Intranasal trigeminal and secretory functions are impaired after topical anaesthesia or surgical treatment of epistaxis

J.J. Vavrina[1], T. Hummel[3], B.N. Landis[2], S. Macario[1,2], M.B. Soyka[1]

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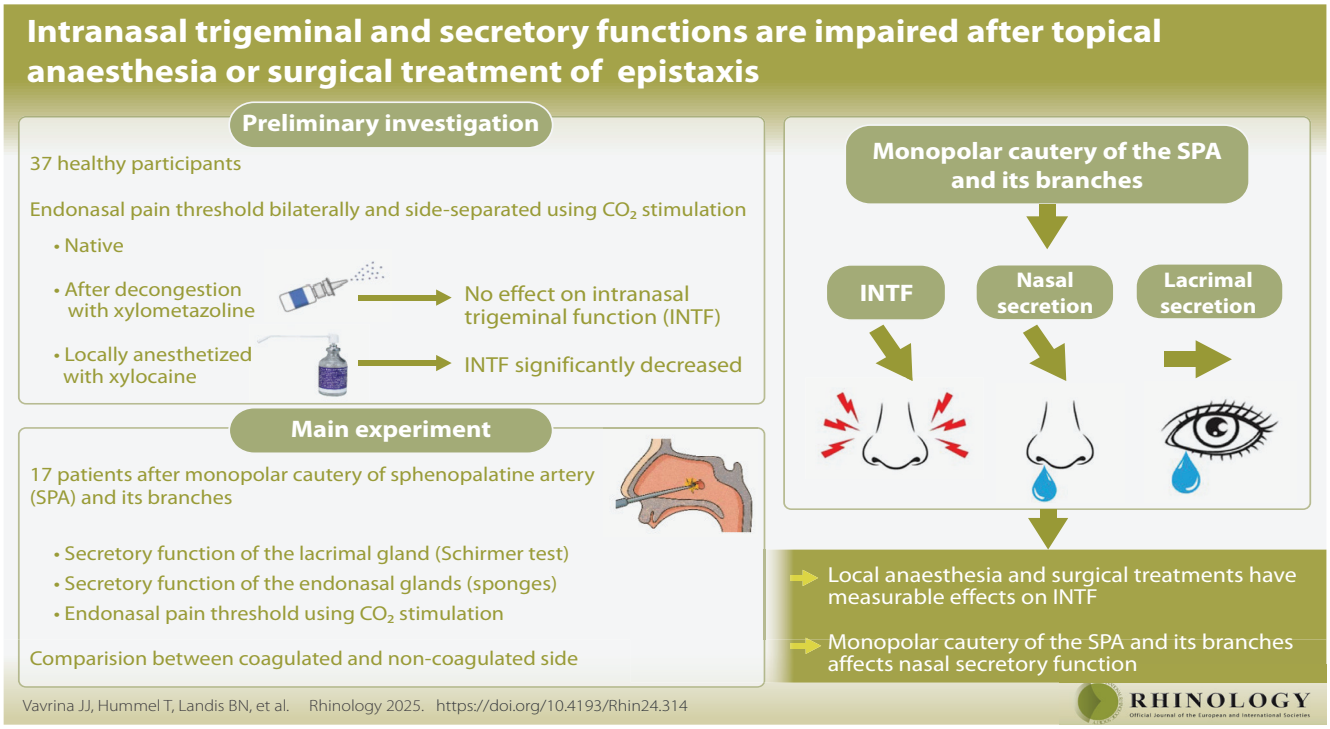

Abstract

Background: The sphenopalatine artery (SPA) runs in close proximity to the branches of the trigeminal nerve and to the sympathetic and parasympathetic secretomotor fibers. In refractory epistaxis, monopolar cautery of the SPA during surgery is of widespread use. The effect of coagulation on adjacent trigeminal and parasympathetic branches, and thus intranasal sensitivity and secretory function, is unknown. **Methods**: To investigate intranasal trigeminal function (INTF) by means of CO_2 stimuli intranasally, at baseline and after decongestion, before and after local anaesthesia (xylocaine) in healthy subjects and after monopolar cautery in patients treated for refractory epistaxis. In the latter, INTF and secretory function were tested by comparing the treated with the untreated side. Nasal and lacrimal secretions were measured with intranasal sponges and Schirmer's tests. **Setting**: Monocentric cohort study in tertiary referral centre. **Results**: A total of 37 healthy participants and 17 patients were included. Nasal decongestion had no effect on CO_2 measurements, whereas local anaesthesia significantly decreased INTF in healthy subjects. In patients, the operated side showed significantly lower INTF, lower nasal secretory function but no significant changes in lacrimal function. **Conclusion**: Local anaesthesia and surgical treatments have measurable effects on INTF. Monopolar cautery of the SPA and its branches affects nasal secretory function. These effects may lead to symptoms and surgeons should be aware of the potential harm in epistaxis treatments.

