

**Alterations in Upper Airway Cross-sectional Area in Response to Lower Body Positive
Pressure in Healthy Subjects**

Running Title: Fluid Shift and Upper Airway Cross-sectional Area

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ABSTRACT

Introduction: Fluid accumulation in the neck during recumbency might narrow the upper airway (UA) and thereby contribute to its collapse in patients with obstructive sleep apnea (OSA). We hypothesized that acute fluid shifts from the legs to the upper body in healthy subjects would increase neck circumference and reduce UA cross-sectional area (UA-XSA).

Methods: In 27 healthy, non-obese subjects (mean \pm SE, 39 \pm 3 years, body mass index 23.2 \pm 0.6kg/m²), studied while supine, we measured leg fluid volume using bio-electrical impedance, neck circumference using a mercury strain gauge and mean UA-XSA between the velum and the glottis using acoustic pharyngometry at end-expiration. Measurements were made at baseline after which subjects were randomly assigned to a 5-minute time-control period or to a 5-minute application of LBPP at 40 mmHg by anti-shock trousers, separated by a 15-minute washout period. Subjects then crossed-over to the opposite arm of the study.

Results: Compared to control, application of LBPP significantly reduced leg fluid volume ($p<0.001$), increased neck circumference ($p<0.001$), both at 1-min and 5-min, and reduced UA-XSA after both 1-min (-0.15 cm²; 95% confidence interval [CI], -0.23 to -0.09 cm², $p<0.001$) and 5 min (-0.20 cm²; 95% CI, -0.33 to -0.09 cm², $p<0.001$).

Conclusion: In healthy subjects, displacement of fluid from the legs by LBPP causes distension of the neck and narrowing of the UA lumen. Therefore, fluid displacement from the lower to the upper body while recumbent may contribute to pharyngeal narrowing and obstruction to airflow in patients with OSA. This may have particular pathological significance in edematous states such as heart and renal failure.

Key Words: upper airway, acoustic pharyngometry, lower body positive pressure, obstructive sleep apnea

INTRODUCTION

Obesity and increased neck circumference are important risk factors for obstructive sleep apnea (OSA) in the general population ¹. However, body mass index and neck circumference only account for approximately 4% and 29%, respectively, of the variability in the frequency of obstructive apneas and hypopneas per hour of sleep (apnea-hypopnea index, AHI) ². Therefore, other factors must be involved in the pathogenesis of upper airway (UA) obstruction in patients with OSA.

One possible factor contributing to UA obstruction in patients with OSA might be fluid displacement from the lower extremities into the neck during sleep. An increase in neck fluid volume could narrow the UA and increase its propensity to collapse. This mechanical force might be of particular clinical relevance in patients with edematous states such as heart and renal failure who have a higher prevalence of OSA than the general population that has yet to be explained ³⁻⁷. Only one study has examined the effect of shifting fluid from the lower extremities to the upper body on UA size. In that study, Shepard and colleagues ⁸ tested the effects of shifting fluid out of the lower body by raising the legs, and of shifting fluid into the legs by applying tourniquets around the thighs in an attempt to displace fluid into and out of the neck, respectively, in patients with OSA. Using computed tomography, they observed a tendency for the UA cross-sectional area (UA-XSA) to decrease and to increase in response to leg raising and tourniquet application, respectively. However, these changes in UA-XSA were not significant, perhaps because these interventions did not cause sufficient fluid displacement to alter UA size. A more effective means of displacing fluid from the lower to the upper body may be application of lower body positive pressure (LBPP) via anti-shock trousers. LBPP displaces fluid into the

upper body ⁹ and increases central venous pressure ¹⁰, but without increasing left ventricular filling pressure ¹¹.

In a recent study, we applied LBPP to healthy euvoletic subjects to mimic the effects of fluid redistribution from the lower to the upper body upon assuming the recumbent position in patients with fluid overload. We demonstrated in 11 healthy subjects that LBPP caused significant increases in neck circumference and pharyngeal resistance to airflow measured by pressure transducers in the hypo- and naso-pharynx ¹². However, upper airway caliber was not measured during those experiments because it could not be assessed concurrently with upper airways resistance. Therefore, to test the hypothesis that this increase in resistance we observed was related to narrowing of the UA, we undertook a separate study to examine the effects of fluid redistribution from the legs to the neck by LBPP on UA-XSA measured by acoustic pharyngometry. Of the 27 subjects taking part in the present experiments, only 5 were subjects for our previous study ¹², so that overlap in subjects was minimal.

