# Voice Reactivity as a Response to Acute Hypobaric Hypoxia at High Altitude

Martine Van Puyvelde; Xavier Neyt; Wim Vanderlinden; Maarten Van den Bossche; Tony Bucovaz; Tony De Winne; Nathalie Pattyn

**BACKGROUND:** Although the understanding of hypobaric hypoxia is increasing, it remains a hazard in aviation medicine. This study examined the feasibility of detecting voice markers sensitive to acute hypobaric hypoxia in an early presymptomatic (PRE-SYMP) stage.

- **METHOD:** Eight subjects qualified with hypobaric training completed a series of standardized speech tests in a hypobaric chamber at 20,000 ft and 25,000 ft (6096 and 7620 m) of altitude. Voice response patterns were analyzed in terms of fundamental frequency (F0), F0 range, and voice onset time (VOT). We hypothesized a PRE-SYMP compensatory stage in voice reactivity.
- **RESULTS:** There was a different dose-response reactivity course at 20,000 ft vs. 25,000 ft, nonlinear to altitude. At 20,000 ft, our hypothesis was confirmed. In comparison to sea level, a PRE-SYMP compensatory stage could be distinguished, characterized by a decreased F0 range, decreased VOT, and increased F0. During a transitional (TRANS) stage, in comparison with sea level, the F0-range reset, VOT decreased, and F0 increased. During a symptomatic (SYMP) stage, F0 increased, F0 range increased, and VOT decreased. At 25,000 ft, in comparison to sea level, voice reactivity showed increased F0 and F0 range and decreased VOT in a PRE-SYMP stage and increased F0 and F0 range in the SYMP stage.
- **DISCUSSION:** The compensatory PRE-SYMP stage is suggested to be the expression of ongoing bottom-up and top-down regulatory mechanisms, whereas the 25,000-ft results are interpreted as a combination of tonic and phasic voice reactivity. This tonic component needs to be foreseen in sea level baseline measures.
- **KEYWORDS:** acute hypobaric hypoxia, voice stress analysis, voice response patterns, Model for Voice and Effort.

Van Puyvelde M, Neyt X, Vanderlinden W, Van den Bossche M, Bucovaz T, De Winne T, Pattyn N. Voice reactivity as a response to acute hypobaric hypoxia at high altitude. Aerosp Med Hum Perform. 2020; 91(6):471–478.

he understanding of hypobaric hypoxia, such as its nature (e.g., be it acute or chronic hypoxia), the individual and situational risk factors for aviators (e.g., physical fitness), or training possibilities, has clearly been improved over the years. Nevertheless, acute hypobaric hypoxia (AHH) remains a hazard in aviation medicine for several reasons (e.g., Ghosh and Pant<sup>12</sup> and Neuhaus and Hinkelbein<sup>20</sup>). An analysis of a military air force reported 656 in-flight hypoxic incidents between 1976-1990 and 221 between 1983-2003.11 The most menacing aspect of hypoxia is its insidiousness. Certainly, when untrained,<sup>2</sup> the moment a person notices the first signs of hypoxia, cognitive and psychomotor functioning may already be too severely impaired for well-thought decision-making and remedial action.<sup>15</sup> Since AHH can be considered a condition of cognitive breakdown<sup>20,22</sup> in which mechanisms of effort become slightly damaged, the challenge is to differentiate subtle

(presymptomatic) substages where remedial action is still possible. This is a complex puzzle since hypoxia has been shown to have an individual signature with regard to both the type of symptoms and the timing and order of its onset.<sup>16,25</sup>

Recently, in a new 'Model of Voice and Effort' (MoVE),<sup>28</sup> the operational relevance of voice stress analysis was conceptualized.

From the VIPER Research Unit, LIFE department, Royal Military Academy, Brussels, Belgium; the Brain Body and Cognition Research Group, and Clinical & Lifespan Psychology, Department of Psychology and Educational Sciences, and MFYS-BLITS, Human Physiology Department, Vrije Universiteit Brussel, Brussels, Belgium; and the Military Hospital Queen Astrid, Center for Aerospace Medicine, Hypobaric Chamber, Brussels, Belgium.

This manuscript was received for review in March 2019. It was accepted for publication in March 2020.

Address correspondence to: Prof. dr. Martine Van Puyvelde, Ecole Royale Militaire, Renaissancelaan 30, Brussels 1000, Belgium; Martine.Van.Puyvelde@vub.be.

Reprint & Copyright © by the Aerospace Medical Association, Alexandria, VA. DOI: https://doi.org/10.3357/AMHP.5390.2020

