Neural mechanism of the pressor response to obstructive and nonobstructive apnea

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Katragadda, Srinivas, Ailiang Xie, Dominic Puleo, James B. Skatrud, and Barbara J. Morgan. Neural mechanism of the pressor response to obstructive and nonobstructive apnea. J. Appl. Physiol. 83(6): 2048–2054, 1997.—Obstructive and nonobstructive apneas elicit substantial increases in muscle sympathetic nerve activity and arterial pressure. The time course of change in these variables suggests a causal relationship; however, mechanical influences, such as release of negative intrathoracic pressure and reflation of the lungs, are potential contributors to the arterial pressure rise. To test the hypothesis that apnea-induced pressor responses are neurally mediated, we measured arterial pressure (photoelectric plethysmography), muscle sympathetic nerve activity (peroneal microneurography), arterial O2 saturation (pulse oximeter), and end-tidal CO2 tension (gas analyzer) during sustained Mueller maneuvers, intermittent Mueller maneuvers, and simple breath holds in six healthy humans before, during, and after ganglionic blockade with trimethaphan (3–4 mg/min, titrated to produce complete disappearance of sympathetic bursts from the neurogram). Ganglionic blockade abolished the pressor responses to sustained and intermittent Mueller maneuvers (−4 ± 1 vs. +15 ± 3 and 0 ± 2 vs. +15 ± 5 mmHg) and breath holds (0 ± 3 vs. +11 ± 3, all P < 0.05). We conclude that the acute pressor response to obstructive and nonobstructive voluntary apnea is sympathetically mediated.

sympathetic nervous system; arterial pressure; obstructive and nonobstructive apneas

SUSTAINED APNEA, with and without intrathoracic pressure change, causes an increase in arterial pressure that is coincident with resumption of breathing. This apnea-induced pressor response is preceded by an increase in sympathetic outflow to skeletal muscle; however, a causal relationship between sympathetic activation and arterial pressure elevation has not been demonstrated in humans. Mechanical influences, such as release of highly negative intrathoracic pressure, may play a role in raising arterial pressure via redistribution of blood volume. On the other hand, several lines of evidence suggest that neural mechanisms are more important than mechanical mechanisms in causing the pressor response to apnea. O’Donnell and co-workers (10) showed that increases in arterial pressure produced by experimental airway occlusion in sleeping dogs are abolished by autonomic blockade. The importance of chemoreflex stimulation was demonstrated in studies where supplemental O2 greatly attenuated apnea-induced increases in sympathetic vasomotor outflow and arterial pressure during voluntary apneas in awake subjects and during episodes of sleep apnea (4, 5, 9, 17). Previous work from our laboratory indicates that chemoreflex stimulation is more important than negative intrathoracic pressure in causing apnea-induced sympathetic activation and arterial pressure elevation during wakefulness (9). In that study, peak increases in sympathetic outflow and arterial pressure were comparable in obstructive and nonobstructive apneas of the same duration.

The purpose of the present study was to test the hypothesis that pressor responses to obstructive and nonobstructive apnea are neurally mediated. Accordingly, we studied the hemodynamic responses to Mueller maneuvers and breath holds during wakefulness in healthy subjects before, during, and after reversible pharmacological blockade of the autonomic nervous system.

METHODS

Four women and two men, aged 21 ± 3 (SD) yr, served as subjects. All subjects were normotensive and free from cardiovascular, pulmonary, and neurological disease as evaluated by history and physical examination. All subjects provided informed consent, and the experimental protocol was approved by the University of Wisconsin Health Sciences Human Subjects Committee.

General procedures. All studies were carried out with the subjects awake, in the supine position, and in the postabsorptive state. A beat-by-beat measurement of arterial pressure was obtained by photoelectric plethysmography (Finapres, Ohmeda, Englewood, CO). Arterial pressure was also measured by using a Dinamap automated sphygmomanometer (Critikon, Tampa, FL) at 1-min intervals. Heart rate was measured from the electrocardiogram. Subjects breathed through a low-resistance mouthpiece and two-way valve assembly. Mouth pressure was measured by using a Statham transducer (model P23-Dg, Gould, Cleveland, OH) located between the mouthpiece and the valve. Expired air was sampled from the mouthpiece-valve assembly for measurement of end-tidal CO2 tension using an LB-2 analyzer (Beckman, Schiller Park, IL). Ventilation was measured using a pneumotachograph (model 3700, Hans Rudolph, Kansas City, MO) coupled to a differential pressure transducer (model DP103–10, Validyne, Northridge, CA). Arterial O2 saturation was measured using a pulse oximeter (Biox 3740, Ohmeda, Madison, WI). All tracings were recorded continuously on paper (Gould) and on videotape (Vetter, Rebersburg, PA).

