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Time-varying closed-loop modeling of autonomic control in pediatric Obstructive Sleep Apnea Syndrome during cold face stimulation

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Abstract—**Adults with obstructive sleep apnea syndrome (OSAS) are known to have impaired autonomic function but the corresponding effects in children appear to be more subtle. Model-based analysis of the cardiovascular response to cold face test (CFT) was used to quantify daytime autonomic dysfunction. The increase in transfer gain between respiration and RRI was not different between controls and OSAS. However, the transfer gain between "surrogate cardiac output" (pulse pressure ÷ R-R interval) and systolic blood pressure (SBP) and the transfer gain between cardiac output and SBP both increased significantly in controls but not in OSAS during CFT. These findings suggest that the parasympathetic function remains relatively normal in pediatric OSAS, but cardiovascular sympathetic reactivity is impaired.**

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I. Introduction

The diving reflex, elicited by face immersion or cold face stimulation, leads to both parasympathetically-mediated bradycardia and sympathetically-mediated increases in peripheral resistance [1,2,3]. We hypothesized that careful analysis of the cardiorespiratory responses to autonomic challenges, such as the cold face test, may provide a more sensitive means of detecting autonomic abnormality in pediatric OSAS. An existing closed-loop minimal model of cardiovascular variability [4], modified to incorporate time-varying parameter changes, was used to estimate the transfer relations among respiration, beat-to-beat systolic blood pressure (SBP), surrogate cardiac output (SCO) or cardiac output (CO), and R-R interval (RRI) before and during CFT.

II. Methodology

A. Participants

Ten pediatric patients with moderate-to-severe OSAS (apnea-hypopnea index = 21± 5.3/hour) before treatment of tonsillectomy and ten normal control were recruited. The average age of the OSAS group was 11.4 ± 0.5 yrs with a mean BMI of 25.7 ± 2 kg m^{-2}, and the average age of the control group was 11.5 ± 0.9 yrs with a mean BMI of 18.3 ± 0.8 kg m^{-2}. None of them had history of lung disease, cardiac arrhythmia, congestive heart failure, or diabetes. The study was approved by the institutional review board of Childrens hospital Los Angeles. Written, informed consent was obtained from each subject before participation in the study.

B. Experiment

After 3 minutes of resting in supine wakefulness, a gel pack (cooled to 0° C) was placed on the subject's forehead for 1 minute. During the experiment; noninvasive arterial blood pressure (arterial tonometer), electrocardiogram (ECG), CO (by impedance cardiography), and respiration air flow (pneumotachometer) were measured continuously.

C. Preprocessing

R-R intervals (RRI) were extracted from the ECG. SBP and Diastolic blood pressure (DBP) were extracted on a beat by beat basis. Instantaneous lung volume (ILV) was calculated from respiration air flow. The thoracic impedance Z_0 and its rate of change dZ/dt were measured continuously. From these parameters, stroke volume was estimated using the Kubicek equation [5], and CO was computed on a beat to beat basis by dividing stroke volume by RRI. Finally, each signal was detrended and uniformly resampled at 2 Hz.

D. Model

To characterize the interrelationships among respiration, RRI and SBP, a time-varying closed-loop model was used.

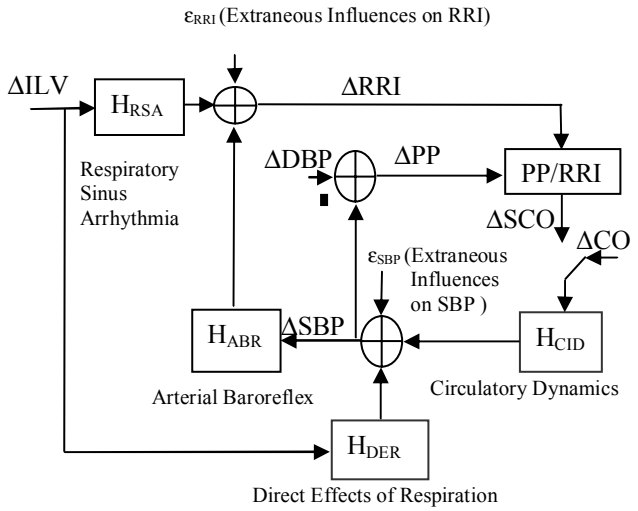

Fig. 1. Model of the circulatory control system.

