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Swallow-breathing coordination during incremental ascent to altitude

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Abstract

Swallow and breathing are highly coordinated behaviors reliant on shared anatomical space and neural pathways. Incremental ascent to high altitudes results in hypoxia/hypocapnic conditions altering respiratory drive, however it is not known whether these changes also alter swallow. We examined the effect of incremental ascent (1,045m, 3,440m and 4,371m) on swallow motor pattern and swallow-breathing coordination in seven healthy adults. Submental surface electromyograms (sEMG) and spirometry were used to evaluate swallow triggered by saliva and water infusion. Swallow-breathing phase preference was different between swallows initiated by saliva versus water. With ascent, saliva swallows changed to a dominate pattern of occurrence during the transition from inspiration to expiration. Additionally, water swallows demonstrated a significant decrease in submental sEMG duration and a shift in submental activity to earlier in the apnea period, especially at 4,371m. Our results suggest that there are changes in swallow-breathing coordination and swallow production that likely increase airway protection with incremental ascent to high altitude. The adaptive changes in swallow were likely due to the exposure to hypoxia and hypocapnia, along with airway irritation.

Keywords

High altitude ascent; Electromyograms; Airflow; Apnea duration; Airway protection; Swallow coordination

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1. Introduction

Swallow and breathing are highly coordinated airway protective behaviors. Swallow is a multi-phase event, however the pharyngeal phase presents the highest risk for aspiration (Paydarfar et al., 1995). During the pharyngeal phase, supra-laryngeal/hyoid musculature moves the larynx superiorly and anteriorly resulting in closure of the airway and a functional apnea (German et al., 2009; Wheeler Hegland et al., 2011; Wheeler Hegland et al., 2009).

The expiratory phase of breathing is the preferred phase for swallow to occur, likely due to the limited inspiratory airflow (Martin-Harris et al., 2003). The central mechanism is thought to be due to interactions of breathing and swallow pattern generators (Dick et al., 1993; Miller, 1982), however this preference can be modified by peripheral feedback (Pitts et al., 2015b) and disease (Brodsky et al., 2010; Leslie et al., 2002; Troche et al., 2011). Specifically, alterations in respiratory mechanics due to chronic obstructive pulmonary disease (Nagami et al., 2017; Pinto et al., 2017) and/or upper abdominal laparotomy can shift swallow occurrences to inspiration, potentially increasing risk of aspiration (Pitts et al., 2015b). Additionally, there is also limited evidence that alterations in blood gasses (i.e., oxygen [O_2] and carbon dioxide [CO_2]) can also increase the likelihood that swallow will occur during inspiration (D'Angelo et al., 2014), (Ghannouchi et al., 2013).

Incremental ascent to high altitudes (>2,000m) produces hypoxia (low O_2) induced hyperventilation, resulting in hypocapnia (low CO_2) (Huang et al., 1984; Weil, 1986). As climbers acclimatize to high altitude they can reach a new "steady-state chemoreflex drive" in which balance is achieved between hypoxia and hypocapnia, while ventilation parameters can return to near baseline conditions (Bruce CD, 2018; Pfoh et al., 2017). Additionally, healthy individuals that are not acclimatized to high altitude conditions can have changes in pulmonary mechanics due to interstitial pulmonary edema, which can be accompanied with accumulation of fluid within and around the airway walls (Cremona et al., 2002; Pratali et al., 2010; Schoene et al., 1988). Early symptoms such as shortness of breath and cough are often overlooked leading to mortality (Dunin-Bell and Boyle, 2009).

Due to the significant coordination necessary for swallow and breathing, it is likely that conditions which significantly alter respiratory drive and mechanics would also affect swallow production and swallow-breathing coordination. We hypothesized that with incremental ascent to high altitude there would be a decrease in swallow duration, and a shift in swallow phase preference to inspiration.

2. Methods

Ethics and Participant Recruitment

This study abided by the Canadian Government Tri-Council policy on research ethics with human participants (TCPS2) and the Declaration of Helsinki, except for registration in a database. Ethical approval was received in advance through Mount Royal University Human Research Ethics Board (Protocol 100012) and was harmonized with the Nepal Health Research Council (Protocol 109–2017). Participants were recruited via email correspondence or direct verbal communication, and provided written, voluntary, informed and ongoing consent.

Ten participants were recruited for the study, while only seven (two males, five females) completed the study. One participant voluntarily withdrew from the study during ascent, another was excluded following baseline data acquisition due to a persistent cough and a third was excluded due to complications with data acquisition. Exclusion criteria included facial hair, as electrodes were unable to effectively adhere to skin, and health status (e.g., persistent cough, severe altitude illness). No pre-existing medical conditions were reported by any participants. Participants avoided rigorous exercise for at least 12 hours prior to data collection.