Recording of muscle sympathetic nerve activity. Direct intraneural recordings of postganglionic muscle sympathetic activity in the right peroneal nerve were made by the technique of Vallbo et al. (21). Details of this procedure have been described previously (8). The neural signals were passed to a differential preamplifier, an amplifier, and an integrator (time constant = 100 ms, total gain = 100,000). Once an acceptable neural recording (pulse synchronous activity with signal-to-noise ratio > 3:1) was obtained, the subject was instructed to maintain the leg in a relaxed position for the...
duration of the study. Sympathetic bursts were identified from the mean voltage neurogram by using a computer program with a sampling rate of 126 Hz (1). Segments of the neural recording that showed evidence of α-motoneuron or mechanoreceptor activity caused by unintentional leg movements were excluded from analysis. For purposes of quantification, muscle sympathetic nerve activity was expressed as minute activity (bursts/min × mean burst amplitude) in arbitrary units.

Breath holds. The subject breathed through the mouthpiece and valve described in General procedures. After a stable baseline was achieved, the subject stopped breathing at end expiration for 20 s. A visual display of mouth pressure was provided to assist the subject in maintaining the required level of pressure. The subject was instructed to exhale immediately after the opening of the valve at the end of the Mueller maneuver so that an end-tidal sample could be acquired for CO2 analysis. To perform intermittent Mueller maneuvers, the subject made brief, repetitive inspiratory efforts (1–3 s in duration) against the closed valve every 5 s for a total of 20 s.

Results

Effect of ganglionic blockade on baseline hemodynamic variables. Infusion of trimethaphan caused disappearance of postganglionic bursts of sympathetic activity from the peroneal neurogram within minutes in all subjects. The dose of trimethaphan required to produce this effect was 3 or 4 mg/min (Fig. 1). The trimethaphan infusion caused a steady-state reduction in mean arterial pressure from 79 ± 3 to 68 ± 1 mmHg (Table 1). Heart rate increased from 70 ± 5 to 89 ± 7 beats/min. Respiratory variations in heart rate and arterial pressure were greatly attenuated during ganglionic blockade. After the infusion was discontinued, sympathetic nerve activity and respiratory variations in heart rate and arterial pressure returned to baseline values in an average of 9 min (range 5–17 min).

Effect of apnea on neurocirculatory variables with and without ganglionic blockade. In the absence of ganglionic blockade, sustained Mueller maneuvers caused a multiphasic arterial pressure response that consisted of an initial decrease with the onset of inspiratory strain, a return to the baseline level by the end of the apnea, and an overshoot in pressure that occurred after the release of the inspiratory effort (Figs. 2 and 3, Table 1). Ganglionic blockade abolished the overshoot after, but not the fall in pressure during, sustained Mueller maneuvers. Muscle sympathetic nerve activity increased ~10-fold during the Mueller maneuver in the intact condition (Table 1). During ganglionic blockade, no bursts of muscle sympathetic nerve activity were detectable on the mean voltage neurogram at rest or during the Mueller maneuver. In the intact condition, heart rate rose by an average of 6 beats/min during the Mueller maneuver (Fig. 3, Table 1). The magnitude of the peak increase in heart rate was unaffected by ganglionic blockade.

In the absence of ganglionic blockade, breath holds caused a progressive increase in arterial pressure (Figs. 4 and 5, Table 1). This increase was abolished by ganglionic blockade. Muscle sympathetic nerve activity increased to 80% of the baseline value during breath hold in the intact condition. During ganglionic blockade, muscle sympathetic nerve activity was absent at rest, and no increase was elicited by breath hold. In the unblocked condition, heart rate decreased by an average of 1 beat/min during the breath hold (Fig. 5, Table 1).
and sustained and intermittent Mueller maneuvers before, during, and after trimethaphan infusion.