METHODS

Subjects

Eligible subjects were healthy men and women, 18 years of age or older, with no history of smoking, cardiovascular, respiratory or neurological disease. Exclusion criteria were obesity (body mass index [BMI] >30 kg/m²), a history of habitual snoring or daytime sleepiness, taking prescribed medications and pregnancy. The protocol was approved by the local research ethics board and subjects gave their written informed consent prior to participating.

Lower body positive pressure

LBPP was applied using medical anti-shock trousers (MAST IIIAT, David Clark, Worcester, MA) that were fitted around the subjects' legs from the ankles to the hips in the deflated state. During experiments only the leg bladders were inflated to 40 mmHg.

Leg fluid volume

Leg fluid volume was measured using a bio-electrical impedance spectrum analyzer (Xitron Hydra ECF/ICF, Model 4200; Xitron Technologies Inc., San Diego, CA)¹³. This is a well validated technique that measures electrical impedance between 2 pairs of electrodes placed on the body. Changes in impedance are proportional to changes in fluid volume^{14, 15}. Electrodes were placed on the ankle and upper thigh to measure fluid volume in one lower limb.

Neck circumference

Percentage changes in neck circumference during experiments were monitored continuously by a mercury-in-silastic strain gauge (D. E. Hokanson, Inc., Bellevue, WA) whose resistance to electrical flow is altered in proportion to change in its length¹⁶. The gauge was placed above the cricothyroid cartilage. This device is ordinarily used to measure changes in cross-sectional area of limbs for determination of blood flow, and is exquisitely sensitive, accurate and reproducible as we have previously described¹⁷.

Upper airway cross-sectional area

To determine UA-XSA, we used acoustic pharyngometry (Eccovision™ Acoustic pharyngometry; Hood Laboratories; Pembroke, MA)¹⁸⁻²⁰. With subjects supine, and their heads

in the neutral position, the device was positioned in the mouth using a mouthpiece designed to secure the tongue in place. The pulse emitter produced five pulses per second. Two microphones detected the amplitude and temporal changes of the reflected pulse. Data were collected and analyzed by a single investigator. During the measurements, the subject's head position was fixed by resting the head in form-shaping sand bags. UA-XSA area was determined at end-expiration as the mean area between the nasal and oropharyngeal junction (velum) and the glottis as previously described ²¹. The mean of four consecutive measurements was used. Acoustic pharyngometry has been validated against computed tomography ²² and magnetic resonance imaging ²³ for assessment of the UA-XSA in non-snores, and in snorers with and without OSA in both the supine and upright positions ^{21, 24-26}.

End-expiratory lung volume and blood pressure

In 6 subjects, change in end expiratory lung volume (EELV) was monitored by a respiratory inductance plethysmograph (Respirace ®; Ambulatory Monitoring Inc., Ardsley, NY) in the DC coupled mode calibrated against a spirometer. Systolic and diastolic blood pressures were measured using an automated sphygmomanometer (Dinamap 1846SX NIBP, Critikon, Tampa, FL) on the upper arm. Heart rate was measured during blood pressure measurements.

Protocol

Following a 5-minute stabilization period, baseline measurements of all variables were made. Subjects were then randomized to a 5-minute LBPP exposure or to a 5-minute control period at the end of which baseline measurements were repeated. This was followed by a 15-

minute washout period during which subjects were seated upright. They then returned to the supine position and underwent a second 5-minute baseline period after which they crossed-over to the other arm of the study for 5 minutes. Measurements of all variables were made at the end of each baseline period, and after 1 and 5 minutes during each of the LBPP and control periods. Reproducibility of UA-XSA measurements was determined from 5 separate measurements in each subject during baseline before the control period, 1 and 5 minutes during the control period, and at 1 and 5 minutes following the control period.

Data Analysis

All variables were analyzed at the ends of the baseline period, and after 1 and 5 minutes of the LBPP and control periods. Data from 5 consecutive breaths at the end of each of these periods were analyzed and averaged to provide changes in neck circumference and in EELV from baseline. Two-way repeated-measures analysis of variance (ANOVA) (Sigma Stat 2.0, SPSS Inc., Chicago, IL) was used to compare values obtained during the baseline, control and LBPP periods, followed by *post hoc* Tukey's test as appropriate. For helium dilution lung volumes, paired t-tests were used to compare values during the control and LBPP periods. **All** data were normally distributed and are presented as mean \pm SEM unless stated otherwise. A two-sided p-value <0.05 was considered significant.

