



ORIGINAL ARTICLE

Displacement of the hyoid bone by muscle paralysis and lung volume increase: the effects of obesity and obstructive sleep apnea

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Work Performed: This work was conducted at Chiba University Hospital.

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Abstract

Study Objectives: Animal studies suggest a pivotal role of the hyoid bone in obstructive sleep apnea (OSA). We aimed to explore the role of the hyoid bone in humans by testing the hypotheses that muscle paralysis and lung volume (LV) changes displace the hyoid bone position particularly in people with obesity and/or OSA.

Methods: Fifty patients undergoing general anesthesia participated in this study (20 participants with nonobese, non-OSA; 8 people with nonobese OSA; and 22 people with obese OSA). Three lateral neck radiographs to assess the hyoid position (primary variable) and craniofacial structures were taken during wakefulness, complete muscle paralysis under general anesthesia, and LV increase under general anesthesia. LV was increased by negative extrathoracic pressure application and LV changes were measured with a spirometer. Analysis of covariance was used to identify statistical significance.

Results: Muscle paralysis under general anesthesia significantly displaced the hyoid bone posteriorly (95% CI: 1.7 to 4.6, 1.5 to 5.2, and 1.1 to 4.0 mm in nonobese non-OSA, nonobese OSA, and obese OSA groups, respectively), and this was more prominent in people with central obesity. LV increase significantly displaced the hyoid bone caudally in all groups (95% CI: 0.2 to 0.7, 0.02 to 0.6, and 0.2 to 0.6 mm/0.1 liter LV increase in nonobese non-OSA, nonobese OSA, and obese OSA groups, respectively). Waist-hip ratio was directly associated with the caudal displacement during LV increase.

Conclusions: The hyoid bone plays an important role in the pathophysiology of pharyngeal airway obstruction due to muscle paralysis and LV reduction, particularly in people with obesity.

Statement of Significance

Among the many characteristic craniofacial features of people with obstructive sleep apnea (OSA), caudal displacement of the hyoid bone has been repeatedly and consistently documented; however, the mechanisms are still yet unknown. This study is the first to evidence that the hyoid bone is displaced as a marker for changes of muscle activation and lung volume, as well as the balance of soft tissue volume for the craniofacial size. Based on the pathophysiological understanding of hyoid bone position, future studies should test the hyoid bone displacement as a possible diagnostic/prognostic indicator for OSA.

Clinical Trial: UMIN Clinical Trial Registry, https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=cR000022635&language=E, UMIN000019578

Key words: craniofacial aspects of OSA; obesity; OSA – pathogenesis; respiratory physiology; upper airway; lung volume

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Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive pharyngeal narrowing and closure during sleep, with both obesity and craniofacial abnormalities being important features associated with the presence and development of OSA [1, 2]. Pharyngeal airway size is determined by an interaction between neural regulation of upper airway muscle activity and structural properties of the pharyngeal airway [3, 4]. Among the many characteristic craniofacial features of people with OSA, the caudal displacement of the hyoid bone has been repeatedly and consistently documented, suggesting the importance of the hyoid bone in the OSA pathogenesis [5–7].

The hyoid bone is a horseshoe-shaped bone located within the soft tissue surrounding the pharyngeal airway between the mandible and the thyroid cartilage. Unlike most other vertebrates, the human hyoid bone does not articulate with any other bones. The position of the hyoid bone is suggested to be neurally determined by the muscle force vector between supra- and infra-hyoid muscles that attach to the hyoid bone [8–10]. These muscles are frequently admitted to inspiratory activity possibly producing anterior and caudal traction force on the hyoid bone and leading to its movement in synchrony with anterior movement of the tongue and caudal movement of the trachea and thyroid cartilage during inspiration [11, 12]. Active traction of the hyoid bone by vector forces produced by the infra- and supra-hyoid muscles appears to be one of the potential mechanisms of recovery from pharyngeal obstruction [11, 13]. This neural mechanism is presumably more active in people with OSA, where greater genioglossus muscle activity is evident during wakefulness [14]. In other words, the hyoid bone position could be a marker of the neurally mediated traction on the hyoid bone. This hypothesis can be tested by comparing the hyoid bone position before and during muscle paralysis under general anesthesia.

In addition to the neurally mediated traction of the hyoid bone discussed above, floating hyoid bone within soft tissue could also be displaced by nonmuscular passive forces derived from surrounding soft tissue [15, 16]. Relatively excessive soft tissue within the maxilla–mandible bony structure could shift the hyoid bone caudally, as well as narrow the pharyngeal airway in people with OSA [6, 17]. Furthermore, lung volume (LV) increase could displace the hyoid bone, as well as the trachea, caudally, which consequently could increase the longitudinal tension of the pharyngeal airway wall [18–22] and decrease the extra-luminal tissue pressure [15]. In fact, our research group confirmed stiffening of the passive pharyngeal airway by LV increase under general anesthesia and paralysis [23]. Notably, there was a body mass index (BMI) dependence of the LV influence on the pharyngeal collapsibility [23]. Lung inflation during sleep in people with morbidly obese OSA significantly improved the OSA severity [24]; however, the result was contradicted in another lung inflation study in people with less obese OSA [25]. At lower LV in people with obesity, contraction of the diaphragm with increased curvature is capable of producing a greater longitudinal tracheal traction force and displaces the hyoid bone more caudally. These factors suggest differences in the LV dependence of pharyngeal collapsibility and the hyoid bone position between obese and nonobese people with OSA. This nonmuscular passive mechanism could be tested by comparing the hyoid bone position before and during LV increase under

general anesthesia and muscle paralysis in people with obese and nonobese OSA.

Despite the possible roles of the hyoid bone position in OSA pathophysiology, no study has yet to explore the mechanical linkages between the hyoid bone position and the pharyngeal airway maintenance mechanisms, such as pharyngeal muscle activation and LV change. We hypothesized that muscle paralysis displaces the hyoid bone cranially and posteriorly, particularly in people with OSA (primary hypothesis-1); moreover, the LV increase displaces it caudally, particularly in people with obese OSA (primary hypothesis-2). We tested the hypotheses by measuring the hyoid bone position during wakefulness, general anesthesia with muscle paralysis, and LV increase under general anesthesia in male patients undergoing surgeries under general anesthesia.

Methods

Study population

The institutional review board of Chiba University Hospital (Chiba, Japan) approved this prospective study (G27029) and the study was registered in UMIN Clinical Trial Registry (UMIN000019578, October 30, 2015: https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=cR000022635&language=E). Written informed consent was obtained from each participant after the aim and potential risks of the study were fully explained. Subject enrollment in this prospective hypothesis testing study was terminated on March 2017. Inclusion criteria were adult male patients undergoing scheduled surgeries under general anesthesia at Chiba University Hospital and exclusion criteria were people with severe co-morbidities, upper airway abnormalities, severe COPD, and uncontrolled asthma. People with respiratory disturbance index (RDI) between 10 and 15 hr⁻¹ were excluded after the sleep study in order to clarify the differences between OSA and non-OSA groups.

