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Abstract

Functional electrical stimulation (FES) has been proposed as a potential treatment for restoring motor functions of denervated motor systems. We investigated whether FES of paralyzed laryngeal adductor muscles could restore adduction to the vocal folds. In addition, we studied the effect of stimulated vocal fold adduction on the intensity and overall quality of voice production. We recorded movement of the vocal fold, electromyographic activity of muscles recruited for vocalization, and sound production in unanesthetized decerebrate cats during FES of the paralyzed thyroarytenoid (TA) muscle. FES of the paralyzed TA muscle induced adduction of the vocal fold. Appropriate stimulus parameters for induction was 1.5 to 3.0 mA intensity pulses delivered at a frequency of 30 to 50 pulses per second (pps). FES of the paralyzed TA muscle prolonged phonation time and increased intensity of voice sounds during vocalization induced by electrical stimulation (0.2 ms, 20-50 µA, 50 pps) of the periaqueductal gray. The quality of voice sounds evaluated by sound spectrography was shown to improve during vocalization with FES. We conclude that FES of the paralyzed laryngeal adductor muscle was effective in restoring adduction of the vocal fold and improving voice sounds impaired by unilateral laryngeal paralysis.

Key Words: Functional electrical stimulation (FES); Unilateral laryngeal paralysis; Laryngeal adductor muscle; Thyroarytenoid muscle (TA); Vocal fold; Voice sound; Cat;

1. Introduction

Recurrent laryngeal nerve injury can cause impairment of both abductive and adductive functions of the vocal folds.   Because a vocal fold is paralyzed in the paramedian position in case of unilateral recurrent laryngeal nerve paralysis, the voice becomes breathy and aspiration can occur.   To eliminate these symptoms, the glottal gap caused by the adductive dysfunction of the paralyzed fold should be corrected. Currently, cordal injection or thyroplasty has been performed to reposition the immobile vocal fold back to the midline.   However, these treatments ignore the long-term effects of muscle atrophy on vocal fold mass and position, important factors in voice production.   The outcome from intervention also depends largely upon the experience and technique of the surgeon.   To overcome the inherent limitations associated with conventional surgery, attempts have been made toward remobilization of the vocal fold using a more physiologic procedure.   In particular, strategies such as nerve-to-nerve anastomosis (Brondbo et al., 1992; Sercarz et al., 1997) or neuromuscular pedicle transfer from an extralaryngeal source (El-Kashlan et al., 2001) have been reported. Unfortunately, these procedures have failed in wide clinical application.

Functional electrical stimulation (FES) has been proposed as a potential treatment for restoring motor functions of denervated motor systems.   In the field of otolaryngology, FES has been proposed as an innovative treatment for the management of patients with laryngeal paralysis or facial palsy (Zealear and Dedo, 1977; Targan et al., 2000).   Numerous studies in acute and chronic animal models have demonstrated that FES restores abduction of the paralyzed laryngeal muscles (Obert et al., 1984; Otto et al., 1985; Bergmann et al., 1988; Sanders, 1991; Zealear et al., 2000).   Moreover, FES of the paralyzed posterior cricoarytenoid muscle of the human larynx has induced

vocal fold abduction and restored ventilation through the glottis in case of bilateral laryngeal paralysis (Zealear et al., 2002; Billante et al., 2002; Zealear et al 2003). However, there are few reports describing the remobilization of paralyzed laryngeal adductor muscle with the use of FES (Kojima et al., 1990; Kojima et al., 1991). We believe that remobilization of the vocal fold adductor muscle with FES may provide a new and better treatment for voice disturbances resulting from unilateral recurrent laryngeal nerve paralysis.

In order to study the effect of FES on sound production in an animal model, an experimental paradigm is generally developed in the awake spontaneously vocalizing animal. In view of the difficulty in training animals and timing of FES with vocalization, an alternative approach has been adopted: induction of vocalization through brain stimulation in the anesthetized or decerebrate animal. In decerebrate cats, repetitive electrical stimulation of the midbrain periaqueductal gray (PAG) induces natural-sounding vocalization (Magoun et al., 1937; Kelly et al., 1946; Kanai and Wang, 1964). After the onset of PAG stimulation, inspiration and vocalization are induced alternately until cessation of PAG stimulation. Respiratory and laryngeal muscles show the same discharge pattern during PAG induced vocalization as they do during normal spontaneous vocalization. The intensity of muscle activity and sounds generated are dependent on the stimulus intensity to the PAG. Thus, it is possible to induce a consistent and stereotypic vocalization in this animal model trial after trial through stimulation of the PAG in a controlled fashion. We have previously employed this animal model to investigate the activities of respiratory neurons in the medulla during vocalization and the effects of auditory inputs on vocalization (Katada et al., 1996; Nonaka et al., 1997). The model may also be suitable for evaluating the effects

of FES on laryngeal paralysis.

In the present study, we examined the capacity of FES of the paralyzed laryngeal adductor muscles to restore vocal fold adduction and improve the function of voice production.   To address this aim, we analyzed EMG activities of respiratory and laryngeal muscles, the timing of vocalization, subglottic pressure and voice quality during PAG induced vocalization in the presence and absence of FES.

2. Methods

All experiments were carried out in accordance with the Guidelines for Animal Experiments of Asahikawa Medical College.

2.1. Denervation of the left thyroarytenoid muscle

Denervation of the left thyroarytenoid (TA) muscle was performed in four adult cats (2.5-3.5 kg) of either sex.   The animals were anesthetized by inhalation of halothane, nitrous oxide, and oxygen in an airtight chamber.   This anesthetic mixture was also delivered via nasal intubation over the course of an experiment to maintain the plane of anesthesia.   All surgeries were performed under aseptic conditions.   A midline incision was made from the hyoid bone to the sternum.   The left recurrent laryngeal nerve (RLN) was identified near the lateral wall of the trachea.   After exposure of the nerve, a thirty-millimeter length of nerve was resected and the nerve stumps ligated to discourage reinnervation.   The electromyogram (EMG) was recorded from the left TA muscle using a pair of teflon insulated (50 μm) stainless steel wires with 1 mm deinsulated tips.   EMG was amplified and band pass filtered 100 Hz to 3 kHz.   It was confirmed that spontaneous activity of the left TA muscle disappeared upon resection of the left RLN.   A rigid endoscope (MACHIDA, Japan) with attached microchip camera (IK-C 30, Toshiba, Japan) was then used to confirm that the left vocal fold was immobilized by the nerve resection.

