Modelling Fluid Accumulation in the Neck Using Simple Baseline Fluid Metrics: Implications for Sleep Apnea

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Abstract— **Obstructive sleep apnea (OSA) is a common respiratory disorder among adults. Recently we have shown that sedentary lifestyle causes an increase in diurnal leg fluid volume (LFV), which can shift into the neck at night when lying down to sleep and increase OSA severity. The purpose of this work was to investigate various metrics that represent baseline fluid retention in the legs and examine their correlation with neck fluid volume (NFV) and to develop a robust model for predicting fluid accumulation in the neck.**

In 13 healthy awake non-obese men, LFV and NFV were recorded continuously and simultaneously while standing for 5 minutes and then lying supine for 90 minutes. Simple regression was used to examine correlations between baseline LFV, baseline neck circumference (NC) and change in LFV with the outcome variables: change in NC (ΔNC) and in NFV (ΔNFV_{90}) after lying supine for 90 minutes. An exhaustive grid search was implemented to find combinations of input variables which best modeled outcomes. We found strong positive correlations between baseline LFV (supine and standing) and ΔNFV_{90}. Models developed for predicting ΔNFV_{90} included baseline standing LFV, baseline NC combined with change in LFV after lying supine for 90 minutes. These correlations and the developed models suggest that a greater baseline LFV might contribute to increased fluid accumulation in the neck. These results give more evidence that sedentary lifestyle might play a role in the pathogenesis of OSA by increasing the baseline LFV. The best models for predicting ΔNC include baseline LFV and NC; they improved accuracies of estimating ΔNC over individual predictors, suggesting that a combination of baseline fluid metrics is a good predictor of the change in NC while lying supine. Future work is aimed at adding additional baseline demographic features to improve model accuracy and eventually use it as a screening tool to predict severity of OSA prior to sleep.

I. INTRODUCTION

Sleep apnea is a common respiratory disorder among adults that occurs in 5% to 10% of the general population [1], which is associated with increased cardiovascular morbidity and mortality [1,2]. Obstructive sleep apnea (OSA) is the most common form of sleep apnea that occurs due to repetitive collapse of the upper airway during sleep. Although various factors could affect the pathophysiology of upper airway during sleep and predispose it to collapse, the underlying mechanisms of this collapse are not fully understood. Recently, we developed a novel theory that sedentary lifestyle causes an increase in diurnal leg fluid retention, which can shift into the neck at night when lying down to sleep [3]. Fluid shifting out of the legs and into the neck could increase neck circumference (NC) [4], increase tissue pressure around the upper airway and decrease its cross-sectional area [5], and increase its collapsibility [6]; all of which could contribute to increased severity of OSA. Also the amount of fluid coming out of legs overnight is strongly correlated to the overnight increase in NC and severity of OSA [3, 7-9].

Although previous studies investigated the change in NC relative to the changes in leg fluid volume (LFV) while supine, they did not examine the effects of other representatives of fluid retention in the legs, such as the baseline values of LFV while standing, or the change in LFV due to posture. Furthermore, due to technical difficulties they only measured LFV, but not neck fluid volume (NFV). The goal of this study is to develop more robust algorithms that can predict fluid accumulation in the neck from different baseline fluid metrics that can be recorded easily. The first objective of this study is to investigate the effects of various factors such as baseline NC, LFV, and change in LFV due to posture and due to lying supine on the changes in NC and NFV while supine. The second objective is to develop models which can predict variations in NC and NFV while supine with high accuracy.

II. METHOD

A. Participants

Healthy non-obese (BMI < 30 kg/m^2) men participated in the study. Only men were included because previous research has shown that pattern of fluid redistribution is different between sexes and men are more susceptible to the adverse effects of fluid shift than women [7,8].

B. Neck Circumference and Fluid Measurements

A tape measure was used to measure NC just above the cricothyroid cartilage. A line was drawn at this level to ensure the NC measurement at the end of the experiment was made at the same level [6,9].