Sleep study and study grouping before radiographic assessments

A sleep study was performed by a nocturnal portable monitor which measured respiratory airflow and SaO₂ (SAS2100, Nihon Kohden, Tokyo, Japan) in all patients with consent. An oximetry finger probe and nasal cannula were attached before sleep and removed on awakening. After checking quality of the recordings by A.K., respiratory and oximetry variables were calculated by a computer software (QP-021W, Nihon Kohden, Tokyo, Japan). Severity of OSA was quantified by RDI, frequency of desaturation 3% or more from the baseline, the percent of time spent at SaO₂ less than 90%, and lowest SaO₂. RDI was calculated by the frequencies of apneas and hypopneas with 3% or more desaturation per hour of the monitoring time. Apnea and hypopnea were determined by absence of airflow for 10 s or more and more than 50% decrease of the nasal pressure signal for 10 s or more, respectively. The participants were divided into three groups based on BMI and the results of the portable sleep study: participants with BMI less than 25 kg/m² and RDI equal to or less than 10 hr⁻¹ were denoted as the nOB-nOSA group; participants with BMI less than 25 kg/m² and RDI greater than 15 hr⁻¹ as the nOB-OSA group; and participants with BMI equal to or greater than 25 kg/m² and RDI greater than 15 hr⁻¹ as the OB-OSA group.

Lateral head and neck radiographs during wakefulness, general anesthesia with muscle paralysis, and LV increase under general anesthesia and paralysis

On the day of the surgery, lateral head and neck radiographs were obtained at three different conditions in the operating room in the supine position while maintaining the neutral head and neck position (no head elevation, with face straight up). An inverter-type mobile X-ray system (Sirius Star Mobile 130H, Hitachi Ltd, Tokyo, Japan) with a wireless digital radiography system (AeroDR1417, Konica Minolta Inc., Tokyo, Japan) was used to obtain high-quality digitized radiograph images with a constant source to image-receptor distance (150 cm) and a constant radiation setting (80 kV, 5 mAs, no removing scatter grid). A scale attached on the center of the sternum was used to obtain absolute values of the radiograph measurements. The mouth was kept closed with a chin strap. The head posture was maintained constant by adjusting the head angle between the operation table and a line connecting two small markers stuck on the side-face skin near the tragus and the corner of the eye immediately before each radiograph. First, a radiograph was taken at the end of quiet expiration during wakefulness (AW) and the second and third radiographs were taken during cessation of mechanical ventilation under general anesthesia and paralysis either with (AN-LV(+)) or without (AN) lung inflation which were randomly determined before the measurements. The quality of the images was confirmed for each radiograph by a diagnostic imaging workstation (CS-7, Konica Minolta Inc., Tokyo, Japan).

General anesthesia and lung inflation procedures

Under standard cardiorespiratory monitoring, general anesthesia was induced by intravenous infusion of fentanyl $2 \mu\text{g kg}^{-1}$ and propofol $1\text{--}2 \text{ mg kg}^{-1}$ and maintained by either continuous infusion of propofol or inhalation of desflurane. Rocuronium 1 mg kg^{-1} produced complete paralysis confirmed by a muscle relaxation monitor (TOF watch SX, Nihon Kohden Inc., Tokyo, Japan) throughout the experiment while the participant was ventilated through an anesthesia full-face mask with positive pressure through an anesthetic machine. The mechanical ventilation was ceased for 1 min to obtain lateral head and neck radiographs for the AN-LV(+) and AN conditions.

LV was increased by application of negative extrathoracic pressure up to $-50 \text{ cmH}_2\text{O}$ through a rigid plastic shell covering the anterior part of the thorax between axilla and ilium. An AN-LV(+) radiograph was taken after measuring the LV change by a spirometer connected to a tightly fitted full face mask at atmospheric pressure. To counteract the possibility of a closed airway during anesthesia and paralysis, the triple airway maneuver (mandible advancement, neck extension, and mouth opening) with anesthesiologist's two hands was performed to open the airway and allow oxygen to flow in order to increase LV during negative extra-thoracic pressure application. Airway opening and absence of mask leak were confirmed by progressive increase of spirometer tracing in response to the negative pressure application. The triple airway maneuver was applied during LV change, but was released for the radiographs.

Analyses of lateral head and neck radiographs

Using an image enhancement processing software (CS-7, Konica Minolta Inc., Tokyo, Japan), digitized radiographic

images were modified to obtain clear boundaries of targeted structures and craniofacial dimensions were measured by the investigator (A.K.) using a cephalometric analysis program (WinCeph version 10, Rise Corporation, Miyagi, Japan), without prior knowledge of the anthropometric and sleep characteristics (Figure 1). To systematically assess the direction and amount of the hyoid bone movement, we defined a coordinate on the lateral radiograph with anterior–posterior (x-axis) and cranial–caudal (y-axis) axes. Frankfort plane was set as the x-axis, and a line perpendicular to the Frankfort plane through the nasion (N) was set as the y-axis (Figure 1). Using the coordinate superimposed on the radiographic images, longitudinal and transverse distances of the hyoid bone to the origin (L-Hyoid and T-Hyoid, respectively) were defined and measured. Due to variable LV increase among the participants, these variables were normalized by a unit LV change (0.1 liter), L-Hyoid/LV and T-Hyoid/LV, respectively, in order to assess the effects of LV increase on the hyoid bone position. As commonly measured in scientific studies and for clinical purposes, the distance between the hyoid and the mandibular plane line (MP-H) was also measured. In addition to the hyoid bone position analyses, other cephalometric variables such as pharyngeal airway spaces, craniofacial bony structures, and soft tissue sizes were also assessed. Narrowest pharyngeal airway spaces above and below the tip of the uvula were measured as the upper pharyngeal airway space (U-PAS) and lower pharyngeal airway space (L-PAS), respectively. Relative position of the mandible to the maxilla was assessed by the angle between the lines subspinale to nasion and supramentale to nasion. Maxillary length and mandibular length were defined as distances between the medial condylar point of the mandible and subspinale, and medial condylar point of the mandible and porion, respectively. Total tongue cross-sectional area was outlined by the dorsum of the tongue surface and lines that connect tongue tip, retrognathion, and base of epiglottis. Tongue cross-sectional area below the mandibular plane line was also measured. To assess constancy of head and neck position during the radiography for each participant, a head and neck angle formed by the x-axis and a line connecting the posterior edge of the odontoid process and posterior inferior tip of the third cervical vertebra (head/neck angle) was measured.