2.2. FES of the paralyzed TA muscle

One month after denervation of left TA muscle, attempts were made to identify the FES stimulation parameters that were most effective in producing adduction

of paralyzed vocal fold.   Two of the four animals were used for this purpose.   All surgical procedures, including precollicular-postmammilary decerebration (Katada et al., 1996), were performed under halothane-nitrous oxide anesthesia.   A midline incision was made from the hyoid bone to the sternum.   To induce vocal fold adduction by FES, a pair of insulated stainless steel wires with 1 mm exposed tips was inserted into the paralyzed (left) TA muscle.   After completion of all surgical procedures, administration of anesthesia was discontinued in the decerebrate animal at least 1 hour prior to data collection.   The animal was placed in a stereotaxic frame with the upper body supported by a thoracic vertebral clamp and the lower body suspended by a rubber hammock.   Body temperature was maintained at 36-38°C using a radiant heating lamp. Movement of the paralyzed (left) vocal fold produced by FES was monitored with the endoscope-video camera and archived on a digital video recorder (DCR-TVR900, Sony, Japan) for off-line image analysis. Vocal fold adduction was indexed by measuring the change in cross-sectional area of the airway at the level of the two vocal folds (i.e. the glottis).   Since the magnification of video images varied with endoscope position, a small ruler was placed on the vocal fold to calibrate a grid superimposed upon the images.   This grid served as a reference for making measurements of glottal area. Video images were digitized and analyzed using computer software (NIH image, NIH, USA).   The pulse duration of FES was set at 0.2 ms for activating denervated muscle fibers.   Stimulus intensities ranging from 0 to 3 mA and stimulus frequencies ranging from 5 to 100 pulses per second (pps) were employed to evoke tetanizing TA contractions and smooth vocal fold adductions.

2.3.   Changes in EMGs, subglottic pressure and voice sounds induced by FES of the

paralyzed TA muscle during evoked vocalization

One month after denervation of the left TA muscle, the remaining two animals were enrolled in a study to determine the effects of FES on EMG, subglottic pressure, and voice sounds during evoked vocalization. Prior to anesthetization, it was noted that spontaneous vocalization was weak and breathy as a consequence of the denervation. These two animals underwent the same anesthetization and surgical procedures as the first two animals. Electrical stimuli (0.2 ms, 20-50 μA, 50 pps) were delivered to the periaqueductal grey (PAG) for induction of vocalization in the unanesthetized decerebrate animal. After inserting a pair of stainless steel electrodes into the left TA muscle, it was confirmed endoscopically that FES (2-5 mA, 0.2 msec, 30 pps) produced vocal fold adduction. EMGs were recorded from the diaphragm (DIA), external oblique abdominal (EA) muscle, and the intact (right) TA muscle. These three muscles were chosen because of their potential roles in inspiration, expiration, and sound production respectively. PAG stimulation recruited all three muscles bilaterally during the act of vocalization: DIA contraction can enhance inhalation in preparation for vocalization; EA contraction may increase subglottic pressure during expiration; and TA contraction primarily repositions the vocal folds medially into the expiratory air stream to initiate vibration and sound production. The change in subglottic pressure during vocalization was recorded using a micro-tip catheter pressure transducer (3 Fr diameter, Millar, USA) placed in the trachea through the mouth. EMGs and subglottic pressure were simultaneously stored on a DAT data recorder (DC-10 kHz; RD-135T, TEAC, Japan) for off-line analysis using AD Instruments MacLab and software (Chart version 4.0) for a Power Macintosh-7300/166 computer. Voice sounds were detected by a microphone placed 10 cm from the mouth,

recorded on a digital audio tape recorder (TCD-D10, Sony, Japan), and analyzed with

computer software for sound analysis (Sound Scope). Statistical analysis was performed

by means of the Wilcoxon signed rank test.   A P-value of less than 0.05 was

considered statistically significant.

3. Results

3.1. *Vocal fold adduction induced by FES of the paralyzed TA muscle*

Endoscopic images of the vocal folds at the end of the expiratory phase are shown in Fig. 1.   Figure 1A shows the vocal folds without FES of the paralyzed (left) TA muscle.   Figure 1B shows the vocal folds with FES (0.2 ms, 3.0 mA, 50 pps). Adduction of the paralyzed (left) vocal fold was appreciable, and a corresponding decrease in glottal area was measured.   To determine the appropriate stimulus parameters for evoking effective adduction of the paralyzed vocal fold, the relationship between the intensity and frequency of the stimulus and vocal fold adduction was investigated.   The degree of vocal fold adduction rose with increasing stimulus intensity, reaching a maximum medialization at 3.0 mA (Fig. 2).   Vocal fold adduction also increased in response to increasing stimulus frequency (Fig. 2).   Stimulation at the highest frequency of 100 pps produced a near maximum adduction at only nominal stimulus intensity, making it difficult to regulate the response.   Therefore, the appropriate stimulus paradigm for inducing controllable adduction of the paralyzed vocal fold was deemed to be a 1.5 to 3.0 mA intensity pulse train delivered at a frequency of 30 to 50 pps.

During this first phase of the study, it was also established that FES of the paralyzed TA muscle had no effect on the respiratory cycle during quiet breathing. Even when using a relatively high stimulus intensity of 3.0 mA and a stimulus frequency ranging from 5 to 100 pps, there was no change observed in either the respiratory rate or the duration of the inspiratory phase.