In this model, fluctuations of RRI are influenced by SBP via the arterial baroreflex (ABR) mechanism and respiration via direct respiratory-cardiac coupling (RSA). Fluctuations in SBP are assumed to be influenced by changes in

intrathoracic pressure that result from respiration (DER), and by variations in cardiac output governed by the Frank-Starling and Windkessel runoff effects (CID). In fact, if the peripheral resistance remains unchanged during each beat, the pulse pressure is roughly linearly correlated with stroke volume [6]. On this basis, we defined a new variable, the "surrogate cardiac output" (SCO), in the following way:
at beat n,

$$SCO(n) = PP(n) / RRI(n) \quad (1)$$

Changes in the gain of the CID transfer function (Fig.1) were assessed in two ways: (a) ΔSCO was used as the input to derive "CID_{SCO} gain", (b) ΔCO was used as the input to the same transfer function to estimate "CID_{CO} gain". Changes in CID_{SCO} gain and CID_{CO} gain were taken to reflect changes in peripheral resistance. Thus, both parameters were used as indices of sympathetic activity. From the model, variables are related by the following equations:

$$\Delta SBP(n) = \sum_{i=0}^{M-1} h_{CID}(i) \cdot \Delta SCO(n - i - T_{CID}) + \sum_{i=0}^{M-1} h_{DER}(i) \cdot \Delta V(n - i) + \varepsilon_{SBP}(n) \quad (2)$$

$$\Delta RRI(n) = \sum_{i=0}^{M-1} h_{RSA}(i) \cdot \Delta V(n - i - T_{RSA}) + \sum_{i=0}^{M-1} h_{ABR}(i) \cdot \Delta SBP(n - i - T_{ABR}) + \varepsilon_{RRI}(n) \quad (3)$$

where M is the length of each impulse response, T_{RSA}, T_{ABR}, and T_{CID} are the latencies associated with the RSA, ABR, and CID, respectively, $\varepsilon_{RRI}(n)$ and $\varepsilon_{SBP}(n)$ represent residuals not accounted for by the model.

The estimation of impulse responses of the two-input one-output model was improved by computationally increasing the orthogonality between the respiration and other input. This was achieved by using an autoregressive model with exogenous input (ARX model) to "filter" out the respiration-correlated component from other input before it was used as an input to the model [7].

E. Impulse response estimation

The time-varying RSA and CID impulse responses were estimated using a technique that employs the Meixner expansion of kernel functions [8] and an algorithm based on the Recursive Least Squares (RLS) method [9]. Finally, the time-courses of the impulse response features - peak, LF gain (0.04-0.14 Hz), HF gain (0.15-0.4 Hz) and overall gain (0.04-0.4) - were calculated.

F. Statistical tests

The percent change of each feature from "pre-CFT", an average of one minute of feature before the test, was calculated. Subsequently, 2 minutes of the percent change of each feature was averaged every 5 seconds. Then two-way repeated measures ANOVA were performed where one factor was subject group (control vs OSAS) and the other factor was time from start of CFT.

III. RESULTS

Mean SBP significantly increased during CFT in both subject groups (Table 1). RRI in OSAS group significantly increased but was unchanged in control group. The consequences of CFT were that CID_{SCO} and CID_{CO} overall gain increased in controls but remained unchanged in OSAS, while RSA gain of both controls and OSAS increased (Table 2 , Figure 2 and 3).

TABLE I
Summary of cardiovascular measures.

Cardiovascular Measure	OSAS Mean ± SE	Control Mean ± SE
SBP_{Pre} (mmHg)	99.4±6.4	105.7±4.9
SBP_{Post} (mmHg)	102.3±6.5*	110.5±5.4*
RRI_{Pre} (ms)	797.6±37.6	787.0±38.2
RRI_{Post} (ms)	817.5±38.2*	798.9±30.9

Pre=1 min before CFT, Post= 1 min during CFT and 1 min after CFT, * P<0.05 from Pre.