Statistical methods

The primary outcome was change of the L-Hyoid after interventions such as induction of general anesthesia with muscle paralysis ($\Delta\text{L-Hyoid}$) and LV increase ($\Delta\text{L-Hyoid/LV}$). Since no previous study measured L-Hyoid, we calculated a sample size by using the reported values of distance between the hyoid and the mandible plane (MP-H: $23.4 \pm 5.8 \text{ mm}$) although the MP-H was obtained by a different radiographic technique and in a different posture from this study [5]. In our preliminary study of 26 people with awake OSA, changes of the LV from residual capacity to total lung capacity resulted in an MP-H change of 8.8 mm on average. We expected a much smaller LV change in this study because our previous experiment revealed only a 0.72 liter LV increase by the same technique [23]. In sample size calculation, a pathophysiologically meaningful change was considered to be 50% of MP-H change (4.4mm) possibly produced by maximum voluntary LV change in the preliminary experiment. The minimum sample size was calculated as 20 participants for each group assuming $\alpha = 0.05$ (two-tailed), $\beta = 0.8$ (SigmaPlot 12.0,

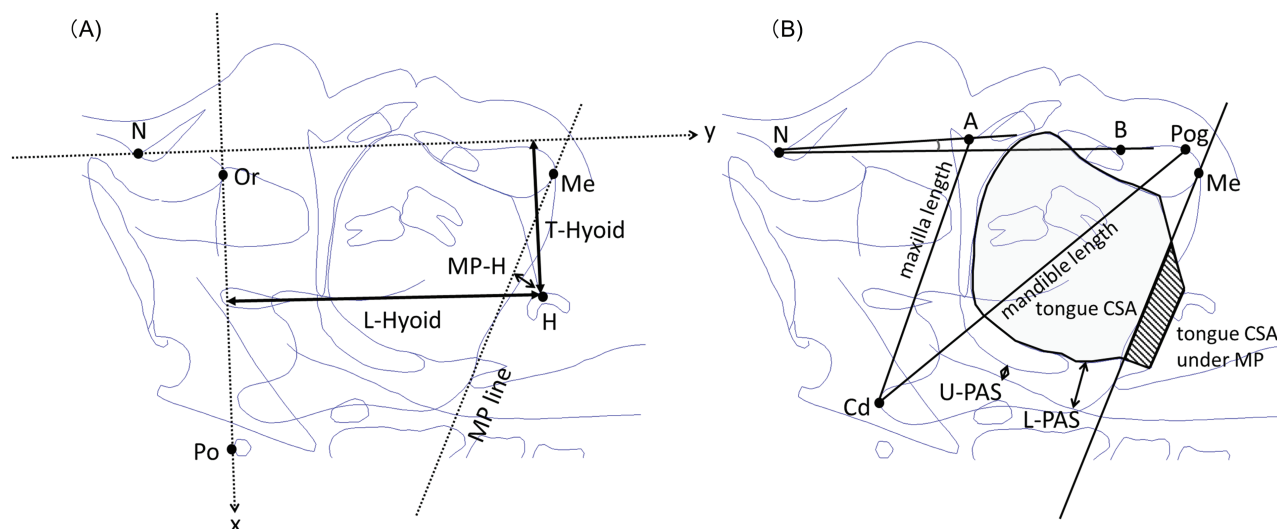


Figure 1. Definitions of the cephalometric variables. (A) Coordinate on the cephalogram with transverse and longitudinal axes was defined with using the Frankfort plane (a line connecting Po and Or) as the transverse axis, and a line perpendicular to Frankfort plane through the nasion (N) as the longitudinal axis. Using the coordinate, the longitudinal and transverse distances of the hyoid bone to the origin were measured as the L-Hyoid and T-Hyoid, respectively. (B) Narrowest pharyngeal airway spaces above and below the tip of the uvula were measured as the U-PAS and L-PAS, respectively. Relative position of the mandible to the maxilla was assessed by ANB angle (angle between the lines A to N and B to N). Maxillary length (Cd-A) and mandibular length (Cd-Po) were defined as distances between the Cd and A, and Cd and Po, respectively. Total tongue cross-sectional area was outlined by the dorsum of the tongue surface and lines that connect tongue tip, retrognathion, and base of epiglottis. Shaded area indicates tongue cross-sectional area below the MP line. A = subspinale; B = supramentale; Cd = medial condylar point of the mandible; H = hyoid bone; Me = menton; MP = mandibular plane; N = nasion; Or = orbitale; Po = porion; Pog = pogonion.

Systat Software Inc., Point Richmond, CA). Accordingly, we set the sample size to be 22 participants for each group.

To assess displacements of the hyoid bone in response to induction of general anesthesia with muscle paralysis and LV increase (primary variables: Δ L-Hyoid and Δ L-Hyoid/LV), intergroup and intragroup comparisons were performed through analysis of a covariance (ANCOVA) model, taking into account the variation caused by using the waist/hip ratio and neck circumference as covariates. As a secondary analysis, we specifically focused on possible changes of the upper and lower pharyngeal airway spaces (Δ U-PAS and Δ L-PAS, respectively) and tongue cross-sectional area (Δ tongue-CSA) in response to induction of general anesthesia with muscle paralysis and LV increase. Statistical differences of patient characteristics and radiographic variables were assessed by analysis of variance (ANOVA) and group comparisons were performed by Turkey's test for multiple comparisons. A value of $p < 0.05$ was considered statistically significant, and all p values were two-sided. Statistical analyses were performed using SAS Ver. 9.4 (SAS Institute, Cary, NC).

Results

The study was successfully performed in 50 patients, but terminated before completing the predetermined sample size particularly in nOB-OSA group due to difficulty in recruiting nOB-OSA participants during the scheduled study period. However, we considered this analysis of the 50 participants as meaningful, as a result of this prospective hypotheses-testing pathophysiological study. Table 1 presents significant differences of background participant characteristics and results of the portable sleep study between the groups in accordance with our study protocol. As shown in Table 2, LV increase was successfully performed in all participants but varied among the participants

(794 ± 312 ml). The maximum level of the negative pressure application was limited particularly in participants with obesity because the shell was filled with the thorax of the participant.

Possible confounding factors associated with the primary variables

The head/neck angle did not statistically differ between the three conditions when the radiographs were taken (95% CI: 93.6 to 98.8, 93.3 to 98.4, and 93.5 to 98.6 degree during wakefulness, general anesthesia with muscle paralysis, and LV increase under anesthesia and paralysis, respectively), suggesting constancy of head and neck position during radiography within the participants. Table 3 presents baseline radiographic variables during wakefulness which were not different between the groups. Table 4 presents results of univariate correlation analyses between the hyoid bone displacement and anthropometric and sleep characteristics. Besides the BMI and RDI used for the classifications in this study, waist/hip ratio and neck circumference, which characterize obesity pattern, were significantly associated with the primary variables and these possible confounding factors were used as covariates for the ANCOVA in this study population.