Fluid was measured in the leg and neck using bioelectrical impedance, a non-invasive technique for measuring fluid volume of the tissues. Bioelectrical impedance of tissues is inversely related to its fluid content and directly related to its length: $V = \rho L^2/R$, where ρ is the resistivity of the fluid, L is the segment's length, and V is the fluid volume [3]. While this relation is based on assuming that each segment is a cylinder, more accurate models are proposed to reflect the conical shape of the segments [10]:

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$$V = \frac{\rho^{2/3}}{3(4\pi)^{1/3}} \left(\frac{L}{C_1 C_2 R}\right)^{2/3} L(C_1^2 + C_2^2 + C_1 C_2), \tag{1}$$

where C_1 and C_2 are the segment's circumference at the level of the sensing electrodes and R is the segment's resistance.

Leg and neck resistances (Equation 1) were recorded simultaneously using the MP150 Biopac System. The system uses two electrodes to inject current (400μA at 25kHz and 50kHz for LFV and NFV, respectively) and two sensing electrodes to measure the bioelectrical impedance of the segments. To measure LFV, sensing electrodes were placed on the ankle and upper-thigh of the right leg, and to measure NFV, on the right side of the neck below the right ear and at the base of the neck. Injecting electrodes are placed 1-inch from the sensing electrodes and all electrodes were secured with adhesive tape. Length and circumferences of the leg and neck were measured by measuring tape and Equation 1 was used to estimate LFV and NFV.

C. Protocol

The protocol was approved by the Research Ethics Board of Toronto Rehabilitation Institute and all participants provided written consent prior to participating in the study. Participants were instrumented for bioelectrical impedance while in the seated position. Then participants were asked to stand for 5-minutes, followed by lying supine on a bed without pillow for 90 minutes. Biolectrical impedance data were recorded continuously and simultaneously while standing and supine, and subjects did not move during the whole study.

D. Input Variables and Outcome Variables

Input variables were selected to be measurements that can be obtained easily, represent fluid retention in the legs, and/or have been shown previously to have a strong correlation with either OSA severity or change in NC. The variables included are NC_{sp1}, NC measured at baseline supine; LFV_{st5}, LFV after standing for 5 minutes; LFV_{sp1}, LFV at baseline supine; ΔLFV_P, change in LFV upon transitioning from standing to supine position ($\Delta LFV_P = LFV_{sp1} - LFV_{st5}$); and ΔLFV_{90}, the change in LFV after 90 minutes supine ($\Delta LFV_{90} = LFV_{sp90} - LFV_{sp1}$), where LFV_{sp90} is the LFV after 90 minutes supine.

Outcome variables represent the amount of fluid accumulation in the neck after lying supine: $\Delta NC = NC_{sp90} - NC_{sp1}$, and $\Delta NFV_{90} = NFV_{sp90} - NFV_{sp1}$; where NC_{sp90} and NFV_{sp90} are the NC and NFV after lying supine for 90 minutes, respectively.

E. Data Analysis

Data analysis was performed in two main steps. In the first step, we investigated the correlations between the input variables and the outcome variables using simple regression. The input variables with significant correlation (P-value < 0.05) were investigated in more detail.

In the second step, we aimed to investigate whether we can develop models based on various combinations of input variables to predict the outcome variables. Given the limited number of input variables, all possible combinations of them were tested using an exhaustive grid search methodology, creating a total of 31 models for each outcome variable. To prevent over-fitting, leave-one-out cross-validation method was used which involved leaving out a single observation (k=1, ... , 13) from the original sample as the validation data, and using the remaining observations as the training data. This is repeated such that each observation in the sample is used once as the validation data. For each combination of input variables, model fit was assessed using the normalized root mean squared error ($RMSE_N$):

$$RMSE_N = \frac{\sqrt[2]{E\left(Y_{actual} - Y_{predict}\right)^2}}{\sqrt[2]{E(Y_{actual})^2}} \times 100 \tag{2}$$

where, Y is the output variable (ΔNC or ΔNFV_{90}), Y_{actual} is the actual output, $Y_{predict}$ is the predicted output, and E(.) represents the average function. For each of the 31 combinations of input variables, $RMSE_N$ was used to evaluate each model and the two models with lowest $RMSE_N$ were selected. All data analysis was performed with Matlab and data was presented as Mean±SD.

