DIPLOMA THESIS

Standardization of cryotherapy for cephalea: a prospective feasibility study

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Graz, November 9th, 2021

Affirmation

I solemnly vow, that this diploma thesis has been written and composed without assistance, independently and by myself only. It has neither been partly nor fully submitted as graded academic work. I herewith assure, that all references and sources – segments used directly or indirectly, exact wording as well as meaning – are stated and labeled as such.

Graz, November 9th, 2021 *Katharina Weiler eh*

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List of Abbreviations

ARS	acute rhinosinusitis
CRP	c-reactive protein
CRS	chronic rhinosinusitis
CRSsNP	chronic rhinosinusitis without nasal polyps
CRSwNP	chronic rhinosinusitis with nasal polyps
CSD	cortical spreading depression
CT	computer tomography
ENT	specialty of ears-nose-throat/otolaryngology
EPOS 2012	European Proposition Paper on Rhinosinusitis and Nasal Polyps in 2012
EPOS 2020	European Proposition Paper on Rhinosinusitis and Nasal Polyps in 2020
ESR	erythrocyte sedimentation rate
GA²LEN	Global Allergy and Asthma European Network project
HNO	Hals-Nasen-Ohren Heilkunde
HLA	human leukocyte antigen
ICHD	International Classification of Headache Disorders
ICHD-III	International Classification of Headache Disorders - III
IFN-γ	interferon gamma
IL-4	interleukin 4
IL-5	interleukin 5
IL-13	interleukin 13
IL-17	interleukin 17
IL-22	interleukin 22
NO	nitrogen oxide
PAMPs	pathogen-associated molecular patterns
PRR	pattern recognition receptors
TTH	tension-type headache

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Zusammenfassung

Einleitung

Kryotherapie ist eine weitläufig applizierte Art der konservativen Therapie von Schmerzen, wie z.B. auch bei jeglicher Form von Cephalgien. Dennoch basiert dessen Anwendung in der Klinik vor allem auf Erfahrung und nicht auf evidenzbasierter Medizin.

Deswegen ist das Ziel dieser Studie die Parameter Temperatur und Lokalisation bei der Anwendung von Kryotherapie am Kopf in Form einer Machbarkeitsstudie zu untersuchen. Es soll ein Standard für die Anwendung der Kryotherapie bei Cephalgien herausgearbeitet werden, welcher am angenehmsten und effizientesten wirkt.

Material und Methoden

15 Teilnehmer*innen wurden in diese klinische Studie der Intervall-Kryotherapie mit ein-minütigen Zyklen von Kühlung und Kühl-Pause inkludiert. Alle Teilnehmer*innen sind über 18 Jahre alt, nicht schwanger, haben bereits unter Kopfschmerz gelitten und haben keine weiteren bekannten Vorerkrankungen. Die Temperatur und die Eindrücke der Teilnehmer*innen werden während der gesamten Durchführung stetig dokumentiert. Über das Programm IBM SPSS Statistics® erfolgt die statistische Auswertung, wobei die Darstellung der Resultate anhand letztgenanntem und Python erfolgt. Die Datenauswertung wird mithilfe von deskriptiver Statistik dargestellt. Der Umgang mit den Daten der Teilnehmer*innen ist anonymisiert.

Resultate

93.3% empfanden Kryotherapie als sehr angenehm oder angenehm. 100% gaben an sie in zukünftigen Kopfschmerzepisoden anzuwenden. Ein Mittelwert der Temperatur von 16.48°C (SD: 2.54) und eine Spannweite zwischen 12°C-19.6°C wurden als am angenehmsten und effektivsten angegeben. Eine etwas höhere Kälteempfindlichkeit der Stirn (33.3%) im Vergleich mit den Schläfen (13.3%) konnte festgestellt werden. Wobei 53.3% keinen Unterschied zwischen den beiden Lokalisationen empfanden.

Konklusion

Das Einführen einer Standardisierung der Parameter Temperatur und Lokalisation für Kryotherapie bei Cephalgien ist erstrebenswert, um Patient*innen eine bestmögliche nichtmedikamentöse Therapieform anbieten zu können. Das standardisierte Schema sollte in zukünftigen Studien an Patient*innen mit akuten Cephalgien weiter untersucht werden.

