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References

1. Sutherland RE, Olsen JS, McKinstry A, Villalta SA, Wolters PJ. Mast cell IL-6 improves survival from *Klebsiella pneumoniae* and sepsis by enhancing neutrophil killing. *J Immunol* 2008;181:5598–5605.
2. Sutherland RE, Xu X, Kim SS, Seeley EJ, Caughey GH, Wolters PJ. Parasitic infection improves survival from septic peritonitis by enhancing mast cell responses to bacteria in mice. *PLoS One* 2011;6:e27564.
3. Verhoef P, Greenberg J, Hrusch C, Krishack P, Sperling A. Type 2/Th2 inflammatory responses protect against the mortality of *Staphylococcus aureus* infection. *Crit Care Med* 2015 [accessed 2016 Sep 1];43(12 Suppl):251. Available from: http://journals.lww.com/ccmjournal/Citation/2015/12001/998__TYPE_2_TH2_INFLAMMATORY_RESPONSES_PROTECT.1001.aspx
4. Bezemer GF, Sagar S, van Bergenhenegouwen J, Georgiou NA, Garssen J, Kraneveld AD, Folkerts G. Dual role of Toll-like receptors in asthma and chronic obstructive pulmonary disease. *Pharmacol Rev* 2012;64:337–358.
5. Tsujimoto H, Ono S, Efron PA, Scumpia PO, Moldawer LL, Mochizuki H. Role of Toll-like receptors in the development of sepsis. *Shock* 2008;29:315–321.
6. Lorenz E, Mira JP, Frees KL, Schwartz DA. Relevance of mutations in the TLR4 receptor in patients with gram-negative septic shock. *Arch Intern Med* 2002;162:1028–1032.
7. Freitas A, Alves-Filho JC, Victoni T, Secher T, Lemos HP, Sônego F, Cunha FQ, Ryffel B. IL-17 receptor signaling is required to control polymicrobial sepsis. *J Immunol* 2009;182:7846–7854.
8. van Walraven C, Austin PC, Jennings A, Quan H, Forster AJ. A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data. *Med Care* 2009;47:626–633.
9. Bang DW, Yang HJ, Ryoo E, Al-Hasan MN, Lahr B, Baddour LM, Yawn BP, Juhn YJ. Asthma and risk of non-respiratory tract infection: a population-based case-control study. *BMJ Open* 2013;3:e003857.
10. Talbot TR, Hartert TV, Mitchel E, Halasa NB, Arbogast PG, Poehling KA, Schaffner W, Craig AS, Griffin MR. Asthma as a risk factor for invasive pneumococcal disease. *N Engl J Med* 2005;352:2082–2090.

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Hyoid Arch Displacement with Hypoglossal Nerve Stimulation

To the Editor:

A new treatment for obstructive sleep apnea (OSA) is unilateral hypoglossal nerve stimulation, an approach shown to decrease the severity and symptoms of OSA in selected patients (1, 2). Drug-induced sedation endoscopy suggests that upper airway stimulation

(UAS) therapy enlarges the oropharyngeal (retroglossal area) and velopharyngeal (retropalate) airway channels, the former through forward movement of the tongue and the latter presumed to be by a linkage through tissues moved by UAS (3). Physiological studies in anesthetized dogs indicate such a linkage exists in that pulling the hyoid bone and its attachments forward opens not only the oropharynx but also the velopharynx (4). This hyoid arch (i.e., the bones, muscles, and ligaments) forms the anterior pharyngeal wall, and is known for its actions in speech and swallowing. A forward movement of the hyoid arch also occurs with glossopharyngeal breathing. This is a useful method for independent breathing in ventilator-dependent patients with post-polio myelitis syndrome, whereby air is first gulped into the oropharynx through the nose and then pushed into lungs (5, 6). The hypothesis here was that UAS would displace the hyoid arch forward, increasing upper airway volume through an action similar to the inspiratory mechanics in this phenomenon.

