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Age-related changes in olfactory processing detected with olfactory event-related brain potentials using velopharyngeal closure and natural breathing

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Abstract

Previous olfactory event-related potential (OERP) studies often employed the Velopharyngeal Closure (VC) method, which prevents respiratory air flow in the nose during odor presentation. However, the use of VC has limited the application of OERPs to populations able to perform this artificial breathing technique. The present study investigated the effects of Natural Breathing (NB) in comparison to VC on OERP latency and amplitude in young (mean age: 24 years) and elderly (mean age: 71 years) adults. OERPs were recorded from three midline scalp electrodes (Fz, Cz, Pz) for 15 trials in each breathing condition with an interstimulus interval of 3.5 min, using amyl-acetate as stimulus. Subjects were asked to report perceived stimulus intensity. A thermistor placed inside one nostril monitored nasal respiration and performance of VC. In the NB condition, subjects were instructed to breathe normally through mouth and nose, while stimulus presentation occurred during inspiration. In both breathing conditions, elderly subjects showed significantly smaller N1–P2 and N1–P3 interpeak amplitudes and longer latencies for N1, P2, P3 than younger subjects. VC generated significantly larger N1–P2 amplitudes across all electrode sites, whereas Natural Breathing produced a trend towards shorter P3 latencies. No significant interaction was found between age and breathing technique. The present investigation showed that the OERP is a sensitive measure for detecting age-related changes in olfactory function regardless of breathing technique. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Breathing; Velopharyngeal closure; Aging; Smell; Olfaction; Olfactory event-related potential (OERP)

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1. Introduction

Electroencephalographical recordings of brain responses to auditory, visual, and somato-sensory stimuli have received much attention by researchers. Findings from these studies contributed to the understanding of human information processing in health and disease, and Event-Related Potentials (ERP) of these modalities are already well established assessment tools in clinical settings (Spehlmann, 1985). Comparably, the development of ERPs to olfactory stimuli progressed much slower. This was mainly due to previous negligence of the chemical senses in research, and the difficulties associated with the control of olfactory stimuli. Reliable recording of Olfactory Event-Related Potentials (OERP) requires rapid rise of odor concentration without stimulation of sensory modalities other than olfactory (Evans et al., 1993); features that were firstly incorporated in a stimulus delivery device for odors by Kobal (1981). Rise times below 20 ms are generally achieved with this and similar olfactometers, yielding reliable neural responses in an ERP paradigm (Lorig, 2000). In addition, smell and taste are generally the least understood human senses, however, in the last decade a growing body of research has emphasized the importance of the chemical senses in mate selection, quality of life, nutrition, as well as in disease, such as in Parkinson's Disease, Huntington's Disease, Korsakoff's Syndrome, Depression, and Alzheimer's Disease (AD) (Harrison and Pearson, 1989). For example, recent evidence suggests that areas in the central nervous system processing olfactory information are affected at the early stages of AD, even before the onset of cognitive decline, and that olfactory dysfunction might be an early indicator of AD (Murphy, 1999). It is this more profound understanding of the importance of olfaction and the constant improvements in OERP research methods which have rendered the OERP a promising candidate to be included in standard clinical assessments.

Much of the previous literature on OERPs used the Velopharyngeal Closure (VC) method as the breathing technique, where subjects are trained to use the levator veli palatini muscle to elevate the soft-palate in order to isolate the pharyngeal cavity from the nasal cavity (Geisler et al., 1999; Huang et al., 1998; Kobal, 1981; Kobal and Hummel, 1991; Murphy et al., 1994; Pause et al., 1996; Wetter and Murphy, 1999) (see Fig. 1).

This procedure prevents intranasal respiratory airflow and ensures the absence of interference from respiration on stimulus presentation (Kobal and Hummel, 1991). However, some populations may not be able to perform VC reliably, and therefore, the use of VC has limited olfactory assessment with OERPs in populations unable to perform this artificial breathing technique. These patients, in particular, should not be automati-

