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Modeling of Deep Breath Vasoconstriction Reflex

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Abstract

Deep breaths akin to sighs have been reported to cause peripheral vasoconstriction. Our previous simulation studies have shown that this phenomenon cannot be reproduced in existing circulatory control models without inclusion of a respiratory-vascular coupling mechanism. To better understand this “sigh-vasoconstriction reflex”, we investigated the effect of spontaneous and passively induced sighs as well as spontaneous breathing on peripheral vasoconstriction during wakefulness and non-rapid eye movement sleep in human subjects. We found that both spontaneous and induced sighs caused vasoconstriction during wakefulness and sleep. The coupling between respiration and vasoconstriction is also present even in an absence of deep breaths. The coupling mechanism is largely linear with increased nonlinearity during induced sighs. Since peripheral vascular resistance modulation is known to be sympathetically mediated, investigation of this coupling could potentially allow us to assess sympathetic function through non-invasive measurements and simple interventions.

I. Introduction

Previous studies have shown that a deep breath akin to a sigh causes vasoconstriction [1, 2]. As well, we previously demonstrated, by means of a simulation model (Fig. 1), that the sigh-vasoconstriction reflex cannot be reproduced without incorporating the respiratory-peripheral vascular conductance coupling (RPC) as a model component, in addition to the baroreflex control of peripheral resistance [3]. In this study, peripheral arterial tonometry (PAT) was employed to detect vasoconstriction. PAT measures the pulsatile changes in blood volume at the fingertip [4]. When peripheral blood vessels constrict (peripheral vascular resistance increases), the amplitude of the PAT pulse decreases. Thus, the beat-to-beat PAT amplitude was taken as a surrogate measure of time-varying changes in peripheral vascular conductance.

Many diseases are associated with autonomic dysfunction, such as sickle cell anemia and sleep-related breathing disorder [2, 5]. Sickle cell anemia, an inherited blood disorder, is characterized by episodes of painful vaso-occlusion and vaso-occlusive crisis. Recent studies showed that sickle cell patients have autonomic dysfunction that may promote neutrally-mediated vasoconstriction, thus raising the likelihood of vaso-occlusive crisis [2]. As well, subjects with sleep-related breathing disorder have increased sympathetic tone and reactivity

[5]. Since the sympathetic nervous system is known to mediate vasoconstriction through the regulation of peripheral vascular resistance [5], investigating the mechanisms that govern these fluctuations, such as the sigh-vasoconstriction reflex, would allow us to assess sympathetic function in these kinds of disorders.

The purpose of this study was to investigate the effect of spontaneous sighs and induced sighs on the vasoconstriction response during wakefulness and non-rapid eye movement (NREM) sleep. We also determined whether the RPC is present during spontaneous breathing (no sighs). Finally, we investigated if the RPC mechanism involves nonlinearity.

II. Methods

A. Protocols and Data Processing

Data analyzed in this paper were obtained from an existing series of studies that were designed to phenotype sleep-related breathing disorders in overweight-to-obese pediatric subjects (mean $\pm$ SD: age = 15.3 ± 1.5 years; body mass index = 34.6 ± 8.1 kg/m²; male/female = 6/12). All data analyzed were taken from subjects identified as snorers following a prior polysomnographic study – however, subjects clinically classified as having obstructive sleep apnea were excluded. In the follow-up overnight study, the subject was put on a bilevel positive airway pressure machine in addition to standard polysomnography. In wakefulness, 3 cmH₂O pressure was constantly applied to reduce the breathing circuit resistance. Once the subject fell asleep, he/she underwent positive airway pressure titration during the first part of the sleep study to determine the therapeutic pressure required to eliminate airflow limitation. During the induced sigh protocol, 2 consecutive breaths of +5 cmH₂O positive airway pressure from 3 cmH₂O during wakefulness and from the therapeutic pressure during NREM sleep were passively administered to the subject. This protocol was repeated for 1–2 times during wakefulness and 3–4 times during NREM sleep. Each set was at least 50 breaths apart (approximately 5 minutes).

Recordings were also made during spontaneous breathing period (with no intervention) to capture any spontaneous sighs that might occur. Data segments with spontaneous sighs and spontaneous breathing without sighs were extracted from the recordings during wakefulness and NREM sleep. A sigh was defined as a breath whose tidal volume (V_t) was greater than the mean V_t for that segment + 2 times its standard deviation. 1–3 of each of these data segments were obtained per subject, depending on data quality and availability. Each segment was 5–10 minute long. For spontaneous sigh segments, data were extracted such that only one spontaneous sigh occurred towards the beginning of the segment. For all protocols, any data segments with arousal detected by EEG were excluded from the analyses.