RESULTS

Characteristics of the subjects

We studied 27 subjects (16 men and 11 women) whose demographic data are summarized in Table 1. They were generally young, non-obese adults.

Table 1. Characteristics of the Subjects

Number (Male/Female)	27 (16/11)
Age, years	39 ± 3
Height, cm	167.5 ± 1.8
Weight, kg	65.5 ± 2.4
BMI, kg/m ²	23.2 ± 0.6
Neck circumference, cm	36.5 ± 0.7

Data are mean ± SEM.

BMI = Body mass index

Leg fluid volume and neck circumference

Table 2 shows that leg fluid volume did not change significantly after 1 and 5 minutes during the control period. In contrast, after 1 and 5 minutes of LBPP, there was a sustained decrease in leg fluid volume compared to baseline that was significantly greater than during 1 and 5 minutes of the control period (difference from control, -0.16 L; 95% confidence interval [CI], -0.19 to -0.12 L, and -0.14 L; 95% CI, -0.18 to -0.09 L, respectively). Neck circumference did not change significantly from baseline during the control period at either 1 or 5 minutes. In contrast, after 1 and 5 minutes of LBPP there was a sustained increase in neck circumference compared to baseline that was significantly greater than at 1 and 5 minutes of the control period (difference from control, 0.34%; 95% CI, 0.23 to 0.45%, and 0.28; 95% CI, 0.12 to 0.43%, respectively).

Upper airway cross-sectional area

Figure 1 shows tracings of UA-XSA as a function of distance from the mouth opening at the end of the baseline period, and after 1 and 5 minutes of LBPP from a representative subject. It demonstrates that LBPP reduced UA-XSA at both 1 and 5 minutes. Measurements of UA-XSA performed on 5 separate occasions under control conditions in each of the 27 subjects were highly reproducible with a mean coefficient of variation of just $3.74 \pm 0.78\%$.

Figure 2 shows grouped data for all 27 subjects. It illustrates that UA-XSA did not change significantly during the control period at either 1 or 5 minutes (from 2.66 ± 0.13 to 2.62 ± 0.13 cm², $p = 0.440$, and to 2.60 ± 0.12 cm², $p = 0.146$). In contrast, after 1 and 5 minutes of LBPP, there was a sustained reduction in UA-XSA (from 2.68 ± 0.13 to 2.47 ± 0.12 cm², $p < 0.001$, and to 2.40 ± 0.12 cm², $p < 0.001$) that was significantly greater than during 1 and 5 minutes of the control period (difference from control, -0.15 cm²; 95% CI, -0.23 to -0.09 cm², and -0.20 cm²; 95% CI, -0.33 to -0.09 cm², respectively). There was also a significant inverse correlation between the magnitude of change in UA-XSA and neck circumference at 1 minute ($r = -0.53$, $p = 0.01$). However, there was no significant correlation between the change in UA-XSA and neck circumference after 5 minutes ($r = -0.15$, $p = 0.50$).

End expiratory lung volume, blood pressure and heart rate

Table 2 demonstrates that neither EELV, systolic nor diastolic blood pressures, nor heart rate changed significantly from baseline during either the control or LBPP periods. There were no side effects during the application of LBPP.

Table 2. Influence of lower body positive pressure (LBPP) on physiological variables

		Baseline	1-min	5-min	P-value for time-treatment interaction
Leg fluid volume, L	Control	4.67 ± 0.18	4.67 ± 0.18	4.66 ± 0.18	
	LBPP	4.57 ± 0.19*	4.41 ± 0.19* [†]	4.43 ± 0.19* [†]	<0.001
Δ in Neck circumference, %	Control	-	-0.01 ± 0.02	0.00 ± 0.05	
	LBPP	-	0.33 ± 0.05* [†]	0.28 ± 0.06* [†]	<0.001
Δ in End expiratory lung volume, L ^{††}	Control	-	-0.024 ± 0.024	0.107 ± 0.044	
	LBPP	-	0.112 ± 0.049	0.198 ± 0.106	0.22
Systolic blood pressure, mmHg ^{††}	Control	119 ± 10	120 ± 9	115 ± 8	
	LBPP	122 ± 10	124 ± 9	121 ± 9	0.61
Diastolic blood pressure, mmHg ^{††}	Control	71 ± 3	70 ± 4	71 ± 4	
	LBPP	74 ± 4	74 ± 4	75 ± 4	0.62
Heart rate, bpm ^{††}	Control	68 ± 6	67 ± 6	66 ± 6	
	LBPP	68 ± 6	68 ± 6	66 ± 6	0.29

