

# Periodic, Profound Peripheral Vasoconstriction—A New Marker of Obstructive Sleep Apnea

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**Abstract:** We report a novel approach to the determination of sleep apnea based on measuring the peripheral circulatory responses in a primary condition of disordered breathing. The apparatus is a finger plethysmograph coupled to a constant volume, variable pressure, pneumatic system. The plethysmograph's tip (measurement site) is composed of two parallel opposing longitudinal half thimbles, which is attached to a contiguous annular cuff. Each compartment consists of an internal membrane surrounded by an outer rigid wall. These provide a uniform pressure field and impart a two-point locking action preventing axial and longitudinal motion of the finger. Subdiastolic pressure is applied to prevent venous pooling, engorgement, and stasis, to inhibit retrograde venous shock wave propagation and partially unload arterial wall tension. The annular cuff extends the effective boundary of the pressure field beyond the measuring site.

In 42 patients with Obstructive Sleep Apnea Syndrome (OSAS) profound, transient vasoconstriction and tachycardia usually of a periodic nature, were clearly seen with each apneic event, possibly related to transient arousal. Good agreement was found between standard total apnea-hypopnea scoring,  $129.5 \pm 22.4$  (Mean  $\pm$  SEM), and transient vasoconstriction and tachycardia events,  $121.2 \pm 19.4$  ( $R = .92$ ,  $p < .0001$ ).

We conclude that the finger tip exemplifies the scope of peripheral vascular responsiveness due to its high density of alpha sympathetic innervation, and its high degree of blood flow rate lability. Given that elevated peripheral resistance and tightly linked transient heart rate elevation is a consistent part of the hemodynamic response to arousal and OSAS, we believe that pulsatile finger blood flow patterns can be clearly diagnostic of OSAS and other sleep-disordered breathing conditions.

## INTRODUCTION

SLEEP-RELATED BREATHING DISORDERS HAVE COME TO BE INCREASINGLY RECOGNIZED IN RECENT YEARS, as has the serious morbidity and excess mortality associated with these disorders. Estimations of the Obstructive Sleep Apnea Syndrome's (OSA) prevalence vary considerably as do its definitive criteria; however it is clear that this condition is very widespread.<sup>1,2</sup> It is well recognized as a major cause of morbidity with a particularly strong association with hypertension, reduced longevity, and as a contributing factor in automotive and industrial accidents.<sup>3-5</sup>

Aside from OSAS which, as its name suggests, involves frank cessations in breathing in sleep, an allied condition, the Upper Airway Resistance Syndrome (UARS) has been more recently described.<sup>6</sup> In UARS frequent apneas and hypopneas do not actually occur, but the condition nevertheless results in frequent arousals and sleep fragmentation. UARS could also cause similar cardiac sequelae as OSAS, perhaps due to high levels of airways resistance.<sup>6</sup> The diag-

nosis of UARS is much more difficult due to the condition's more subtle symptomatology.<sup>6</sup>

Upper airway patency during inspiration depends largely on the interaction between UAW anatomical and mechanical factors, on the one hand, and the forces exerted by the UAW dilating muscles that support its walls on the other.<sup>7-9</sup> Methods for determining the presence and severity of OSA have been directed at the combination of standard polysomnographic measurements, and measurements of the respiratory aspects of the disorder, which include monitoring of airflow at nose and mouth, and respiratory movements of the thorax and abdomen by non-invasive means. Apart from the disadvantage of being limited to the sleep laboratory, the traditional approach is likely to underestimate hypopneas and particularly UARS since respiratory parameters are not sufficiently sensitive.<sup>10</sup> Attempting to evaluate OSAS by monitoring blood oxygen saturation using pulse oximetry is liable to result in low specificity since minor variations in SaO<sub>2</sub> accompanying hypopneas and UARS may be missed.<sup>11</sup>

A precise but not necessarily accurate way of evaluating UAW obstruction is by the invasive measurement of resistance based on the measurement of the pressure difference between two points within the airway system, together with

Accepted for publication April 1999

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**TABLE 1—PATIENTS' ANTHROPOMETRIC DATA**

	<u>MEAN</u>	<u>SD</u>	<u>SEM</u>
Age (years)	47.6	9.9	1.5
Height (cm)	171.8	6.7	1.0
Weight (kg)	87.4	15.0	2.3
BMI (kg/meter <sup>2</sup> )	29.7	5.2	0.8

the simultaneous measurement of the flow rate.<sup>12</sup> This is uncomfortable for the patient and may also be inaccurate since foreign bodies in the UAW could have indeterminate effects on UAW resistance. Thus, a convenient yet accurate method for apnea scoring and for evaluating UARS, particularly for screening of large populations is not presently available.