Airflow, mask pressure and PAT were continuously recorded at 200 Hz throughout the sleep study. V_t was calculated by integrating airflow and extracting the peak volume from each breath to obtain breath-to-breath V_t. The mean of the baseline V_t was subtracted from V_t to obtain ΔV_t , fluctuations of V_t around zero. PAT amplitude was extracted from PAT on a beat-to-beat basis. Since PAT is a relative measurement (arbitrary units), PAT amplitude was normalized to its own baseline mean and standard deviation to allow comparison among

subjects. The normalized PAT amplitude (PATampN) represents fluctuations in peripheral vascular conductance around the baseline. Both V_t and PATampN were then downsampled to 2 Hz for further analysis.

B. Linear Model

A minimal (non-parametric) modeling approach was employed to investigate the RPC during wakefulness and NREM sleep under 3 breathing patterns: spontaneous sigh, induced sigh and spontaneous breathing. One-input-one-output linear model relating changes in respiration (V_t) to changes in peripheral vascular conductance (PATampN) was applied on the experimental data to quantify the coupling. The linear model can be represented mathematically as

$$y(t) = \sum_{i=0}^{M-1} h(i) x(t-i-T) + \varepsilon(t). \quad (1)$$

x represents the input, V_t ; y represents the output, PATampN; $h(t)$ represents an impulse response; T represents the mechanism latency; M represents the system memory = 25 seconds; and ε represents other influences that are not captured by the model. The impulse response was estimated using basis function expansion technique as previously described by [3] and [6] – that is the $h(t)$ can be represented as a weighted sum of orthogonal set of Meixner basis functions (MBF) [7] where each expansion coefficient (weight) can be estimated using least-squares minimization. The minimization process was repeated for all combinations of model parameters which were allowed to vary in the following ranges: model order (number of MBF) = 2–6, order of generalization = 2–8, and T of RPC = 0–3 seconds. For each combination, the minimum description length (MDL) [8], a cost function which optimizes the goodness of fit and the model complexity, was computed. The optimal model was chosen based on the global minimum MDL.

C. Wiener (LN) Cascade Model

In addition to the linear coupling, we also investigated the nonlinearity in this mechanism using a Wiener (LN) cascade model (Fig. 2). The dynamic linear (L) part was represented by an impulse response, $h(t)$, and the static nonlinear (N) part was represented by $f(u)$.

x and y are the input and the output of the Wiener system, respectively, where $x = V_t$ and $y = \text{PATampN}$. The output of the L component, u , is a convolution of x with $h(t)$. u was then fed to the N component,

$$f(u) = Au^2 + u. \quad (2)$$

The rationale behind choosing the nonlinearity to take a form of a quadratic equation was that we suspected the vasoconstriction response might be augmented further with large V_t such as during a sigh.

The technique used to identify the model parameters of the Wiener cascade model was adapted from [9] and [10]. The iterative identification process was implemented as follows:

- 1) Estimate $\hat{h}$ from x and u_N using the aforementioned basis function expansion technique. Let initial $u_N = y$.
- 2) Convolve x with $\hat{h}$ to obtain an estimate of u_L , the output of the L component.
- 3) Fit the static nonlinear function between u_L and y . The quadratic coefficient, $\hat{A}$, was estimated using simplex algorithm [11]. Let initial $\hat{A}=0$. Moreover, a constraint was imposed on the estimation such that $\hat{A} \leq 0$.
- 4) Predict the model output, $\hat{y}$, using u_L from step 2) and $\hat{A}$ from step 3).
- 5) Update $u_N: u_N = u_N + y - \hat{y}$.
- 6) Compute normalized mean square error (NMSE). If the current NMSE is lower than the NMSE of the previous iteration, go to step 1). Otherwise, terminate iterations.

The median of the RPC impulse response (h_{RPC}) from both the linear and the Wiener cascade models as well as the static nonlinearity coefficient, A , of each breathing pattern and sleep stage were computed and later employed as the representative RPC mechanism in the parametric model.

D. Feature Extraction and Statistical Tests

The peak drop in peripheral vascular conductance (i.e. peak vasoconstriction) caused by a spontaneous or induced sigh was extracted from PATampN. The peak drop was defined as the magnitude of the maximum drop in PATampN within the first 15 seconds from the onset of the sigh (Fig. 3). Similarly, h_{RPC} peak magnitude of each breathing pattern and sleep stage was also extracted (Fig. 5).