Key words: Carbon dioxide, coagulation, epistaxis, lacrimal function, nose, secretory function, trigeminal perception

Introduction

Epistaxis is among the most frequent reasons for otorhinolaryngology-related emergency department visits [1]. In approximately 80-90% of nosebleeds, the source can be identified in the anterior nasal septum through anterior rhinoscopy, classifying it as anterior epistaxis [2]. The remaining 10-20% are categorized as posterior epistaxis, most commonly arising from the sphenopalatine artery (SPA) [3, 4].

Various therapeutic options are available for managing epistaxis, with coagulation being an established and effective method depending on the bleeding site. When classical treatments like nasal packing fail, surgical closure of the SPA either by endoscopic clipping or monopolar cautery are indicated [5-7].

The SPA enters the nasal cavity through the sphenopalatine foramen, accompanied by nerve branches from the pterygopalatine ganglion. It supplies the lateral nasal wall, nasal septum, and superior portion of the pharynx. The parasympathetic pterygopalatine ganglion, located near the SPA's entry point, sends postsynaptic axons to the mucous membranes of the palate, nose and lacrimal gland. Additionally, branches of the maxillary nerve pass through the ganglion, carrying afferent sensory fibers from the nasal, throat and palatal mucosa. Sympathetic postganglionic fibers follow the sensory nerves and act on adrenoceptors promoting vasoconstriction and widening of the nasal airway [8]. The anterior ethmoidal artery (AEA) and its accompanying anterior ethmoidal nerve (AEN), a branch of the ophthalmic nerve, supply and innervate the mucosa of the anterior ethmoidal cells, anterior septum and lateral nasal wall. Similarly, the posterior ethmoidal artery (PEA) and posterior ethmoidal nerve (PEN) serve and innervate the posterior ethmoidal air cells, portions of the lateral nasal wall and septum and the sphenoid sinus [9].

Thermal coagulation can lead to diminished blood supply to the nasal mucosa and damage to sensory and autonomic fibers due to the close anatomical proximity of SPA, AEA and PEA. A previous study has shown histologically and histochemically evidence of reduced size and secretory activity in nasal seromucous glands following endoscopic SPA coagulation [10]. However, the extent to which thermal coagulation of the SPA, AEA, or PEA impacts the sensitivity and secretory function of the nasal cavity and lacrimal gland remains unclear. The present study aims to investigate whether a thermal coagulation lead to a substantial reduction in the secretory function of the endonasal and lacrimal glands or impair trigeminal sensitivity. To answer this primary research question, we needed to be able to measure INTF unilaterally. In a preliminary study, we demonstrated that unilateral assessment of INTF using CO_2 is feasible. Previous studies have exclusively applied CO_2 bilaterally resulting in a non-differentiated measurement of the entire nasal cavity.

Materials and methods

The cohort study was conducted at the Department of Otorhinolaryngology Head and Neck Surgery at the University Hospital Zurich. The study was performed according to the Declaration of Helsinki and approved by the Cantonal Ethics Committee of Zurich (application number/BASEC number: 2020-02012). All participants were of legal age. Participants were provided with detailed information about all testing procedures, and written informed consent was obtained prior to study participation. Patients were included only if the surgical steps differed minimally from each other. In each surgery, the posterior third of the middle concha was partially removed and if necessary, septal spurs might need corrections in some cases. The mucosa was elevated, and the SPA was thermally coagulated, using a monopolar suction cautery device, and transected including the septal branch, that was identified after sphenoidotomy. The surgical procedure had to be performed no less than 30 days before inclusion into the study.