Data are mean ± SE: * p<0.001 versus control by Tukey's test; [†] p<0.001 versus baseline by Tukey's test; ^{††} n=6

DISCUSSION

In this study of healthy, non-obese subjects, we made several interesting and novel observations. First, we demonstrated that application of 40 mmHg of LBPP, which displaced approximately 320 ml from both legs (assuming the fluid shift was twice that of one leg), increased the circumference of the neck. This indicated that a portion of this fluid was shifted into the nuchal structures. Second, this distension of the neck was accompanied by a significant 9% reduction in UA-XSA. Because LBPP caused no significant effect on EELV, blood pressure or heart rate, the most likely explanation for this decrease in UA-XSA was fluid accumulation in the nuchal structures, including the great veins and/or soft tissues. These observations show that the LBPP-induced increase in upper airway resistance that we recently described¹² was related to constriction of the pharynx. Taken together, these findings may have implications for the pathogenesis of UA obstruction in patients with OSA, particularly in those with co-existing edematous states. The very low coefficient of variation under control conditions in our 27 subjects also provides evidence of the high reproducibility of measurements UA-XSA using acoustic pharyngometry.

We limited our application of LBPP to 5 minutes because we found empirically during pilot studies that 5 minutes was a time beyond which some subjects began to feel uncomfortable from leg compression while maintaining constant body and head position during measurement of UA-XSA by acoustic pharyngometry. We did not assess the duration of the effect of LBPP on UA-XSA following deflation of the trousers. However, because there was a 15-minute washout period between conditions, and because there were no differences in baseline values for the control and LBPP conditions for any variable except for leg fluid volume, we can assume that

any potential carry over effect lasted less than 15 minutes. With respect to leg fluid volume, it was significantly less at baseline during LBPP than at baseline during control. However, since leg fluid volume fell after 1- and 5-min of LBPP, we cannot attribute the higher baseline fluid volume during control to a carry over effect of LBPP.

Although subjects and experimenters were not blinded to the control and LBPP conditions, measurements of leg fluid volume, neck circumference and UA-XSA are performed automatically, and are therefore not subject to observer interpretation.

The only other study to examine the effect of fluid shift from the legs on UA-XSA, apart from our present and previous ones¹², was performed by Shepard and colleagues⁸. They studied 10 patients with OSA and shifted fluid out of the legs by raising them 33° from the horizontal, and shifted fluid into the legs by applying venous occlusion tourniquets to the upper thighs for 10 minutes each. UA-XSA was assessed at baseline and at the end of these two 10-minute interventions by computed tomography. However, they did not measure either the amount of fluid displaced out of, or into the legs in response to these interventions; nor did they assess whether any fluid was displaced into or out of the neck. They observed a tendency for UA-XSA to decrease in response to leg raising and to increase in response to tourniquet application, but neither of these changes was significant. The reason why they did not find a significant reduction in UA-XSA in response to leg raising may be that the amount of fluid displaced was not sufficient to alter fluid volume in the nuchal structure or to cause neck distension or UA narrowing. For example, using radionuclide scintigraphy, it has been reported that leg raising reduces leg blood volume by 30-35%, or approximately 150 ml or less for both legs^{27, 28}. This is less than half the volume we displaced using LBPP of 40 mmHg. The mean 320 ml displacement of fluid from the legs by LBPP in our study is similar to the 240-360 ml that is displaced from

the legs of healthy subjects when moving from standing to the recumbent position, and so is liable to be physiologically and clinically relevant²⁹. It has also been shown, in healthy subjects, that LBPP displaces fluid into the upper body⁹ and increases central venous pressure¹⁰. Thus, it is possible that fluid influx into the jugular veins might displace the lateral pharyngeal walls medially and contribute to UA narrowing and obstruction to airflow³⁰.