TABLE II
Estimates of percent change of model parameters and spectral indices

Features		OSAS Mean± SE	Control Mean±SE	P-values Group	Time
CID_{SCO}	LF	-1.1±3.3	33.0±5.7	0.086	0.182
	HF	0.8±3.9	40.8±7.2	0.042*	0.899
	OA	-1.1±3.1	35.7±5.7	0.041*	0.518
CID_{CO}	LF	0.6±4.6	51.6±8.2	0.052	0.432
	HF	-9.8±4.3	29±7.4	0.098	0.708
	OA	-5±3.9	39±6.9	0.04*	0.342
RSA	LF	84.0±11.9	94.2±16.0	0.842	0.010*
	HF	30.5±6.9	50.1±10.1	0.554	0.086
	OA	56.3±8.8	68.1±12.2	0.767	0.020*
RRI	HF	22.4±3.6	28.1±4.9	0.782	0.23
RRI	LHR	-28.1±2.9	-17.9±3.6	0.512	<0.001*
SBP	LF	-32.5±3.8	-6.9±5	0.137	<0.001*

OA= Overall Gain, * P<0.05.

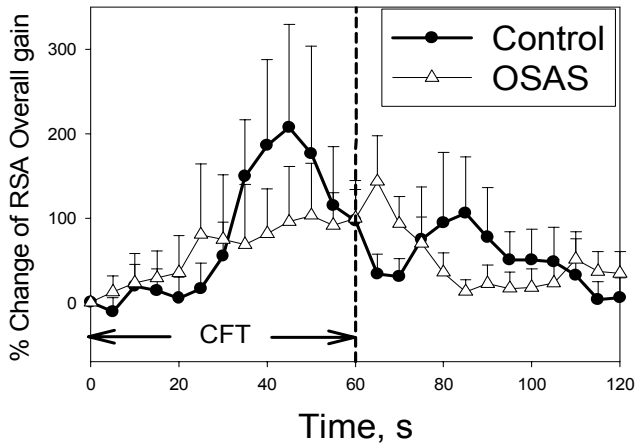

Fig. 2. Mean and SE of percent change of RSA overall gain in control and OSAS group.

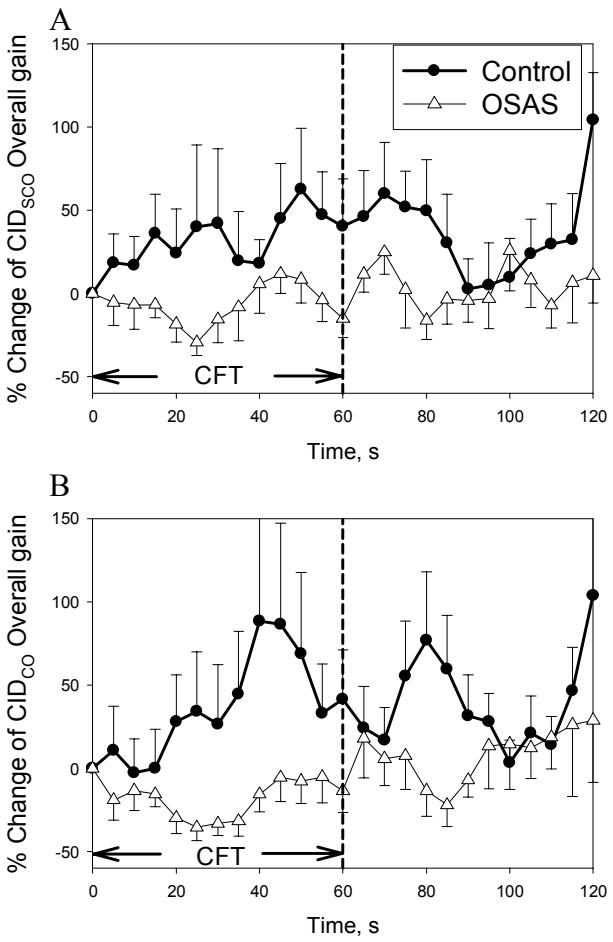

Fig. 3. Mean and SE of percent change of A) CID_{SCO} overall gain, and B) CID_{CO} overall gain in control and OSAS group.

IV. Discussion

RSA gain, the index of parasympathetic activity, significantly increased in both groups. However, the sympathetic index, CID gain, significantly increased in control group but remained unchanged in OSAS. These findings suggest that parasympathetic function remains normal in pediatric OSAS, but the cardiovascular sympathetic response is impaired.

We conclude that model-based analysis of the cardiovascular response to CFT is useful as a noninvasive tool for quantifying daytime autonomic dysfunction in children with OSAS. Moreover, assessment of CID transfer gain using CID_{SCO} and CID_{CO} gains led to similar results, suggesting that it is possible to perform this test without the need to directly measure cardiac output.

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