Incremental ascent to high altitude

Baseline measurements were recorded at 1,045m (Calgary) prior to the departure to Nepal. Following arrival in Kathmandu (1,400m), participants spent up to 3 days in Kathmandu before flying to Lukla (2,860m) where the trek to high altitude commenced (Figure 1). Consecutive measurements were obtained on rest days at 3,440m (Namche; day 3 at altitude) and 4,371m (Pheriche; day 5 at altitude) on every second day following arrival in Lukla (Figure 1), following one night sleep at each respective altitude.

Data Collection

Data acquisition was performed using an analog to digital data acquisition system [Powerlab/16SP ML880; AD Instruments (ADI), Colorado Springs, CO, USA], and data was collected, archived and analyzed offline using commercially available software (LabChart Pro software version 8) and a personal laptop computer. Surface electromyogram (sEMG) (ADI MLA2503 & ADI FE132) electrodes were placed approximately 3 cm posterior to the mental region of the mandible, on each side of the midline, capturing the submental complex. The grounding electrode was placed inferior to the participant's left clavicle. Voluntary swallow was performed in advance to ensure an adequate electrical signal through the sEMG electrodes.

A pneumotachometer (800L flow head; Series 3813; Hans Rudolph Inc.) and spirometer amplifier (ADI ML141) were used to monitor respiratory variables using a mouthpiece and nose-clip. Calibration of the flow head was performed with a 3L calibration syringe before data acquisition in each participant. Respiratory flow (L/s) was measured directly by the pneumotachograph. Inspired volume (V_{TI}; L) and respiratory frequency (f_R; min^{-1}) were derived from respiratory flow. The product of V_{TI} and f_R was used to determine instantaneous minute ventilation ($\dot{V}_I$; L/min). The pressure of end-tidal $P_{ET}CO_2$ was measured using a portable, calibrated capnograph (Masimo EMMA, Danderyd, Sweden) with a personal mouthpiece and nose clip and peripheral oxygen saturation (SpO_2) was measured with a portable finger pulse oximeter (Masimo SET® Rad-5, Danderyd, Sweden). Electrocardiography (ECG; ADI MLA2503 & ADI FE132; lead II configuration) was utilized to derive instantaneous heart rate (HR; 1/R-R Interval in min^{-1}). The protocol was carried out with participants sitting comfortably in a dark, quiet room with ear plugs and eyes closed. Resting ventilation at each altitude was analyzed from a one-minute representative period near the end of a 10-min baseline period, whereas $P_{ET}CO_2$ and SpO_2 measures were obtained after stability was achieved.

Swallow stimulation

1. Swallows produced during the baseline respiratory data via normal saliva collection in the mouth, termed *saliva swallows*.

2. *Water swallows* were trigged via water delivery from a 250 mL wash bottle (Nalgene 2089–0008 Narrow-Mouth Economy Bottle; Thermo Scientific, Waltham, MA, USA) inserted approximately 5 cm into the participant's mouth, lateral to the pneumotachometer mouthpiece. The wash bottle was positioned by each participant to ensure comfort with the water delivery. The infusion protocol began by recording a thirty-second baseline with all instrumentation in place. Following this baseline, water was infused at ~1 mL/second for 30 seconds into the participants' mouths. Finally, a 30 second washout was conducted after all instrumentation remaining in place. In all instances, participants were instructed before the introduction of water to swallow normally as needed.

Statistical Analysis

Data was analyzed from seven participants (5 female and 2 male) ages 19–23 at 1,045m (Calgary), 3,440m (Namche; day 3 at altitude), and 4,371m (Pheriche; day 7 at altitude) (Figure 1). All results were expressed as means ± standard deviation (SD) using SPSS software (IBM).

To examine changes in swallow phase preference the following designations were used for respiratory phase: A) transition from inspiration to expiration (In-Ex); within expiration (Ex-Ex); transition from expiration to inspiration (Ex-In); and within inspiration (In-In). Then the following assigned coding system was used with In-Ex = 1; Ex-Ex = 2; Ex-In = 3; and In-In = 4 to categorize where each swallow occurred (Table 1). Finally, Wilcoxon signed ranks tests were run to determine changes across swallow-type and altitude, as we have previously used (Pitts et al., 2015b).