Results related to the primary hypothesis-1: influences of muscle paralysis and general anesthesia on hyoid positions and other radiographic variables

The Δ L-Hyoid (primary variable) ranged widely (-0.5 ± 5.2 mm, -16 to 9 mm) and direction of the longitudinal hyoid bone displacement was significantly associated with severity of RDI ($r = -0.404$, $p = 0.004$, $n = 50$) (Figure 2, left). Cranial hyoid bone displacement was more commonly observed in people with OSA

Table 1. Background participant characteristics and results of the portable sleep study for each of the groups

	All participants	nOB-nOSA	nOB-OA	OB-OA	P
Number of participants	50	20	8	22	
Age (year)	59.3 ± 12.8	56.9 ± 15.4	67.9 ± 5.4	58.5 ± 11.1	0.102
Height (cm)	168.5 ± 6.2	170.3 ± 7.1	168.0 ± 5.1	166.9 ± 5.5	0.146
Weight, kg	71.8 ± 13.5	63.3 ± 7.1	64.0 ± 6.2	82.3 ± 12.7	<0.0001
BMI, kg/m ²	25.3 ± 4.5	21.8 ± 2.0	22.6 ± 1.4	29.4 ± 3.4	<0.0001
Neck circumference (cm)	38.4 ± 3.1	36.1 ± 2.2	37.1 ± 1.2	40.9 ± 2.5	<0.0001
Waist circumference (cm)	90.1 ± 12.1	80.5 ± 6.8	86.9 ± 6.8	99.9 ± 9.5	<0.0001
Hip circumference (cm)	95.9 ± 8.9	89.7 ± 5.5	93.9 ± 4.7	102.4 ± 8.2	<.0001
Waist/hip ratio	0.936 ± 0.059	0.897 ± 0.049	0.925 ± 0.044	0.976 ± 0.047	<.0001
Mallampati (I/II/III/IV)	6, 4, 9, 31	6, 3, 5, 6	0, 0, 0, 8	0, 1, 4, 17	0.002
RDI, events/hr	21.8 ± 18.2	4.7 ± 2.6	20.8 ± 5.5	37.6 ± 14.7	<0.0001
3% ODI, events/hr	17.2 ± 15.0	4.2 ± 2.6	15.1 ± 4.0	29.8 ± 13.7	<0.0001
CT90, %	3.0 ± 5.7	0.1 ± 0.2	0.9 ± 0.9	6.4 ± 7.2	<0.0001
Nadir SaO ₂ , %	92.7 ± 2.6	94.6 ± 1.2	93.4 ± 0.9	90.7 ± 2.4	<0.0001
Lowest SaO ₂ , %	84.4 ± 7.8	90.5 ± 3.5	82.8 ± 7.8	79.5 ± 7.1	<0.0001

Values are means ± SD. Group differences were assessed by ANOVA.

nOB-nOSA = people with non-obese non-OA; nOB-OA = people with non-obese OA; OB-OA = people with obese OA; ODI = oxygen desaturation index; CT₉₀ = percent of time spent SaO₂ < 90%; SaO₂ = arterial oxygen saturation; 3%ODI = 3% oxygen desaturation index.

Table 2. Baseline radiographic variables during wakefulness for each of the patient groups

Lateral radiograph during wakefulness	All participants	nOB-nOSA	nOB-OA	OB-OA	P
ANB angle (degree)	4.4 ± 3.1	4.4 ± 2.6	5.1 ± 3.3	4.3 ± 3.6	0.91
maxilla length (mm)	89.1 ± 6.0	90.7 ± 4.8	86.6 ± 8.3	88.6 ± 6.0	0.25
mandible length (mm)	122 ± 7.9	123 ± 7.4	118 ± 12.8	122 ± 6.0	0.27
L-Hyoid (mm)	99.9 ± 8.6	99.3 ± 5.6	98.1 ± 15.0	101 ± 8.0	0.47
T-Hyoid (mm)	52.3 ± 16.1	50.5 ± 16.8	52.6 ± 15.2	54.0 ± 16.3	0.78
MP-H (mm)	16.6 ± 6.3	14.2 ± 4.0	18.0 ± 7.7	18.3 ± 7.0	0.16
U-PAS (mm)	5.4 ± 3.1	5.3 ± 2.5	5.1 ± 3.8	5.7 ± 3.5	0.79
L-PAS (mm)	11.7 ± 5.1	11.5 ± 4.2	10.5 ± 4.5	12.3 ± 6.0	0.53
tongue CSA (cm ²)	3300 ± 387	3212 ± 317	3170 ± 594	3428 ± 331	0.052
tongue CSA under MP (cm ²)	603 ± 229	538 ± 205	630 ± 318	653 ± 210	0.19

Values are means ± SD. Group differences were assessed by ANOVA.

ANB = angle between the lines subspinale to nasion and supramentale to nasion; CSA = cross-sectional area; L-Hyoid = longitudinal distance of the hyoid bone to the origin; L-PAS = lower pharyngeal airway space; MP-H = distance from the mandibular plane to the hyoid bone; nOB-nOSA = people with nonobese non-OA; nOB-OA = people with non-obese OA; OB-OA = people with obese OA; T-Hyoid = transverse distance of the hyoid bone to the origin; U-PAS = upper pharyngeal airway space.

See [Figure 1](#) for definitions of the radiographic variables.

with RDI greater than 20 hr⁻¹ (14 out of 20 patients), whereas caudal hyoid bone displacement was more common in people with normal or less severe OA (19 out of 30 patients) as clearly illustrated in [Figures 2](#) and [3](#) (Fisher exact test: $p = 0.042$, $n = 50$). Similar indirect association was noted between Δ tongue CSA under MP and RDI ($r = -0.441$, $p = 0.001$, $n = 50$; [Figure 2](#), right).

Results of the ANCOVA for the Δ L-Hyoid between AW and AN indicated no significant differences among the groups ($p = 0.726$) and within the group (95% CI: -3.0 to 2.5, -2.8 to 4.3, and -3.9 to 1.6 mm in nOB-nOSA, nOB-OA, and OB-OA groups, respectively; [Table 5](#)). In contrast, the ANCOVA for the Δ T-Hyoid between AW and AN revealed significant increase in all groups (95% CI: 1.7 to 4.6, 1.5 to 5.2, and 1.1 to 4.0 mm in nOB-nOSA, nOB-OA, and OB-OA groups, respectively), whereas no significant group difference was indicated ($p = 0.815$).

Muscle paralysis and anesthesia induction significantly narrowed the pharyngeal airway space in all groups and no group difference was indicated ([Table 5](#)). Δ U-PAS and Δ L-PAS were not significantly associated with Δ T-Hyoid between AW and AN ($p = 0.955$, 0.958 , respectively, $n = 50$). The tongue CSA

significantly increased with muscle paralysis and general anesthesia suggesting tongue musculature volume shift from lateral to anteroposterior direction. The tongue musculature was significantly displaced to the submandibular region in nOB-nOSA and nOB-OA groups, but not in the OB-OA group. The Δ tongue CSA under MP between AW and AN was significantly associated with the Δ L-Hyoid ($r = 0.573$, $p < 0.001$, $n = 50$).