The alternating cyclic pattern of sleep and arousal typifying OSAS suggests that other physiological aspects related to apneic events and to interval phase arousals, could be monitored to provide an index of sleep disordered breathing. Morgan et al. showed that auditory-induced arousal from non-rapid-eye-movement (NREM) sleep resulted in bursts of sympathetic nervous system activity associated with increased systolic and diastolic blood pressure, increased heart rate and decreased cardiac output. Auditory stimuli, which failed to induce EEG frequency changes or alter muscle nerve sympathetic activity, were nevertheless still associated with hemodynamic changes consistent with increased peripheral resistance and transient tachycardia.<sup>13</sup> Pitson and Stradling evaluated the relationships between indices of sleep fragmentation (EEG arousals, apnea/hypopnea index (AHI), and SaO<sub>2</sub> drops) and autonomic markers of arousal, (heart rate change and the pulse transition time, an analogue of blood pressure). They found that the indirect blood pressure index correlated better than heart rate change to the AHI ( $r=0.65$  and  $r=0.51$ ) respectively.<sup>14</sup>

Given that the arterial vascular beds of the finger tips are very densely innervated by sympathetic vasoconstrictor efferents, and that blood flow through the finger tips is capable of very great modulation, we felt that the finger could be an exemplary site for evaluating the level and time course of peripheral vascular resistance. We therefore studied the relationship between OSAS and the vasoactivity of peripheral vascular beds of the fingers and on heart rate derived from the pulsatile blood volume changes accom-

**TABLE 2—MEAN APNEA-HYPOPNEA INDICES AND DIFFERENCES**

	<u>MEAN</u>	<u>SD</u>	<u>SEM</u>
Standard Method	129.5	145.4	22.4
New Method	121.2	125.7	19.4
Difference (Standard-New)	8.4	56.0	8.6

panying each heart beat.

## METHODS AND MATERIALS

### Finger Peripheral Vascular Resistance Measuring Apparatus

The apparatus<sup>1</sup> we developed is essentially based on a finger plethysmograph coupled to a constant volume, variable pressure pneumatic system. The human interface consists of a plethysmograph, which is composed of three compartments, two parallel,<sup>1</sup> (Patent pending). Longitudinal half cylinders closed off at the terminal end, and an annular cuff. Each of these elements consists of an internal membrane surrounded by an outer rigid wall. The two parallel longitudinal half cylinders which are placed in opposition form the tip of the plethysmograph, and apply a uniform pressure field over the distal part of the finger including the finger tip. These paired elements are pneumatically interconnected and impart a two-point locking action which effectively locks the plethysmograph onto the finger thereby preventing axial and longitudinal motion of the finger relative to the detector. The pulse signals were recorded as pressure changes within these elements. The third segment, an annular cuff, which is effectively an upstream extension of the front part of the detector, is primarily provided to prevent venous pooling adjacent to the actual measuring part and, in effect, extends the effective boundary of the plethysmograph's pressure field to beyond the actual measuring site. Additionally, it further immobilizes the distal finger joint, helping to eliminate finger bending. It is not actually used for measuring the pulse signal. The finger sensor is shown in Figure 1.

For each finger, the paired semi-cylinder components and the annular components of the plethysmograph were respectively connected via 1.5 meters of 1.0 mm id. and 3.0 mm od. flexible tubing (Tygon Norton Performance Plastics Co., Akron, Ohio, USA), to separate volume reservoirs for the purpose of buffering pressure changes within the plethysmograph itself. A further volume reservoir unconnected to the finger served as a pressure reference. The pressure changes accompanying finger volume changes are electronically transduced, (Micro Switch PD1 141PC, Honeywell USA) and the signal is band passed filtered (0.3–30Hz), amplified, and then stored to memory.

Pressure within the system is generated by a minicompressor and the partitioning and pneumatic isolation of various pressurized compartments is accomplished using a series of two-way solenoid pneumatic taps. The latter elements are controlled by a dedicated central processor. When all the compartments of the plethysmograph are collectively pressurized to the same level, the plethysmograph prevents venous engorgement and stasis within the instrumented part of the finger and allows pulsatile finger blood flow patterns to be comfortably monitored throughout the night.