Figure 1. Three-dimensional rendering images of the upper airway with cone beam computed tomography for one patient. The segmented airway is colored yellow. The arrow labeled with an H points to the hyoid bone. The stimulation cuff electrode (on the right hypoglossal nerve) is represented by the three linear, yellow dots above the hyoid. *Top left:* Resting breathing. Sagittal view during a cycle of resting breathing showing an upper airway volume (yellow area) of 29.5 cm³. *Top right:* Stimulation. Sagittal view during stimulation of the hypoglossal nerve with an increase in upper airway volume (43.7 cm³, +48%) from baseline. The hyoid bone (H) and the submental soft tissue (haziness resulting from movement artifact) move anteriorly during stimulation and produce an outward bulge in submental contour. *Bottom left:* Application of negative pressure (–2 cm H₂O) by facemask, shown as a shadow on the face. Sagittal view during application of –2 cm H₂O with a decrease in upper airway volume (20.9 cm³, –29%). The velopharynx is completely closed, explaining the lack of yellow in that region. The position of the hyoid and the cuff electrode are unchanged. *Bottom right:* Application of positive pressure (+10 cm H₂O) by facemask. Sagittal view during application of +10 cm H₂O with an increase in airway volume (37.8 cm³, +28%). The position of the hyoid and the cuff electrode are unchanged.

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Table 1. Comparison among Variables: Resting Breathing versus Upper Airway Stimulation

Variable	Resting	Stimulation	% Change (<i>P</i> Value)
Total airway volume, cm ³ , mean $\pm$ SD	29.5 $\pm$ 9.7	43.6 $\pm$ 16.1	+48 (0.001)
Hyoid horizontal, mm, mean $\pm$ SD	19.62 $\pm$ 3.8	14.82 $\pm$ 5.9	+29 (0.026)
Hyoid to mandibular plane, mm, mean $\pm$ SD	27.38 $\pm$ 4.1	35.58 $\pm$ 6.5	−24 (0.019)
Tongue length, mm, mean $\pm$ SD	60.5 $\pm$ 5	55.0 $\pm$ 3.0	−9 (0.03)

After informed consent was obtained, seven patients (four men and three women; age range, 39–68 yr) with moderate-to-severe OSA (apnea–hypopnea index, mean $\pm$ SD, 37 $\pm$ 20/h) were recruited for study. All had been regularly using UAS therapy for 1 to 3 years with varying degrees of success (apnea–hypopnea index, 11.9 $\pm$ 12/h; *P* < 0.01). Subjects were evaluated while seated, with the head positioned naturally. Cone beam computed tomography (CB MercuRay scanner; Hitachi Medical Systems, Twinsburg, OH) was used to collect anatomic images (2 mA, 120 kVp, and a 12-inch field of view setting over 6 s) (7). Each image was composed of 512 slices, with a slice thickness of 0.3777 mm, a resolution of 1,024 $\times$ 1,024 pixels, and 12 bits per pixel (4,096 shades of gray). The radiation dose was approximately 80 μ Sv. Images were collected under four conditions: during a cycle of resting breathing, during a 4-second stimulation at the therapeutic voltage amplitude, during breathing on continuous positive pressure (+10 cm H₂O) using a facemask (ResMed, Sydney, Australia), and during continuous negative pressure (−2 cm H₂O) using the same facemask. The mask pressures were produced by a positive/negative pressure source (Pcrit 3000; Philips Respironics, Murrysville, PA).

Sagittal and vertical positions of the hyoid bone were calculated by identifying the most anterosuperior point on the hyoid bone to the posterior pharyngeal wall and the mandibular plane, respectively, with calculations of linear distance (8). A linear tongue length was measured from the tip of the tongue to the base of the epiglottis. After identification of landmarks, scans were automatically segmented to define the channel from the nasopharynx to the hypopharynx (the region from the superior border of the epiglottis to the level of the fourth cervical vertebra) and a volume was calculated. Intrarater reliability, over successive measurements blinded to prior results, ranged from 0.893 to 0.900. For statistical comparisons, *P* < 0.05 was considered significant (SPSS version 22; IBM Corporation, Armonk, NY).