Swallow apnea duration was measured as the period of zero airflow in the event of a swallow (Figure 2). The apnea duration then was divided into three sub-phases: a) pre-swallow apnea, b) duration of submental sEMG, and c) post-swallow apnea (Figure 2). Pre-swallow apnea began at the time of zero airflow before the submental activation. Submental sEMG duration was measured as the activation and inactivation of submental sEMG. Post-swallow apnea was measured as the zero airflow after the inactivation of submental complex (Figure 2). Additionally respiratory rate, heart rate, mean arterial pressure (MAP), $\dot{V}_I$, SpO_2, $P_{ET}CO_2$ and steady-state chemoreflex drive (SS-CD) were measured. The SS-CD was computed by calculating a stimulus index (SI; $P_{ET}CO_2/SpO_2$), and then comparing minute ventilation against SI (Bruce CD, 2018; Pfoh et al., 2017). A repeated measures ANOVA was used to determine differences in swallow motor pattern and respiratory parameters across the three elevations with significance at $p \le 0.05$, and if significance was met the LSD post-hoc test was used. A $p \le 0.07$ was designated as "approaching significance".

3. Results

Swallow was present during baseline respiratory measurements (saliva swallows), and reliably elicited with infusion of water in all subjects (water swallows). A total of 379 swallows (122 saliva and 257 water) were analyzed across the three altitudes (142 at 1,045m; 121 at 3,440m; and 116 at 4,371m).

Swallow-breathing coordination

Table 1 reports percent of swallow occurrences across each respiratory phase/transition. Water swallows had a strong In-Ex phase preference (69–79%) which was maintained through the ascent protocol. For saliva swallows at 1,045m only 43% occurred during In-Ex [significantly different than water ($Z = -3.3$, $p < 0.001$)], but this shifted at 3,440m with 76% of swallows occurring during In-Ex [significantly different than 1,045m ($Z = -3.3$, $p < 0.001$)]. At the highest altitude 4,371m the percent of swallows which occurred during the In-Ex transition reduced to 55% ($p = 0.07$). Interestingly, at 1,045m 21% of saliva swallows occurred during inspiration (In-In), which reduced to 6% at 3,440m and at 4,371m none occurred. In contrast <6% of water swallows occurred during inspiration (Table 1).

Change of swallow motor pattern with increasing altitude

Figure 3 demonstrates changes in pre-swallow apnea, submental duration, and post swallow apnea plotted by subjects across the three altitude locations. For swallows elicited by water, the average submental duration (ms) approached significance [1170 ± 539, 1038 ± 218, and 710 ± 227 respectively ($F_{2,\,12} = 4.19$, $p = 0.07$)]. As elevation increased pre-swallow apnea duration (ms) significantly decreased [−256 ± 236, −115 ± 99, and −5 ± 172 respectively ($F_{2,\,12} = 4.218$, $p = 0.06$)], and post-swallow apnea duration (ms) significantly increased [56 ± 109, 111 ± 171, and 241 ± 218 ($F_{2,\,12} = 6.137$, $p < 0.05$)] (Table 2 and Figure 2 and 3). Of note, pre-swallow submental sEMG activity was seen during swallows at each elevation and of each type (Figure 2). For saliva swallows there was no significant change in submental sEMG and apnea duration, or swallow frequency (Table 2).

Breathing related variables

Table 2 also illustrates resting minute ventilation ($\dot{V}_I$), the pressure of end-tidal $P_{ET}CO_2$, peripheral oxygen saturation (SpO_2), stimulus index (SI) and measurement of steady-state chemoreflex drive (SS-CD) during incremental ascent to high altitude. All variables changed in predictable ways with incremental ascent. Heart rate [81.6 ± 9.5, 97.8 ± 7.9, and 93.5 ± 5.8 respectively ($F_{2,12} = 10.29$, $p < 0.05$)], MAP [90.4 ± 8.4, 96.0 ± 6.5, and 99.1 ± 9.2 respectively ($F_{2,12} = 11.88$, $p < 0.05$)] and SS-CD significantly *increased* as altitude increased [36.8 ± 8.5, 49.3 ± 12.7, and 58.7 ± 19.5 respectively ($F_{2,12} = 7.41$, $p < 0.05$)]. SpO_2 [96.2 ± 1.0, 88.1 ± 2.3, and 83.3 ± 5.3 respectively ($F_{2,12} = 37.44$, $p < 0.001$)] and $P_{ET}CO_2$ [31.1 ± 4.2, 25.9 ± 2.7, and 21.3 ± 2.3 respectively ($F_{2,12} = 31.61$, $p = 0.001$)] significantly *decreased* as altitude increased. Additionally, respiratory rate and instantaneous minute ventilation remained stable across all elevations (Table 2).