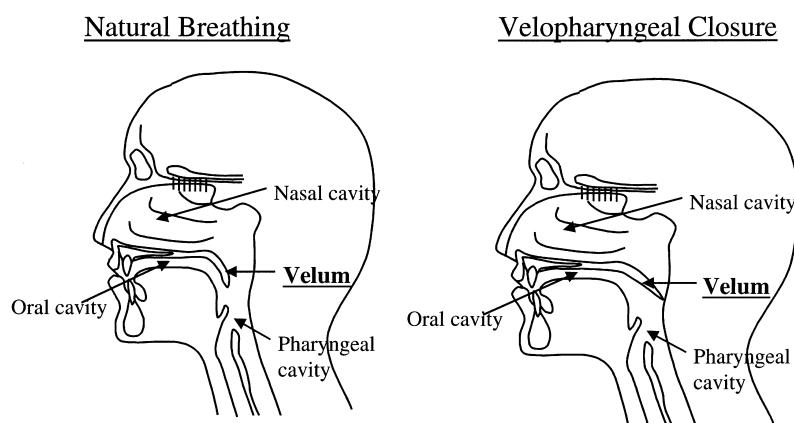


Fig. 1. Schematic drawing of human head showing velum position for natural breathing and velopharyngeal closure. No respiratory airflow enters the nasal cavity during velopharyngeal closure.

cally excluded from OERP assessment, since OERPs require minimal effort and cooperation from the patient compared with traditional psychophysical testing, and are therefore especially well-suited for these populations. However, when using an alternative to VC, the OERP components can be expected to differ in amplitude and latency from those recorded with VC.

Two procedural variables that have been identified in OERP studies are breathing technique and administration of the stimulus with respect to the respiratory cycle. In a recent study, Pause et al. (1999) recorded OERPs with a short ISI (8 s) from eight subjects performing VC and normal mouth breathing. In both instances, odor presentation occurred non-synchronously to the breathing cycle. In an off-line analysis, trials were separated into whether the odor was delivered during phases of inspiration or expiration. In this study, mouth breathing yielded shorter N1 latencies and larger P3 amplitudes than VC, which the authors attribute to the division of attention between stimulus processing and maintenance of breathing technique. Lorig et al. (1996) examined the difference between synchronous and non-synchronous odor presentation. If the stimulus was delivered during nasal inspiration, the amplitude of the positive peak at approximately 800 ms latency was generally found to be smaller than if stimulus presentation in the nose occurred randomly during mouth breathing. However, these studies used only normal, young adults with similar olfactory function as participants. To this point, no previous study has investigated the effects of the above mentioned variables in populations with different olfactory function.

Psychophysical measures have demonstrated an age-related decline in olfactory function, including odor detection threshold (Murphy, 1983), odor identification (Murphy and Cain, 1986) and odor memory (Murphy et al., 1991, 1997). Moreover, anatomical changes across the life span in peripheral olfactory structures (e.g. olfactory receptor cells) and central olfactory areas such as temporal lobe, entorhinal cortex, hippocampus, and amygdala have been identified (Cowell et al., 1994; Liss and Gomez, 1958; Price et al., 1991). Recent OERP studies reported decreased amplitudes and longer

latencies from older subjects compared to younger subjects (Morgan et al., 1997, 1999; Murphy, 1999; Murphy et al., 1994).

In the present study, the effects of Natural Breathing (NB) in comparison to Velopharyngeal Closure on OERP latency and amplitude were investigated in two populations who are known to exhibit different olfactory function, but are able to perform Velopharyngeal Closure: young and elderly adults.

2. Methods and materials

2.1. Participants

Participants were 12 normal young adults (6 male, 6 female, mean age: 24 years), and 12 older adults (6 male, 6 female, mean age: 71 years). The older participants were recruited from a longitudinal study on chemosensory function and had been previously screened for general, nasal, and mental health. All older participants tested negative for the $\epsilon 4$ allele of apolipoprotein E (ApoE), a gene known to compromise olfactory function in old age (Murphy et al., 1998a). All participants reported normal nasal health and the absence of nasal obstructions or current allergies. Participants were paid for participation or received course credit.