Figure 1 displays the cone beam computed tomography lateral images in one subject for four conditions. The emphasis is on the position of the hyoid bone and the shape of the anterior neck, and the relative volumes in the upper airway. With stimulation, there is anterior displacement of the hypoglossal nerve cuff electrodes and the hyoid bone. Despite an unchanged position of the mandible, the submental soft tissue is displaced anteriorly and a bulge appears on the skin surface. The haziness of the hyoid bone and tissue in this region is the result of the artifact of a 4-second UAS in a 6-second acquisition window, and it emphasizes the anterior displacement of the hyoid arch. With UAS and +10 cm H₂O, total airway volume increases, and with −2 cm H₂O, it decreases. With negative or positive pressure, no displacement of the mandible, hyoid bone and arch, or electrode occurs.

Table 1 presents the group results in total upper airway volume, two measures of hyoid position (hyoid horizontal and hyoid to mandibular plane), and tongue length. As a result of

stimulation, there was a forward and upward movement of the hyoid, with a reduction in tongue length. With negative and positive pressure, there was no displacement of the hyoid or tongue length, whereas total airway volume decreased or increased by −29 and +36%, respectively; hyoid position and tongue length did not change with pressure forcing (data not shown).

The hypothesis that the actions of UAS result from movement of the hyoid is confirmed. Airway volume changes with negative or positive pressure, but it is not airway size that changes hyoid position or tongue length. Oral appliance therapy (9) and maxillomandibular advancement (10) both result in volume increases from the velo- to the hypopharynx, associated with anterior positioning of the tongue base and hyoid arch; however, unlike UAS, this is accomplished by intentional forward movement of the mandible. With UAS, oropharyngeal volume increases through movement of the tongue and the hyoid arch, by mechanical coupling to the airway walls. More detailed analyses of segmental effects are beyond the scope of this format and may require further imaging. Finally, these observations on UAS patients producing upper airway volume increases by anterior displacement of the submental wall suggest that the actions of the hypoglossal nerve on hyoid position are important in the voluntary actions of glossopharyngeal breathing to move air into the oropharynx (5). ■

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References

1. Woodson BT, Soose RJ, Gillespie MB, Strohl KP, Maurer JT, de Vries N, Steward DL, Baskin JZ, Badr MS, Lin HS, *et al.*; STAR Trial Investigators. Three-year outcomes of cranial nerve stimulation for obstructive sleep apnea: the STAR trial. *Otolaryngol Head Neck Surg* 2016;154:181–188.
2. Strollo PJ Jr, Soose RJ, Maurer JT, de Vries N, Cornelius J, Froymovich O, Hanson RD, Padhya TA, Steward DL, Gillespie MB, *et al.*; STAR Trial Group. Upper-airway stimulation for obstructive sleep apnea. *N Engl J Med* 2014;370:139–149.
3. Safiruddin F, Vanderveken OM, de Vries N, Maurer JT, Lee K, Ni Q, Strohl KP. Effect of upper-airway stimulation for obstructive sleep apnoea on airway dimensions. *Eur Respir J* 2015;45:129–138.
4. Van de Graaff WB, Gottfried SB, Mitra J, van Lunteren E, Cherniack NS, Strohl KP. Respiratory function of hyoid muscles and hyoid arch. *J Appl Physiol* 1984;57:197–204.
5. Collier CR, Dail CW, Affeldt JE. Mechanics of glossopharyngeal breathing. *J Appl Physiol* 1956;8:580–584.
6. Mazza FG, DiMarco AF, Altose MD, Strohl KP. The flow–volume loop during glossopharyngeal breathing. *Chest* 1984;85:638–640.
7. Palomo JM, Rao PS, Hans MG. Influence of CBCT exposure conditions on radiation dose. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2008;105:773–782.
8. El H, Palomo JM. Measuring the airway in 3 dimensions: a reliability and accuracy study. *Am J Orthod Dentofacial Orthop* 2010;137(4 Suppl): S50.e1– S50.e9; discussion S50–S52.
9. Ryan CF, Love LL, Peat D, Fleetham JA, Lowe AA. Mandibular advancement oral appliance therapy for obstructive sleep apnoea: effect on awake calibre of the velopharynx. *Thorax* 1999;54:972–977.
10. Zaghi S, Holty JE, Certal V, Abdullatif J, Guillemainault C, Powell NB, Riley RW, Camacho M. Maxillomandibular advancement for treatment of obstructive sleep apnea: a meta-analysis. *JAMA Otolaryngol Head Neck Surg* 2016;142:58–66.