The model associated the balance between bottom-up arousal and top-down regulatory activity as an attempt by the body to compensate for experienced stress (e.g., different types of workload or environmental challenges such as hypoxia) with certain voice stress patterns. Indeed, speech demands the complex coordination of three processes (i.e., breathing, phonation, and resonance) involving both the central and peripheral nervous system<sup>3</sup> and may, therefore, intervene with the psychophysiological processes of stress regulation<sup>28</sup> (see Table I for an overview of operationally relevant speech variables and its definitions). With regard to hypoxia, Johnston et al.<sup>16</sup> observed that slurred speech was the most stable symptom in recurrent hypobaric hypoxia trainings. A study on chronic hypoxia at the Concordia Station in Antarctica (3233 m/10,606 ft) also showed a faster recovery pattern for  $S_{\mathrm{p}}\mathrm{o}_2$  than for the speech-related muscular deterioration.<sup>17</sup> Moreover, MRI studies demonstrated that essential speech-related brain regions such as the basal ganglia-and more specifically the globus pallidus-are vulnerable to hypobaric hypoxia<sup>19</sup> and that hypoxia-related brain damage in these regions can even be permanent.<sup>10</sup> Nevertheless, only a small number of studies has examined the direct impact of hypoxia on voice output. Two studies<sup>17,19</sup> examined the impact of chronic hypoxia on microspeech articulation, making use of the variable 'voice onset time' (VOT; see Table I for an overview and explanation of speech variables). Chronic hypoxia at medium<sup>17</sup> as well as high<sup>19</sup> altitude resulted in a significantly decreased VOT. Regarding acute exposure, AHH during a fatal crash was related with increased VOT.<sup>24</sup> In this study, Saito et al.<sup>24</sup> reported a decreased fundamental frequency or F0 (Table I) and blurred formants. Finally, a recent study<sup>26</sup> found no impact of chronic normobaric or medium hypobaric hypoxia on formants (Table I). In the above described MoVE, 28 a top-down compensatory stage was hypothesized to involve a more rigid

voice use typified by an increased F0 but diminished F0 range, whereas a serious case of hypoxia—based on the findings of Saito et al.<sup>24</sup>—was proposed to be announced by the loss of control characterized by a decrease in F0 and increase in F0 range.

In the current study, we opted for an in-depth analysis of a small number of subjects who were tested at two altitudes. Firstly, we aimed at testing whether it is possible to detect voice markers sensitive to hypoxia in a presymptomatic substage, secondly at understanding potential explanatory underliers, and thirdly, we wanted to test the eventual dose-effect of altitude. Based on the above mentioned former studies,<sup>17,19,23</sup> we targeted F0 on the level of voice phonation and VOT, which are speech variables that may carry the capability to be integrated in future real-time radio contact analyses, as an articulatory measure. We designed a standardized speech sample with twosyllable nonsense words to avoid potential confounds related to language-specific vowel and consonant constellations as well as breathing patterns (e.g., Eklund<sup>8</sup> and Van Puyvelde et al.<sup>28</sup>) and the position and/or linguistic meaning during voice production.9,16 We have chosen to test higher altitudes at 20,000 ft and 25,000 ft (6096 and 7620 m), congruent to air force pilots' training altitudes for operational purposes. Based on the MoVE,<sup>28</sup> we hypothesized we would observe increased F0 and decreased F0 range along with a decreased VOT during a presymptomatic hypoxic stage and a combined increased F0 and F0 range as well as increased VOT when hypoxia set in.

# METHODS

# Subjects

The study was approved by the Medical Ethics Committee of the University Hospital Brussels (B.U.N. 143201731931). The

Table I. Overview of the Speech Processes (i.e., Breathing, Phonation, and Resonance) and Their Speech Parameters Relevant for the Purpose of Operational Hypoxia Detection.

BREATHING: RESPIRATION						
MEASURE	DEFINITION	ANATOMIC LINK VOICE	OPERATIONAL RELEVANCE			
Respiration rate	The number of respirations within a given amount of time.	Nervus vagus (Cranial Nerve X)	Inappropriate breathing pauses may be indicative of ongoing work/overload.			
Respiration time	The time needed to take a breath.					
BREATHING: ARTICULATION						
Speech rate	The number of speech units of a given type within a given amount of time.	Articulatory organs (lips, tongue, epiglottis, larynx)	A deteriorated articulatory output may be indicative of ongoing work/overload.			
VOT	Time between release of a plosive (e.g., 'p') and vocal fold vibration onset of subsequent vowel.					
PHONATION: PITCH OR FUNDAMENTAL FREQUENCY (F0)						
Mean FO	Mean number of closure-opening pulses of vocal folds per second (Hz) within a given amount of time.	The laryngeal nerves and cricothyroid muscle system (tension causes increased F0)	F0 has been related with the impact of work/ overload and coping efforts.			
F0 range	The difference in F0 between the min-max measured mean value (e.g., vowel 1 vs. 2)		The FO-range can offer extra insight in a person's attempt to control the situation.			
F0 peak and floor values	The min-max values measured during a period of interest.		Lower floor/higher peak values may be a preliminary overload indicator.			
RESONANCE: FORMANTS						
Mean F1–FN	Frequency components that refer to resonance cavities and position of the vocal tract and articulators.	Articulatory organs (lips, tongue, epiglottis, larynx)	Indicates changes in the laryngeal/pharyngeal system and vowel pronunciation; potential preliminary overload indicator.			

The overview is based on previous literature<sup>28</sup> as well as the eventual feasibility of future automatic processing.

subjects were eight male adults with a military 'Very High Altitude' (VHA) training including hypoxia training. These persons are trained on the recognition of their hypoxia symptoms. They all participated at 20,000 ft and 25,000 ft. The mean age of the subjects was 33 yr (M = 32.6; SD = 7.3) at the time of experiment 1 at 20,000 ft. The experiments took place in the hypobaric chamber of the Center for Aerospace Medicine, Military Hospital Queen Astrid, Brussels, Belgium.