2.2. OERP apparatus and stimulus

Olfactory stimulation was accomplished by means of an olfactometer described previously (Murphy et al., 1994) and incorporated features used by Kobal (1981). Clean air established a flow rate of 7.4 l/min, with an 80% relative humidity achieved by passing the air stream through deionized water of a constant temperature. In a second circuit, liquid amyl-acetate in its pure form was substituted for water. Plastic tubing delivered the air, which was heated to body temperature (36.5°C) before it passed into the nostril through a Teflon tube (1.6 mm inner diameter) placed just inside the nostril. At each stimulus presentation an electromagnetic valve opened for 200 ms, dur-

ing which time a portion of the main air flow was replaced by an equal portion of odor flow (2.1 l/min). Excess air/odor was exhausted via a vacuum pump that led to an exhaust vent located in another room. The switching valves were acoustically isolated and a constant flow rate into the nostril was maintained at all times during OERP data collection. The concentration of amyl-acetate (1493 ppm) was safely below the threshold for nasal pungency of 1648 ppm (Cometto-Muniz and Cain, 1991). Stimuli rise time was below 20 ms (Murphy et al., 1994). Stimuli were presented with a long interstimulus interval (ISI) of 3.5 min to avoid adaptation and habituation, and to produce robust OERPs (Morgan et al., 1997).

2.3. OERP recordings

Electroencephalographic (EEG) activity was recorded using gold-plated electrodes, affixed with Grass electrode cream and tape, from the Fz, Cz, and Pz electrode sites referenced monopolarly to linked earlobes and grounded to the forehead, according to the international 10/20 system. Impedance was in most cases kept below 5 k Ω and never exceeded 10 k Ω . Neuroelectric activity and nasal respiration were recorded for 2000 ms (500 ms prestimulus and 1500 ms poststimulus), amplified 20 000 times (Astro-Med Grass Instrument, Model 12 Neuro-Data Acquisition System) through a 0.1–30 bandpass filter (6 db per octave) and digitized at 1000 Hz (Biopac Systems, MP100) and stored on disk. Artifactual activity was assessed between trials at all electrode sites; including electro-ocular activity, which was monitored with electrodes placed at the outer canthus and supraocularly to the right eye. Trials with eye blinks or EEG activity exceeding ± 50 μ V were excluded from further analysis. Fifteen individual trials were averaged off-line to isolate the OERP from the background EEG.

2.4. Procedure

Participants were seated comfortably in a reclining chair adjacent to the olfactometer arm to reduce muscle movement. Before each trial, participants placed the nostril on the nasal piece.

Stimulus onset occurred randomly within a 10–25-s time window. The time window was chosen to reduce expectancy effects (Loveless and Sanford, 1974). All participants were exposed to both VC and NB in a counterbalanced block design. Before each session, participants were trained to perform VC using a thermistor ($t_c = 6$ s; Model F-TCT, Grass Instruments, USA) placed inside one nostril, which monitored nasal air flow at all times. Nasal respiration was recorded simultaneously with EEG activity and displayed on an oscilloscope not visible to the participant. In the VC condition, participants were instructed to use the soft palate to close the nasal cavity from the pharyngeal tract until correct performance of VC was achieved. Stimulus presentation in the VC condition was triggered manually non-synchronously to the breathing cycle. In the NB condition, participants were instructed to breathe normally through mouth and nose while stimulus presentation was triggered manually during inspiration. The experimenter judged the phase of inspiration heuristically based on oscilloscope readings (see Fig. 2).

The relationship between stimulus administration and inspiration was not explicitly stated. Correct performance of VC was monitored throughout the experiment. Trials showing nasal respiration were rejected and repeated. If necessary, VC was practiced between trials.

2.5. Magnitude estimation and single-stimulus paradigm

Immediately after each trial, participants were asked to report the perceived intensity of the stimulus they had just received on the Labeled Magnitude Scale (LMS). The LMS is a semantically labeled scale with logarithmic spacing of its verbal labels (e.g. strongest imaginable, strong, weak, barely detectable, etc.), developed by Green et al. (1993) for magnitude estimation of oral somatosensation and gustation, and was subsequently validated for olfaction (Green et al., 1996). In addition to eliciting a subjective measure of the participant's olfactory perception, the estimation of odor magnitude for each stimulus insured that the participant was attending to the stimulus,