Student's t-test (or Wilcoxon rank-sum test as applicable) was employed to test the following: the peak drop in PATampN during induced vs. spontaneous sigh and wakefulness vs. NREM sleep, and the peak magnitude of h_{RPC} during wakefulness vs. NREM sleep. One-way analysis of variance (or Kruskal–Wallis test as applicable) was employed to test the difference in h_{RPC} peak magnitude as well as the % change in NMSE from the linear to the Wiener cascade model among 3 breathing patterns. Student's t-test (or Wilcoxon test as applicable) was then used to test the pairwise differences.

III. Results

A. Sigh-vasoconstriction Response from Raw Data

The peak drop in PATampN, reflecting the degree of vasoconstriction, was extracted from spontaneous sigh and induced sigh segments during wakefulness and NREM sleep (Fig 4). There was no significant difference between the degrees of vasoconstriction in spontaneous and induced sighs during either wakefulness or NREM sleep.

B. Linear Component in RPC

The median h_{RPC} estimated using the Wiener cascade model, and the h_{RPC} peak magnitude of each breathing pattern and sleep stage are shown in Fig 5–6. The peak magnitude of h_{RPC} during wakefulness was not different among breathing patterns. However, the h_{RPC} peak magnitude of spontaneous breathing during NREM sleep was different from the other breathing patterns ($p=0.002$). Pairwise comparisons revealed that it was significantly higher than both spontaneous and induced sigh ($p=0.034$ and $p=0.001$, respectively).

C. Nonlinear Component in RPC

The quadratic coefficients of the Wiener cascade model in each breathing pattern and sleep stage are shown in Fig. 7. Even though the coefficient of spontaneous breathing during NREM sleep showed a tendency to be more nonlinear than the rest, the degree of nonlinearity was not different among breathing patterns or between wakefulness and NREM sleep.

The performance of the Wiener cascade model was compared to the linear model by computing the % change in NMSE from the linear model for each breathing pattern (Fig. 8). One-way ANOVA indicated that there was a difference in % NMSE change among the 3 breathing patterns ($p=0.049$). Pairwise comparisons showed that induced sigh had significantly larger drop in NMSE compared to spontaneous sigh ($p=0.02$).

IV. Discussion

In this study, we found that both spontaneous and passively induced sighs produced similar vasoconstriction responses during both wakefulness and NREM sleep (Fig. 5). This suggests that the vasoconstriction reflex likely involves lung stretch receptors and/or the expansion of the chest wall, but not necessarily central respiratory motor output. A previous study reported that taking a deep breath using chest wall muscles while the abdomen was tightly bounded resulted in vasoconstriction, but the opposite did not lead to vasoconstriction [1]. This suggests that the expansion of chest wall is primarily responsible for the reflex. It was previously shown also that vasoconstriction occurred following a voluntary sigh [5].

We further investigated the RPC during spontaneous breathing (with no sighs). The strength of the coupling, reflected by the peak magnitude of h_{RPC} during spontaneous breathing was similar to those during spontaneous and induced sighs in wakefulness (Fig. 6, left). However, the coupling strength during spontaneous breathing was significantly higher than spontaneous and induced sighs in NREM sleep (Fig. 6, right). This finding suggests that RPC exists even in an absence of a sigh although the effect is not evident, as the change in V_t during spontaneous breathing is much smaller than during a sigh. Lastly, we investigated if nonlinearity is involved in the RPC mechanism. We found by incorporating a quadratic nonlinearity into the model, the NMSE was significantly reduced only in induced sigh (Fig. 8). This suggests that the coupling is predominantly linear during spontaneous breathing and spontaneous sighs, while the nonlinear component becomes more evident when a large breath is passively induced.

Our findings demonstrate that vasoconstriction detected by PAT during wakefulness and NREM sleep can be the result of a sigh. Since PAT is now frequently employed for detection of arousal [12], one should be cautioned that peripheral vasoconstriction could also occur following deep breaths without associated arousals. A limitation of this study is that our estimates of RPC dynamics did not take into account blood pressure changes following sighs that may have affected peripheral vascular resistance via the baroreflex.

The identified RPC mechanism can be incorporated into a simulation model of cardiovascular system to better represent the control of peripheral vascular resistance (Fig. 1). We can see how RPC in different breathing pattern and sleep stage affect the cardiovascular system when it operates in a closed-loop manner. Another application is that the peak magnitude of h_{RPC} can potentially be used to identify sickle cell disease subjects who are more prone to having vasoconstriction, which may be associated with higher chance of having vaso-occlusive crisis.