# Materials

General materials. During the experiment, for security reasons,  $S_p o_2$  was monitored with a live monitor system in the hypobaric chamber. We also registered SpO2, ECG, and respiration by the BioRadio TM system (Great Lakes NeuroTechnologies Inc., Cleveland, OH, USA), consisting of a primary module or wireless acquisition system connected to a PC. For S<sub>p</sub>O<sub>2</sub> registration, a pulse oximeter finger clip sensor with interface cable and BioRadio Sensor Pod were used. For ECG, we used a standard single-channel ECG registration (II derivation) in correspondence with standard configurations. The ECG signals were recorded with a 960-Hz sampling frequency, lowpass Bessel filter order 4, with a lower cutoff at 100 Hz. To register the breathing movements, a thoracic and abdominal respiratory effort belt were applied. Registration was made with a lowpass Bessel filter order 2, lower cutoff at 1 Hz. For the voice recordings we used a Shure Beta 58A Microphone (Shure, Essex, UK) connected on an Interface Focusrite Scarlett 2i2 (© Focusrite Audio Engineering Plc., High Wycombe, UK) by a NCMB900 XLR-XLR cable. Audio was registered with a sampling frequency of 44,100 Hz by means of Ableton Live, v.9 (Ableton Inc., Pasadena, CA, USA) and analyzed in Matlab and PRAAT<sup>1</sup>. The Statistical Package for Social Sciences Version 25.0 (SPSS 25.0) was used to perform the statistical analyses.

Speech set of two-syllable nonsense words. We designed a standardized speech set of two-syllable nonsense words. The subjects were asked to read the standard text within a time window of 45 s, then a pause of 15 s, after which they restarted. A two-syllable nonsense test was chosen to avoid language interference (e.g., Eklund<sup>8</sup> and Talbot et al.<sup>27</sup>) and to test for possible syllable order effects. It has been shown that a potential impairing impact on VOT may worsen in unstressed syllables<sup>9</sup> and in speech that lacks timing and/or rhythmical structure.5 Therefore, we asked the subjects to structure their reading by stressing the initial syllable of each word (e.g., 'tipa, 'tepa, 'tapa, ...). Doing this, each word had an initial stressed and second unstressed syllable. Furthermore, to allow the applicability in many languages of the sample set of words, we chose only words with voiceless (i.e., /t/, /p/ and /k/) and not voiced (i.e., /d/, /b/, /g/) stop phonemes since they may have different VOT formations. For instance, in French, voiced stops such as /d/ or /b/ require the voicing to start before the oral closure release, called negative VOT.<sup>18</sup>

# Procedure

*Experimental procedure.* The entire experiment proceeded under continuous medical supervision with a medical doctor,

two inside observers, and a technical instructor. After briefing and signing an informed consent, the preparation of the experiment commenced, and the first sea level (SL) baseline speech test was recorded. Subsequently, the subject and the inside crew received 30 min of prebreathing 100% oxygen to prevent decompression sickness. Once ascended to 20,000 ft or 25,000 ft (6096 or 7620 m), the subject was instructed to remove his mask at a sign from the experimenter. At that point, the speech test immediately started. To differentiate a presymptomatic from a symptomatic stage of hypoxia, the subjects were asked to indicate the moment they felt their first symptom. Similar as in an AHH training procedure, the subject was free to put on the mask when he preferred to stop the experiment. If not, a limit rule of 65% S<sub>p</sub>O<sub>2</sub> as bottom value was applied. Once the speech test was finished and the subject had recovered to 99%  $S_pO_2$ , the descent commenced and a debriefing took place (Fig. 1).

The duration of the experiment differed with altitudes and between subjects. At 20,000 ft, there were several rounds. To test the current hypothesis, we targeted four substages, i.e., SL, measure 1 (M1), measure 2 (M2), and measure 3 (M3) in which M1 was intended to be a presymptomatic (PRE-SYMP) symptom-free stage, M2 a transition (TRANS) stage, during which the first and second symptom were indicated, and M3 a symptomatic (SYMP) stage just before the end of the experiment (more than two symptoms). At 25,000 ft, there was only a SL, M1, and M2 measure since hypoxia appeared much faster at this altitude (see **Table II**).

*Missing Data.* In four out of the eight subjects, the BioRadio stopped working once at altitude. We were not able to recover these data. Hence, the physiological data are presented as descriptive statistics. With regard to the speech data, at 20,000 ft, all of the subjects completed at least three speech rounds (M1, M2, and M3). However, at 25,000 ft, two subjects desired to stop the experiment in the start of the second round (M2), which did not deliver enough data for these two subjects to conduct a reliable analysis at M2-25,000 ft. Hence the analyses at 25,000 ft for M2 are based on the data of six subjects.

## **Speech Analyses**

**Data preparation.** All of the speech samples were prepared for automatic presegmentation in Matlab by manually removing noise such as clearing the throat, words that were read for a second time due to a reading error [N = 3 or 1.16% at 25,000 ft (7620 m)] and by indicating reading errors [N = 6 at 20,000 ft (6096 m) or 1.04%; N = 11 or 2.16% at 25,000 ft].

**Presegmentation for F0-analysis.** In order to ease further processing, the audio signal was automatically presegmented using a custom program written in Matlab. The principle of the segmentation is that a syllable is deemed present if the running average (over 100 samples) of the signal amplitude is larger than a fraction (5%) of the maximum average amplitude. In practice, low amplitudes during a syllable may occur and short (< 2500 samples) interruptions are still considered part of the same syllable.



Fig. 1. Overview of the experiment.