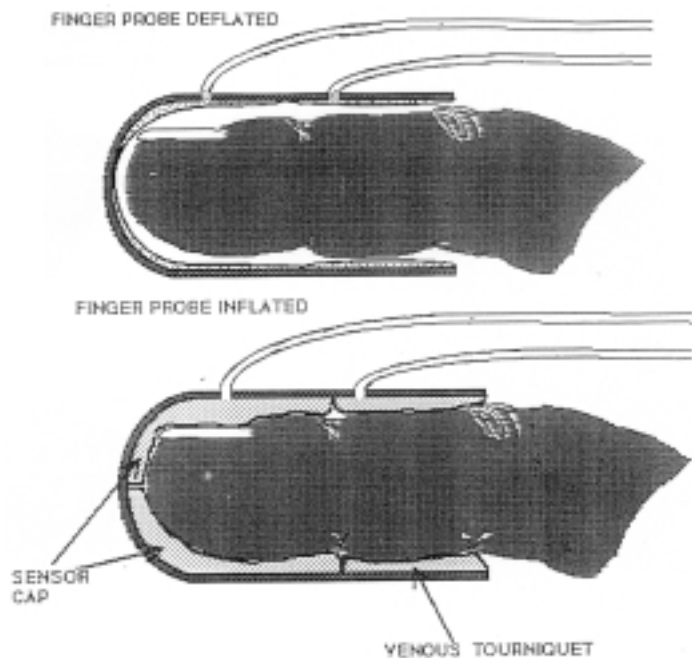


Figure 1—Schematic diagram of the finger probe in deflated and inflated conditions.

### Pulsatile Volume Measurements

We recorded pulse signals from the first and third fingers respectively of one hand. Only data from one finger were used for analysis. A constant pressure of 70mm Hg or 40 mm Hg was applied within the plethysmograph for the purposes of preventing venous pooling and inhibiting retrograde venous shock waves in the measurement site. In addition, the counter pressure served to partially unload arterial wall tension thus improving the dynamic range of the system. In cases where an individual's diastolic blood pressure was lower than 70 mm Hg the higher level of pres-

sure was associated with some discomfort.

The measurements were conducted in comfortable, thermoneutral environment conditions that would be expected to optimize peripheral vasoactivity. Signals were amplified and band pass filtered (0.3 Hz - 30 Hz, 6 pole Butterworth each).

### Subjects

We measured pulsatile finger blood flow throughout the night in a group of 42 unselected patients who were referred to the sleep lab for standard diagnostic polysomnographic testing because of suspected OSAS. Anthropometric data for the subjects are given in Table 1.

### Polysomnography

Signals recorded were: Electrooculography (EOG), Electrocardiography (ECG), submental Electromyography (EMG), Electroencephalography (EEG, C3-A2 connections), respiratory abdominal motion (respiratory belt), air flow (oronasal thermistor) rate, arterial oxygen saturation  $\text{SaO}_2$ , body movements, and breathing sound intensity, were all recorded to computer memory after amplification and signal conditioning via a multichannel polygraph (EEG 4214; Nihon Kohden, Kogyo Co., Tokyo, Japan). Studies were performed from about 10–11 PM to 6 AM the following day. The polysomnographic signals were analyzed according to standard practice, as were the apnea/hypopnea indices. An apnea was defined as a cessation of airflow at the mouth and nostrils lasting at least 10 second, and hypopnea was defined as a decrease in airflow of at least 50% which was associated with brief arousal and/or body movement.