Demographic data were collected from all participants. A focused medical history regarding medication, co-morbidities, allergies and previous nasal surgeries was taken and a clinical workup including nasal endoscopy was performed. No skin prick test was conducted. Exclusion criteria included regular analgesic intake, alcohol or drug abuse, previous nasal surgery (excluding the treatment of epistaxis), radiotherapy in the head and neck region or diseases that could influence trigeminal sensitivity (e.g. neurological diseases, any form of chronic rhinosinusitis, granulomatosis with polyangiitis, severe diabetes etc.). In addition, exclusion criteria of the preliminary investigation were previous coagulation in the nasal cavity and contraindications such as allergies to the substances used in the study and symptoms of allergic rhinitis. Participants were instructed not to eat or drink within one hour prior to the examination. For CO_2 stimulation, we used a technique that allows to measure trigeminal sensitivity for CO_2 [11]. It had been modified to measure unilateral sensitivity. The exact procedure is described in the paragraph measurement of the intranasal trigeminal function (INTF). All measurements were performed and supervised by the same investigator (JJV).

Preliminary investigation and setup of methods

INTF was determined in healthy participants bilaterally, as well as separately for each side, using CO_2 gas stimulation. To validate unilateral testing, we also explored the influence of xylometazoline-containing spray (decongestant) and xylocaine spray (topical anaesthesia) on endonasal sensitivity, since the device had not been used for mononostril testing before. Data were collected first at baseline, then after application of a decongestant nasal spray (xylometazoline HCl (Xylo-Mepha 0.1%, Mepha Pharma Inc., Basel, Switzerland)) and finally after endonasal application of a mucosa surface anaesthetic (xylocaine spray 10%,

Lidocainum, Aspen Pharma Ltd., Zug, Switzerland).
Intranasal trigeminal function (INTF) is not routinely assessed in typical clinical settings but several methods exist which provide reliable results [12-14]. One of them is intranasal application of odorless carbon dioxide (CO_2) by means of a special stimulation device [11]. The psychophysical device is based on a semi-quantitative assessment of INTF. CO_2 is a selective chemical trigeminal stimulus [15-17]. Pure CO_2 (100%) was delivered via an oxygen nasal cannula. The measurements took place 3 minutes after application of the decongestant nasal spray and 8 minutes after application of the mucosa surface anaesthetic spray. In contrast to the olfactory system that recognizes mainly concentration changes of airborne stimuli, the INTF is also able to integrate the sum of weak stimuli over a given temporal period. This temporal summation effect was used in our experimental setup to administer stimuli with CO_2 intranasally, which were continuously increased regarding the duration of the stimulation, until the participant perceived a painful stinging and burning sensation in the nose. This pain quasi-threshold, defined as the stimulus duration in milliseconds until the first pain sensation, is the main outcome parameter that reflects a certain dimension of the INTF. The exact procedure is listed in the appendix.

Main study procedures

First, a functional measurement of the lacrimal gland using a bilateral ophthalmic Schirmer's test was performed followed by a unilateral functional measurement of the endonasal glands using sponges inserted into the nasal cavity. Subsequently, endonasal sensitivity was measured unilaterally by means of CO_2 stimulation, as described above.

Functional measurement of the lacrimal glands

Tear fluid was collected using sterile ophthalmic strips, so-called Schirmer's strips made of Whatman No 41 filter paper (Bio Schirmer, Bio-Tech Vision Care Pvt. Ltd., Gujarat, India). The Schirmer's strip was bent and hooked into the lower eyelid. Both eyes were tested simultaneously. After 5 minutes the flow distances of the tear fluid on the Schirmer's strips were measured in millimeters; with a maximum length of 35mm [18]. The results of the coagulated side were compared with the non-coagulated side.

Functional measurement of the endonasal seromucous glands

To measure the secretory function of the endonasal glands, surgical sponges (Merocel Ambrus Ear Pack, size 15mm x 20mm, REF 400354, Medtronic Xomed, Jacksonville, FL, USA) were inserted into the nasal cavity of the patients. The sponges were cut in half lengthwise. Half a sponge weighed between 0.10g and 0.12g. The sponges were placed in the anterior 3cm of the nasal cavity in the upper region in front of the middle meatus, so that no tear fluid, which flows into the inferior nasal meatus, was collected [19, 20]. The sponges were left in the nose between 5min and 16min (average 10.9min). The difference between the initial and the final weight was determined. The endonasal secretion, adjusted to the mean sponge weight in grams per minute, corresponds to the secretory output. The results of the coagulated side and the non-coagulated side were compared.