*Frequency analyses for F0.* For each segmented syllable as described in the previous paragraph, the fundamental frequency (F0) was computed. The 'pitch' routine of Matlab was used with its default parameters, with the exception of a window length equal to 52 ms, an overlap between the windows of half the window length, and a median filter length of 7. An estimate of the F0 is thus obtained for each window position. In addition to that, the average of the F0 over the entire syllable is computed. The F0 range was the difference between the F0 values of syllables 1 and 2.

*Frequency analyses—logarithmic scale.* The difference in pitch, i.e., the perceived interval between two tones one octave separated in the middle octave (e.g., between C' and a C") and the higher octave (e.g., between C" and C""), is perceived similarly. However, the frequency difference between C' and a C" (i.e., 264 Hz) is half the frequency difference between C" and C"" (i.e., 528 Hz). Therefore, to compare frequency differences, a logarithmic scale log10(F0) needed to be applied.

*VOT.* The time interval of VOT was marked in PRAAT.<sup>1</sup> The onset of the stop release (i.e., start of the consonant 'p' or 't') was based on the presegmentation timings calculated by MatLab, taking the first zero-crossing before the segmentation point. The onset of the vocal fold vibration of the following vowel was performed in PRAAT based on the spectrogram to detect the

regular voicing pattern using the second zero-crossing of the glottal pulse to mark the beginning of voicing<sup>9</sup> (**Fig. 2**).

#### **Statistical Analyses**

For the data on 20,000 ft (6096 m), to test the impact of hypoxia on F0, we conducted two  $4 \times 2$  [Hypoxia (SL, M1, M2, and M3)  $\times$  Syllable (First, Second)] mixed ANOVAs with hypoxia as the within-subjects factor, syllable as the between-subject factor, and the log10(F0) as the dependent variable in the

first test and VOT in the second to test a position effect of the stressed vs. unstressed syllable on VOT. We also performed a one-way ANOVA [Hypoxia (SL, M1, M2, and M3)] test with F0 range as the dependent variable. For the data on 25,000 ft (7620 m), similar tests were conducted with only three Hypoxia conditions, i.e., SL, M1, and M2. Further, F0 range at SL vs. M1 was compared by a paired-samples *t*-test. At a post hoc level, to control for differences in the SL onset absolute values, we conducted a paired samples *t*-test to compare the absolute log10(F0 range) of SL at 20,000 ft vs. 25,000 ft and to test a post hoc interpretation (see Results for the rationale) of M1 25,000 ft vs. M3 20,000 ft and M2 25,000 ft vs. M3 20,000 ft. When the assumption of sphericity was violated, indicated by Mauchly's test, we applied Huynh-Feldt ( $\epsilon > 0.75$ ) or Greenhouse-Geisser ( $\epsilon <$ 0.75). In case of extra evaluations of the ANOVA analyses in pairwise comparisons between conditions, we used post hoc tests with the critical P-value for significance adjusted with Bonferroni correction.

# RESULTS

At 20,000 ft (6096 m), there was a significant impact on the log10(F0 range) [F(2.68, 685.52) = 46.11, P < 0.001,  $\eta p^2 = 0.153$ ]. Fig. 3 shows that a significant decrease from SL (M = 0.054, SD = 0.046) to M1 (M = 0.033, SD = 0.030) (P < 0.001)

Table II. Overview of the Conditions, Number of Participants, and Stages of Hypoxia at 20,000 ft and 25,000 ft.

20,000 ft						
CONDITION	SL	M1	M2	M3		
STAGE	Sea level	PRE-SYMP	TRANS	SYMP		
Ν	8	8	8	8		
SYMPTOMS	Symptom-free baseline at sea-level	No symptoms reported	First and second symptom reported	More than 2 symptoms reported		
S <sub>P</sub> O <sub>2</sub> [M (SD)]	99.0 (0.0)	89.8 (6.1)	80.4 (6.4)	75.3 (3.8)		
25,000 ft						
CONDITION	SL	M1	M2	/		
STAGE	Sea-level	PRE-SYMP	SYMP	/		
Ν	8	8	6	/		
SYMPTOMS	Symptom-free baseline at sea-level	No symptoms reported	2 or more symptoms reported	/		
S <sub>P</sub> O <sub>2</sub> [M (SD)]	99.0 (0.0)	90.1 (3.4)	67.9 (3.3)	/		

PRE-SYMP is presymptomatic; TRANS is transition stage; SYMP is symptomatic stage.



Fig. 2. Example of analysis of VOT.

was followed by a significant increase from M1 to M2 (M = 0.054, SD = 0.055) (P < 0.001), and again a significant increase from M2 to M3 (M = 0.076, SD = 0.056) (P < 0.001). F0 range at M3 was significantly larger than at baseline (Fig. 3). There was a significant impact of the degree of hypoxia on VOT [ $F(2.73, 594.71) = 44.35, P < 0.001, \eta p^2 = 0.169$ ]. VOT significantly decreased from SL (M = 0.0169, SD = 0.005) to M1 (M = 0.0133, SD = 0.004) (P < 0.001). There was no change between M1 and M2 (M = 0.0132, SD = 0.005) (P = 1.000). The VOT increased again from M2 to M3 (M = 0.0146, SD = 0.005). There was no interaction effect between the syllable and degree of hypoxia [ $F(2.73, 594.71) = 0.561, P = 0.625, \eta p^2 = 0.003$  (Fig. 3)]. The degree of hypoxia significantly impacted the log10(F0) [ $F(2.802, 1364.815) = 77.43, P < 0.001, \eta p^2 =$ 



**Fig. 3.** At the top, the course of F0 range and VOT at 20,000-ft altitude. At the bottom, the course of F0 and the two syllables separated. The fine-dotted line presents the course of syllable 2.