Abstract

Introduction

Cryotherapy is a commonly applied form of therapy in the event of pain, e.g. for all kinds of headache. However, its application in the event of headaches, is often based on experience rather than on evidence-based medicine. Therefore, this study aims to investigate the parameters temperature and localization of cryotherapy on the head in the form of a prospective feasibility study, in order to provide a standardized treatment regimen for cryotherapy for headaches.

Material and Methods

15 participants are included in this clinical trial of an interval cryotherapy which consists of ten cycles of one minute cooling and one minute without cooling. All participants are over 18 years old, non-pregnant, have experienced headaches before and do not have any other diseases. The temperature and impressions of participants is consistently documented. For statistical evaluation descriptive statistic is used. For plotting the results IBM SPSS Statistics® and Python was used. Participants' data is anonymized.

Results

Out of the 15 participants 93.3% identified cryotherapy as very pleasing or pleasing and a 100% envisaged using cryotherapy during future headache episodes. A mean temperature of 16.48°C (SD: 2.54), with a range between 12°C-19.6°C, was found to be the most effective and pleasant temperature. A slightly higher sensitivity to cold of the forehead could be noticed (33.3%) in comparison to the temples (13.3%). However, 53.3% were indifferent towards the sensitivity of both cooling sites.

Conclusion

In this study we showed that the implication of a standard treatment regimen for the parameters temperature and localization in cryotherapy on the head is desirable in order to provide patients a non-pharmaceutical form of therapy. With a mean temperature of 16.48°C, further studies are required to fully investigate the effect of cryotherapy on patients with acute headache.

1 INTRODUCTION

Cryotherapy is frequently used in clinical routines for diverse indications. In the field of otolaryngology (ENT), an example would be the application in the event of postoperative cephalea or (acute) rhinosinusitis, which is often accompanied by facial pain or a headache (1,2). Otherwise, cryotherapy also provides relief for patients with migraine or tension-type-headache (TTH) which belong to the most common headache disorders in society (3-5). Cryotherapy is the most common non-pharmacological method that relieves pain (1). Nonetheless, there is no standardized treatment regimen for its application.

The aim of this study is to find out an optimum temperature as well as the most comforting localization on the head in the form of a feasibility study in order to optimize cryotherapy and to propose a standard treatment regimen for its application.

1.1 CRYOTHERAPY

1.1.1 Definition

Cryotherapy is the therapeutic usage of cold in order to cool the body either systemically or locally by aiming to reduce inflammatory processes, edema and pain.

It is subdivided in short-term (10-15 minutes) and long-term (1-2 hours) cryotherapy (6).

1.1.2 Administration/Application

In current routines there are various sorts of application (6):

- Whole body exposition in a cold chamber (-110°C)-(-160°C) for 1-3 minutes
- Cold water immersion – whole body or certain body parts 6-12°C
- Cooling spray (chloraethyl spray) (-0,5°C)-(-1°C)
- Cold gases as nitrogen (-110°C)-(-160°C) or cold air -30°C
- Ice compresses 1°C-3°C

- Ice bags with water (massage, packages, dabbing) 0°C
- Ice packs with silicate -30°C

Out of all mentioned types one should choose according to the indication. The indications include several postoperative conditions, for example after sinus surgery in ENT, (rheumatoid) arthritis, injuries of muscles, ligaments or junctions, burns, spastic muscle tensions as well as benign and malign skin alterations (6). Furthermore, it is often used to treat headaches (3).

1.1.3 Effects

The effect of cryotherapy depends on several factors, including the time and type of application, as well as the localization it is used on (7).

A short-term application causes a vasoconstriction and therefore decreases the vascularization. During the first 5-10 minutes, this phenomenon only occurs superficially. During another following 5 minutes, it also starts affecting the deeper muscle layers. After removing the cooling device, a reactive persisting hyperemia eventuates and increases the pain threshold in the long-term (6).

In case of long-term application (1-2 hours), cold causes a decrease of tissue perfusion accompanied by a reduction of metabolism. The activity of enzymatic processes and phagocytose diminishes (6).

In addition, it initiates a reduction in neuronal activity regarding refractory period, nerve conduction velocity, and reflective inhibition of pain transmission, thus providing significant pain relief as the pain threshold increases. Total analgesia can be documented at a skin temperature of 15°C because the skin's sensitivity to cold exceeds its sensitivity to pain. Otherwise, effects of cryotherapy on muscles can also be observed. Bleedings and the development of edema can be inhibited (6).