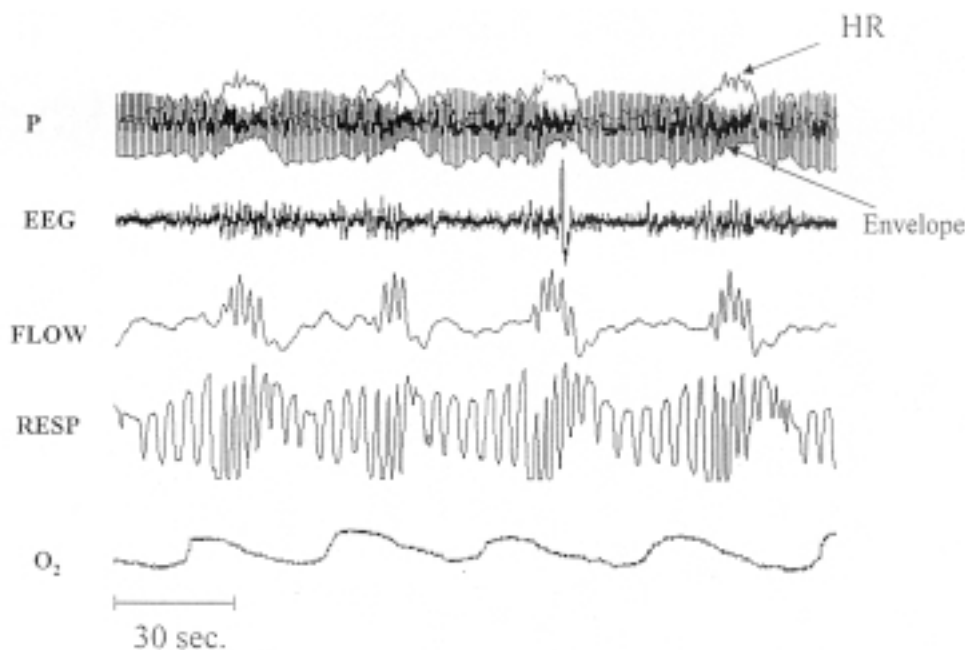


Figure 2a—A three-minute record of obstructive apneas. The envelope of the finger pulse wave was added to further emphasize the apnea-related attenuation in its amplitude. Note also that the apnea-related attenuation in the pulse wave was associated with concomitant increase in heart rate. PAP-finger pulse wave, HR-Heart Rate, EOG-Electrooculogram, EEG - Electroencephalogram, Flow-Naso-oral thermistor, Resp-Respiratory effort,  $\text{O}_2$  - Arterial oxygen saturation.

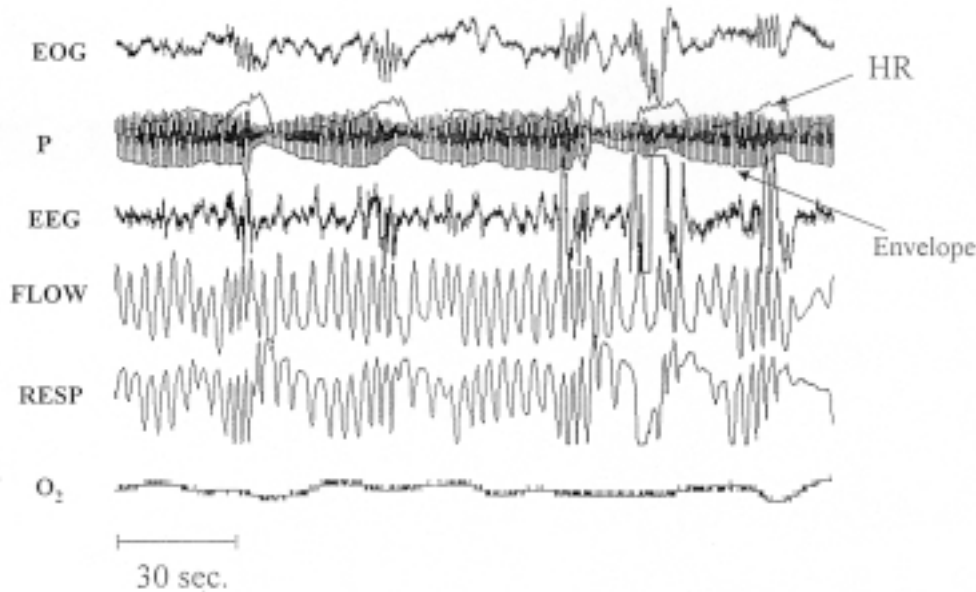


Figure 2b—A three-minute record of hypopneas. See Caption of Figure 2a.

### Analysis of Signals

The polysomnographic signals were evaluated by skilled personnel using conventional protocol to provide apnea-hypopnea indices. The finger plethysmograph signals were analyzed by a dedicated computer program, in terms of relative peak to peak amplitude, heart rate, and the linkage and duration of changes in the two parameters. Apneas or hypopneas were deemed to have occurred when there was a combination of relative vasoconstriction of 33% or greater (i.e. at least a one third fall in amplitude) and relative tachycardia of 15% compared to the pre-vasoconstricted phases. These periods of vasoconstriction lasted between 3 and 30 seconds, during which period at least 35% of the pulse-waves in the slope showed a reduction in amplitude.

### RESULTS

A representative trace of 180 seconds of the polysomnographic and finger plethysmographic signals in frank OSA is shown in Figure 2a. It is clearly seen that the apneas' associated vasoconstriction is accompanied by transient periods of increased heart rate. Three-minute traces of hypopnea (Figure 2b) show a similar pattern; however spontaneous vasomotion associated with Mayer waves (Figure 2c) does not show the transient tachycardia, nor any associations with changes in breathing. Figure 2d shows a further example of vasoconstriction occurring without associated tachycardia related to a series of leg movements each of which was followed by vasoconstriction. The cyclic nature of these changes in severe OSA can be seen in Figure 3a, which shows a 15-minute period of recording. Figure 3b, shows a 15-minute period of record-