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Durability of Weaning Success for Liberation from Invasive Mechanical Ventilation: An Analysis of a Nationwide Database

To the Editor:

The definition of weaning success plays a crucial role in epidemiological and clinical studies of invasive mechanical ventilation (MV). Weaning success is typically defined as a period of 1 to 7 consecutive ventilator-free days after liberation

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from a ventilator (1–4). In acute care settings in the intensive care unit, a 2-day ventilator-free period is commonly used as the definition for weaning success (2). On the other hand, a 7-day ventilator-free period is suggested for patients with prolonged mechanical ventilation (PMV), which is defined as being under MV for at least 21 days (3). However, the rationale for the establishment of these definitions is unclear. Although experts in this field have advocated for more scrutiny regarding the definitions of weaning success (3), there is as yet no consensus. Here we aimed to select a threshold for defining weaning success by evaluating the durability of weaning success on each day after ventilator liberation, using a nationwide database in Taiwan.

This nationwide cohort study used the entire population database of Taiwan's National Health Insurance (NHI) and death registration data (5). Our study was part of a governmental project to investigate MV use in Taiwan. Established in 1995, the NHI is a universal and compulsory health insurance program that covers more than 99% of Taiwanese citizens (5). The NHI covers MV use, with no restrictions on use initiation or limitations on the length of use. Taiwan's National Health Insurance Administration maintains the quality of NHI data by routinely auditing the data.

The inclusion criterion in our study was receipt of invasive MV for at least 2 consecutive days between March 1, 2010 and September 30, 2011. The exclusion criteria were an age younger than 18 years on MV initiation and death on the day of ventilator liberation. We followed each patient from the day of MV initiation until death, disenrollment from NHI, or March 31, 2012, whichever came first. Our study protocols were approved by the Institutional Review Board of Cardinal Tien Hospital in Taiwan (CTH-104-4-6-002). Because all individual identification numbers in our research database were encrypted to protect the privacy of study participants, informed consent was waived.

Weaning success may be regarded as a time point when the probability of reinstituting MV is adequately low in the time-to-event analysis. We estimated the survival function of ventilator-free time after liberation from ventilator and subsequently calculated the probability of reinstituting MV for every single day after the day of liberation by density function. The estimate of the density function is equivalent to the absolute value of the slope along the survival curve that depicts the speed of reinstitution of MV after liberation. We used SAS software version 9.2.1 (SAS Institute Inc., Cary, NC) to extract the NHI data and used Stata software version 12 (StataCorp, College Station, TX) to conduct the survival analysis.

During the study period, there were a total of 199,713 acute respiratory failure events requiring MV for at least 2 days. The median patient age was 72 years (interquartile range, 57–81 yr), 37% of the cases were women, and 35% of the cases were patients undergoing surgery. The clinical courses of these 199,713 events of acute respiratory failure, which occurred in 143,094 patients, are summarized in Figure 1. Among the 199,713 events of acute respiratory failure, 157,581 (78.9%) were followed by ventilator liberation. Figure 2A shows Kaplan-Meier estimates of the cumulative probability of reinstituting MV after the day of ventilator liberation. The cumulative probabilities for the initial 7 days were 11, 15, 17, 18, 19, 20, and 21% in the total cohort (Figure 2A). We used the density function of ventilator-free time to calculate the probability of the reinstitution of MV for every single day after the day of liberation. Figure 2B shows the