0.137]. Log10(F0) significantly increased from SL (M = 2.046, SD = 0.076) to M1 (M = 2.081, SD = 0.072) (P < 0.001). The F0 remained unchanged from M1 to M2 (M = 2.082, SD = 0.086) (P = 1.000) and significantly decreased from M2 to M3 (M = 2.055, SD = 0.083) (P < 0.001). SL also significantly differed from M2 (P < 0.001) and M3 (P = 0.025). A significant interaction effect between the degree of hypoxia and the syllable position (i.e., first or second syllable) [F(2.802, 1364.815) = 23.431, P < 0.001,  $\eta p^2 = 0.046$ ] showed that the decrease in log10(F0) at M3 was primarily the result of a decrease at the second syllable. Log10(F0) at the first syllable increased from SL to M1 and to M2, whereas log10(F0) of the second syllable started to decrease from M1 onwards (Fig. 3).

At 25,000 ft (7620 m), there was a significant impact on the log10(F0 range) [ $F(1.677, 313.67) = 20.21, P < 0.001, \eta p^2 =$ 0.098]. Log10(F0 range) significantly increased from SL (M = 0.041, SD = 0.041) to M1 (M = 0.056, SD = 0.048), P < 0.001, followed by a significant increase from M1 to M2 (M = 0.068, SD = 0.065) (P = 0.024; Fig. 4). The degree of hypoxia had a significant impact on VOT [F(1.344, 290.249) = 10.83, P <0.001,  $\eta p^2 = 0.048$ ]. VOT significantly decreased from SL (M = 0.0144, SD = 0.004) to M1 (M = 0.0123, SD = 0.003) (P <0.001) and increased again from M1 to M2 (M = 0.0139, SD =0.007; P = 0.11). There was no difference between SL and M2 (P = 1.000; Fig. 4). There was a significant impact of the degree of hypoxia on the log10(F0) [F(1.706, 543.100) = 34.85, P <0.001,  $\eta p^2 = 0.085$ ]. Log10(F0) significantly increased from SL (M = 2.045, SD = 0.088) to M1 (M = 2.062, SD = 0.077) (P < 0.077)0.001) and again to M2 (M = 2.075, SD = 0.092; P = 0.001). SL also significantly differed from M2 (P < 0.001). A significant interaction effect between the degree of hypoxia and the syllable position (i.e., first or second syllable) [F(1.706, 543.100) =4.33, P = 0.018,  $\eta p^2 = 0.011$ ] showed that between M2 and M3, the two syllables started to gain distance, with a steep increase in syllable 1 and the onset of a smoothing syllable 2 (P = 0.012; Fig. 4).

The results above show a correspondence between the vocal reactivity from BL to M1 at 25,000 ft and BL to M3 at 20,000 ft, i.e., a significantly decreased VOT in combination with an increased F0 range. However, at 25,000 ft, there was an immediate increase in F0 range from SL to M1; the absolute values of M1 and even M2 at 25,000 ft were smaller than the absolute value of the F0 range of M3 at 20,000 ft. Also, the absolute F0 range values at SL were smaller at 25,000 ft than at 20,000 ft. Therefore, we conducted a paired samples *t*-test to compare the absolute log10(F0 range) of the SL at 20,000 ft vs. 25,000 ft, M1 25,000 ft vs. M3 20,000 ft, and M2 25,000 ft vs. M3 20,000 ft. The log10(F0 range) of SL 25,000 ft was significantly smaller than at 20,000 ft [t(219) = 4.181, P < 0.001] and significantly smaller at M1 25,000 ft than at M2 20,000 ft [t(219) = 6.910], *P* < 0.001]. The difference between M2 25,000 ft and M3 20,000 ft was not significant [t(219) = 0.688, P = 0.469].

With regard to the physiological results, **Table III** shows the descriptive statistics of the physiological measures [respiration rate, heart rate, and respiratory sinus arrhythmia (RSA)] of four subjects. RSA refers to the parasympathetic or regulatory



Fig. 4. At the top, the course of F0 range and VOT at 25,000-ft altitude. At the bottom, the course of F0 and the two syllables separated.

component of a person's natural heart rate variability. It expresses the coupling between the heart period and respiration cycle, mediated by the nervus vagus (cranial nerve X)—hence vagal activity—that has a pivotal function both in regulation processes and voice production.<sup>28</sup>

# DISCUSSION

In the current study, we examined the feasibility of detecting voice markers sensitive to acute hypobaric hypoxia in an early PRE-SYMP stage. Based on the MoVE,<sup>28</sup> we hypothesized the presence of a PRE-SYMP compensatory stage during which the voice would respond to the changed conditions due to hypoxia to cope with the situation before clinical deterioration set in. This compensation mechanism was supposed to be characterized by a decrease in both F0 range and VOT and an increase in F0. At 20,000 ft (6096 m), our hypothesis was confirmed. During the PRE-SYMP stage at 20,000 ft, the voice markers showed the hypothesized changes in phonation and articulation. The additional analyses on the two syllables showed that the decreased F0 range was mainly due to a raised pitch of the

**Table III.** Descriptive Statistics of Physiological Variables of Four Participants

 During a Baseline Measure at Sea Level.