Measurement of the intranasal trigeminal function (INTF)

The measurement of INTF was carried out using CO_2 gas, which was released into the nasal cavity in a computer-controlled, side-separated manner. The device has already been used in several studies (Figure S1) [11]. CO_2 was delivered into the nasal cavity via a nasal cannula (Comfort Soft Plus Oxygen Goggles for Adults 1.2m (WEME0194, REF 0194, LOT 070320N18), Westmed Inc., 5580 S. Nogales Highway, Tucson, AZ, USA). To ensure better fitting, sponge nose adapters were placed onto the prongs, which are inserted into the nostrils (nose adapter Cube size 1, REF 512.1061.0, Atmos MedizinTechnik GmbH & Co. KG, Lenzkirch, Germany). For unilateral measurement the respiratory cannula was fitted into one nostril only. CO_2 stimulation delivery was computer-controlled and started with a gas-flow-time of 50ms. The gas-flowtime was consecutively presented in a stairway reversal paradigm. At intervals of 10 seconds, the gas-flowtime was increased by 50ms. Participants pressed a button at the first sensation of pain. The stimulation-time was again gradually reduced by 50ms until the subjects no longer felt any pain. Subsequently, the duration was increased again. The average of the last four stimulation durations at which a pain sensation has been perceived was documented as the pain quasi-threshold. The maximum stimulation duration was 2000 milliseconds.

Statistical analysis

A linear regression analysis was performed to study factors, which may have an impact on the INTF and the effect of time after surgery on INTF and on endonasal secretion using R statistical software (R Core Team, The R Foundation for Statistical Computing, Vienna, Austria). T-tests for paired samples and independent samples comparisons were performed by using SPSS Statistics 29.0.0.0 (241) for Windows (Statistical Package for the Social Sciences, SPSS Inc., IBM, Chicago, IL, USA). The Alpha-level of significance was set at a p-value of < 0.05. G-Power 3.1.9.7 was used to confirm that the population was large enough.

Results

Effect of local anaesthesia and decongestant

37 healthy volunteers (14 females, 23 males; median age 29 years, mean age 31.8 years; SD 11 years) were enrolled in the preliminary investigation. All healthy participants had no history of nasal surgery, radiation or trauma and showed a normal nasal