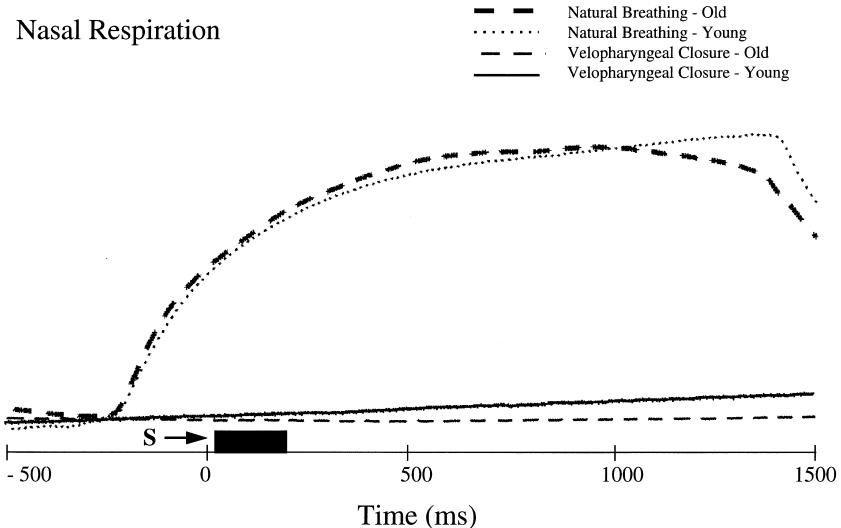


Fig. 2. Nasal respiration for both age groups and breathing conditions, monitored with thermistor placed inside one nostril. Upward slope indicates inspiration. Straight line indicates absence of nasal airflow (S = stimulus).

eliciting cognitive OERP components in a single-stimulus paradigm. Generally, a P3 component can be elicited when subjects attend to a novel stimulus (Donchin and Coles, 1988), and is usually produced with an oddball paradigm. However, P3 components can also be obtained with a single-stimulus, where only one stimulus is presented to which the subject has to respond. Longer ISI's are used in this paradigm to allow for the memory trace to be updated, rendering each trial 'novel' (Polich et al., 1994). This paradigm produces virtually identical scalp topographies as the oddball paradigm, and has been shown to exhibit the same effects for many experimental variables (Cass and Polich, 1997; Polich and Heine, 1996). The single-stimulus paradigm is especially useful for cognitive ERP testing in the olfactory modality (Geisler et al., 1999; Geisler and Murphy, 2000; Morgan et al., 1999), where a rapid succession of stimuli would produce strong adaptation and habituation effects.

3. Results

Measurements included N1–P2, N1–P3 interpeak amplitudes and N1, P2, P3 latencies. P3 was

identified as the largest peak within the Late Positive Complex (LPC) of the OERP following P2. A repeated measures multivariate analysis of variance (MANOVA) was utilized for each OERP component, with age as between-subject factor and breathing condition and electrode site as within-subject factors. Greenhouse–Geisser adjustments were made to correct for degrees of freedom (Greenhouse and Geisser, 1959). Grand averaged OERP waveforms at Fz, Cz, Pz, and EOG electrode sites are illustrated for younger participants and older participants in both breathing conditions (see Fig. 3).

Fig. 4 displays mean N1–P2 amplitudes for each group in each breathing condition.

Analyses demonstrated a significant decrease in amplitude for older subjects for each OERP component: N1–P2 [$F_{1,23} = 6.1, P < 0.05, (\eta^2 = 0.217)$] and N1–P3 [$F_{1,23} = 18.74, P < 0.001 (\eta^2 = 0.46)$]. A significant age effect was found for latency for all OERP components: N1 [$F_{1,23} = 16.88, P < 0.001 (\eta^2 = 0.434)$], P2 [$F_{1,23} = 33.82, P < 0.001 (\eta^2 = 0.606)$], and P3 [$F_{1,23} = 46.62, P < 0.001 (\eta^2 = 0.679)$]. Additionally, P2 latency was subtracted from P3 latency. This measure of adjusted P3 latency also yielded longer latencies for elderly subjects [$F_{1,23} = 7.16, P = 0.014 (\eta^2 = 0.246)$].