3.2. *Changes in EMGs, subglottic pressure and voice sounds induced by FES of the*

paralyzed TA muscle during PAG evoked vocalization

Repetitive electrical stimulation of the PAG induced consistent vocalizations in the decerebrate cat with unilateral laryngeal paralysis.   During the periods of PAG stimulation, inspiration and vocalization were induced alternately with reciprocal activations of DIA and intact (right) TA muscle.   During the vocalization phase, the subglottic pressure was observed to increase with the production of a voice sound (Fig. 3A).   When FES (0.2 ms, 3.0 mA, 50 pps) was applied to the paralyzed (left) TA simultaneous to PAG stimulation (Fig. 3B), the FES appeared to prolong activity in the intact (right) TA muscle during the vocalization.   Moreover, the peak subglottic pressure and the amplitude of voice sound both appeared to increase during FES. Detailed analysis of the change in these parameters with FES is shown for all nine trials in Fig. 4.   The average duration of the intact (right) TA muscle activity during vocalization was found to be significantly prolonged by FES (Fig. 4A, discussion). However, the duration of DIA activity did not change during FES delivery (Fig. 4B). The average latency from the end of first inspiration to the activation of EA muscle significantly decreased with FES (Fig. 4C).   Detailed examination of the subglottic pressure waveform demonstrated that both the positive peak during expiration (Fig. 5A) and the negative peak during inspiration (Fig. 5B) increased significantly when FES was applied during PAG stimulation.   As expected, the increase in subglottic pressure during the expiratory vocalization phase was paralleled by a significant increase in the average peak sound level generated when FES was present (Table 1).   Moreover, the quality of the voice sound improved significantly at the higher magnitude of sound production suggesting that vocal fold vibration became more normal.   Perceptually, the breathy voice sounds noted during spontaneous vocalization in unanesthetized animals

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as well as the stimulated vocalization in the decerebrate animals clearly improved in their resonance quality with FES.   The improved quality was directly demonstrated by comparing the voice sounds generated with and without FES by sound spectograpy.   A representative example of this comparison is shown in Fig. 6.   In every case in which the PAG induced vocalization was accompanied by FES on the paralyzed side, the formants exhibited greater definition, consistency, and signal-to-noise ratio throughout the animal's call.   Table 1 summarizes the average value and standard deviation for each parameter studied during this investigation.

4. Discussion

Previous studies in acute and chronic animal models have demonstrated that FES restores abduction of the paralyzed laryngeal muscle (Obert et al., 1984; Otto et al., 1985; Bergmann et al., 1988; Sanders, 1991; Zealear et al., 2003).   However, there are few reports describing remobilization of the paralyzed laryngeal adductor muscle by means of FES (Kojima et al., 1990; Kojima et al., 1991).   In this study, we identified the optimal conditions for evoking effective adduction of the paralyzed vocal fold using an objective measure of the response (i.e. glottal area decrease).   The appropriate stimulus parameters for inducing controllable adduction of the paralyzed vocal fold in decerebrate cats were 1.5 to 3.0 mA intensity pulses delivered at a frequency of 30 to 50 pps.   These results were similar to those from a previous study for inducing vocal fold abduction through stimulation of the paralyzed laryngeal abductor muscles in the canine (Zealear et al., 1994).   Furthermore, we confirmed that the stimuli did not alter the respiratory cycle during quiet breathing.   These results indicate that FES of the paralyzed laryngeal adductor muscles reanimate the vocal folds without interfering with normal breathing.   The null effect on respiration is an important observation, since it is prerequisite to any consideration of clinical application of FES to patients with laryngeal paralysis.

In this investigation, we also confirmed that FES of the paralyzed vocal fold adductor muscles improved the function of vocalization.   In the previous study by Kojima et al, 1990, observations were made that stimulation of the paralyzed adductor muscle improved the quality of vocalization.   However, these observations were made in a lightly anesthetized spontaneously vocalizing animal wherein the vocalizations may not have been reproducible. In the present study, the timing and consistency of animal

vocalization was guaranteed by the PAG stimulation, so that the additive effect of FES on an animal call could be objectively examined.   The results of this study convincingly demonstrated that both the intensity and harmonic quality of sound production improved with FES.   This is a critical finding, since the primary goal of FES intervention is to restore voice quality in paralyzed humans.

By using PAG to induce consistent and representative vocalizations in the decerebrate cat (Katada et al., 1996), it was also possible to study the mechanisms underlying FES effects on vocalization.   During FES application to the unilaterally paralyzed TA muscle, changes were observed in EMG activity of respiratory and laryngeal muscles, subglottic pressure, intensity of voice sounds, and the quality of voice sounds during vocalization. The findings of this study along with the interpretation of results can be summarized as follows. 1) EMG activity of the intact TA muscle was prolonged during FES application.   The consequent prolongation of vocal fold adduction on the intact side in conjunction with the stimulated vocal fold adduction on the paralyzed side must have increased the airway resistance during the expiratory phase.   In turn, the increase in airway resistance resulted in both 2) an increase in subglottic (positive) pressure and 3) a prolongation of vocalization.   Finally, the increased subglottic pressure in conjunction with a near approximation of both vocal folds 4) increased the intensity of the sound produced and 5) improved the vibratory pattern of the vocal folds and harmonic quality of the sound.   Parenthetically, the impact of stimulating the paralyzed TA in prolonging activity of the intact TA was an unexpected finding.   Although the mechanism remains to be discovered, FES was shown to have no impact on the respiratory cycle in the nonvocalizing animal.   One possible explanation would invoke the Hering-Breuer Reflex.   More specifically,

retardation in lung deflation may have provided sensory feedback to the PAG center to prolong expiration and vocalization until normal FRC (i.e. functional residual capacity) had been reached.   Similarly, advanced recruitment of the EA muscle by the PAG may have reflected some homeostatic mechanism to overcome the increased glottal resistance and reduced airflow during expiration.