4. Discussion

This is the first evidence of a significant change in swallow-breathing coordination as well as swallow production during incremental ascent to high altitude. There was a significant change in swallow phase preference comparing saliva to water swallows during baseline and approached significance at the highest elevation (4,371m). This was due to a shift in the dominance of the In-Ex pattern seen during water swallows and at 3,440m for saliva swallows. Additionally, in the water trials there was a significant increase in the post-swallow apnea period and a decrease (approaching significance) in the submental duration and pre-swallow apnea, while the overall swallow apnea duration did not change.

Phase Preference

Swallow phase preference has been intensely studied in humans (Martin-Harris, 2008; Martin-Harris et al., 2008; Martin-Harris et al., 2003; Martin-Harris and McFarland, 2013; Pratali et al., 2010; Wheeler Hegland et al., 2011; Wheeler Hegland et al., 2009), as well as in cats (Dick et al., 1993; Pitts et al., 2015a; Pitts et al., 2013; Pitts et al., 2015b), goats (Bonis et al., 2011; Feroah et al., 2002a; Feroah et al., 2002b), and rats (Saito et al., 2002a, b). However, all the peripheral stimulations and/or central mechanisms which regulate their interactions are not entirely understood. In the present study there was *not* a strong expiratory phase preference (~80%) which is observed in single swallow studies in which a 5 or 10 mL bolus is placed in the mouth (Wheeler Hegland et al., 2009). Saliva swallows (probably most akin to the typical single swallow task) demonstrated only 9% occurred during expiration, with 43% occurring in the transition of In-Ex, and of great interest is that 21% of these swallows occurred during inspiration (Table 1).

The dominance of In-Ex preference may be due in part to the mouthpiece which forces an “open mouth” swallow. It has been shown that muscle spindle afferents, in the masseter muscle, increase in discharge frequency during active opening of the jaw (Taylor et al., 1997). It has also been shown that input of muscle spindle afferents influence other central pattern generators [i.e. locomotion (Pearson, 1995)], and has been speculated that muscle spindle afferents influence mastication CPG output (Kolta et al., 1990; Lund, 2011). This information allows speculation that position of the jaw, indicated by proprioception of muscle spindle afferents can modulate the interaction between the swallow and breathing CPGs.

These changes could also be related to the effects of hypoxia and/or hypocapnia on swallow. Although there are limited studies, there are also conflicting results. In mice an increase in swallow frequency was reported (Khurana and Thach, 1996), no change in rat (Ghannouchi et al., 2013), and a decrease in the cat (Nishino et al., 1986). Hypoxia has also been studied in nonnutritive swallow in newborn lambs which showed a decrease in frequency during quiet sleep (Duvareille et al., 2007). Interestingly, hypercapnia shifts swallows towards In and Ex-In (D’Angelo et al., 2014) while we found that hypocapnia with hypoxia shifts swallow toward In-Ex. In light of the present data, further studies may need to investigate swallow-breathing coordination not only with variation of respiratory drive but swallow drive as well. We speculate that the water trials increased swallow excitability, which likely altered and stabilized its relationship with breathing.

Swallow motor pattern

In contrast to the swallow-breathing coordination data, the largest changes in the swallow motor pattern with ascent were on the water swallows, with a 39% decrease in the submental duration (Figure 2–3) at the highest altitude (compared to Calgary). This effect has been demonstrated in cats when swallow was coordinated with cough (airway irritation discussed below) (Leow et al., 2006); however we could find no study demonstrating a decrease in submental sEMG in healthy adults when using a mechanical/cold stimulus on the back of the mouth (Sciortino et al., 2003) or altering oral stimulation with taste (Leow et al., 2006).

To protect the airway during the pharyngeal phase of swallow the vocal folds must be adducted (zero flow; swallow apnea) during the laryngeal exposure to the bolus (Butler et al., 2004; Chi-Fishman and Sonies, 2000; Ding et al., 2003; Kijima et al., 1999; Martin-Harris et al., 2003; Martin et al., 1994; Paydarfar et al., 1995; Wheeler Hegland et al., 2011). In a review by Martin-Harris (2008), she stated that increases in the timing from the onset of the submental activity to the apnea period is related to significant clinical risk for aspiration. Evidence of this has been demonstrated in patients with Parkinson's disease with dysphagia (Ertekin, 2014). Based on this current data, we speculate that the decrease in submental sEMG and the shift in its activity to closer to the start of the swallow apnea period could increase airway protection. Of note, Ertekin and colleagues (Ertekin, 2014; Gürgör et al., 2013) demonstrated an activation of the submental complex during the pre-swallow respiratory phase that is likely related to infusion of water into the mouth (termed foreburst). Figure 2 demonstrates the difference between swallow-related and pre-swallow submental activity.