Several observations suggest that fluid accumulation in the neck and peripharyngeal soft tissues might play a role in narrowing the UA and increasing its resistance to airflow. For instance, systemic vasodilatation in cats by sodium nitroprusside reduces pharyngeal volume and increases UA closing pressure, whereas systemic vasoconstriction does the opposite²⁹. In humans, topical application of the vasoconstrictor phenylephrine reduced UA resistance^{30,31}. In patients with OSA, surgical specimens from uvulopalatopharyngoplasty revealed vascular congestion and diffuse interstitial edema³³. In another study involving patients with OSA, peripharyngeal edema apparent on MRI scanning prior to therapy decreased following chronic application of CPAP³⁴. Two of the present observations support this concept by demonstrating that: 1) fluid displacement from the legs into the neck causes UA narrowing, and 2) there is a significant inverse correlation between changes in UA-XSA and in neck circumference after 1 minute of LBPP. However, this relationship was no longer significant after 5 minutes of LBPP, possibly because factors other than distension of the neck veins, such as edema formation, intervened during this time and contributed to this effect.

Obesity and increased neck circumference are important risk factors for OSA, but these only explain about 33% of the variance in the AHI². Additional factors that may contribute to severity of OSA could include alterations in UA sensory, reflex and motor control as well as variations in the bony structures surrounding the UA³⁵. The physiological data presented herein

suggest that fluid retention in general, and in the nuchal structures in particular might also predispose to UA obstruction. Redistribution of fluid from the lower extremities to the upper body upon assuming the recumbent position could narrow the UA overnight during sleep, especially in subjects with fluid retaining states. This might explain, in part, why OSA is more common in patients with heart and renal failure than in the general population^{4,36}. It may also help to explain the recent observation of Tang et al³⁷ that removal of 1.47 liters of fluid more during the night by nocturnal than by 24 hour peritoneal dialysis caused a 76% reduction in the frequency of obstructive apneas and hypopneas during sleep. These authors speculated that this effect was due to removal of excess fluid accompanied by a reduction in UA edema, although they did not make any measurements of UA properties. In any case, their data are compatible with ours in suggesting that fluid accumulation in the neck and UA structures can contribute to pharyngeal narrowing and collapse.

Acoustic pharyngometry assesses UA lumen size, but does not define the structures surrounding the lumen. In addition, because the sound waves are only transmitted through the mouth down the pharyngeal lumen below the velum, we could not evaluate the XSA of the retropalatal pharynx. Nevertheless, many studies using acoustic pharyngometry have shown consistently that the mean UA-XSA from the velum to the glottis in the awake state is narrowed in patients with OSA compared to those without OSA, in obese and non-obese patients alike, both while upright and supine^{24,38,39}. Furthermore, our recent demonstration that in healthy subjects, LBPP causes a large, 102% increase in UA resistance¹² indicates that the reduction in UA-XSA we observed is physiologically significant.

UA-XSA is, to some extent, lung volume dependent⁴⁰. However, since we demonstrated that EELV did not change significantly in response to LBPP (indeed, they tended to increase) ,

the decrease in UA-XSA we observed in response to LBPP cannot be explained by a reduction in lung volume.¹² These findings are consistent with those of Regnard et al⁴¹ who also showed that application of LBPP of 60 mm Hg caused no significant change in functional residual capacity or vital capacity in healthy subjects.

Since our measurements were performed while subjects were awake, the present finding may not be entirely applicable to the sleeping state. However, since the UA narrows at sleep onset owing to withdrawal of neural input to the pharyngeal dilator muscles, fluid displacement into the nuchal structures during sleep should cause an even greater degree of narrowing than during wakefulness. Our finding that LBPP causes UA narrowing does not necessarily indicate that fluid shift into the nuchal structures increases the propensity of the UA to collapse. Nevertheless, it does indicate that LBPP can increase the degree of obstruction to airflow in the UA. We did not perform sleep studies to ascertain whether subjects had OSA or not. However, it is likely that none or only a very small minority had OSA, since none of our subjects was obese, had a history of habitual snoring or daytime sleepiness, and were young (mean age of 39 years). In any case, future experiments will be required to determine whether there are differences in the effects of LBPP on UA-XSA between subjects with and without OSA.

