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Effects of intermittent hypoxia on sympathetic activity and blood pressure in humans

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Abstract

Sympathetic nerve activity and arterial pressure are frequently elevated in patients with obstructive sleep apnea (OSA). The mechanisms responsible for chronic sympathetic activation and hypertension in OSA are unknown. To determine whether repetitive apneas raise sympathetic nerve activity and/or arterial pressure, awake and healthy young subjects performed voluntary end-expiratory apneas for 20 s per min for 30 min (room air apneas). To accentuate intermittent hypoxia, in a separate group of subjects, hypoxic gas (inspired O_2 10%) was added to the inspiratory port for 20 s before each apnea (hypoxic apneas). Mean arterial pressure (MAP) and muscle sympathetic nerve activity (MSNA, peroneal microneurography) were determined before and up to 30 min following the repetitive apneas. Following 30 hypoxic apneas (O_2 saturation nadir 83.1 ± 1.2%), MSNA increased from 17.4 ± 2.7 to 23.4 ± 2.5 bursts/min and from 164 ± 28 to 240 ± 35 arbitrary units respectively ($P < 0.01$ for both; $n = 10$) and remained elevated while MAP increased transiently from 80.5 ± 3.7 to 83.1 ± 3.9 mm Hg ($P < 0.05$; $n = 11$). In contrast, in the subjects who performed repetitive apneas during room air exposure (O_2 saturation nadir 95.1 ± 0.8%), MAP and MSNA did not change ($n = 8$). End-tidal CO_2 post-apnea, an index of apnea-induced hypercapnia, was similar in the 2 groups. In a separate control group, no effect of time on MAP or MSNA was noted ($n = 7$). Thus, repetitive hypoxic apneas result in sustained sympathetic activation and a transient elevation of blood pressure. These effects appear to be due to intermittent hypoxia and may play a role in the sympathetic activation and hypertension in OSA.

Keywords: Sleep apnea; Hypertension; Sympathetic activity; Intermittent hypoxia

1. Introduction

Sympathetic nerve activity and arterial pressure are frequently elevated in patients with obstructive sleep apnea (OSA) (Fletcher et al., 1987; Kales et al., 1984; Carlson et al., 1994) and are thought to contribute to cardiovascular complications. Large cross-sectional and prospective studies suggest that OSA may cause hypertension (Bixler et al., 2000; Nieto et al., 2000; Peppard et al., 2000). However, the mechanisms responsible for sympathetic activation and hypertension in OSA are not known.

Several studies reported elevated discharge rates of sympathetic vasoconstrictor nerves in patients with OSA (Somers et al., 1995; Hedner et al., 1988; Leuenberger et al., 1995) and raise the possibility that hypertension in OSA is linked to heightened sympathetic tone. Because treatment with nasal continuous positive airway pressure (CPAP) or tracheostomy reduces sympathetic nerve activity (Waravdekar et al., 1996; Hedner et al., 1995; Fletcher et al., 1987) and blood pressure (Pepperell et al., 2002; Becker et al., 2003), physiological stress resulting from acute obstructive apneas is likely responsible for chronic sympathetic activation and hypertension in OSA.

Acute obstructive apnea is associated with transient surges of sympathetic activity and vasoconstriction that

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appear to be triggered by hypoxia and/or arousal from sleep (Morgan et al., 1996; Leuenberger et al., 1995; Imadojemu et al., 2002). It has been suggested that the acute sympathoexcitatory stimuli evoked by obstructive apnea may over time contribute to chronic (long-term) sympathetic activation. In support of this concept, Fletcher et al. reported that rats exposed to intermittent hypoxia develop hypertension (Fletcher et al., 1992c). This effect appeared to be mediated via the sympathetic nervous system and activation of peripheral chemoreceptors (Fletcher et al., 1992b,a). Recent studies in humans suggest that short-term (20 min) exposure to combined hypoxia and hypercapnia (Morgan et al., 1995) and intermittent asphyxia (Xie et al., 2000) during spontaneous breathing result in sustained sympathetic activation but no change of blood pressure following exposure to these stimuli. However, these studies did not specifically address the role of intermittent cessation of breathing (apnea). Apnea is known to enhance chemoreflex-induced sympathetic activation and transient peripheral vasoconstriction (Leuenberger et al., 2001).