Airway Irritation

Exposure to high altitude conditions is also associated with airway irritation from dry air and insensible water loss, which results in a chronic cough (Freer, 2004). The most common diagnosis in the Nepal Himalaya is "Khumbu cough", also known as "high altitude hack" (Freer, 2004), thought to be caused by dry air, sub-zero temperatures, dust, and exposure to yak dung stoves in the lodges (Linoby et al., 2013). There is evidence that dry air increases airway responsiveness (Van Oostdam et al., 1986), and prolonged exposure results in an inflammatory response, desquamation of the epithelium, and edema of submucosa (Florey et al., 1932). While each subject did have evidence of coughing across the recording period, none were actively coughing during the measurement period. It is possible that activation of irritant receptors can alter swallow production without cough as a presenting feature.

Respiratory Drive

The changes in swallow and swallow-breathing coordination were also accompanied by changes/adaption of the chemoreflexes driving breathing. It is known that these reflexes become more dynamic as individuals acclimatize to their respective environment (Pfoh et al., 2017) (Steinback and Poulin). To asses this adaptation, Pfoh and colleagues (2017) created an index of steady-state chemoreflex drive (SS-CD), taking into account resting ventilation indexed against the overall contributions of both low O_2 and low CO_2 during exposure to hypoxia. Based on the magnitude of this index the significant change in the SS-

CD from 1,045m to 3,440m is evidence of respiratory acclimatization in our participants [see also (Huang et al., 1984)].

Blood levels of O_2 and CO_2 are maintained in part by central (brainstem) and peripheral (carotid body) chemoreceptors. Central chemoreceptors, located throughout brainstem, detect $PCO_2/[H^+]$ accumulation (Guyenet and Bayliss, 2015). Peripheral chemoreceptors located bilaterally within carotid bodies detect rapid changes in both O_2 and CO_2 synergistically (Fitzgerald and Parks, 1971; Lahiri and DeLaney, 1975; López-Barneo et al., 2016). A primary location for integrating these signals is in the nucleus tractus solitarius (NTS) (Jordan and Spyer, 1986; Paton et al., 2001). Due to the overlap in sensory integration in the NTS for breathing and swallow (Jean, 1984, 2001), this may be a site of shared central excitability which affects both respiratory and swallow central pattern generators.

Clinical Implications

Altitude exposure has inherent risks with 1–2% experiencing high altitude pulmonary edema (HAPE) (Houston, 1960; Hultgren, 1969; Schoene et al., 1986), a form of high altitude sickness, and of those 65% are diagnosed with a concomitant respiratory infection (most commonly pneumonia) (Leshem et al., 2008). It would be of interest to know if climbers with pneumonia display the same adaptations in swallow, especially in light of our knowledge of pneumonia rates with dysphagia.

5. Conclusions

Our results suggest that there are changes in swallow-breathing coordination and swallow motor production that increase airway protection with incremental ascent to high altitude. In conclusion, we suspect the adaptive changes in swallow were likely due to the exposure to superimposed hypoxia and hypocapnia, along with the increased airway irritation.