	20,000 ft [M (SD)]	25,000 ft [M (SD)]
RSA	60.33 (27.68)	37.2355 (9.08)
RRI	0.914 (0.100)	0.905 (0.104)
<i>f</i> R	12.088 (1.22)	14.07 (3.05)
<i>f</i> R	12.088 (1.22)	14.07 (3.05)

RSA = respiratory sinus arrhythmia; RRI = R-R interval; fR = respiration frequency rate.

second syllable, resulting in a rather monotone speech with little difference in F0 between the first and second syllable. As hypothesized in the MoVE,<sup>28</sup> this voice response pattern of increased F0 and decreased F0 range may be the expression of a compensation attempt of the body to rebalance ongoing bottom-up arousal by regulatory top-down coping mechanisms.<sup>28</sup> During this PRE-SYMP stage, S<sub>p</sub>O<sub>2</sub> decreased to 89.9%.

After this PRE-SYMP stage, a TRANS stage, during which S<sub>p</sub>O<sub>2</sub> decreased toward 80%, started. During TRANS, the subjects reported one or two symptoms, pointing to the onset of the hypoxic process. With increasing hypoxia and symptoms during M2 and M3, the F0 of both syllables started to decline again. This decline was steeper in the second syllable than in the first one. Consequently, the F0 range increased once again, but it was only in M3 that this increase became significantly higher than measured at SL. In fact, the TRANS stage M2 is characterized by the breakdown of the PRE-SYMP phonetic compensatory mechanisms, resulting in a "reset" of the F0 range. At an articulatory level however, VOT remained unchanged during the TRANS stage M2. The fact that-contrary to articulationthe phonation resets itself after the compensatory PRE-SYMP stage has finished, may point to a faster dose-response pattern in phonation than in articulation. This may correspond with the observations of a slower VOT adaptation than SpO2 adaptation in chronic hypoxic conditions.<sup>17</sup> However, it also implies that during a hypoxic course, there is a period (during the TRANS stage) during which the F0 range is not informative to detect hypoxia because, at that point, there is no difference with the initial baseline reference measure of F0 range at SL.

Subsequent to this TRANS stage, M3 was characterized by a significantly increased F0 range in comparison with any stage before. Moreover, during M3, VOT started to rise again. However, unlike the F0 range, although VOT during M3 was significantly higher than during the PRE-SYMP and TRANS stage, it still remained smaller than measured during SL, again confirming its slower dose-response pattern.

Summarized, this means that, at 20,000 ft, both a decreased VOT and increased F0 compared to SL functioned as a warning signal in all of the hypoxic stages. A decreased F0 range compared to SL acted as a secure warner, marking in particular a PRE-SYMP stage, and an increased F0 range as a red flag for a symptomatic hypoxic stage. Moreover, at 20,000 ft, once hypoxia had settled in, VOT showed a slower dose-response curve than F0 range.

At 25,000 ft (7620 m), voice reactivity was different. Primarily, at 25,000 ft, we did not observe the above described compensatory top-down reactivity that was found at 20,000 ft. In fact, the vocal reactivity from BL to the PRE-SYMP stage M1 at 25,000 ft corresponded with the reactivity from BL to M3 observed at 20,000 ft of altitude; that is, a decreased VOT in combination with an increased F0 range. We propose that there may be a similar nonlinear relationship between altitude and voice reactivity as between altitude and ambient pressure and time of useful consciousness (TUC).<sup>6</sup> Whereas a person's TUC is still approximately 20 min at 20,000 ft, it is decreased to 3-5 min at 25,000 ft.<sup>6</sup> Hence, a comparable nonlinear time aspect may influence speech functionality, resulting in the omission of the above described PRE-SYMP and TRANS stage voice features.

Nevertheless, notwithstanding the similarities between M3 at 20,000 ft and M1 at 25,000 ft, there were some differences as well between both. At 25,000 ft, we did not observe the F0 decline when hypoxia settled in, neither in M1 nor in M2. On the contrary, at M2, the first syllable continued to increase in pitch. With regard to F0 range, although it increased at M1 at 25,000 ft (in place of the expected compensatory decrease) in comparison with SL, its absolute values remained significantly smaller than those at M3 at 20,000 ft. Moreover, the absolute F0 range values at SL were already significant smaller at 25,000 ft than at 20,000 ft. Since this was a within-subjects design, it is doubtful that this is coincidental.

We suggest that a combination of two processes may play a role in these results. Pattyn et al.<sup>21</sup> showed that reactivity can involve the interaction between a phasic activation component and a tonic activation component; the first being a transient reactivity that may reset over time-on-task and being respiration driven; the latter being a rather constant throughout during arousal, typically independent from the experimental manipulation and being typified by a cardiac vagal withdrawn. In Pattyn et al.,<sup>21</sup> tonic reactivity was observed in a pre-experimental baseline stage in pilot students going through an exam period where it was not present in those that were not having exams. Obviously, an initial aroused state of tonic reactivity can overrule the following experimentally induced arousal and hinder cardiac reactivity occuring due to a floor effect [see the Law of Initial Values (LIV) that states that both the magnitude and direction of a psychophysiological response can highly vary in function of its initial values]. Hence, a rigid reactivity in response to an experimental manipulation may be both the consequence of the experimental task as well as the pre-experimental conditions of the subject.<sup>21</sup> Knowing that speech is a psychophysiological response,<sup>28</sup> we can expect it to be subject to the LIV as well.