Results related to the primary hypothesis-2: influences of LV increase under general anesthesia on hyoid positions and other radiographic variables

As demonstrated in [Figure 4](#), LV increase under general anesthesia and muscle paralysis displaced the hyoid bone and the tongue musculature caudally, whereas no anteroposterior hyoid bone displacement was observed. The already closed pharyngeal airway remained closed even during LV increase. The ANCOVA analyses revealed caudal hyoid bone displacement (95% CI: 0.2 to 0.7, 0.02 to 0.6, and 0.2 to 0.6 mm/0.1 liter LV increase in nOB-nOSA, nOB-OA, and OB-OA groups, respectively), whereas no

Table 3. Lung volume change in response to application of negative extra-thoracic pressure or each of the patient groups

	All participants	nOB-nOSA	nOB-OSA	OB-OSA	P
Extrathoracic pressure (cmH ₂ O)	30.5 ± 13.7	39.4 ± 13.9	32.6 ± 14.8	21.7 ± 6.0	0.0002
Lung volume change (ml)	794 ± 312	910 ± 311	841 ± 95	671 ± 327	0.16

Values are means ± SD. Group differences were assessed by ANOVA.

nOB-nOSA = people with non-obese non-OSA; nOB-OSA = people with non-obese OSA; OB-OSA = people with obese OSA.

Table 4. Results of univariate correlation analyses between the hyoid bone displacement and background variables

n = 50	Wakefulness to general anesthesia with muscle paralysis				Lung volume increase under general anesthesia with muscle paralysis			
	ΔL-Hyoid		ΔT-Hyoid		ΔL-Hyoid/LV		ΔT-Hyoid/LV	
	r	P	r	P	r	P	r	P
Age	-0.032	0.826	0.028	0.85	-0.098	0.5	-0.021	0.886
BMI	-0.451	0.001	-0.301	0.034	0.161	0.263	0.063	0.665
Neck circumference	-0.352	0.012	-0.235	0.1	0.026	0.858	0.065	0.656
Waist/hip ratio	-0.375	0.007	-0.281	0.048	0.312	0.027	0.218	0.128
RDI	-0.404	0.004	-0.23	0.107	-0.029	0.839	-0.065	0.656

Values are correlation coefficient (*p* value) obtained by Pearson correlation analyses.

ΔL-Hyoid = the amount of caudal displacement of the hyoid bone by induction of general anesthesia and muscle paralysis; ΔL-Hyoid/LV = change of longitudinal distance of the hyoid bone to the origin per 0.1 liter lung volume increase; ΔT-Hyoid = the amount of posterior displacement of the hyoid bone by induction of general anesthesia and muscle paralysis; ΔT-Hyoid/LV = change of transverse distance of the hyoid bone to the origin per 0.1 liter lung volume increase.

significant group difference was identified ($p = 0.776$; [Figure 5](#), [Table 5](#)). Notably, the ANCOVA identified the waist/hip ratio to be a significant confounding factor for the ΔT-Hyoid/LV ($p = 0.001$). The amount of the ΔL-Hyoid/LV was directly associated with the waist/hip ratio ($r = 0.312$, $p = 0.03$, $n = 50$; [Figure 5](#)) and the Δtongue CSA under MP/LV ($r = 0.679$, $p < 0.001$, $n = 50$). No significant change of the ΔT-Hyoid/LV was indicated by the ANCOVA.

Discussion

This is the first study which demonstrates hyoid bone displacement with anesthesia and muscle paralysis and subsequent LV increase. Consistent with pharyngeal airway narrowing during muscle paralysis and anesthesia, the hyoid bone was posteriorly displaced, but its longitudinal movements varied and were associated with severity of obesity and OSA. LV increase caudally displaced the hyoid bone regardless of the severity of BMI and OSA, and the waist/hip ratio was directly associated with the amount of caudal hyoid bone displacement. The longitudinal hyoid bone movement was significantly associated with changes of the tongue volume at submandible region. These results strongly suggest the hyoid bone position as a marker for changes of upper airway muscle activation and longitudinal pharyngeal wall tension due to LV change as well as the balance between soft tissue volume and craniofacial size.

Limitations of the study

Clearly, this study has many methodological limitations. First, complete muscle paralysis under general anesthesia differs from the reduction of upper airway muscle activity during sleep [26, 27]. Therefore, the results do not directly reflect the conditions of sleeping humans but should be able to clarify

fundamental roles of the upper airway muscle activation in the maintenance of the pharyngeal airway patency. Secondly, distribution of forces experimentally produced by negative extra-thoracic pressure application for increase of the LV in this study would significantly differ from that produced by contraction of the chest wall muscles. The difference would also be significantly influenced by obesity as indicated by smaller LV increase in response to negative extra-thoracic pressure in obese OSA group. Thirdly, the initial LV and the amount of LV reduction by induction of general anesthesia and paralysis were not measured and controlled [28]. In fact, the functional residual capacity is reported to decrease by more than 1 liter in people with obesity immediately after induction of general anesthesia; consequently, this study would have only reversed part of the LV reduction (0.67 liter) [29]. Accordingly, the changes of hyoid bone position from wakefulness to general anesthesia with muscle paralysis are the sum of muscle paralysis and LV reduction and would be more significant in people with obesity. Fourthly, the amount of LV increase was not controlled and significantly differed between participants as evident in [Table 2](#). Since no difference in variation was observed between groups, intergroup comparisons were possible. Potential nonlinearity of LV dependence of the hyoid bone displacement would result in inaccurate quantitative estimation of the effect. Fifthly, the sample size for the nOB-OSA group is insufficient, and therefore comparisons between nOB-OSA and other groups are underpowered. We tried to minimize this limitation by using ANCOVA. Sixthly, we did not study patients with RDI between 10 and 15 hr⁻¹ who would be habitual snorers with less apnea. Although responses to muscle paralysis and LV increase would be intermediate between those in the nOSA and OSA as indicated by [Figure 2](#), future studies need to include this unique population. Lastly, we used neither a three-dimensional imaging technique nor a lateral cephalogram technique both of which are commonly used to characterize