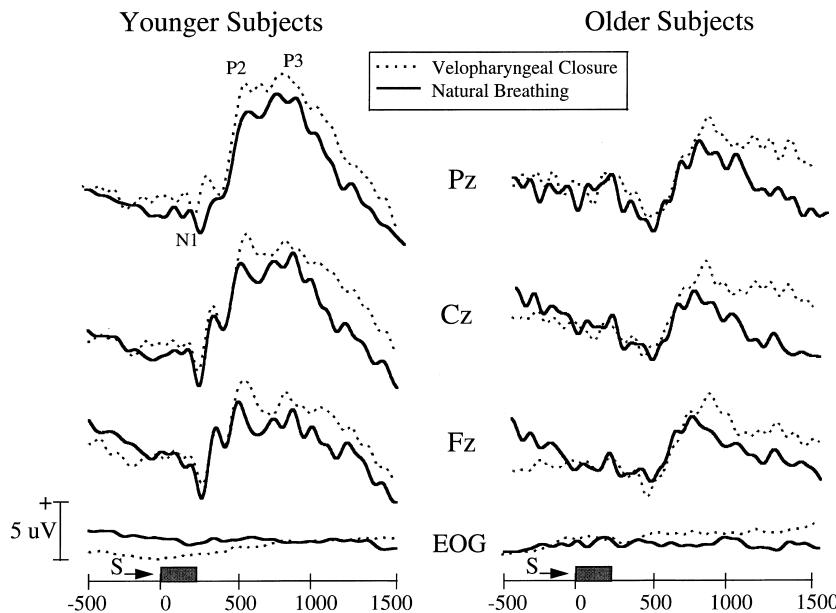


Fig. 3. Grand averaged olfactory event-related potential waveforms at each electrode site for each breathing condition in young (left panel) and older (right panel) adults (S = stimulus).

Analyses indicate a significant main effect for breathing technique for N1–P2 amplitude: $[F_{1,23} = 5.04, P < 0.05 (\eta^2 = 0.187)]$ (see Fig. 4), but not for N1–P3 amplitude: $[F_{1,23} = 0.21, P = 0.652]$ at all electrode sites.

No significant effect for breathing technique was found for latency: N1 ($F_{1,23} = 0.18, P = 0.678$), P2 ($F_{1,23} = 0.82, P = 0.374$), and P3 ($F_{1,23} = 2.76, P = 0.111$); however, NB produced a trend towards shorter P3 latencies at all electrode sites. Table 1 summarizes mean numbers for amplitudes and latencies by breathing condition and electrode site.

Magnitude estimation was found to be significantly higher in younger subjects: $[F_{1,23} = 5.85, P < 0.05 (\eta^2 = 0.21)]$, but was not significant for breathing technique ($F_{1,23} = 1.48, P = 0.237$).

4. Discussion

The findings from the Velopharyngeal Closure condition were consistent with those observed in previous studies in which OERPs were recorded in different age groups using VC (Morgan et al.,

1997, 1999; Murphy et al., 1994, 1998b). Increasing age was associated with smaller N1–P2 and N1–P3 amplitudes across all electrode sites. For both age groups, maximum amplitudes were observed at Cz and Pz electrode sites. Elderly subjects also showed prolonged latencies for N1, P2, and P3.

Similar effects were observed for Natural Breathing. In this condition, older participants

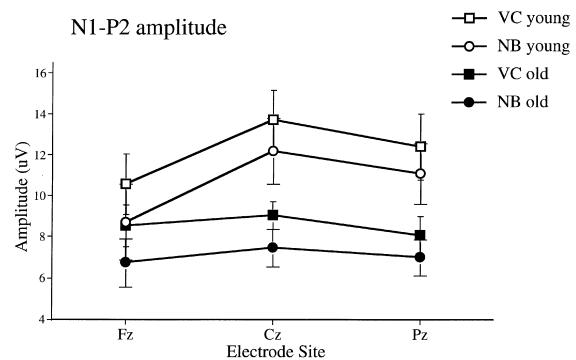


Fig. 4. Mean (± 1 S.E.) N1–P2 amplitudes by age and breathing condition at each electrode site (Fz, Cz, and Pz). Older subjects show decreased amplitude; velopharyngeal closure produces larger amplitudes in both age groups.