We suggest that, related to hypoxia-induced arousal, the phasic component is the well-known physiological sympathetic or physiological adrenal compensatory response to AHH.<sup>13</sup> AHH is known to evoke the activation of sympathetic reactivity (i.e., augmented resting heart rate and blood pressure and decreased heart rate variability),<sup>4,7,23</sup> having a direct influence on the vascular smooth muscles,<sup>13</sup> and which would thus be stronger at higher altitude as described above. Although studies on the adrenal response were conducted for rather longer periods of time and lower altitudes than targeted in the current study [e.g., 6 d at 14,271 ft<sup>4</sup> (4350 m); 22 h at 14,950 ft<sup>7</sup> (4557 m); 2–13 d at 15,748 ft<sup>23</sup> (4800 m)], their results support our observations since the impact of hypoxia on the pulmonary vascular smooth muscle system is stated to be rapid, with a maximum response occurring within 5 min of exposure.<sup>23</sup> We suggest that—in correspondence with the above described nonlinear response course of the TUC-this phasic adrenal compensatory response is stronger at 25,000 ft than at 20,000 ft, having its immediate effect on the laryngeal and respiratory smooth muscle system.

On the other hand, we propose that the more rigid voice output during the 25,000-ft SL measures in comparison with those at 20,000 ft are the expression of tonic reactivity due to the attempt to cope with anticipatory arousal when preparing for and undergoing the 25,000-ft experiment. The observed aroused voice reactivity is in line with the physiological descriptive measures at SL before the 25,000-ft experiment compared to 20,000 ft, showing a vagal withdrawn or cardiac-driven reactivity with a decreased heart period and RSA, which also corresponds with the findings of Pattyn et al.<sup>21</sup> Hence, this would imply that situationally related tonic reactivity can intervene with the detection of hypoxia in a PRE-SYMP stage and that the use of an operational baseline in mapping a person's anticipatory state of readiness should be taken into account.<sup>14</sup> Indeed, tonic reactivity and the need to cope with it in an anticipatory stage is a recognized phenomenon under military personnel well-trained for an occupational specialty. Operators and pilots are known to enter-anticipatory to the task-a so called ready-state, which involves a cognitive state of readiness or compensation to prepare for the targeted stress of an operation (e.g., Hancock and Krueger<sup>14</sup>). Within this stage, the perceived level of control is an important factor in the actual stress outcome in such a way that even low stress can be detrimental when seeming unchangeable or uncontrollable.<sup>14</sup> At all times, operational people search to compensate for a nearby potential perceived loss of mastery.<sup>14</sup> The impact of these type of coping processes on the voice output has been shown during emergency situations in which two communicators displayed two different voice stress responses toward the same shared situation due to their respective degree of top-down regulation expected in their particular role, position, and training (Van Puyvelde et al.<sup>28</sup>). The voice output of those in charge of the most mediating and regulating communication task during emergency was marked by the hypothesized compensatory top-down voice variables,<sup>28</sup> whereas the other communicator showed mainly voice arousal in the sense of increased F0.

In conclusion, voice stress analysis has some promising potentials in the detection of PRE-SYMP hypoxia in an operational aviation context. At 20,000 ft, we could distinguish a PRE-SYMP stage with F0 range as a secure warner. At 25,000 ft, both a phasic and tonic component (i.e., an anticipatory state of readiness) were at work in the voice output, showing that, in an operational context, a tonic component always should be taken into account in SL baseline measures. Finally, we suggest a nonlinear relationship between altitude and voice reactivity similar to between altitude and ambient pressure and TUC.

## ACKNOWLEDGMENTS

We want to thank the Center for Aerospace Medicine, Military Hospital of Brussels, Belgium, and the participating subjects.

*Financial Disclosure Statement:* The current study was funded by Belgian Defence HFM-1602. The authors have no competing interests to declare.

*Authors and affiliations:* Martine Van Puyvelde, Prof. dr., Xavier Neyt, Prof. dr. Ir., and Nathalie Pattyn, Prof. dr. Med. Maj., VIPER Research Unit, LIFE Department, Royal Military Academy, Brussels, Belgium; Martine Van Puyvelde, Brain Body and Cognition Research Group and Clinical and Lifespan Psychology, Department of Psychology and Educational Sciences, and Nathalie Pattyn, MFYS-BLITS, Human Physiology Department, Vrije Universiteit Brussel, Brussels, Belgium; and Wim Vanderlinden, Dr., Maarten Van den Bossche, Tony Bucovaz, and Tony De Winne, Military Hospital Queen Astrid, Center for Aerospace Medicine, Hypobaric Chamber, Brussels, Belgium.