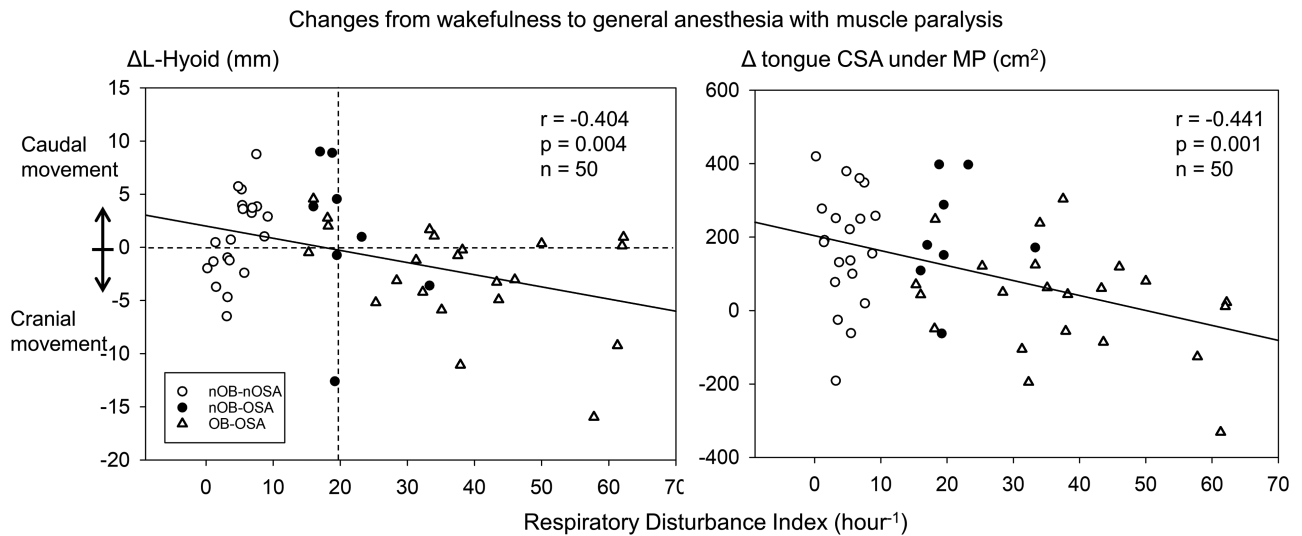


Figure 2. Relationships between respiratory disturbance index and Δ L-Hyoid (left panel), and Δ tongue CSA under MP (right panel) from wakefulness to general anesthesia and muscle paralysis. Pearson's correlation analysis was performed. Values are correlation coefficient, p value, and the number of participants. Δ L-Hyoid = the amount of caudal displacement of the hyoid bone by induction of general anesthesia and muscle paralysis; Δ tongue CSA under MP = the amount of increased tongue cross-sectional area under mandibular plane by induction of general anesthesia and muscle paralysis.

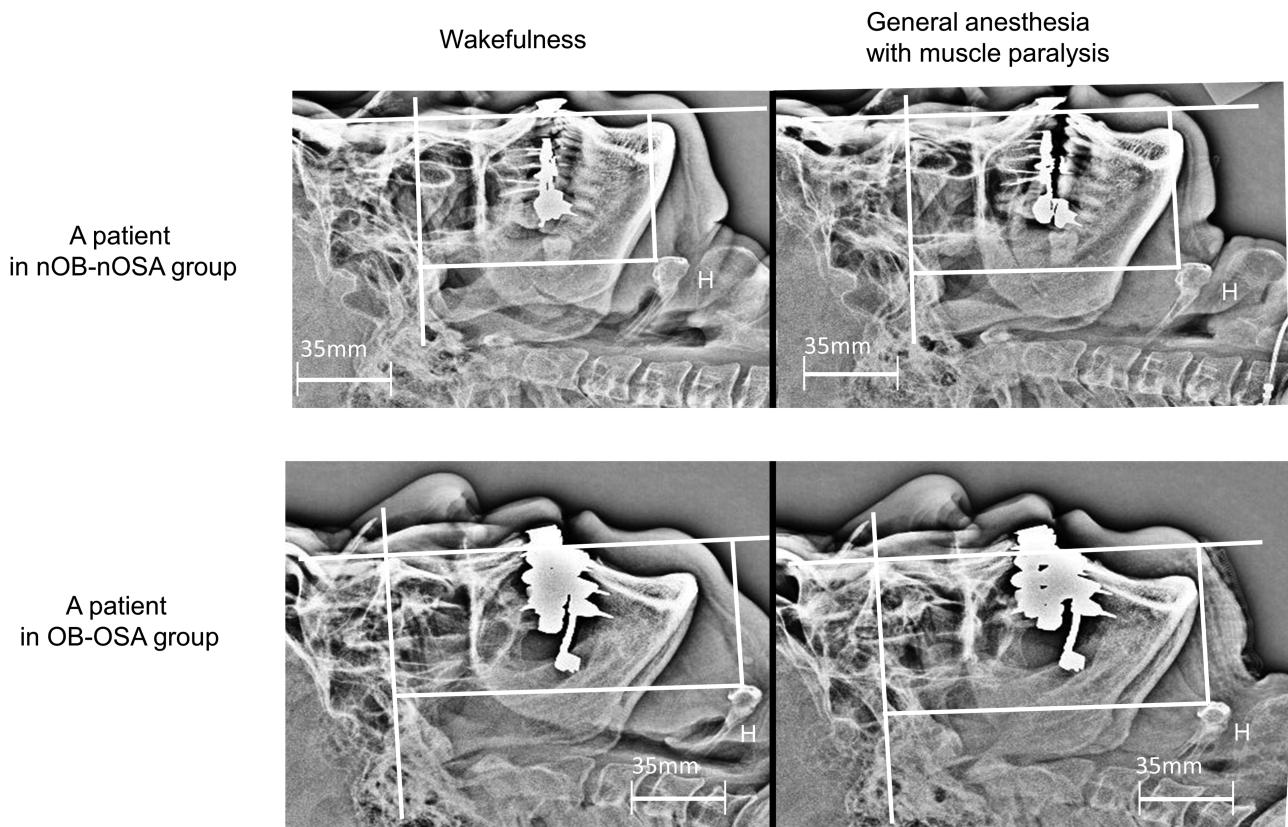


Figure 3. Lateral head and neck radiographs during wakefulness and during muscle paralysis under general anesthesia in a participant of non-obese and non-OSA (nOB-nOSA) group (upper panel) and a participant of obese and OSA (OB-OSA) group (lower panel). (Upper panel) In this 58-year-old male patient with BMI 23.7 kg/m^2 , and RDI 7.5 hr^{-1} , the hyoid bone was posteriorly (6.0 mm) and cranially (8.8 mm) displaced during general anesthesia with muscle paralysis. Note the increase of submandible tongue CSA and reduction of posterior pharyngeal airway space. (Lower panel) In this 66-year-old male patient with BMI 26.9 kg/m^2 and RDI 37.9 hr^{-1} , the hyoid bone was posteriorly (3.7 mm) and caudally (11.1 mm) displaced during general anesthesia with muscle paralysis. Note the reduction of submandible tongue CSA and reduction of posterior pharyngeal airway space. CSA = cross-sectional area; nOB-nOSA = non-obese and non-OSA; OB-OSA = obese and OSA; OSA = sleep-disordered breathing.

the craniofacial structures, and therefore, the accuracy of our craniofacial measurements might be questioned. To improve and assure accuracy of the measurements, the head posture

was checked immediately before each radiograph by measuring the head angle relative to the operation table and the mouth opening was prevented by using a chin strap. Furthermore, we

Table 5. Results of an analysis of variance (ANCOVA) analyses for assessing craniofacial responses to induction of general anesthesia with muscle paralysis with and without lung volume increase