Table 1. Baseline values and peak changes in neurocirculatory and ventilatory responses during breath holds and sustained and intermittent Mueller maneuvers before, during, and after trimethaphan infusion

<table>
<thead>
<tr>
<th></th>
<th>Predrug Baseline</th>
<th>Peak change</th>
<th>Trimethaphan Baseline</th>
<th>Peak change</th>
<th>Postdrug Baseline</th>
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<tr>
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<tr>
<td>Mean arterial pressure, mmHg</td>
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<td>68±1*</td>
<td>−4±1*</td>
<td>78±2</td>
<td>+11±2</td>
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<tr>
<td>Heart rate, beats/min</td>
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<td>+6±3</td>
<td>91±6*</td>
<td>+5±3</td>
<td>71±6</td>
<td>+7±3</td>
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<td>MSNA, %baseline</td>
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<tr>
<td>PETCO₂, Torr</td>
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<td>SaO₂, %</td>
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<td>97±1</td>
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<td>−2±1</td>
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<td>Tidal volume, liters</td>
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<td>+14±0.2</td>
<td>0.6±0.1</td>
<td>+1.1±0.3</td>
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<td><strong>Breath holds</strong></td>
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<tr>
<td>Mean arterial pressure, mmHg</td>
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<td>+11±3</td>
<td>68±1*</td>
<td>0±3*</td>
<td>78±2</td>
<td>+14±3</td>
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<td>Heart rate, beats/min</td>
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<td>−1±3</td>
<td>89±7*</td>
<td>+4±1</td>
<td>71±7</td>
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<td>39±2</td>
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<tr>
<td>SaO₂, %</td>
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<td>−2±1</td>
<td>97±1</td>
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<tr>
<td>Tidal volume, liters</td>
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<td>+0.9±0.3</td>
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<td>+1.2±0.2</td>
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little, if any, independent effect on the arterial pressure rise that follows apnea.

Critique of methods. A limitation of this study is that we recorded sympathetic discharge only in postganglionic neurons that innervate vascular structures in leg muscle. During trimethaphan infusion in our experiments, no muscle sympathetic nerve activity was detectable on the peroneal neurogram under resting conditions and none was elicited by apneas. Although this discharge is representative of sympathetic outflow to skeletal muscle vascular beds elsewhere in the body (11), our measurements do not allow inferences about the effects of trimethaphan on neural outflow to other organs and vascular beds. However, because trimethaphan abolished the pressor response to apnea, it is likely that the drug, in the doses we used, provided nearly complete blockade at all sympathetic ganglia.

We are less confident that trimethaphan caused complete blockade at parasympathetic ganglia. In our subjects, heart rate increased with breath holds during ganglionic blockade and decreased during breath holds in the intact condition. Our interpretation of these findings is that the predominant effect of apnea on heart rate in the intact condition was a decrease that occurred because baroreceptors were stimulated by a rise in blood pressure. In the blocked condition, no baroreceptor stimulation occurred (blood pressure did not rise) and a less powerful mechanism that produced parasympathetic withdrawal was unmasked. These findings suggest that parasympathetic control of sinus node activity was at least partially intact in our ganglionic blockade experiments and that the dose of trimethaphan we used was not sufficient to produce complete autonomic blockade. This inability to confirm complete autonomic blockade would have complicated the interpretation of our data if we had seen only small attenuations of the apnea-induced pressor response during trimethaphan infusion; however, ganglionic blockade completely abolished this pressor response in our subjects. Therefore, the inability to demonstrate complete parasympathetic blockade should not limit our interpretation of the findings.

We assume that trimethaphan had no effect on chemoreceptor function. In the present study our only means of testing this assumption was to examine the ventilatory responses following termination of apneas. Ventilation and tidal volume increased after apneas under control conditions and during ganglionic blockade. This finding indicates that the ventilatory control system remained responsive to apneic events during ganglionic blockade. However, in three of six subjects the ventilatory responses following apnea were smaller in the blocked than in the intact state, perhaps because...
of removal of the mild, modulatory influence of sympathetic activity on carotid body function (2). We cannot determine whether these decreased responses to voluntary apnea in the awake state represent altered chemoreceptor function or the overriding effects of behavioral inputs, which can be highly variable (16).

Potential mechanical influences on arterial pressure during and after apnea. The role of mechanical influences in causing the pressor response following an obstructive apnea has been a matter of controversy. Although the negative intrathoracic pressures generated during inspiration temporarily augment venous return by increasing the pressure gradient between the extrathoracic veins and the right atrium (7), increasingly negative pressures may actually limit venous return by collapsing the great veins at their point of entry into the thorax (14). Previous studies in experimental animals have shown that negative intrathoracic pressure, produced by inspiratory loading or airway occlusion, causes a decrease in stroke volume that is thought to be caused by alterations in preload and afterload (13, 14, 19). A similar decrease in stroke volume has been observed during obstructive sleep apnea in humans (3, 18, 20). Thus it is possible that the release of negative intrathoracic pressure at apnea termination could, via removal of this constraint on cardiac output, result in a pressor response of purely mechanical origin.