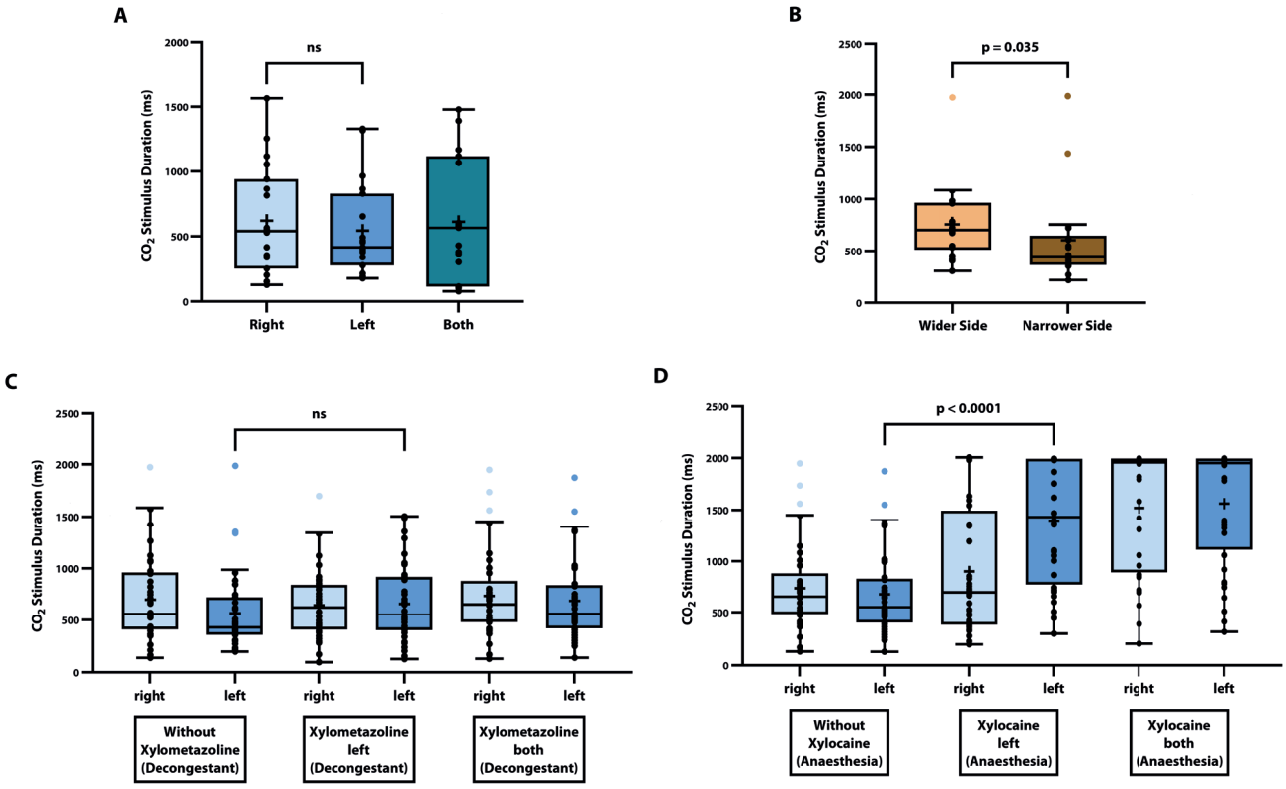

Figure 1. A) INTF without septal deviation. Solid line: Median, Cross: Mean, ns: not significant. B) Effect of septal deviation on INTF. C) Effect of decongestion with xylometazoline on INTF. D) Effect of anaesthesia with xylocaine on INTF.

endoscopy. The INTF determined in the preliminary investigation when testing the endonasal sensitivity using the CO_2 stimulation in both nostrils was 702ms (SD = 496) on average. Using a linear regression model, two factors were identified that influence INTF: the age of the subjects ($p < 0.01$) and a septal deviation ($p < 0.05$). Allergies, gender, hay fever and previous Covid-19 infections had no influence on INTF.

In the group without septal deviation, there was no significant difference between the two sides (right: M = 643ms; SD = 417; left: M = 566ms; SD = 357; t = 1.16; p = 0.26) [Figure 1A]. In contrast, the group with a septal deviation showed a significantly higher INTF and thus reduced pain threshold on the narrower side. (narrower side: M = 607ms; SD = 437; wider side: M = 760ms; SD = 381; t = 2.3; p = 0.035) [Figure 1B].

After decongestion with xylometazoline, there was no significant difference compared to the baseline measurement (baseline left: M = 573ms; SD = 374; xylometazoline left: M = 657ms; SD = 372; t = 1.25; p = 0.22) [Figure 1C].

After topical anaesthesia with xylocaine, there was a highly significant difference in INTF compared to the baseline measurement (native left: M = 687ms; SD = 396; xylocaine left: M = 1392ms, SD = 583; t = 8.4; p < 0.0001) [Figure 1D].

Effect of epistaxis treatment

The 17 patients who had undergone surgical treatment for refractory epistaxis (9 females, 8 males; 33 to 91 years; median age: 64 years; mean age: 64.6 years; SD 16.8 years) were examined once 42 to 499 days after monopolar cautery (median: 161; mean: 184.5; SD 131.7). In 14 patients, only the SPA was coagulated. In 3 patients, the ethmoidal artery/arteries were also coagulated in addition to the SPA. In 9 patients, surgery was performed on the left side and in 8 patients on the right side.

We found no significant difference between the left and the right sides in the Schirmer's test (coagulated: M = 12.1mm; SD = 10.9; non-coagulated: M = 14.2mm; SD = 11.2; t(16) = 1.6; p = 0.14) [Figure 2A]. In contrast, INTF measured by CO_2 stimulation time was significantly reduced and pain threshold was significantly increased on the coagulated side (coagulated: M = 1597ms; SD = 603; non-coagulated: M = 1191ms; SD = 579; t(16) = 3.1 ; p = 0.007) [Figure 2B]. Local anaesthesia with xylocaine significantly (p = 0.036) reduced INTF more than surgery did [Figure 2C]: mean of paired percentage differences between coagulated side and non-coagulated side was 52.3%; SD = 87.1; mean of paired percentage differences between anaesthetized side and non-anaesthetized side was 141.7%; SD = 156.8. We also found a significantly reduced endonasal mucosal secretion on the coagulated side (coagulated: M = 0.0046g/min; SD =