V. Conclusions

Our findings suggest that the “deep breath vasoconstriction reflex” is present even in the absence of deep breaths (sighs) during both wakefulness and NREM sleep. Thus, respiration should be taken into account when PAT is used to detect vasoconstriction associated with arousal. The mechanism of this reflex is largely linear but may involve increased nonlinearity when the sigh is passively induced. Lastly, the respiratory-vascular coupling identified using our nonparametric approach can be incorporated into a simulation (parametric) model to better explain the fluctuations in peripheral resistance and to determine its interaction with other mechanisms when the system operates in a closed-loop manner.

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References

- [1]. Bolton B, Carmichael EA, Sturup G. Vaso-constriction following deep inspiration. *J Physiol.* Jan 15; 1936 86(1):83–94. [PubMed: 16994738]
- [2]. Sangkatumvong S, Khoo MC, Kato R, Detterich JA, Bush A, Keens TG, Meiselman HJ, Wood JC, Coates TD. Peripheral vasoconstriction and abnormal parasympathetic response to sighs and transient hypoxia in sickle cell disease. *Am J Respir Crit Care Med.* Aug 15; 2011 184(4):474–81. [PubMed: 21616995]
- [3]. Chalacheva P, Khoo MC. An extended model of blood pressure variability: incorporating the respiratory modulation of vascular resistance. *Conf Proc IEEE Eng Med Biol Soc.* 2013; 2013:3825–8. [PubMed: 24110565]
- [4]. Schnall RP, Shlitner A, Sheffy J, Kedar R, Lavie P. Periodic, profound peripheral vasoconstriction--a new marker of obstructive sleep apnea. *Sleep.* Nov 1; 1999 22(7):939–46. [PubMed: 10566912]
- [5]. O'Brien LM, Gozal D. Autonomic dysfunction in children with sleep-disordered breathing. *Sleep.* Jun; 2005 28(6):747–52. [PubMed: 16477962]

- [6]. Belozeroff V, Berry RB, Sassoon CS, Khoo MC. Effects of CPAP therapy on cardiovascular variability in obstructive sleep apnea: a closed-loop analysis. *American journal of physiology. Heart and circulatory physiology*. Jan; 2002 282(1):H110–21. [PubMed: 11748054]
- [7]. Asyali MH, Juusola M. Use of meixner functions in estimation of Volterra kernels of nonlinear systems with delay. *IEEE transactions on bio-medical engineering*. Feb; 2005 52(2):229–37. [PubMed: 15709660]
- [8]. Rissanen J. Estimation of structure by minimum description length. *Circ Syst Sig Process*. 1982; 1:395–406.
- [9]. Hunter IW, Korenberg MJ. The identification of nonlinear biological systems: Wiener and Hammerstein cascade models. *Biol Cybern*. 1986; 55(2-3):135–44. [PubMed: 3801534]
- [10]. Paulin MG. A method for constructing data-based models of spiking neurons using a dynamic linear-static nonlinear cascade. *Biol Cybern*. 1993; 69(1):67–76. [PubMed: 8334191]
- [11]. Lagarias JC, Reeds JA, Wright MH, Wright PE. Convergence Properties of the Nelder--Mead Simplex Method in Low Dimensions. *SIAM Journal on Optimization*. 1998; 9(1):112–147.
- [12]. Pillar G, Bar A, Shlitner A, Schnall R, Shefy J, Lavie P. Autonomic arousal index: an automated detection based on peripheral arterial tonometry. *Sleep*. Aug 1; 2002 25(5):543–9. [PubMed: 12150321]

Figure 1.
Simulation Model of Cardiovascular System [3]

Figure 2.
Schematic diagram of the Wiener (LN) cascade model

Figure 3.

A representative spontaneous sigh data during NREM sleep. Bottom panel shows how a peak drop in $\Delta PATampN$ is extracted.

Figure 4. Peak drop in $\Delta PATampN$ (mean $\pm$ SE) following spontaneous and induced sighs during wakefulness and NREM sleep.

Figure 5.

Median h_{RPC} in each breathing pattern during wakefulness (thick line) and NREM sleep (thin line). Left panel shows how a peak magnitude in h_{RPC} is extracted.

Figure 6.
 h_{RPC} peak magnitude (mean $\pm$ SE) in each breathing pattern during wakefulness and NREM sleep

Figure 7.
Quadratic coefficient (mean $\pm$ SE) in each breathing pattern during wakefulness and NREM sleep

Figure 8.
% change in NMSE (mean $\pm$ SE) from the linear model