The present data do not support this concept. In our ganglionically blocked subjects, arterial pressure, which had fallen during the Mueller maneuver, returned slowly to control level on release of the inspiratory strain. We did not observe the characteristic overshoot in arterial pressure that normally occurs after voluntary Mueller maneuvers and obstructive apneas during sleep. We considered the possibility that repetitive inspiratory efforts, similar to those that occur during episodes of obstructive sleep apnea, might have a cumulative mechanical effect on arterial pressure. However, in our ganglionic blockade experiments, brief repetitive Mueller maneuvers also failed to produce an overshoot in arterial pressure (Fig. 6, Table 1). Taken together, these findings suggest that mechanical factors play no independent role in causing the pressor response to apnea.

Neural mechanism of the pressor response to apnea. The present findings, which are consistent with the previous observation that hexamethonium prevents the pressor response to airway obstruction in sleeping dogs (10), suggest that during apnea an increase in sympathetic vasoconstrictor outflow raises arterial pressure via increased peripheral vascular resistance. However, because trimethaphan blocks transmission at parasympathetic as well as sympathetic ganglia, we
also considered the possibility that parasympathetic withdrawal contributed to the rise in arterial pressure via heart rate acceleration and increased cardiac output. Previous investigators demonstrated that atropine blunts the arterial pressure fluctuations associated with apneas in patients with central and obstructive sleep apnea (15). Arousal-induced tachycardia has been shown to augment the pressor response to obstructive apnea in sleeping dogs (10). In contrast, the pressor response to the Mueller maneuver is unaffected by vagotomy in anesthetized dogs (13).

We consider it unlikely that a parasympathetically mediated increase in cardiac output contributed importantly to the apnea-induced pressor response in our subjects for several reasons. First, the pressor response to breath hold was accompanied by a decline in heart rate (−1 beat/min), and the pressor response to Mueller maneuvers was accompanied by an increase in heart rate (+5–6 beats/min). Even if combined with a sympathetically mediated increase in myocardial contractility and stroke volume, it is unlikely that such a small increase in heart rate could raise cardiac output. This concept is supported by the previous clinical finding that cardiac output does not increase after obstructive apneas in patients with sleep apnea syndrome. In these patients, postapneic tachycardia is accompanied by a reduction in stroke volume (3, 18). Second, in one subject in whom incomplete parasympathetic blockade was suspected even though trimethaphan caused complete disappearance of sympathetic activity from the neurogram, heart rate increased by an average of 19 beats/min during Mueller maneuvers. Despite this more substantial increase in heart rate, arterial pressure did not rise. Most importantly, the apnea-induced increases in heart rate were as large or even larger in the blocked than in the intact condition; nevertheless, the pressor responses to breath holds and Mueller maneuvers were completely abolished during trimethaphan infusion. These findings strongly suggest that sympathetic activation is the primary cause of the arterial pressure rise that accompanies apnea through an increase in peripheral vascular resistance and/or an increase in myocardial contractility.

What is the trigger for sympathetic activation during apnea? Our previous work and that of other investigators point to chemoreflex stimulation as a key feature of this neural response (4, 9, 22). In all these previous studies the pressor response to apnea was greatly attenuated by administration of supplemental O2. These observations of experimental apneas during wakefulness are in good agreement with clinical observations of obstructive apneas during sleep (5, 17); however, we recognize that voluntary apneas performed during wakefulness fail to reproduce all the respiratory and neurocirculatory disturbances that occur during sleep. Most importantly, these maneuvers fail to reproduce the effect of sleep state. Many aspects of cardiovascular regulation are known to vary with sleep state (6), and the arousal that occurs at the termination of sleep apneas is likely to contribute importantly to the pressor response, in an additive or a synergistic manner (12).

In conclusion, the pressor response to obstructive and nonobstructive apneas in awake humans is mediated by the autonomic nervous system, because it is abolished by ganglionic blockade. Our data indicate that this arterial pressure rise is caused by sympathetically mediated increases in peripheral vascular resistance and/or sympathetically mediated increases in stroke volume. In contrast, parasympathetically mediated increases in cardiac output do not play an important role in causing this pressor response, because heart rate responses to apnea were unaffected by ganglionic blockade. We further conclude that the mechanical influence of highly negative intrathoracic pressure has little or no independent effect on the acute pressor response to voluntary apnea.

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