Measurement conditions and craniofacial variables		Adjusted mean value (95% confidential interval)			Group difference p value	
		nOB-nOSA	nOB-OSA	OB-OSA		
AW control position	L-Hyoid (mm)	100 (94.1 to 104)	98.1 (91.6 to 105)	101 (96.3 to 106)	0.755	
	T-Hyoid (mm)	54.8 (45.8 to 63.8)	55.4 (43.6 to 67.1)	49.0 (39.9 to 58.0)	0.673	
changes (Δ) from AW to AN-LV(-)	Δ L-Hyoid (mm)	-0.26 (-3.0 to 2.5)	0.77 (-2.8 to 4.3)	-1.14 (-3.9 to 1.6)	0.726	
	Δ T-Hyoid (mm)	3.1 (1.7 to 4.6)*	3.3 (1.5 to 5.2)*	2.5 (1.1 to 4.0)*	0.815	
	Δ MP-H (mm)	-1.3 (-3.6 to 1.0)	-1.5 (-4.5 to 1.5)	-3.2 (-5.6 to -0.9)*	0.569	
	Δ U-PAS (mm)	-4.2 (-6.0 to -2.4)*	-4.8 (-7.2 to -2.5)*	-5.8 (-7.6 to -4.0)*	0.58	
	Δ L-PAS (mm)	-9.0 (-11.5 to -6.5)*	-9.3 (-12.6 to -6.0)*	-9.6 (-12.1 to -7.1)*	0.96	
	Δ tongue CSA (mm ²)	218 (95 to 341)*	285 (124 to 445)*	263 (139 to 387)*	0.768	
	Δ tongue CSA under MP (mm ²)	155 (68 to 242)*	194 (81 to 307)*	50 (-37 to 138)	0.165	
	changes (Δ) from AN-LV(-) to AN-LV(+) (per 0.1 liter LV increase)	Δ L-Hyoid/LV (mm)	0.4 (0.2 to 0.7)**	0.3 (0.02 to 0.6)**	0.4 (0.2 to 0.6)**	0.776
		Δ T-Hyoid/LV (mm)	0.20 (-0.03 to 0.4)	0.004 (-0.3 to 0.3)	0.1 (-0.1 to 0.4)	0.564
		Δ MP-H/LV (mm)	0.2 (0.03 to 0.4)**	0.1 (-0.2 to 0.3)	0.2 (0.02 to 0.4)**	0.44
Δ U-PAS/LV (mm)		0.1 (-0.06 to 0.2)	0.03 (-0.1 to 0.2)	-0.1 (-0.24 to 0.01)	0.232	
Δ L-PAS/LV (mm)		-0.2 (-0.4 to 0.1)	-0.10 (-0.4 to 0.2)	-0.3 (-0.5 to -0.1)**	0.566	
Δ tongue CSA/LV (mm ²)		17 (-3 to 36)	4 (-22 to 29)	5 (-14 to 25)	0.652	
Δ tongue CSA under MP/LV (mm ²)		15 (6 to 23)**	8 (-3 to 19)	13 (5 to 22)**	0.596	

Between-groups and within-group comparisons were performed by the ANCOVA model with taking into account the variation caused by using the waist/hip ratio and neck circumference as covariates.

* $p < 0.05$ versus AW; † $p < 0.05$ versus AN.

AW = wakefulness; AN = general anesthesia with muscle paralysis without lung volume increase; AN-LV(+) = general anesthesia with muscle paralysis with lung volume increase; Δ = difference between the conditions; Δ L-Hyoid = the amount of caudal displacement of the hyoid bone; Δ MP-H = the amount of hyoid bone displacement relative to the mandibular plane; Δ T-Hyoid = the amount of posterior displacement of the hyoid bone; Δ L-PAS = the amount of increase of lower pharyngeal airway space; Δ U-PAS = the amount of increase of upper pharyngeal airway space; Δ tongue-CSA = the amount of increase of tongue cross-sectional area; MP = mandibular plane; nOB-nOSA = people with non-obese non-OSA patients; nOB-OSA = people with non-obese OSA; OB-OSA = people with obese OSA. See Figure 1 for definitions of radiographic variables.

used a digitized radiography technique that increases the accuracy of determining boundaries of the soft tissue and bony structures. In fact, we confirmed no difference in the craniofacial variables for the three radiographs taken in this study.

Hyoid bone and muscle activation

Changes of the hyoid bone position after induction of general anesthesia and muscle paralysis mainly reflect activation of the supra- and infra-hyoid muscles (neurally mediated caudal traction of the hyoid bone). In accordance with the previous study [30], the hyoid bone was posteriorly displaced in response to induction of general anesthesia and muscle paralysis. This would be the result of abolition of wakeful genioglossus and suprahyoid muscle activity. Interestingly, changes of the anteroposterior hyoid bone position were not associated with narrowing of the retroglossal or retropalatal airways. This suggests that although the anteroposterior hyoid position is possibly a marker of pharyngeal dilator muscle activity, the pharyngeal airway space is influenced by both neural and mechanical factors.

Dependency of the longitudinal hyoid bone displacement on severity of OSA found in this study has never been documented in the literature. Interestingly, Lim et al., orthopedic surgeons, recently alerted the use of the hyoid bone position as a surgical landmark for the C3 cervical level because of variable and significant hyoid bone displacement by induction of general anesthesia and paralysis [31]. They found no significant association between the degree of the hyoid bone displacement and gender, obesity, and age. We consider that the association between the

longitudinal hyoid bone position and the OSA severity does not mean a causal relationship but rather reflects possible increased activity of the infra-hyoid muscles during wakefulness as evidenced in animal studies which demonstrated electrical stimulation of the infra-hyoid muscles to decrease the upper airway closing pressure [32]. However, this speculation needs to be tested by assessing the magnitude of infra- and supra-hyoid muscle activities in people with OSA in future studies.

Hyoid bone and LV change

In people with OSA, we previously reported that a 0.72 liter increase of the LV decreased the velopharyngeal closing pressures by 1.2 cmH₂O [23]. Although this suggests mechanical linkage between the lung and the pharynx, no human study has provided its evidence. Recently, in anesthetized rabbits spontaneously breathing through tracheostomy, Amatoury et al. demonstrated that caudal tracheal displacement resulted in smaller caudal hyoid bone displacement (approximately 20% of the tracheal displacement) and proportional reduction of extraluminal tissue pressure [15]. Although the magnitude of hyoid bone displacement during lung inflation appears to be small in our study, the observed hyoid bone displacement (0.4 mm longitudinal hyoid bone displacement in response to 100 ml LV increase) would correspond to 2 mm tracheal displacement per 100 ml LV increase according to the Amatoury's findings [15]. The hyoid bone position would reflect the magnitude of mechanical linkage between the lung and the pharyngeal airway. The results of the present study are the first to provide direct