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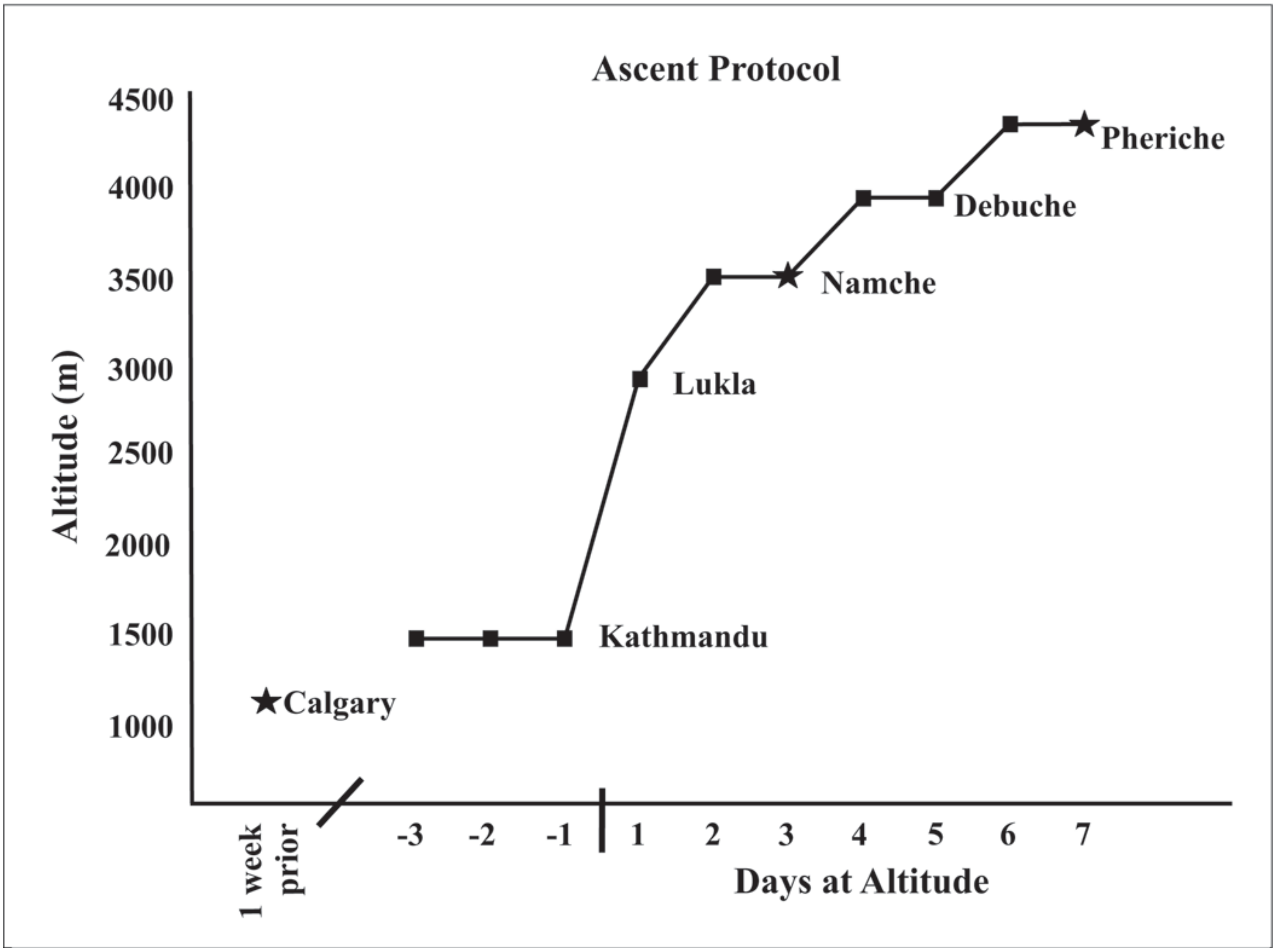

Figure 1.

Timeline of travel, ascent, and recording locations. The (★) represents where data was collected, and (✈) indicates flights.