It is well known that the loss of vocal fold mobility and mass following laryngeal paralysis are responsible for deterioration in the resonance quality of the voice. Loss of vocal fold mass is caused by atrophy of paralyzed laryngeal adductor muscles. Atrophy of denervated adductor muscles becomes significant from 4 to 7 months after denervation, if reinnervation dose not occur (Shindo et al., 1992).   It has been reported that FES not only restores the mobility of denervated muscle but also prevents atrophy and fibrosis of muscle after denervation (Zealear et al., 2000).   Therefore, there is a possibility that early intervention of FES of the paralyzed TA muscle can prevent or delay deterioration of the voice because of the preservation of vocal fold mass. Further investigation on the effect of FES on preservation of muscle integrity is important to eventual clinical application.

The results of this study indicate that FES of the paralyzed TA muscle was effective in restoring adduction of the paralyzed vocal fold and improving the voice impaired by unilateral laryngeal paralysis.   This study strongly supports the feasibility of electrical stimulation as a treatment for unilateral recurrent nerve paralysis.   FES of the paralyzed laryngeal muscle offers tremendous promise in a patient population for whom traditional surgical therapies are not optimal.   Further investigation will be necessary to determine whether FES of paralyzed laryngeal muscles can become the treatment of choice for unilateral laryngeal paralysis.   Given the rapid advance in

biological technology, FES is likely to emerge as an accessible treatment method in the future.

Acknowledgements

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Figure legends

Fig. 1.

Endoscopic images of the glottis with unilateral (left) laryngeal paralysis. (A) glottis at the end of the expiratory phase without FES.　(B) glottis at the end of the expiratory phase with FES.　FES induced adduction of the left paralyzed vocal fold and the area of the glottal airway decreased.

Fig. 2.

Relationship between stimulus parameters (intensity; frequency) and cross sectional area of the glottis.　The area of the glottal airway decreased in response to increasing stimulus intensity or increasing stimulus frequency.

Fig. 3.

Representative changes in muscle activities, subglottic pressure and voice sounds during vocalization with FES of the paralyzed TA muscle.　(A) induced vocalization without FES.　Stimulus period of the PAG is indicated by the solid line at the bottom of the figure.　(B) induced vocalization with FES.　The period of FES is indicated by the solid line at the top of the figure.　"TA (right)": right unparalyzed thyroarytenoid muscle.　"DIA": diaphragm.　"EA": external oblique abdominal muscle.　"SP": subglottic pressure.

Fig. 4.

Change in measured parameters with FES application over all nine trials in cat 3 (n=5) and cat 4 (n=4).　(A) Change in duration of intact TA muscle activity, (B)

change in duration of DIA activity, and (C) change in latency of EA activation following end inhalation.   All measurements were made from the first PAG induced inspiratory-vocalization cycle.   Intact TA activity increased significantly and EA activation latency decreased significantly with the application of FES.   The duration of DIA activity was not altered by FES.

Fig. 5.

Change in subglottic pressure when FES was applied during PAG stimulated vocalization.   (A) During the vocalization phase, the positive peak in subglottic pressure significantly increased with FES application.   (B) During the inspiratory phase, the negative peak in subglottic pressure also increased significantly with FES.

Fig. 6.

Representative sound spectogram of recorded voice in the absence (left) and presence (right) of FES.   The resonance quality of the voice was clearly improved by FES of the paralyzed TA muscle.

Table 1.

Summary of the changes in measured parameters with and without FES application over all nine trials in cat 3 (n=5) and cat 4 (n=4).

A   B

FES(-)   FES(+)

Dorsal

Right ←→ Left

Ventral

Fig. 1.

(mm²)

