BP and an urgent call for antihypertensive treatment modification. These observations suggest a potent hypotensive action of oral theophylline via Cheyne-Stokes respiration with CSA elimination. Our data suggest that CSA may be a mechanism that raises BP even during the daytime. CHEST 2014; 146(1):e8–e10

Abbreviations: AHI = apnea-hypopnea index; CSA = central sleep apnea; CSR = Cheyne-Stokes respiration; LVEF = left ventricular

ejection fraction; SpO_2 = oxygen saturation by pulse oximetry; TIA = transient ischemic attack

Cheyne-Stokes respiration (CSR) with central sleep apnea (CSA) is frequently encountered in pathologic conditions (eg, neurologic dysfunction or congestive heart failure), where it may be implicated in increased morbidity and mortality.^{1–3} Although sleep apnea has been linked to arterial hypertension, only the obstructive type of sleep apnea, and not CSA, is believed to be a causative factor in developing hypertension.^{4,6} In this case report, we show that attenuation of CSR-CSA during sleep with oral theophylline treatment in a patient with hypertensive heart failure (left ventricular ejection fraction [LVEF] = 45%) significantly improved BP control.

CASE REPORT

A 41-year-old man with a longstanding history of complicated, essential hypertension refractory to seven antihypertensives was noted to have CSR-CSA during sleep (Fig 1), exclusively in the supine position. His BP control was poor and showed measurements up to 280/180 mm Hg on home and office measurements and up to 200/140 mm Hg without nocturnal BP dip on 24-h ambulatory BP. The patient had an atherogenic lipid profile, was overweight (BMI = 28), smoked cigarettes, frequently drank alcohol to excess, and had a strong family history of cardiovascular disease. He had left ventricle hypertrophy with segmental contractility impairment, a history of two non-ST segment elevation myocardial infarctions, transient ischemic attack (TIA), retinopathy, and chronic kidney disease (plasma creatinine level, 150 $\mu\text{mol/L}$). The patient was free of diabetes mellitus. Several forms of secondary hypertension (renovascular, hormonal, vasculitis) as well as noncompliance with medications were excluded.

Sleep-Related History

Despite poor sleep quality for approximately 20 years, the patient did not seek professional medical help for this particular problem; however, he occasionally used hypnotics. Diagnostic sleep study revealed CSR-CSA in the supine position (apnea/hypopnea index [AHI] = 16.6; AHI supine = 49.3; oxygen saturation by pulse oximetry [SpO_2] = 93.4%).

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FIGURE 1. A 10-min epoch sample taken from the baseline study. Curves represent (from top to bottom) blood oxygen saturation, ECG, pulse, position (supine), airflow, and respiratory movements.

Intervention

The patient was administered sustained-release oral theophylline 250 mg bid (serum concentration $< 10 \mu\text{g/mL}$). A sleep study while on theophylline therapy showed marked attenuation of CSR-CSA (AHI = 0.6; AHI supine = 4.1; $\text{SpO}_2 = 95.3\%$). These changes were associated with not only a marked improvement in subjective sleep quality and sleep prolongation but also a remarkable BP fall confirmed by 24-h ambulatory BP (103/68 mm Hg). Following these observations, two antihypertensive drugs were discontinued, and dosages of three other medications were reduced. Since theophylline administration was the only treatment change coinciding with the BP fall, we decided to assess the effects of a period of withdrawal. On the morning of the third day after theophylline discontinuation, BP increased substantially, and the patient developed TIA (Fig 2). At the time, we decided to resume theophylline therapy, and a progressive improvement in the patient's BP control was noted over the next few days.

Follow-up

BP control was satisfactory, and no substantial change in antihypertensive drug therapy was required over the next year. At 1-year follow-up visit, mean plasma theophylline level was $3.4 \mu\text{g/mL}$, and sleep monitoring revealed AHI = 1.8, AHI supine = 3.8, and $\text{SpO}_2 = 95.1\%$.

DISCUSSION

Theophylline has been previously suggested as a possible therapy for CSR-CSA both in patients with systolic heart failure and in those with normal LVEF.^{7,8} Most studies of theophylline in CSA examined subjects with concomitant advanced systolic heart failure.^{9,10} These patients in general are hypotensive. However, this patient had an LVEF of

45% and still had extremely high BP. A major effect of sleep apnea on the cardiovascular system is sympathetic excitation.¹⁰ Since we had previously sought to alleviate effects of neurohormonal activation in this patient (two β -blockers, angiotensin-converting enzyme inhibitor, and angiotensin receptor blocker), we then gave priority to eliminating CSR during sleep.

FIGURE 2. Office SBP and DBP recordings before, during, and after theophylline was administered. On the first day of theophylline therapy experimental withdrawal the theophylline level equalled 8.4 mg/dL , and on the morning of day 3, plasma theophylline concentration was 0 mg/dL . On the third day of the experiment, the patient developed TIA, and radical hypotensive drug modifications were implemented, including theophylline resumption. Data are shown as mean $\pm$ SD. DBP = diastolic BP; SBP = systolic BP; THEO = theophylline; TIA = transient ischemic attack.

There are peripheral and central mechanisms of theophylline actions that may result eventually in BP lowering, including endothelium-dependent and -independent vasorelaxation,^{11,12} a diuretic effect, and central apnea elimination via adenosine antagonism resulting in attenuation of hypoxemias and hypercapnias.⁷ Other potential factors contributing to our findings include pharmacologic interactions between the antihypertensive drugs and theophylline and a history of smoking and regular alcohol consumption. In the reported case, during theophylline discontinuation the rise in BP was not linear, as drug concentration was decreasing over time but was more dependent on that level of BP that was set after a nighttime sleep (Fig 2). This suggests a central mechanism of action of theophylline in BP regulation, namely via the alleviation of sleep-disordered breathing, improvement in sleep quality, and blood gas chemistry. Although a direct influence of theophylline on vascular tone cannot be entirely disregarded, our data suggest that this is unlikely to be of major relevance.

CONCLUSIONS

In conclusion, we report a potent antihypertensive action of oral theophylline therapy in a unique patient diagnosed with position-dependent CSR-CSA. These data suggest that CSA may be a mechanism that raises BP even during the daytime.

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