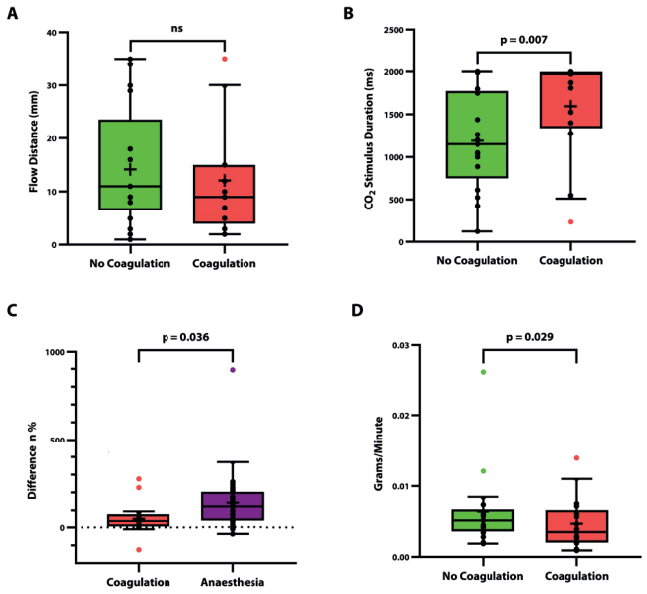

Figure 2. A) Effect of coagulation on tear secretion. B) Effect of coagulation on INTF. C) Effect of coagulation vs. anaesthesia on INTF; Y-axis: Paired percentage differences between coagulated side and non-coagulated side resp. paired percentage differences between anaesthetised side and non-anaesthetised side. D) Effect of coagulation on endonasal secretion.

0.0036; non-coagulated: M = 0.0064g/min; SD = 0.0055; The paired percentage difference between coagulated and non-coagulated side was 70.8%; t(16) = 2.4; p = 0.029) [Figure 2D]. Using regression analysis, we aimed to determine whether postoperative measurements in our patient population indicate an improvement in INTF over time. The difference between the coagulated and non-coagulated side even appears to increase slightly over time; but the effect was not significant (p = 0.7; R = 0.103; SD = 0.170) [Figure S2]. Finally, no significant increase in endonasal secretion was observed over time since surgery (p = 0.58; R = 0.145; SD = 0.184) [Figure S3]. All significant results underwent a power test and showed that population size was large enough.

Discussion

The present study provides novel findings: we could show that unilateral INTF measurement using the CO_2 device is possible and valid, which is an important finding for future research in this area. Clinically we could show that not only sensory but also endonasal secretory function seems to be long-lastingly impaired after surgical treatment for refractory epistaxis, while not affecting tear production.

We observed an influence of the endonasal anatomy on trigeminal sensitivity, in agreement with other reports [21]. Interestingly, the narrower side is more sensitive than the unobstructed one, a finding, that was not described before and difficult to explain in a straightforward way. This could be due to the higher flow velocity on the narrower side (Venturi effect), the different intranasal airflow distribution on the side [22], the higher density of thermoreceptors in the nasal vestibule [23] and the higher sensitivity to CO_2 of the anterior part of the nasal cavity [24, 25]. In the study by Masala et al. the subjects responded more sensitively to CO_2 stimuli the smaller the minimum cross-sectional area in acoustic rhinometry was [21]. Another explanation could be that the wider nasal cavity has more airflow and thus shear stress that may induce inflammation. Inflammation has been shown to reduce INTF [26, 27]. The endonasal anatomy must be considered when comparing side-to-side threshold measurements using a CO_2 device.

Topical anaesthesia of one side with xylocaine leads to a clear, measurable decrease in INTF. Other studies have also shown that superficial local nasal anaesthesia can cause a sensation of a congested nose [28] and increase pain threshold after endonasal CO_2 application [15]. On the other hand, oxymetazoline (decongestant) appeared to have little or no negative effects on intranasal chemosensory function [29].

Our findings suggest that both INTF and endonasal mucosal secretion can be reduced by surgical cautery. The high temperatures up to 800°C around the electrode lead to significant tissue injury with submucosal damage and necrosis. Salzano et al. showed an endonasal hyposensitivity in patients who underwent treatment with different hot techniques. The hyposensitive nasal mucosa showed histologically a devitalization of nervous fibers after electrocautery [30]. Another study showed long-term histological effects after inferior turbinate radiofrequency treatment with significant fibrosis, glandular and venous sinusoid depletion and epithelial shedding due to reduced perfusion [31]. Elwany et al. found a histologically and histochemically decreased size, number and secretory activity of nasal seromucous glands after endoscopic coagulation of SPA [10]. Thermal damage to nerves and vessels appears to have a greater impact on endonasal sensitivity and secretory function than believed and compared to cold steel procedures such as septoplasty and sinus surgery [12, 32-34]. The long-term histological changes in the mucosal architecture with fibrosis could explain the lack of improvement in INTF over time, but our study leaves us uncertain, because each participant was tested only once.