Table 1

Mean numbers for amplitudes and latencies (± 1 S.E.M.) by breathing condition and electrode site for young and old subjects^a

Electrode site/ component	Breathing condition	Young subjects			Old subjects		
		Fz	Cz	Pz	Fz	Cz	Pz
<i>Amplitudes (µV)</i>							
N1-P2	VC	10.57 (1.84)	13.73 (1.44)	12.41 (1.48)	8.51 (1.16)	9.04 (0.91)	8.05 (0.87)
	NB	8.71 (1.5)	12.17 (1.61)	11.08 (1.61)	6.73 (1.02)	7.45 (0.68)	6.98 (0.94)
N1-P3	VC	9.12 (1.7)	12.81 (1.75)	13.66 (1.44)	5.03 (1.39)	6.67 (1.06)	5.67 (1.14)
	NB	8.74 (1.79)	13.31 (1.41)	13.38 (1.64)	4.69 (0.9)	4.25 (1.12)	5.65 (1.08)
<i>Latencies (ms)</i>							
N1	VC	334 (21)	335 (23)	331 (24)	458 (32)	447 (34)	469 (30)
	NB	333 (24)	304 (25)	322 (22)	448 (28)	459 (28)	460 (27)
P2	VC	509 (15)	528 (13)	527 (17)	697 (29)	698 (29)	696 (29)
	NB	502 (28)	495 (28)	522 (27)	695 (27)	673 (28)	672 (28)
P3	VC	850 (29)	851 (32)	833 (30)	1116 (34)	1120 (38)	1152 (40)
	NB	800 (26)	797 (29)	794 (23)	1102 (59)	1067 (49)	1061 (54)

^aVC, velopharyngeal closure; NB, natural breathing.

showed significantly smaller N1-P2 and N1-P3 amplitudes and prolonged P2 and P3 latencies relative to younger participants. However, NB consistently yielded smaller N1-P2 amplitudes at Fz, Cz, and Pz than Velopharyngeal Closure. No difference in N1-P3 amplitude was observed between the two breathing techniques. Means for P3 latency showed a trend towards shorter latencies for NB. No interaction between age and breathing technique was found in this study.

The N1-P2 component of the OERP has been identified as a predominantly exogenous component, and demonstrates a strong positive correlation with psychophysical odor threshold tests (Murphy et al., 1994, 1998b). The components of the late positive complex have been shown to be modulated by attention and stimulus probability, and are thus considered to be predominantly endogenous in nature (Geisler et al., 1999; Geisler and Murphy, 2000; Morgan et al., 1999).

The amplitude decrease in N1-P2, but not in

N1-P3 components during Natural Breathing in this study may be due to varying rates of respiratory air flow during Natural Breathing. Transporting odorous molecules to the nasal epithelium at different velocities might have resulted in a larger deviation of latency between single trials. This latency jitter, when averaged, leads to an observed decrease in peak amplitude and, thus, may not represent a real difference in stimulus processing (Moecks, 1981). In fact, stimulus intensity perception was found to be the same for both breathing conditions.

Considering the possibility that inspiration increases the already high flow rate supplied by the olfactometer, findings by Mozell et al. (1990, 1991) offer another potential explanation. They studied the effects of flow rate on the neuronal discharge of olfactory neurons in animals. Testing with stimuli with different mucosal sorption properties, the authors found that when using amyl-acetate (the stimulus used in the present study), increased

flow rate was associated with fewer odorous molecules absorbed by the olfactory mucosa, an effect that was attributed to the average to low mucosal sorption properties of the stimulus. By increasing the flow rate and, at the same time, keeping the total number of odor molecules constant, low sorbed odorants have less dwell time to diffuse to the olfactory mucosa, which leads to decreased activity of the olfactory nerves.

The tendency towards shorter P3 latencies in the Natural Breathing condition observed for both age groups might result from differences in expectancy for the stimulus. In everyday olfaction, odor perception is rarely independent of inspiration. An odor experience synchronous to inspiration, like in the NB condition, might be considered to be 'primed', and might require less stimulus evaluation time. Indeed, this view is supported by studies with ERPs from visual and auditory modalities, where P3 latency is considered to be a measure of classification and evaluation speed (Kutas et al., 1977; Polich, 1986).

The present investigation showed that the OERP is a sensitive measurement for detecting age-related changes in olfactory function regardless of breathing technique. Results support the use of Natural Breathing in OERP paradigms, and thereby make electrophysiological assessment of olfactory processing possible in populations that were previously excluded from OERP experiments due to their inability to perform Velopharyngeal Closure. However, in populations where it is feasible, Velopharyngeal Closure will produce a higher amplitude response and results that can be compared with normative data (Murphy et al., 2000). Thus, in many cases it will be the technique of choice.

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