0	

5 pps
10 pps
20 pps
30 pps
50 pps
100 pps

-1
-2
-3
-4

0   1.5   3.0

(mA)
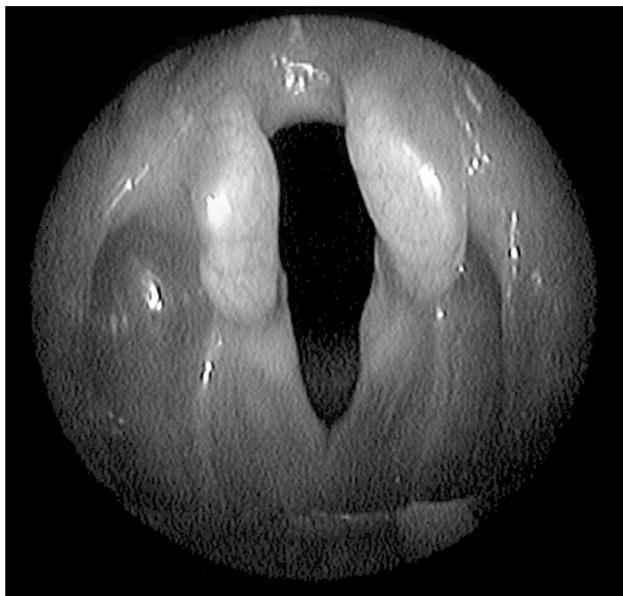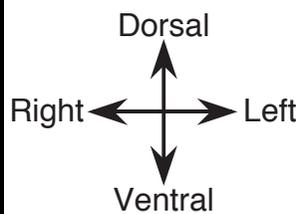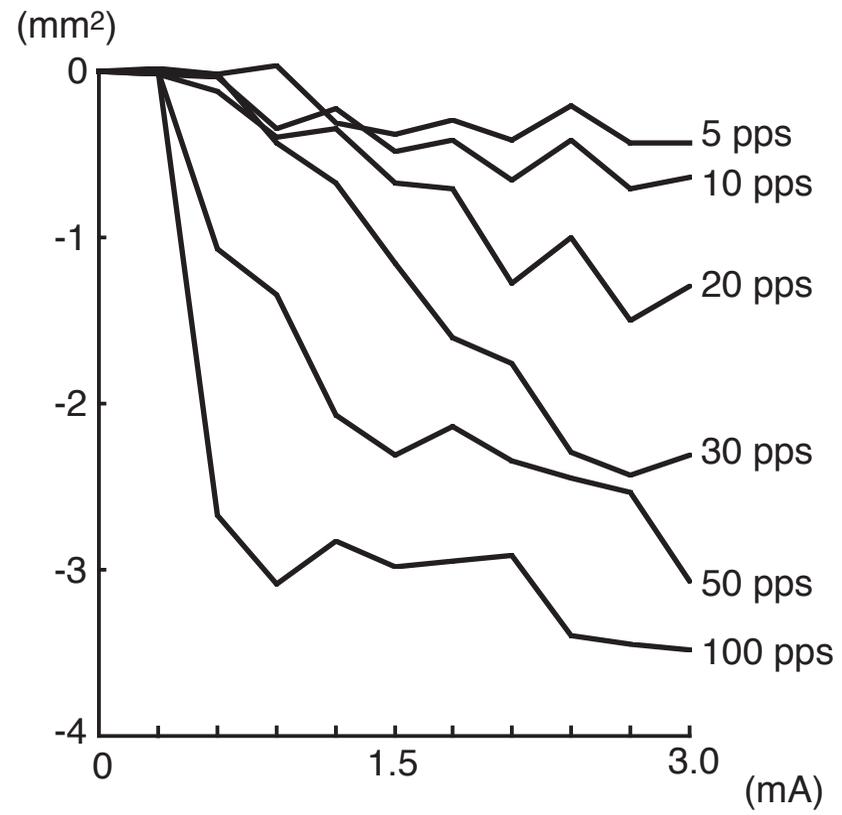
Fig. 2.
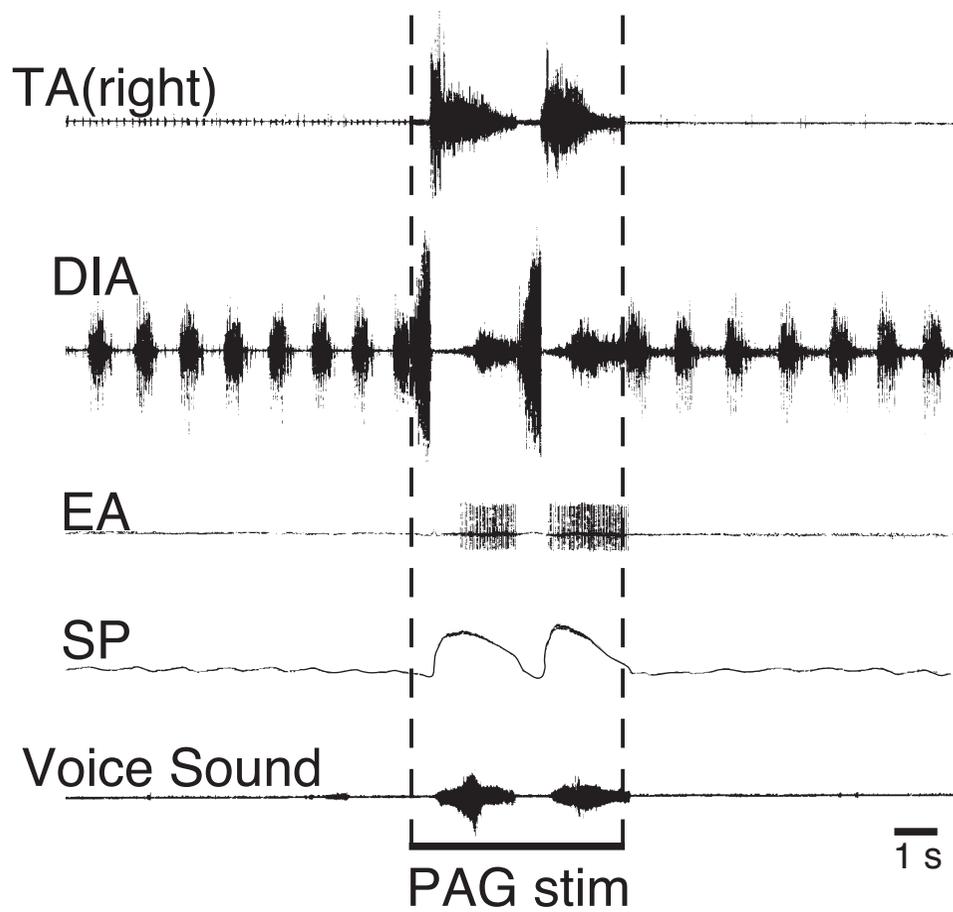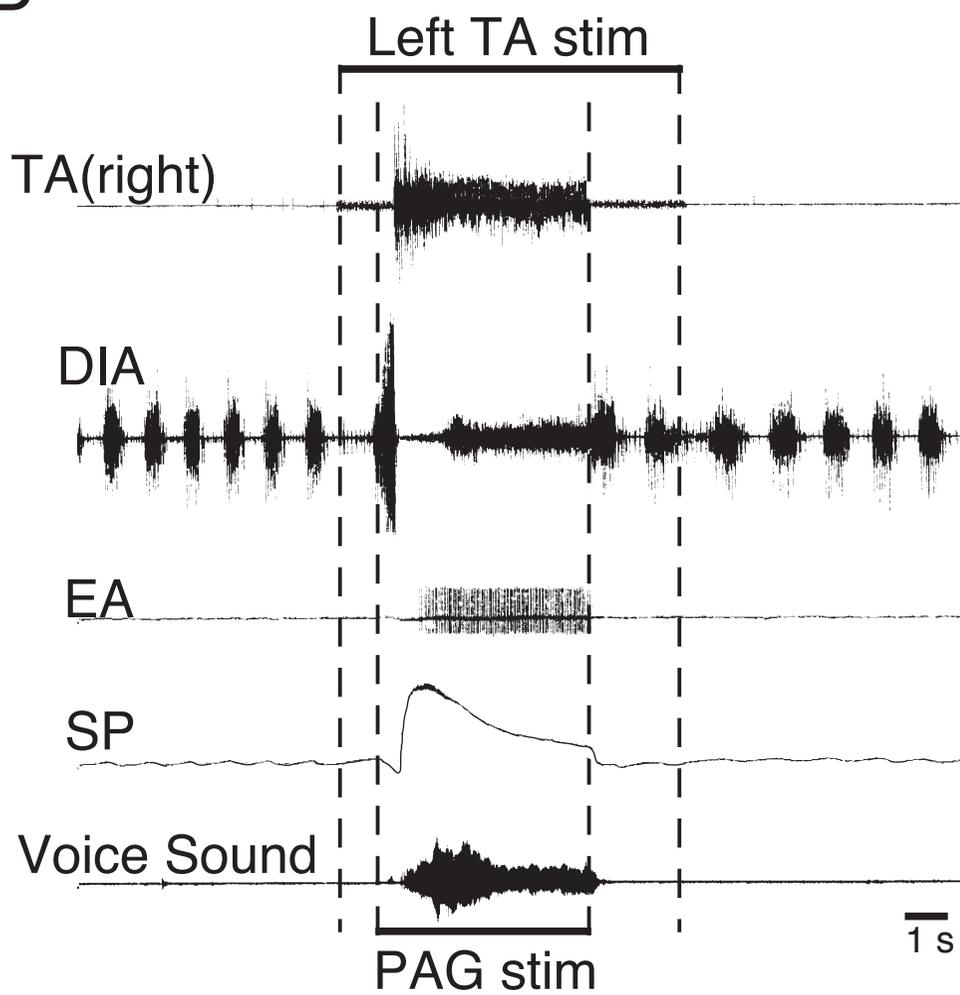