III. RESULTS

Thirteen healthy men, aged 39.5±13.4 years, BMI of 23.8±3.1 kg/m_2 and baseline NC of 40.1±2.5cm participated in this study. Our results show that compared to standing for 5 minutes, after lying supine for 1 minute, there was a significant decrease in LFV (ΔLFV_P: 65.1±37.3 ml, $p<0.001$) and increase in NFV (ΔNFV_P: 12.4±10.7 ml, $p<0.001$). These changes in fluid volumes represent the effects of posture on the quick transitions in intravascular fluid out of the legs into the neck. After lying supine for 90 minutes, there was a significant decrease in LFV (ΔLFV_{90}: 149.9±43.4 ml, $p<0.001$), and significant increases in NC (ΔNC: 0.8±0.3 cm, $p<0.001$) and in NFV (ΔNFV_{90}: 17.5±5.2 ml, $p<0.001$). These results confirm that upon lying supine, there are further changes in fluid redistribution out of the legs towards the upper body and neck.

The results of the simple regression analysis are summarized in Table I. No significant correlations were found between the independent variables and ΔNC, except a borderline significant correlation between ΔLFV_{90} and ΔNC ($p = 0.067$). This indicates that with more fluid coming out of the legs in supine position, there would be a tendency for bigger increase in NC after 90 minutes.

Among all independent variables, baseline LFV when standing (LFV_{st5}) and supine (LFV_{sp1}) were significantly correlated with ΔNFV_{90} (Table I). This demonstrates that with an increase in baseline LFV, there would be a bigger increase in NFV after lying supine for 90 minutes. Figure 1 shows the relationship between ΔNFV_{90} and baseline standing LFV.

Table I. Results of Correlation Between Individual Predictor Variables and ΔNC and ΔNFV_{90} (*$P<0.05$, $^{\updownarrow}P<0.1$)

Variables	NC_{sp1}	LFV_{st5}	LFV_{sp1}	ΔLFV_P	ΔLFV_{90}
ΔNC	-0.447	-0.257	0.193	0.491	$0.522^{\updownarrow}$
ΔNFV_{90}	0.084	0.592^{*}	0.619^{*}	0.158	$0.480^{\updownarrow}$

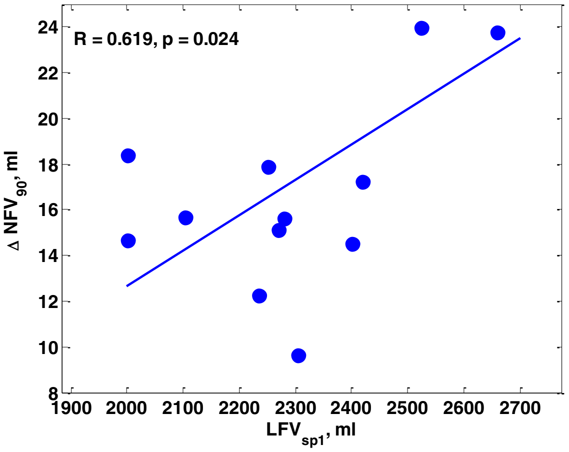

Figure 1. Correlation between baseline LFV at supine position (LFV$_{sp1}$) and change in NFV after lying supine for 90 minutes (ΔNFV$_{90}$). The solid line shows the regression line.

Table II. Average RMSE$_N$ (%) for Top Two Models and Individual Features for Each Outcome Variable (*P<0.05, ‡P<0.1 compared to model 1).