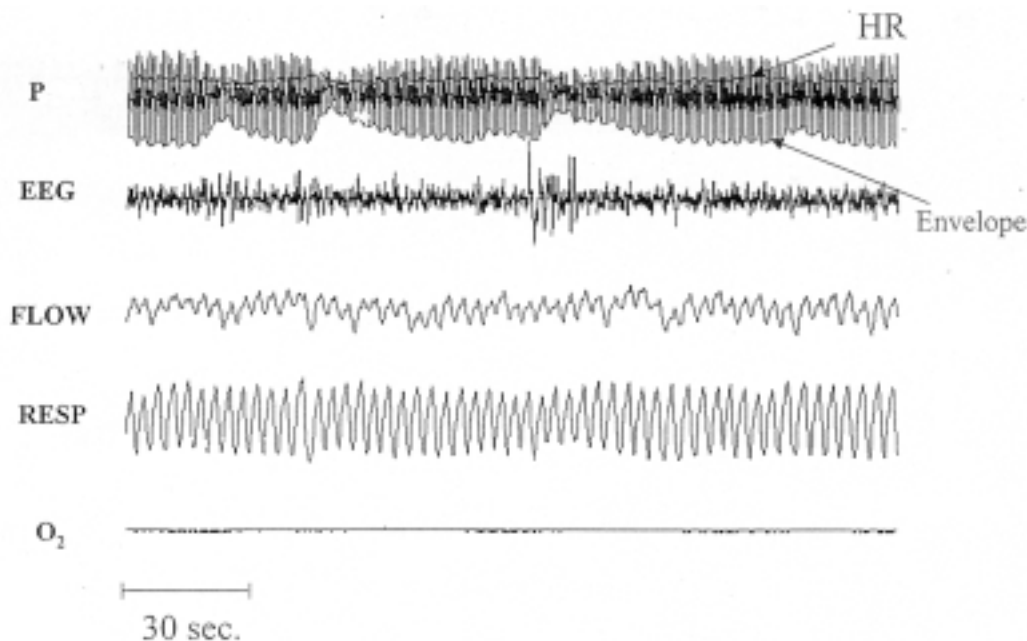


Figure 2c—A three-minute record of spontaneous changes in vasomotion (Mayer waves). Note that the changes in the pulse wave are not accompanied by changes in respiration nor in heart rate.

ing during which there is a period of apneas preceded by and then followed by apnea-free sleep. In the preceding period there are four episodes of vasomotion, none of which is associated with tachycardia. In contrast, each apneic episode is clearly associated with tachycardia of abrupt onset.

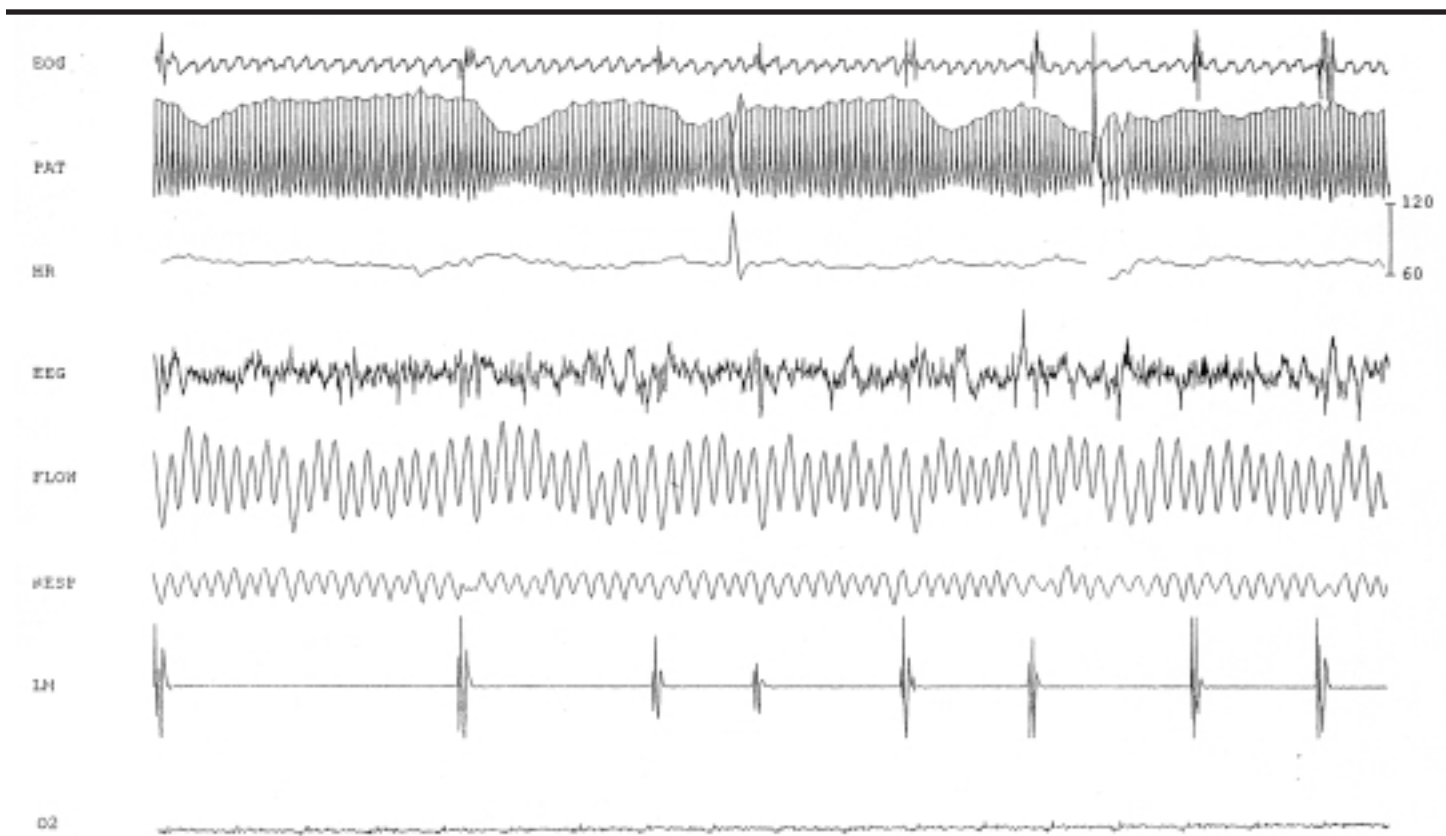
The mean apnea-hypopnea indices for the two methods and their differences are summarized in Table 2. The relationship between apnea-hypopnea indices of the two methods is shown in the scatter graph in Figure 4. Data were highly significantly correlated  $R = 0.92$  ( $p < .0001$ ). The regression equation [New score =  $0.80X$  standard score - 17.57], suggests that below A/H score of about 85 the new method tended to somewhat overestimate A/H indices while tending to underestimate A/H index at higher values.