# REFERENCES

- Boersma P, Weenink D. Doing phonetics by computer, version 6.0.29, 2013. [Accessed 15 June 2017]. Available from http://www.fon.hum.uva. nl/praat/.
- Cable GG. In-flight hypoxia incidents in military aircraft: causes and implications for training. Aviat Space Environ Med. 2003; 74(2):169–172.
- Câmara R, Griessenauer C. Anatomy of the vagus nerve. In: Tubbs RS, Rizk E, Shoja MM, Loukas M, Barbaro N, Spinner RJ, eds. Nerves and nerve injuries. Vol. 1. History, embryology, anatomy, imaging, and diagnostics. Cambridge (MA, USA): Academic Press, Elsevier Ltd.; 2015:385–397.
- Cornolo J, Mollard P, Brugniaux JV, Robach P, Richalet JP. Autonomic control of the cardiovascular system during acclimatization to high altitude: effects of sildenafil. J Appl Physiol (1985). 2004; 97(3):935–940.
- Davidow JH. Systematic studies of modified vocalization: the effect of speech rate on speech production measures during metronomepaced speech in persons who stutter. Int J Lang Commun Disord. 2014; 49(1):100–112.
- Davis JR, Johnson R, Stepanek J, eds. Fundamentals of aerospace medicine. Philadelphia (PA, USA): Lippincott Williams & Wilkins; 2008.
- Duplain H, Vollenweider L, Delabays A, Nicod P, Bärtsch P, Scherrer U. Augmented sympathetic activation during short-term hypoxia and high-altitude exposure in subjects susceptible to high-altitude pulmonary edema. Circulation. 1999; 99(13):1713–1718.
- Eklund R. Languages with pulmonic ingressive speech: updating and adding to the list. Proceedings from Fonetik, Lund University Sweden, 2015:31–34. [Accessed July 2, 2017]. Available from https://konferens. ht.lu.se/fileadmin/user\_upload/sol/ovrigt/konferens\_fonetik2015/docs/ WP55\_Fonetik2015\_hela.pdf.
- 9. Falk S, Müller T, Dalla Bella S. Non-verbal sensorimotor timing deficits in children and adolescents who stutter. Front Psychol. 2015; 6:847.
- Fayed N, Modrego PJ, Morales H. Evidence of brain damage after highaltitude climbing by means of magnetic resonance imaging. Am J Med. 2006; 119(2):168.e1–168.e6.
- Files DS, Webb JT, Pilmanis AA. Depressurization in military aircraft: rates, rapidity, and health effects for 1055 incidents. Aviat Space Environ Med. 2005; 76(6):523–529.
- 12. Ghosh PC, Pant P. In-flight hypoxia still a worrying bane. Ind J Aerosp Med. 2010; 54(1):7–12.

- Hainsworth R, Drinkhill MJ, Rivera-Chira M. The autonomic nervous system at high altitude. Clin Auton Res. 2007; 17(1):13–19.
- Hancock PA, Krueger GP. Hours of boredom, moments of terror. Temporal desynchrony in military and security force operations. Washington (DC): National Defense University Center for Technology and National Security Policy; 2010.
- Harding RM, Mills FJ. Aviation medicine. Problems of altitude I: hypoxia and hyperventilation. BMJ. 1983; 286(6375):1408–1410.
- Johnston BJ, Iremonger GS, Hunt S, Beattie E. Hypoxia training: symptom replication in experienced military aircrew. Aviat Space Environ Med. 2012; 83(10):962–967.
- Kiss G, Sztahó D, Vicsi K, Golemis A. Connection between body condition and speech parameters - especially in the case of hypoxia. In: 5th IEEE Conference on Cognitive Infocommunications (CogInfoCom). New York (NY, USA): IEEE; 2014:333–336.
- Klatt DH. Voice onset time, frication, and aspiration in word-initial consonant clusters. J Speech Lang Hear Res. 1975; 18(4):686–706.
- Lieberman P, Morey A, Hochstadt J, Larson M, Mather S. Mount Everest: a space analogue for speech monitoring of cognitive deficits and stress. Aviat Space Environ Med. 2005; 76(6, Suppl.):B198–B207.
- Neuhaus C, Hinkelbein J. Cognitive responses to hypobaric hypoxia: implications for aviation training. Psychol Res Behav Manag. 2014; 7:297–302.
- Pattyn N, Migeotte PF, Neyt X, van den Nest A, Cluydts R. Comparing real-life and laboratory-induced stress reactivity on cardio-respiratory parameters: differentiation of a tonic and a phasic component. Physiol Behav. 2010; 101(2):218–223.
- Petrassi FA, Hodkinson PD, Walters PL, Gaydos SJ. Hypoxic hypoxia at moderate altitudes: review of the state of the science. Aviat Space Environ Med. 2012; 83(10):975–984.
- Richalet JP, Larmignat P, Rathat C, Keromes A, Baud P, Lhoste F. Decreased cardiac response to isoproterenol infusion in acute and chronic hypoxia. J Appl Physiol. 1988; 65(5):1957–1961.
- Saito I, Fujiwara O, Utsuki N, Mizumoto C, Arimori T. Hypoxia-induced fatal aircraft accident revealed by voice analysis. Aviat Space Environ Med. 1980; 51(4):402–406.
- Smith AM. Hypoxia symptoms in military aircrew: long-term recall vs. acute experience in training. Aviat Space Environ Med. 2008; 79(1):54–57.
- Sondhi S, Khan M, Vijay R, Salhan AK, Sharma SK. Effect of normobaric and hypobaric hypoxia on formant characteristics of human voice. Int J Comput Appl. 2015; 122(15):32–37.
- Talbot NP, Balanos GM, Dorrington KL, Robbins PA. Two temporal components within the human pulmonary vascular response to ~2 h of isocapnic hypoxia. J Appl Phys (1985). 2005; 98(3):1125–1139.
- Van Puyvelde M, Neyt X, McGlone F, Pattyn N. Voice stress analysis: a new framework for voice and effort in human performance. Front Psychol. 2018; 9:1994.