Similarly, no significant difference but only a tendency towards reduced tear production on the coagulated side compared to the non-coagulated side could be measured. Vidian neurectomy was shown to affect tear production with patients suffering from dry eyes and less rhinorrhoea, as well as crusting of the nasal cavity [35, 36]. Studies showed that electrical stimulation of sensory neurons of the nasal cavity can increase tear production and improve the signs and symptoms of dry eye disease [37]. Also, chemical stimulation of trigeminal receptors in the nose can trigger a number of reflexes such as tearing, sneezing, coughing,

transient apnea and secretion of mucus [38]. We interpret the differences anatomically, as our intervention was more distal than classical Vidian neurectomy. Nevertheless, slight affection of tear production cannot be ruled out completely. Whether decreased INTF and tear production recover over time remains a critical question for a follow-up study.

An intact endonasal trigeminal sensitivity is an important prerequisite for the perception of nasal airflow [12]. Nasal mucosal cooling with activation of TRPM8 thermoreceptors is believed to be the underlying stimulus that results in the perception of a non-congested nose [39-42]. A reduced endonasal sensitivity can lead to the perception of nasal congestion [28]. Our study shows that damage to the endonasal afferent blood vessels and sensory nerves can lead to a reduction in INTF. When providing information before surgical treatment, the possibility of reduced secretion and sensitivity should be discussed with the patients. Furthermore, heat producing coagulative techniques in nasal surgery should be avoided and techniques should be favoured that are gentle to the mucous membranes, vessels and nerves.

Limitations

During surgical hemostasis, a septum correction must occasionally be performed to improve visualization of the sphenopalatine foramen [43]. Correcting the septum alone does not appear to significantly reduce overall endonasal sensitivity [12, 32, 44]. Nevertheless, the intranasal air flow distribution and thus cooling is changed [45], which may affect trigeminal sensitivity [21]. In addition to coagulation, this could also have an impact on CO_2 sensitivity in some patients in our study.

We had no subjects complaining of olfactory loss and did not perform a side-separated olfaction test as it was not the focus of the study, yet would be very interesting. Rhinometry or rhinomanometry was not performed, as the results may vary significantly and does not correlate with subjective measures. Consistent with multiple previous studies a reduction of CO_2 pain responsiveness with aging was found [11, 45, 46]. The question arises whether this age-related loss of intranasal trigeminal sensitivity is because of the physiologic effects of the aging nose or of geriatric rhinitis and comorbidities, such as in olfactory disorders [47].

Determining an INTF baseline in a healthy population proved to be difficult due to the relatively wide distribution of the values. The anatomy of each nose like a septal deviation differs between individuals. Furthermore, the exact size of the coagulation area in the nose is not known. Also, the timing of post-interventional testing was very different for each patient (42-499 days). Since our study was not specifically designed to measure regeneration because each participant was tested only once, we cannot completely rule out regeneration and its effects on the measurements. Furthermore, the different tests can influence each other. The procedure was meticulously planned to ensure that the tests exerted minimal influence on one another. Furthermore, the Schirmer's test strip is limited to 35mm and the test time is always 5 minutes. In three measurements, the 35mm were reached before the end of the 5 minutes. However, there was no significant change in the results by extrapolating the run length to 5 minutes. Lastly, the maximum stimulus duration of 2000 milliseconds was reached in 7 measurements on the coagulated side and in 2 on the non-coagulated side. The maximum stimulus duration after local anaesthesia was reached in 29 of 72 measurements. It can therefore be assumed that endonasal coagulation and anaesthesia have even a stronger effect on INTF than we measured in this study.

Conclusion

The present study showed that it is possible to measure the endonasal trigeminal pain threshold unilaterally using CO_2 stimulation. The anatomy of the nose must be considered as it can affect perception. Monopolar cautery of the SPA and its branches can lead to reduced endonasal secretion and trigeminal sensitivity. This should become part of preoperative patient information.

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Authorship contribution

Study concept and measurement planning: JJV, MBS; Measurements: JJV; Data analysis: JJV; Figures: JJV, SM; Manuscript written by: JJV, MBS, BNL; Critical review of the manuscript: MBS, BNL, TH

Conflict of interest

There are no conflicts of interest.