Models		ΔNC	ΔNFV$_{90}$
Developed models	Model 1	24.8±35.2	26.5±27.8
	Model 2	27.1±34.0	26.6±23.5
Individual Features	NC$_{sp1}$	38.9±44.3*	29.4±24.8
	LFV$_{st5}$	39.0±60.1	26.5±23.6
	LFV$_{sp1}$	40.5±60.5	26.1±22.6
	ΔLFV$_P$	37.0±46.1‡	27.9±23.8
	ΔLFV$_{90}$	39.6±30.3‡	25.1±28.1

Table II shows the RMSE$_N$ of the top two models and the models based on the individual input variables for predicting ΔNC. The top two models for predicting ΔNC both included baseline NC and the change in LFV due to posture change (model 1, Equation 3), with model 2 also including baseline standing LFV (Equation 4).

$$\Delta NC = -0.69NC_{sp1} - 0.38\Delta LFV_P + 1.06 \qquad (3)$$

$$\Delta NC = -0.75NC_{sp1} + 0.24LFV_{st5} - 0.44\Delta LFV_P + 2.8 \qquad (4)$$

These models improved prediction of ΔNC compared to each individual predictor (Table II) however this was only significant for differences between model 1 and NC$_{sp1}$ (p=0.02) and borderline significant for differences between model 1 and ΔLFV$_P$ (p=0.08) and ΔLFV$_{90}$ (p=0.09). Plots of the actual versus predicted ΔNC for both models are illustrated in Figure 2. The figure shows that predictions of ΔNC are similar between both models, and close to the unity line. Models 1 and 2 for predicting ΔNC demonstrate that a combination of baseline measures are better predictors of the change in NC than the change in LFV after lying supine for 90 minutes.

Equations 5 and 6 show the best models for ΔNFV$_{90}$:

$$\Delta NFV_{90} = 1.49LFV_{sp1} + 0.21\Delta LFV_{90} + 0.05 \qquad (5)$$

$$\Delta NFV_{90} = 0.86NC_{sp1} + 0.62\Delta LFV_{90} + 0.19 \qquad (6)$$

These models suggest that baseline LFV and NC contribute to neck fluid accumulation in addition to shift in fluid out of the legs after laying supine for 90 minutes. The developed models had a lower RMSE$_N$ compared to most of the individual input variables (Table II), however differences were not significant. They improved prediction error over individual inputs ΔLFV$_P$ and NC$_{sp1}$, and had similar performances to LFV$_{sp1}$, LFV$_{st5}$, and ΔLFV$_{90}$.

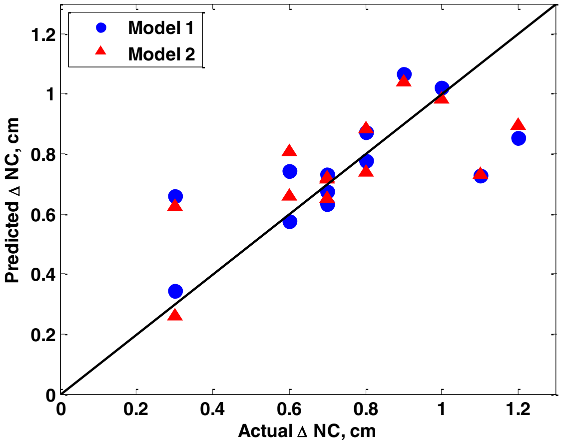

Figure 2. Actual ΔNC versus predicted ΔNC for models 1 and 2, described by Equations 3 and 4, respectively. The solid line shows the unity line.

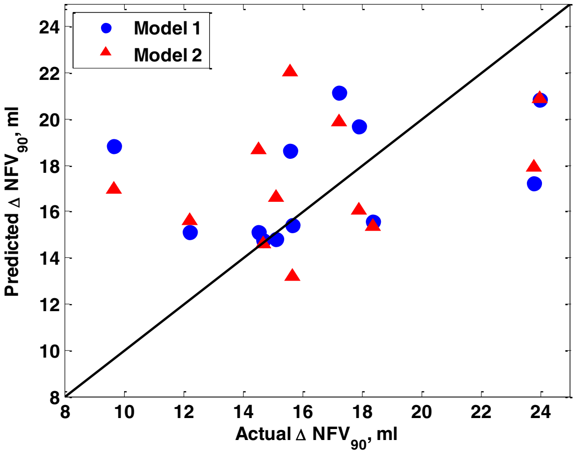

Figure 3. Actual ΔNFV$_{90}$ versus predicted ΔNFV$_{90}$ for models 1 and 2 described by Equations 5 and 6, respectively. The solid line shows the unity line.