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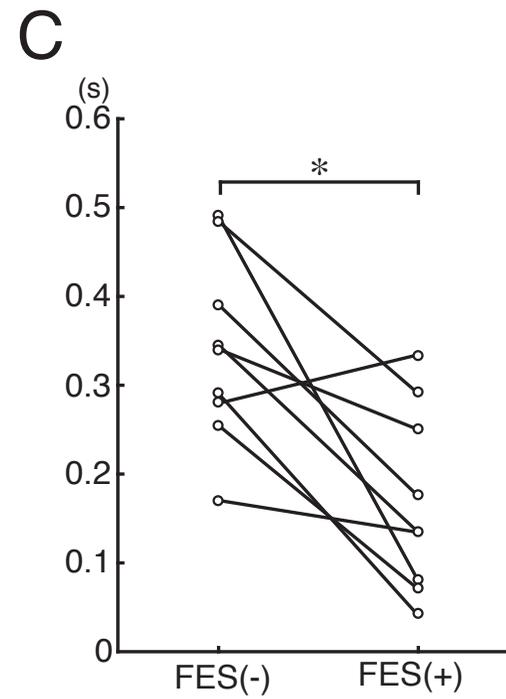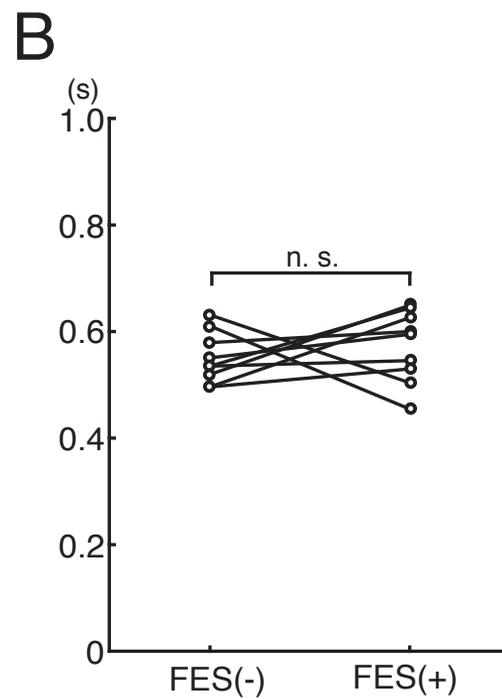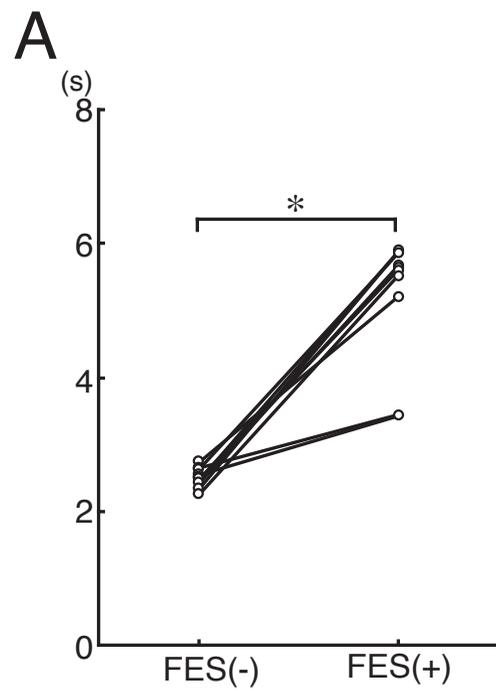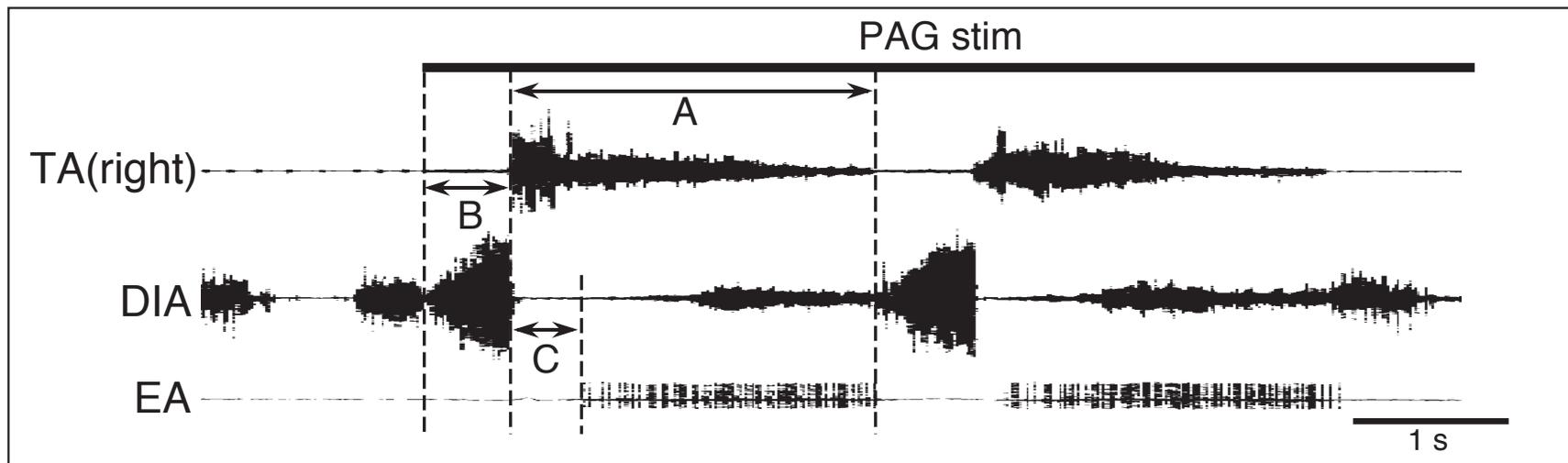
Fig. 4.
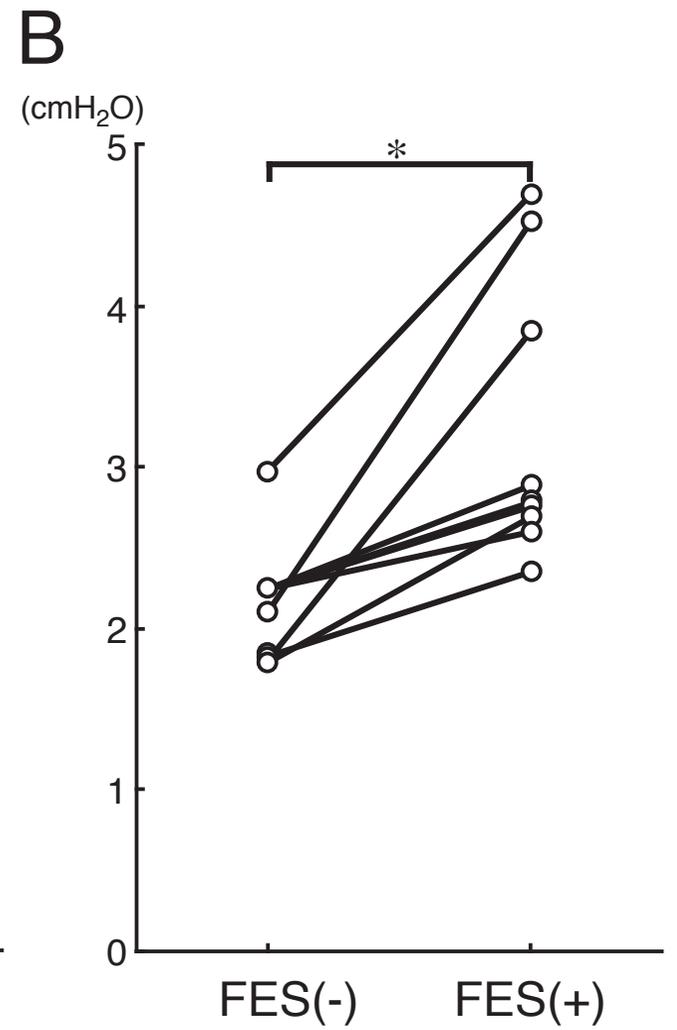