## DISCUSSION

In this study we report the use of a novel approach to the determination of disordered breathing in sleep which is based on the circulatory responses of what is primarily a condition of disordered breathing. In light of the ready accessibility of the fingers, and the benign nature of the measurement, we believe that this approach may have important implications upon the screening of OSA on the one hand, and provide valuable insight into the cardiovascular consequences of OSA on the other. The special design

of our plethysmograph represents a departure from previously available plethysmographs, since the device is capable of being pressurized without being forced off the finger. It is therefore able to clamp firmly to the finger, and can thus engender important physiological benefits by avoiding the problem of induced venous distention distal to the cuff, since the pressure field also encompasses the fingertip. This is in contrast to segmental cuffs and circumferential tubes,<sup>15</sup> which neither cover the finger tip nor impart their full pressure near their boundaries. The result of leaving the distal end of the finger unexposed to counterpressure is to cause venous distention distal to the cuff. This is known to induce local reflex veno-arteriolar vasoconstriction which could mask the response to sympathetic activation, and causes the finger tip to become cold and cyanotic, and is very uncomfortable.<sup>16</sup>

The peripheral vascular beds located at the distal parts of the limbs are major sites of sympathetic vasoconstrictor activity, and hence play an important role in circulatory regulation.<sup>17-19</sup> This is particularly true of the soles of the feet, the plantar surfaces of the toes, and the palmar surfaces of the hands and fingers at which sites there is a high density of arteriovenous anastomoses, and a correspondingly high density of alpha sympathetic innervation.<sup>20</sup> Functionally, finger blood flow can vary enormously, with values ranging from 1 ccm/100 ccm tissue/min to 100



**Figure 2d**—Three-minute record showing periodic leg movements and associated vasoconstriction. Note that the changes in the pulse wave are not accompanied by changes in heart rate. LM—Leg movements

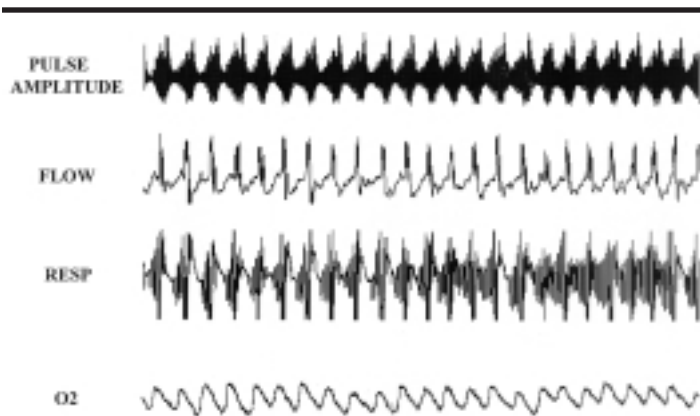


Figure 3a—A 15-minute record of obstructive apneas.