Figure 3 shows the results of predicted versus actual ΔNFV$_{90}$ for models 1 and 2. Larger deviations from the unity line are apparent, but the greatest errors occur in the subjects at the extreme ends of ΔNFV$_{90}$. This suggests that including demographic features into the model such as weight and height may improve prediction accuracies for these outliers.

IV. DISCUSSION AND CONCLUSION

In this study we investigated how the baseline NC, baseline fluid volumes of the legs, and change in LFV due to the posture and due to lying supine contribute to the fluid accumulation in the neck. To our knowledge, this is the first time that the effect of these variables on fluid accumulation in the neck have been considered and compared.

One important finding is that baseline standing and supine LFV have a positive and significant correlation with changes in NFV after lying supine for 90 minutes. Previous studies have shown that sitting time and baseline leg edema are correlated to OSA severity and overnight ΔLFV [8,9]. However, for the first time we show that with increasing baseline LFV, there is a corresponding increase in the change in NFV after lying supine. This relationship demonstrates that not actively preventing leg fluid accumulation through sedentary living can contribute to the overnight fluid accumulation in the neck. We have shown previously that nocturnal fluid shift into the neck increases the severity of OSA [3] and it is therefore possible that larger volumes of baseline LFV plays a role in this. Although we did not find a relationship between ΔNC and ΔLFV_{90} or LFV_{sp1} as has been shown previously [3,9], it is either because our subjects did not lay in bed long enough or because they were awake. This discrepancy should be investigated in future work.

Sedentary lifestyle can increase baseline LFV and nocturnal fluid shift out of the legs [3,9]. Our first developed model for ΔNFV_{90} (Equation 5) predict that with increases in baseline LFV and ΔLFV while supine, NFV would increase more. This gives more support to our hypothesis that sedentary lifestyles could magnify the effects of nocturnal fluid redistribution on the severity of OSA. Sedentary living has been attributed to the modern occupation which requires sitting at a desk for the majority of the day. This puts a large proportion of the population at risk of accumulating excess fluid in the legs during the day. Therefore it is important to investigate interventions to prevent diurnal LFV accumulation. We have shown that wearing compression stockings during the day can attenuate LFV and OSA severity by 30% in non-obese population [11]. Future work could involve developing more convenient and effective methods for reducing diurnal LFV accumulation.

Baseline neck girth is a strong predictor of OSA severity [12]. Our second developed model for ΔNFV_{90} (Equation 6) shows that increases in baseline NC and ΔLFV while supine are associated with a bigger increase in NFV after lying supine. The positive effect of baseline NC in combination with ΔLFV on the increases in ΔNFV could be one of the mechanisms through which NC contributes to the pathogenesis of OSA.

Previous studies have shown that the overnight ΔLFV is correlated to ΔNC, which is also correlated to OSA severity [3]. Our proposed models in Equations 3 and 4 for predicting ΔNC based on baseline NC, baseline standing LFV, and immediate LFV shift upon lying supine, improved ΔNC prediction accuracy compared to the model based on only ΔLFV. Furthermore, our proposed models only use the baseline variables that can be recorded conveniently before sleep. In future studies, if we show that similar models can predict ΔNC after sleep, we would be able to develop simple screening tools to predict severity of OSA prior to sleep.

This study is subject to some limitations which are mainly imposed due to the sensitivity of bioelectrical impedance measurements to movement. Since our participants could not remain still without movement for more than 90 minutes, the duration of study was limited to 90 minutes. Our study was performed during wakefulness to limit involuntary body movements during sleep. Since, the pattern of fluid redistribution out of the legs and into the neck could be different during wakefulness and sleep, future work should include studies during sleep. We only investigated men in this study and future work should also include women and test if the developed models are different between sexes.

Future work aims to improve the developed models by including demographic features, validating the models on data of women participants, evaluating the accuracies of the models during sleep, and whether the developed models can be used to predict the severity of OSA.

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