Lung volume increase under general anesthesia

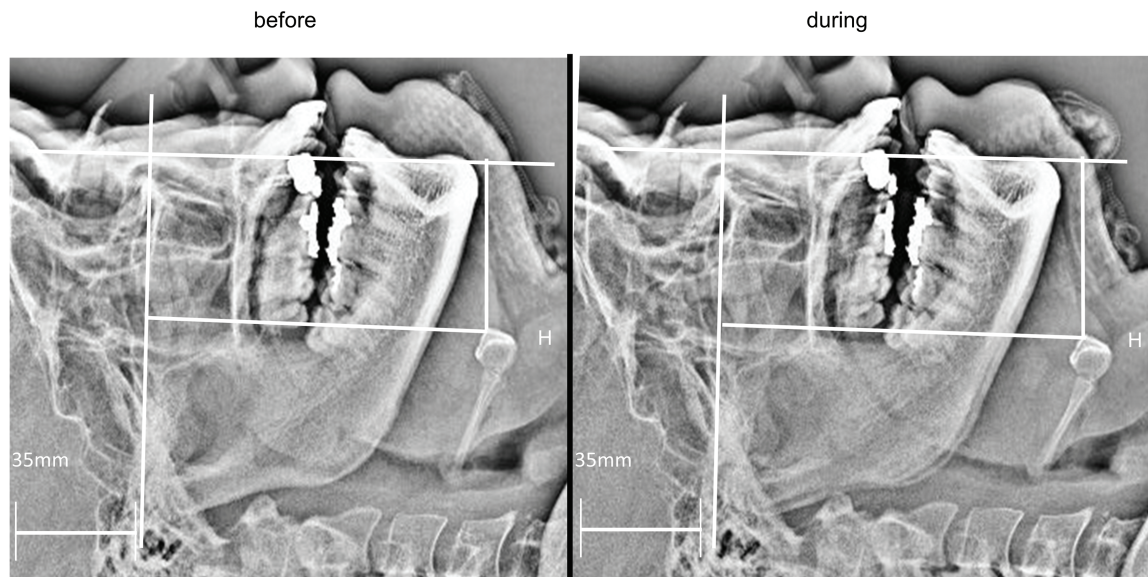


Figure 4. Lateral head and neck radiographs before and during LV increase under general anesthesia with muscle paralysis in a participant of OB-OSA group (46-year-old male patient with BMI 26.1 kg/m² and RDI 16 hr⁻¹). Note 1 liter LV increase under general anesthesia and paralysis caudally displaced the hyoid bone by 6.1 mm. OB-OSA = obese and OSA.

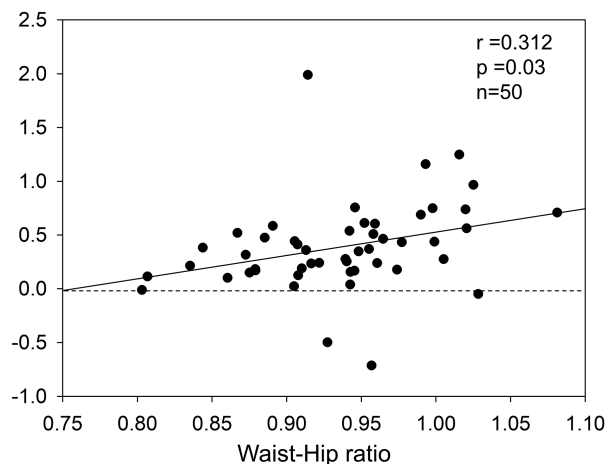
 Δ L-Hyoid/LV (mm/0.1 liter LV increase)

Figure 5. Relationship between the amount of the Δ L-Hyoid/LV and waist/hip ratio. Pearson's correlation analysis indicates direct association between them. Values are correlation coefficient, *p* value, and the number of participants. Δ L-Hyoid/LV = the amount of longitudinal displacement of the hyoid bone under general anesthesia with muscle paralysis by increase of 0.1 liter LV.

evidence suggesting that the mechanical link between lung inflation/tracheal traction and caudal hyoid bone displacement is an important mechanism mediating effects on the human upper airway.

Furthermore, the direct association between the waist/hip ratio and the amount of caudal hyoid bone displacement also agrees with the previous finding that the BMI was directly associated with the magnitude of LV dependence of the pharyngeal collapsibility [23]. Interestingly, the Hoffstein's pioneer work demonstrated that the pharyngeal cross-sectional area decreased significantly more during slow exhalation from

total lung capacity to residual volume in people with obese OSA than in weight-matched control participants without OSA [20]. Notably, the functional residual capacity of participants with obese OSA was significantly lower than that of participants with obese non-OSA [20]. Similarly, lung inflation during sleep was only effective for reducing OSA severity in people with morbidly obese OSA [24], and not in people with less obese OSA [25]. Increased curvature of the diaphragm in a person with obesity at a lower initial LV could mechanically produce greater longitudinal tracheal traction force and displace the hyoid bone more caudally. These observations suggest a BMI dependence of the LV influence on the hyoid bone position. Results of our study clarified that the type of obesity does matter and supports that LV dependence of the pharyngeal collapsibility is augmented particularly in people with central obesity.

Hyoid bone and the balance of the soft tissue volume for the craniofacial structure

The pharyngeal airway is a space inside rigid craniofacial bony enclosure formed by mandible, maxilla, and cervical vertebrae. When the upper airway muscle activation is eliminated, the anatomical balance of the soft tissue volume for the craniofacial structure is considered to determine the airway space and one of the significant mechanisms for pharyngeal airway obstruction in people with OSA [6, 17]. In this context, displacement of the tongue musculature to the outside of the bony enclosure could decrease extra-luminal tissue pressure [33] and serve to compensate for the pharyngeal airway narrowing during muscle paralysis. As evident from Figures 2 and 3, this compensation was less evident, but rather lost during muscle paralysis in people with severe OSA. Accordingly, the results of this study indicate that the upper airway muscles dilate the pharyngeal airway partly by displacing the upper airway soft

tissue to submandible region, particularly in people with severe OSA during wakefulness, and the neural mechanism is lost when the muscle activation is suppressed [14]. The hyoid bone locates at the bottom of the tongue, and therefore, the displacement of the tongue is perceived by the movement of the hyoid bone as a marker of the anatomical balance surrounding the pharyngeal airway [6, 17]. The interaction between the upper airway soft tissue and the hyoid bone position is relevant to the effects of neck circumference changes caused by nocturnal fluid shift in people with OSA with cardiac failure [34].

Clinical implications of the study

The results of this study clearly demonstrated a role of the hyoid bone position as a marker for neural and structural mechanisms for pharyngeal airway maintenance. Therefore, we consider that the caudally located hyoid bone commonly seen in people with OSA is a result of interactions between the infra-hyoid muscle activation [11, 12], compensatory displacement of the excessive soft tissue outside the enclosure [33, 35], and tracheal traction by lung inflation [19, 36]. It should be noted that the hyoid bone is displaced anteriorly or caudally in people with OSA whenever the pharyngeal airway collapsibility is improved either by neural or structural mechanisms mentioned above. It is widely believed that longer pharyngeal airway (caudally located hyoid bone position) increases pharyngeal airway resistance and is a disadvantage for breathing [37], but this does not mean that the intervention to shorten the pharyngeal airway length leads to improvement of the OSA severity [38]. Similarly, the association between the pharyngeal length and upper airway critical closing pressure does not mean that the longer pharyngeal airway increases pharyngeal airway collapsibility [6, 7]. On the contrary, our results strongly suggest that interventions to displace the hyoid bone anteriorly and caudally should decrease the pharyngeal collapsibility and the frequency of obstructive events in people with OSA while interventions such as mandible advancement cranially displace the hyoid bone but decrease the pharyngeal collapsibility [38, 39].

In conclusion, both muscle paralysis and LV influence the hyoid bone position. Anterior and caudal displacement of the hyoid bone are considered to be linked to improvement of the pharyngeal airway patency and collapsibility particularly in people with OSA. Changes of the hyoid bone position should be interpreted in terms of the balances in neural and structural influences involved in pharyngeal airway maintenance.

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