ccm/100 ccm tissue /minute have been reported.<sup>17</sup>

Given that at extremes of vasodilation, blood flow through these regions could reach values approaching perhaps half the mass of the hands and feet, it is apparent that a very large fraction of the resting cardiac output could be channeled through these regions. Since blood flow of 1ccm/100ccm/min is still compatible with tissue viability, and blood flow increases with ambient temperature, the enormous potential excess flow has generally been believed to be associated with a heat dissipating role in body thermoregulation.<sup>21,22</sup>

Several factors have been shown to affect finger blood flow. These include local finger temperature changes, heating or cooling of the torso or other large body masses, and

vasoconstriction in response to being startled.<sup>17-22</sup> An interesting cause of reduced finger blood flow is the taking of a very deep breath that results in a substantial and rapid decline in blood flow which may persist long after normal breathing has resumed.<sup>23</sup> The mechanism of the peripheral vascular response to a deep breath has not been elucidated, however it is postulated that pleural stretch receptors may provide the afferent input. It is possible that the initial deep breath after termination of the obstruction may give rise to such an effect in OSAS. Both the responsiveness both to temperature changes and to deep breaths appears to be sympathetically mediated since they are abolished following sympathectomy. In the absence of sympathetic neural control, a state of near-maximal blood flow prevails.

Prolonged breath-holding during wakefulness has been observed to produce vasoconstriction in a progressive manner,<sup>23</sup> and other respiratory acts such as the Valsalva and Mueller maneuvers produce characteristic multi-phasic responses.<sup>23</sup> The latter may be related to direct intrathoracic pressure changes, which directly affect venous return to the heart and to direct effects on carotid sinus and aortic arch baroreceptors. Inherent rhythmic blood pressure fluctuations have long been recognized; these include the variability associated with the respiratory sinus arrhythmia, and also the lower frequency blood pressure variations known as Traube-Hering or Mayer waves.<sup>17,19,23</sup>

During episodes of obstructive sleep apnea and in the period of post-apneic arousal, many circulatory, respiratory, and autonomic neural control changes that might affect