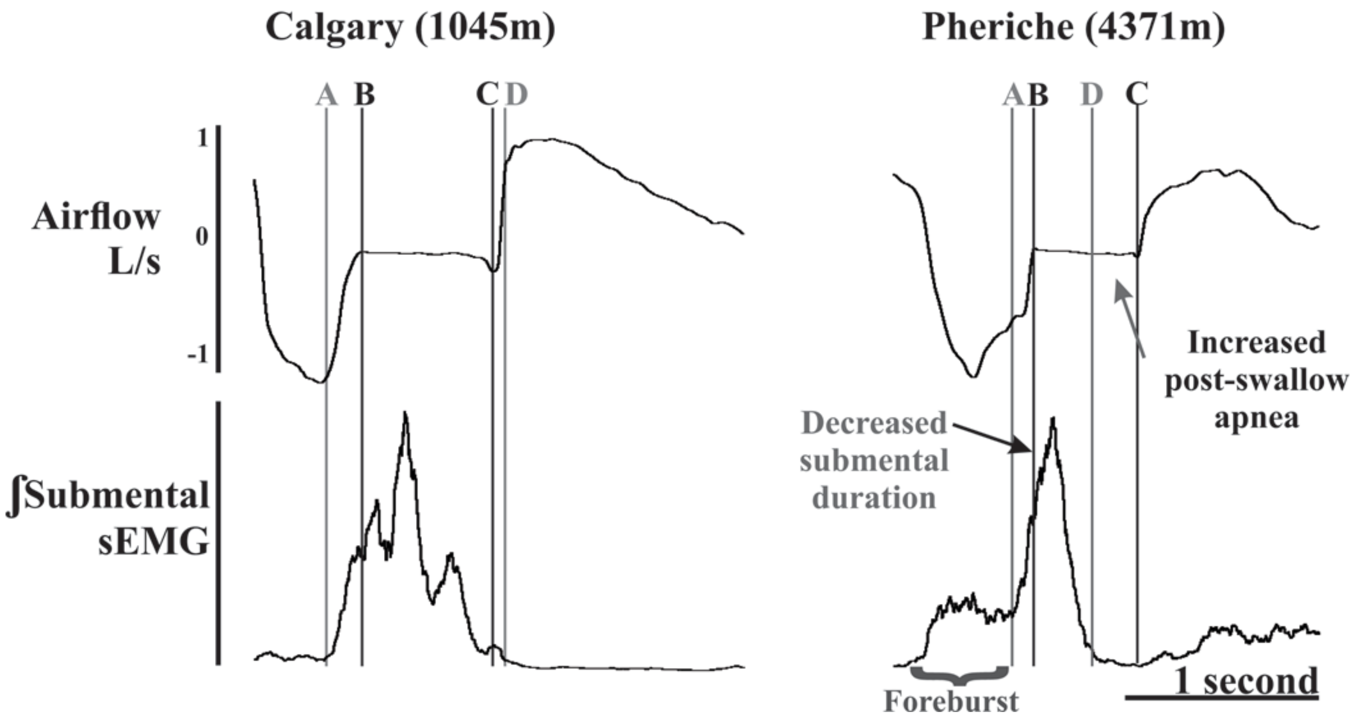

Figure 2.

Example of submental sEMG and airflow from the same participant from Calgary (1,045m) and Pheriche (4,371m) during the water swallow protocol. B to C marks the swallow apnea period. A to B is the pre-swallow submental activity, A to D is the submental duration and C to D is the post-swallow apnea period. At 4,371m, there was a significant increase in the post-swallow apnea as well as a decrease submental duration. The "foreburst" is activity related to water being introduced to the oral cavity.