In summary, the present data provide novel evidence in healthy, non-obese subjects that fluid displacement from the legs into the neck can constrict the UA lumen. Fluid displacement from the lower to the upper body while recumbent may therefore contribute to pharyngeal narrowing and predispose to its collapse during sleep in patients with OSA. This may be of even greater clinical relevance in edematous states. Further studies will be required to determine whether fluid shifts into and out of the neck facilitate, or alleviate, respectively, UA obstruction during sleep in patients with OSA.

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Figure legends

Figure 1. Tracing of upper airway cross-sectional area (UA-XSA) as a function of distance from the mouth in a representative subject. UA-XSA is the mean area between the velum and glottis as indicated by the arrows. Note that compared to baseline (black line, 2.83 cm²), lower body positive pressure application caused a reduction in UA-XSA after 1 minute (red line, 2.44 cm²) and 5 minute (blue line, 2.37 cm²).

Figure 2. Grouped data showing changes in upper airway cross-sectional area (UA-XSA) in response to lower body positive pressure (LBPP). The P-value for the time-treatment interaction from 2-way repeated measures ANOVA is <0.001. Compared to the control period, UA-XSA decreased significantly at both 1 and 5 minutes after applying LBPP. P-values shown in plots are adjusted for multiple comparisons by Tukey's test.

Figure 1

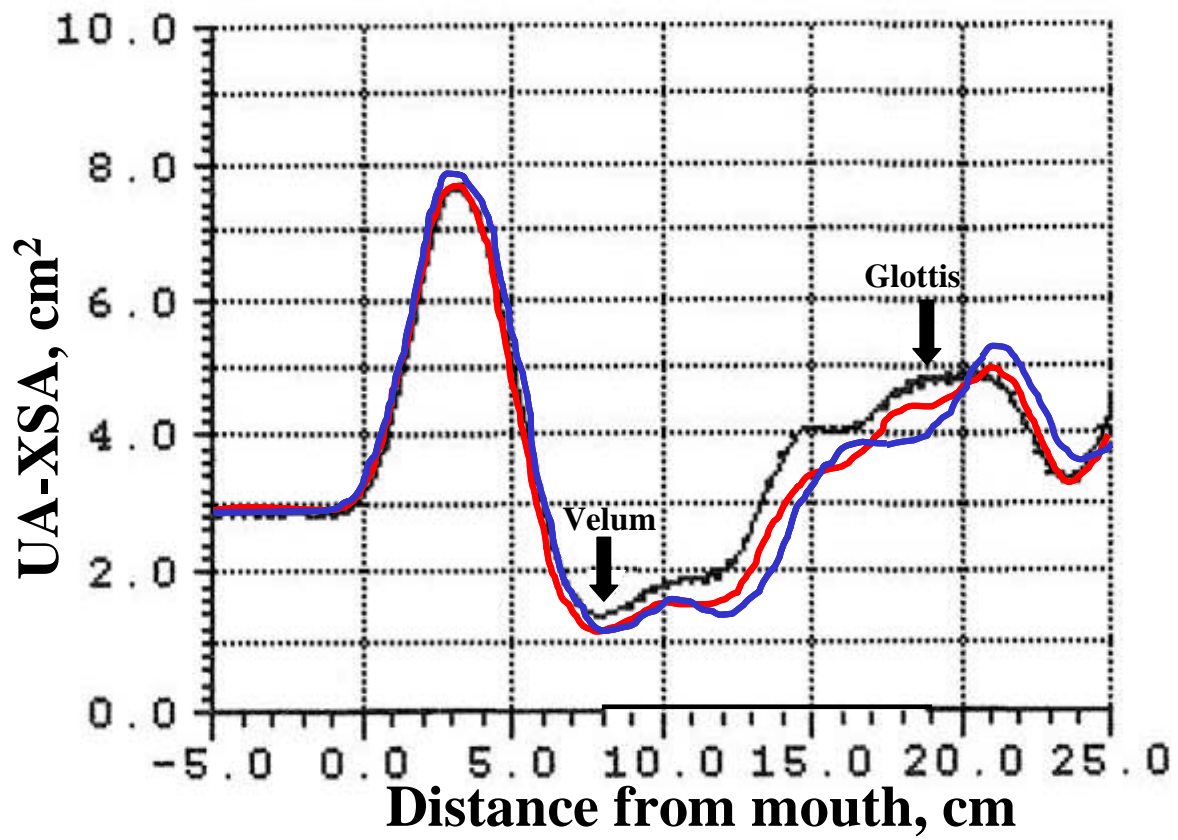


Figure 2