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Prof. Dr. Michael B. Soyka
University and University Hospital Zurich
Frauenklinikstrasse 24
8091 Zurich
Switzerland

E-Mail: michael.soyka@usz.ch

J.J. Vavrina[1], T. Hummel[3], B.N. Landis[2], S. Macario[1,2], M.B. Soyka[1]

[1] Department of Otorhinolaryngology Head and Neck Surgery, University of Zurich and University Hospital Zurich, Zurich, Switzerland

[2] Rhinology-Olfactology Unit, Department of Otorhinolaryngology - Head and Neck Surgery, Geneva University Hospitals (HUG), Geneva, Switzerland

[3] Interdisciplinary Center Smell and Taste, Department of Otorhinolaryngology, Medical Faculty Carl Gustav Carus, TU Dresden, Dresden, Germany

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SUPPLEMENTARY MATERIAL

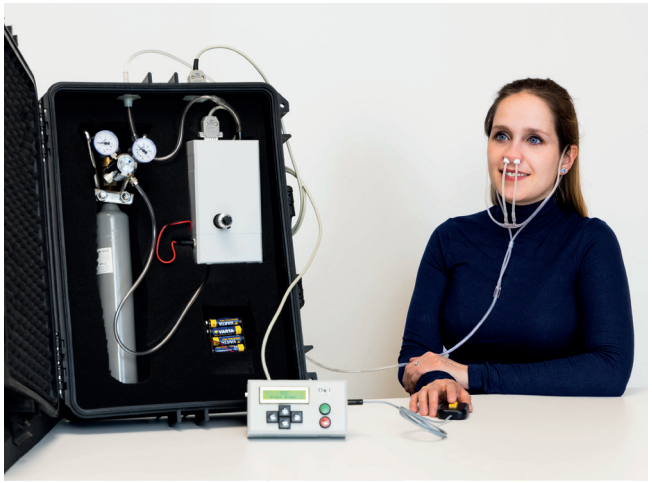

Figure S1. Experimental setup of the CO_2 device; determination of the INTF resp. Pain Threshold.

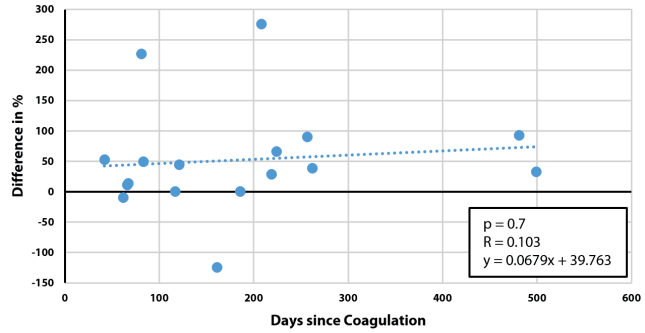

Figure S2. Effect of time since coagulation on INTF; Y-axis: Paired percentage differences between coagulated side and non-coagulated side.

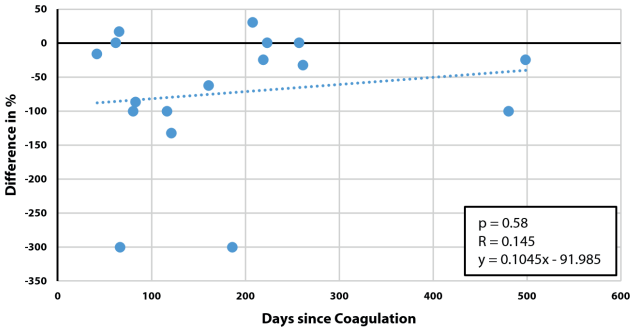

Figure S3. Effect of time since coagulation on endonasal secretion; Y-axis: Paired percentage differences between coagulated side and non-coagulated side..

Appendix

Measurement of the intranasal trigeminal function (INTF) in the preliminary investigation.

1. Simultaneous stimulation of the right and left nasal cavity without substance (native)
2. Mononostril stimulation without substance (native). First right then left nasal cavity.
3. Mononostril stimulation 3 minutes after xylometazoline application on the left nasal cavity. Stimulation first of right, then on left nasal cavity.
4. Simultaneous stimulation 3 minutes after xylometazoline application now also on the right nasal cavity. Simultaneous stimulation of the right and left nasal cavity.
5. Mononostril stimulation after xylometazoline application on both nasal cavities. First stimulation on right, then on left nasal cavity.
6. Mononostril stimulation after xylometazoline application on both nasal cavities and 8 minutes after additional xylocaine application only on the left nasal cavity. First stimulation on right, then on left nasal cavity.
7. Mononostril stimulation after xylometazoline and 8 minutes after xylocaine application on both sides (now xylocaine also on the right nasal cavity). First stimulation on the left then on the right nasal cavity.