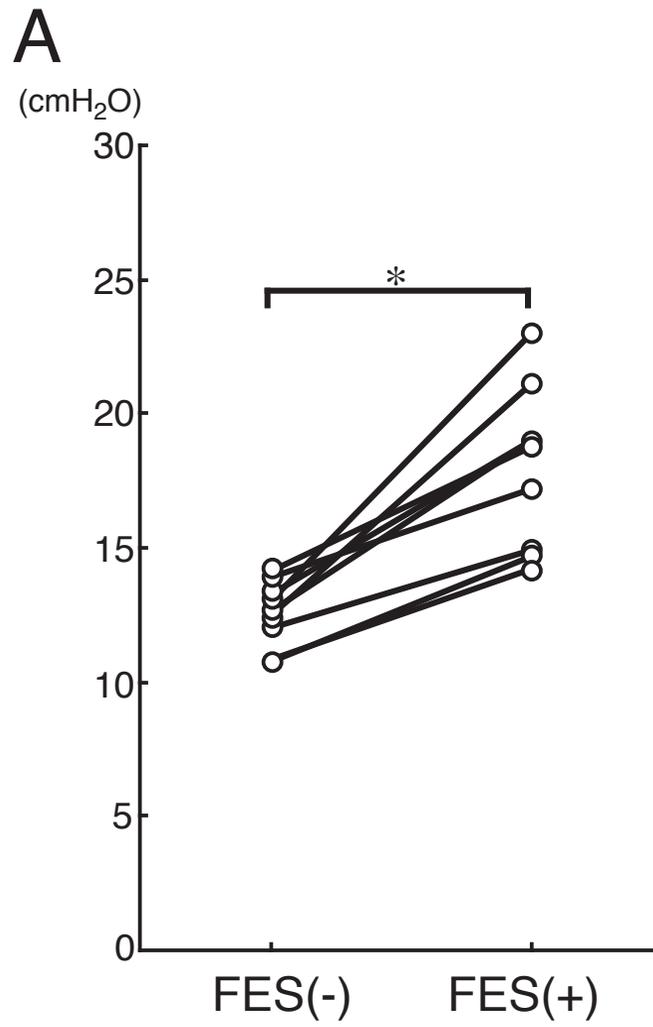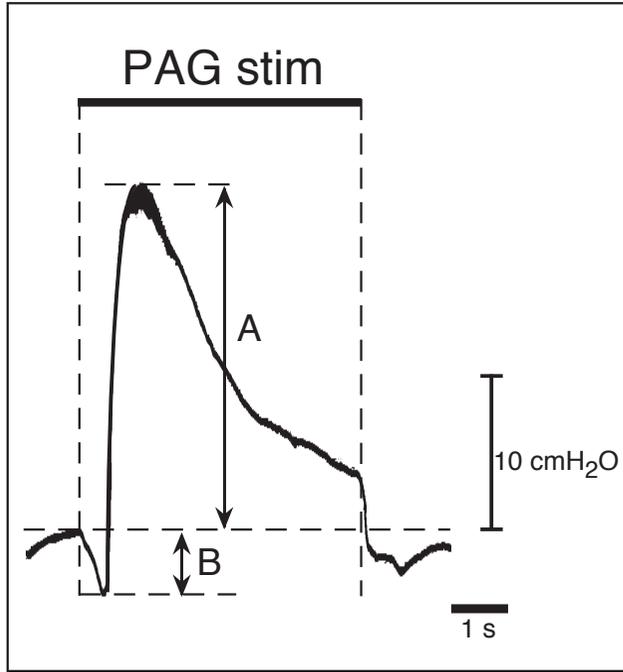
Fig. 5.
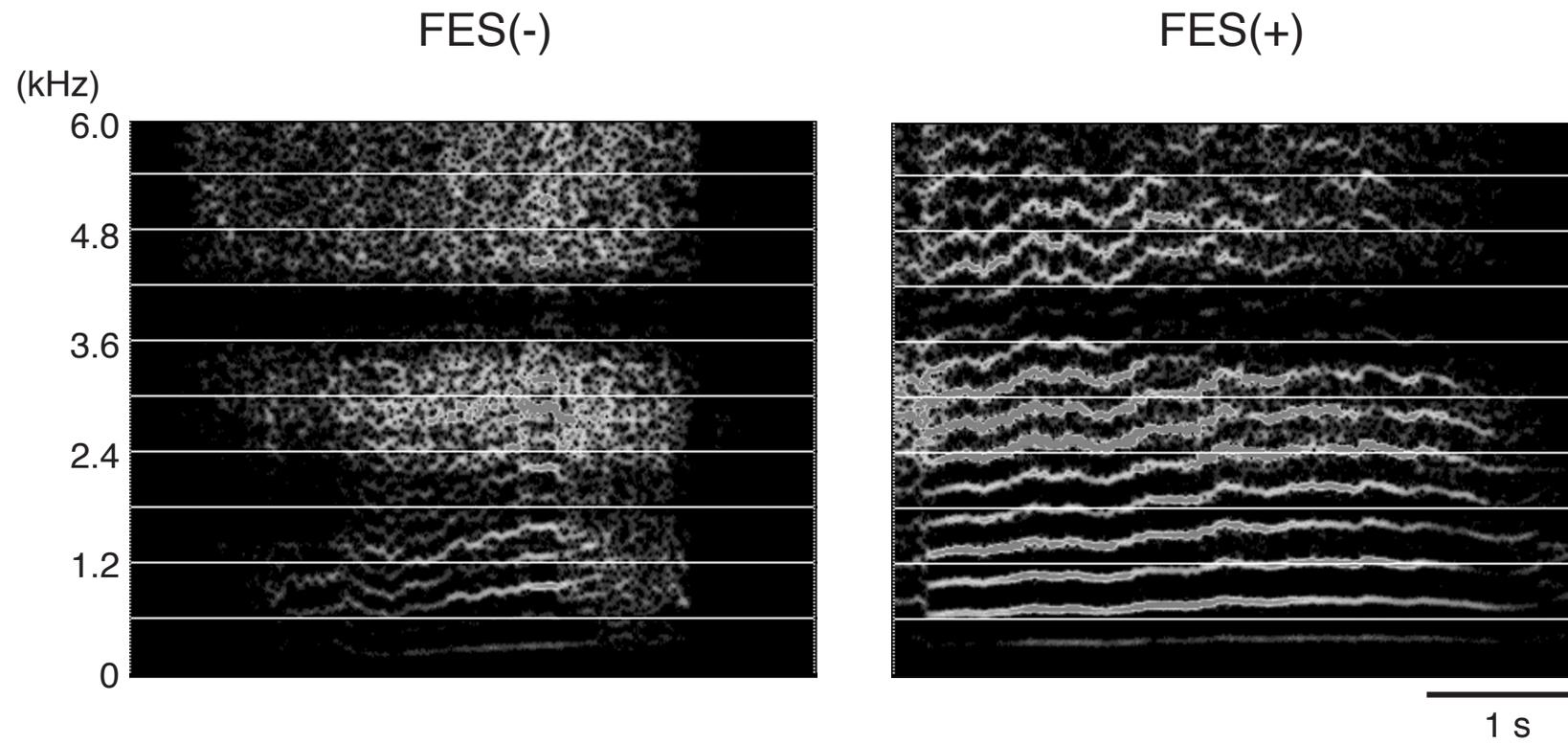
Fig. 6.

	FES (-) (n=9)	FES (+) (n=9)	p value
Duration of intact TA activity (s)	2.05±0.16	5.10±1.00	p=0.008
Duration of DIA activity (ms)	550±47.8	572±67.3	p=0.374
Latency of EA activity (ms)	338±105	168±103	p=0.015
Peak positive subglottic pressure (cmH$_2$O)	12.6±1.14	18.0±2.84	p=0.008
Peak negative subglottic pressure (cmH$_2$O)	2.17±0.369	3.23±0.880	p=0.008
Maximum amplitude of recorded voice (V)	0.219±0.016	0.235±0.016	p=0.036

Table 1