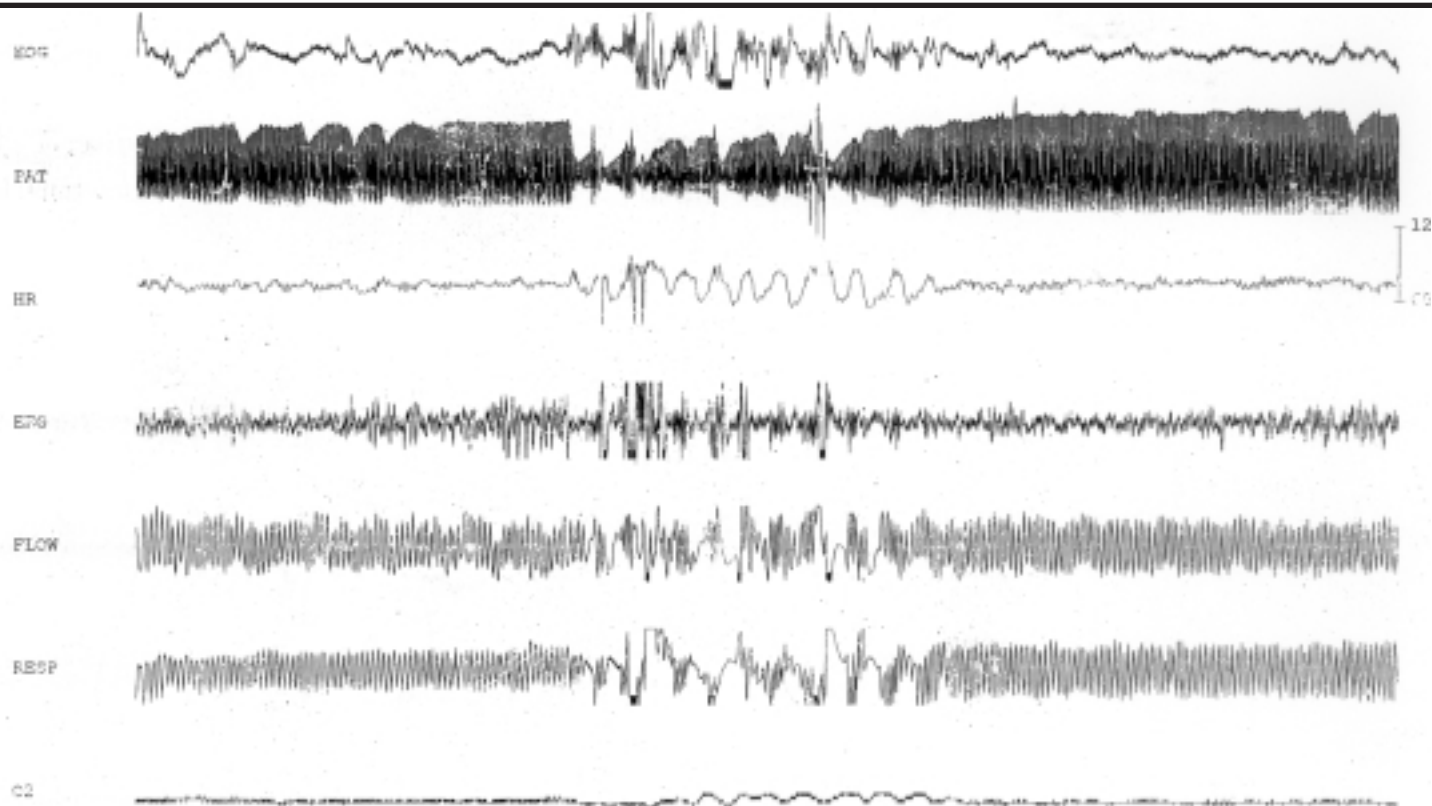
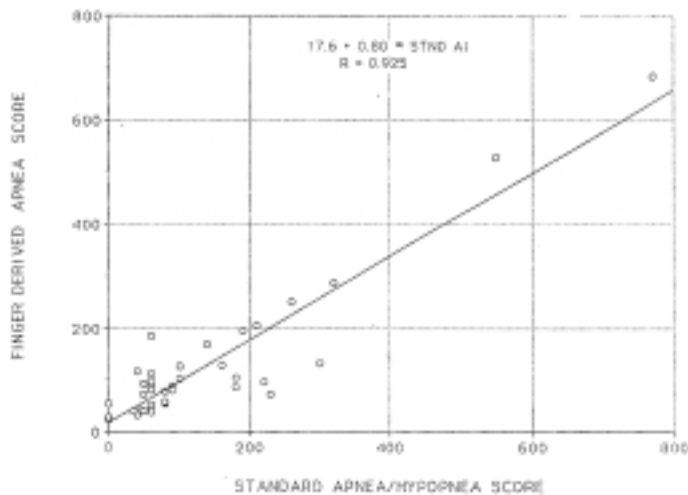


Figure 3b—A 15-minute record showing unobstructed breathing followed by a period of obstructive apneas and return to unobstructed breathing.



**Figure 4**—A scatter diagram of the total number of apneas plus hypopneas as determined by the automatic algorithm based on the attenuation of the pulse wave and increased heart rate, and by conventional scoring.

the peripheral circulation, are brought into play, including prolonged breath-holding, the Mueller maneuver, post-apnea deep breaths and microarousal. The relative contributions of these changes are likely to be complex and remain to be elucidated.

Finger vasoconstriction but negligible heart rate changes were tightly linked to periodic leg movement during sleep in one subject. It is possible that the magnitude of the vascular response and the absence of relative tachycardia may be different under such circumstances than following apnea, since the metabolic consequences of hypercapnea and hypoxia, and their associated reflex responses may be different. These questions are currently being investigated in our laboratory. Whatever the mechanism, it is nevertheless clear that peripheral vascular changes of a striking character repeatedly and reproducibly occur after each apnea.

In previous studies, it was shown that the pulse amplitude bears a strong relationship to the actual blood flow.<sup>17,24</sup> The measurement of pulsatile volume rather than flow per se, has enabled us to observe beat-to-beat variations in the nature and time-course of finger blood flow. Previous reports of autonomic correlates of arousal such as the pulse transmission time showed significant but lesser degrees of correlation to standard AHI.<sup>14</sup> This may have been partly related to the simultaneous increase in HR which would, in the absence of an increase in cardiac output, tend to reduce stroke volume thus lessening the blood pressure response. Since peripheral pulse amplitude would further decline with reduced stroke volume, the vasoconstrictive response to arousal would, in this case, be reinforced.

## CONCLUSION

The configuration and dynamics of the blood flow patterns associated with apneas may serve as clear markers of

the occurrence and possibly the severity of each apnea, and provide a robust and extremely easily applied measurement method. The vascular response to arousal may also enable the less clear-cut manifestation of sleep-disordered breathing, such as hypopneas and UARS, to be identified in a convenient, non-invasive manner. This may have been related to the slight overestimation of total apneas in cases with low A/H indices in the present study.

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