The purpose of this study was to test whether a series of repetitive voluntary apneas would result in sympathetic activation and blood pressure elevation that persist following this intervention. We hypothesized that if intermittent hypoxia due to intermittent airway occlusion is responsible for chronic sympathoexcitation and hypertension in OSA, sympathetic nerve activity and blood pressure would be elevated in healthy humans after an exposure to a series of repetitive voluntary apnea maneuvers.

2. Methods

2.1. Subjects

Eighteen healthy men and 8 women, age 27.3 ± 1.3 yrs (mean ± SE; range 21–48 yrs) with a body-mass-index of 23.3 ± 0.6 kg/m^2 who had no significant medical history and were on no medications participated in the studies. The study protocol was approved by the Institutional Review Board of The Milton S. Hershey Medical Center and informed written consent was obtained. All studies were performed in the General Clinical Research Center at Penn State University's College of Medicine with the subjects in the supine position.

Before instrumentation, the subjects were instructed to perform 20-s voluntary apnea maneuvers in end-expiration at functional residual capacity and to avoid straining that might constitute a Müller or Valsalva maneuver. To allow us to assess the apnea-induced transient hypercapnia, they were instructed to exhale briefly (~1 s) at the end of apnea before resumption of spontaneous breathing. For timing of the apnea-breathing cycle, a clock with markers at the 0 and 20-s positions (to indicate the beginning and the end of voluntary apnea) was placed within the subject's visual field.

2.2. Blood pressure and heart rate measurements

Mean arterial blood pressure (MAP) was determined every minute with an automated sphygmomanometer (Dinamap, Critikon, FL) on the upper arm and was used for statistical analysis. Care was taken to assure that the blood pressure cuff remained at the level of the heart throughout the study. Throughout the repetitive apnea protocol, beat-by-beat blood pressure was also monitored with a Finapres device (Ohmeda, Madison, WI). The electrocardiogram was monitored to determine heart rate (HR).

2.3. Microneurography

Muscle sympathetic nerve activity (MSNA), the sympathetic efferent vasoconstrictor signal directed to skeletal muscle, was determined via peroneal microneurography as described previously (Leuenberger et al., 2001; 1995; Waravdekar et al., 1996). Briefly, a tungsten microelectrode was inserted into the peroneal nerve below the fibular head to record activity in efferent sympathetic fascicles carrying skeletal muscle vasoconstrictor nerve traffic to the lower leg. The nerve traffic signal was filtered, amplified, rectified and integrated and recorded on a Gould TA 4000 recorder (Gould, Valley View, OH). Standard techniques were used to demonstrate that the nerve signal in fact represented MSNA (Leuenberger et al., 2001; 1995; Waravdekar et al., 1996). No site adjustments were made once the nerve recordings began. MSNA was expressed as burst incidence (bursts/min) and arbitrary units/min (average burst height × bursts/min).

2.4. Ventilatory parameters

To administer hypoxic gas and to determine minute ventilation (V_E, l/min) and end-tidal CO_2 (CO_{2ET}, %), a tight sealing facemask was positioned and was connected to an Ohmeda respiratory gas monitor (Ohmeda RGM 5200, Ohmeda, Colorado). Arterial oxygen (O_2) saturation (SaO_2, %) was determined with a pulse oximeter (Ohmeda, CO) via an earlobe probe. Respiration was monitored qualitatively with a strain-gauge pneumograph.

2.5. Protocol 1: repetitive apnea during room air exposure (repetitive room air apneas)

Following instrumentation and a 10-min period of acclimatization to the facemask, baseline parameters were measured over 5 min. The subjects then began the repetitive apnea paradigm as follows: following spontaneous breathing a 20 s end-expiratory apnea at functional residual capacity was performed. At the end of apnea, the subjects exhaled for 1 s before resuming spontaneous breathing to allow sampling of CO_{2ET} at end-apnea. Thus, every apnea-breathing cycle consisted of 40 s of breathing room air and