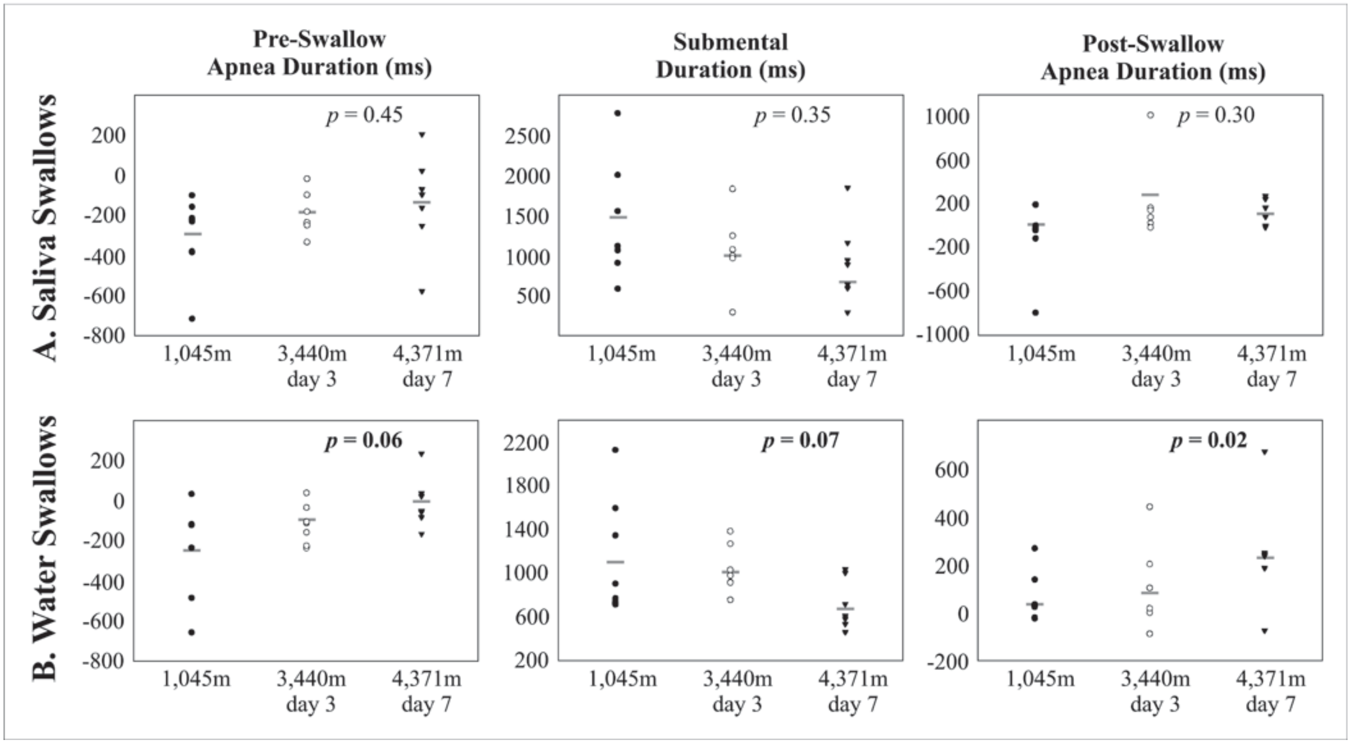

Figure 3.

Scatter plot of duration measures (pre-swallow, submental and post-swallow) for each subjects across th e recording locations for the saliva (A) and water (B) swallow tasks. Repeated measures ANOVA *p*-value reported for each dependent measure, and gray line represents group mean.

Table 1.

Percent of swallow occurrence during breathing across the three levels of ascent.

	In-Ex	Ex-Ex	Ex-In	In-In
Saliva Swallow				
1,045m	43	9	27	21
3,440m	76	12	6	6
4,371m	55	15	30	0
Water Swallow				
1,045m	79	9	9	2
3,440m	69	14	11	6
4,371m	76	11	11	2

Table 2.

Means, standard deviations (SD), and *p*-values comparing ventilatory, cardiac and acclimation values, as well as saliva and water swallows at the three different elevations are shown in this table. Resting respiratory rate (RR), mean arterial pressure (MAP), peripheral O_2 saturation (SpO_2), end tidal CO_2 pressure ($P_{ET}CO_2$), instantaneous minute ventilation ($\dot{V}_I$), and steady-state chemoreflex drive (SS-CD) are recorded. Submental (swallow) duration, swallow apnea duration, pre-swallow apnea and post-swallow apnea (Figure 2) are recorded in both saliva and water conditions. Figure 3 displays swallow data by participant.

	Calgary (1,045m)			Namche (3,440m)			Pheriche (4,371m)			*p*-values
	Mean	**±**	**SD**	**Mean**	**±**	**SD**	**Mean**	**±**	**SD**	
Resting RR (min^{-1})	14.0	±	6.0	15.2	±	3.9	15.5	±	5.2	0.42
Resting Heart Rate	81.6	±	9.5	97.8	±	7.9 ***	93.5	±	5.8 **	**0.004**
MAP (mm Hg)	90.4	±	8.4	96.0	±	6.5 **	99.1	±	9.2 ***	**0.004**
SpO_2 (%)	96.2	±	1.0	88.1	±	2.3 ***	83.3	±	5.3 ***††	**<0.001**
$P_{ET}CO_2$ (Torr)	31.1	±	4.2	25.9	±	2.7 **	21.3	±	2.3 ***†††	**0.001**
$\dot{V}_I$ (L/min)	11.9	±	2.7	14.2	±	2.6	14.7	±	3.8	0.07
SS-CD (V_I/SI)	36.8	±	8.5	49.3	±	12.7 *	58.7	±	19.5 **†	**0.02**
Saliva Swallow Data										
Submental Duration (ms)	1480	±	804	1070	±	490	1015	±	457	0.35
Swallow Apnea Duration (ms)	1088	±	433	1121	±	253	1010	±	374	0.77
Pre-Swallow Apnea (ms)	−296	±	220	−183	±	113	−141	±	265	0.45
Post-Swallow Apnea (ms)	−99	±	363	233	±	385	174	±	101	0.30
Water Swallow Data										
Submental Duration (ms)	1170	±	539	1038	±	218	710	±	227 *†††	*0.07*
Swallow Apnea Duration (ms)	973	±	398	1030	±	165	946	±	285	0.60
Pre-Swallow Apnea (ms)	−256	±	236	−115	±	99	−5	±	126 *	*0.06*
Post-Swallow Apnea (ms)	56	±	109	111	±	171	241	±	218 **†	**0.02**

Reported *p*-values are for repeated measures oneway ANOVA and significant values are **bolded**

* Significant difference from Calgary *$p \leq 0.06$,

** $p<0.05$

***$p<0.01$

†Significant difference between Namche and Pheriche † $p\leq 0.06$

††$p<0.05$

†††$p<0.01$