1.1.4 Side effects and contraindications

In general, cryotherapy has a low risk of side effects (8). However, it can cause cold injury if the temperature is too low and application too long. Therefore, it is important

that patients are well informed and that, depending on the type of cryotherapy, the process is supervised by qualified staff.

In case of peripheral vascular diseases, angina pectoris, Raynaud-Syndrome, allergies against cold, cryoglobulinemia, cold hemoglobinuria or in case of an acute nephropathy or bladder disease, cryotherapy is contra-indicated. Neither is it recommended for elderly patients nor chronic pain patients (6).

1.2 HEADACHE

1.2.1 Definition

Headache is described as a painful neurological detection in the cranial region. It is induced by several stimuli, which can source from a primary or secondary origin. The brain tissue itself has no receptors for pain so the actual impulses are drawn by pain-sensitive structures such as the skull cap, the meninges, brain vessels or cranial nerves (9).

1.2.2 Primary and secondary headache

Headache can be distinguished according to its origin, namely a primary or secondary cause.
The difference between the two types is that a primary headache features no traceable lesions of the intracranial structures, whereas the secondary headache is caused by organic diseases of the cranial vessels or by diseases of other tissue structures of the head (10). Overall, 92% of the cases are primary headaches, only 8% are secondary ones (11).

Several key criteria play an important role in diagnosing the exact origin such as episodic occurrence, duration of headache, its specific characteristics, and the concurrent presence of other diseases (3).
Primary headaches therefore represent a disorder itself. Typical primary headaches with specific symptoms include migraine, TTH and cluster headache. A primary headache is present when no other demonstrable organic disease can be found (12). The most common ones are those mentioned above (10).

A headache is secondary if it occurs simultaneously with other diseases, which can, based on evidence-based medicine, represent a cause of headache as well. If, on the other hand, there is already a confirmed diagnosis of an existing headache that worsens at the same time as another disorder that causes headaches, it is more appropriate to speak either of a primary headache only or, taking into account the worsening of the pain, of a primary and an additional secondary headache (11). Secondary headaches can be caused by intracranial space requirements, an

anomaly of the cerebrospinal fluid's circulation or by liquor hypervolemia. They can also be triggered by infections of or surgical interventions of the paranasal sinuses. As well as by eye-related, medical-induced, dental associated or psychogenetic pathologies (10).

1.2.3 Pathogenesis and symptoms of headache

1.2.3.1 Pathogenesis and symptoms of primary headache

Generally, in 92% of the cases a headache appears as a primary headache. The primary headache's pathogenesis is always influenced by several parameters (11).

1.2.3.1.1 Pathogenesis of TTH

The pathogenesis of TTH is still not yet completely understood. Although it is known that there are multiple contributing factors in its development, the exact process remains unknown. Factors like stress, tensions of the neck musculature, as well as alcohol and nicotine abuse are said to trigger this kind of headache (13). Nowadays it is usually assumed that a neurobiological mechanism is responsible for TTH, especially in severe cases (4).

In relation to TTH, a distinction can be made between infrequent episodic TTH and frequent episodic TTH, which are believed to occur out of peripheral mechanisms. Another differentiation is chronic TTH which, contrarily, has most probably a central pain mechanism (4).
Even though TTH is the most common headache among society, it is also the one that is least studied (4).

1.2.3.1.2 Symptoms of TTH

TTH is generally characterized by a heavy and constrictive pain on both sides of the head. It depends on the frequency of occurrence to which type of TTH, episodic or

chronic, the particular headache relates to. It can last from thirty minutes up to seven days for the episodic type, whereas in case of chronification its occurrence reaches from several hours to continuous presence. The intensity of pain varies from light to modest intensity and is not increased by physical routine activities. Episodic and chronic TTH may be accompanied by phono- or photophobia, but not by both at the same time. Additionally, in case of chronic TTH, nausea can occur as well, but does not occur in any type of episodic TTH (4).

All types of TTH can be presented with or without increased pericranial pain sensitivity. Whereby the actual pain sensitivity increases with the intensity and frequency of the TTH's attacks and is even enhanced during a headache (4). Cryotherapy therefore provides a suitable non-pharmaceutical solution because it increases the pain threshold. It could either interrupt a light or modest THH or support a severe one (6).

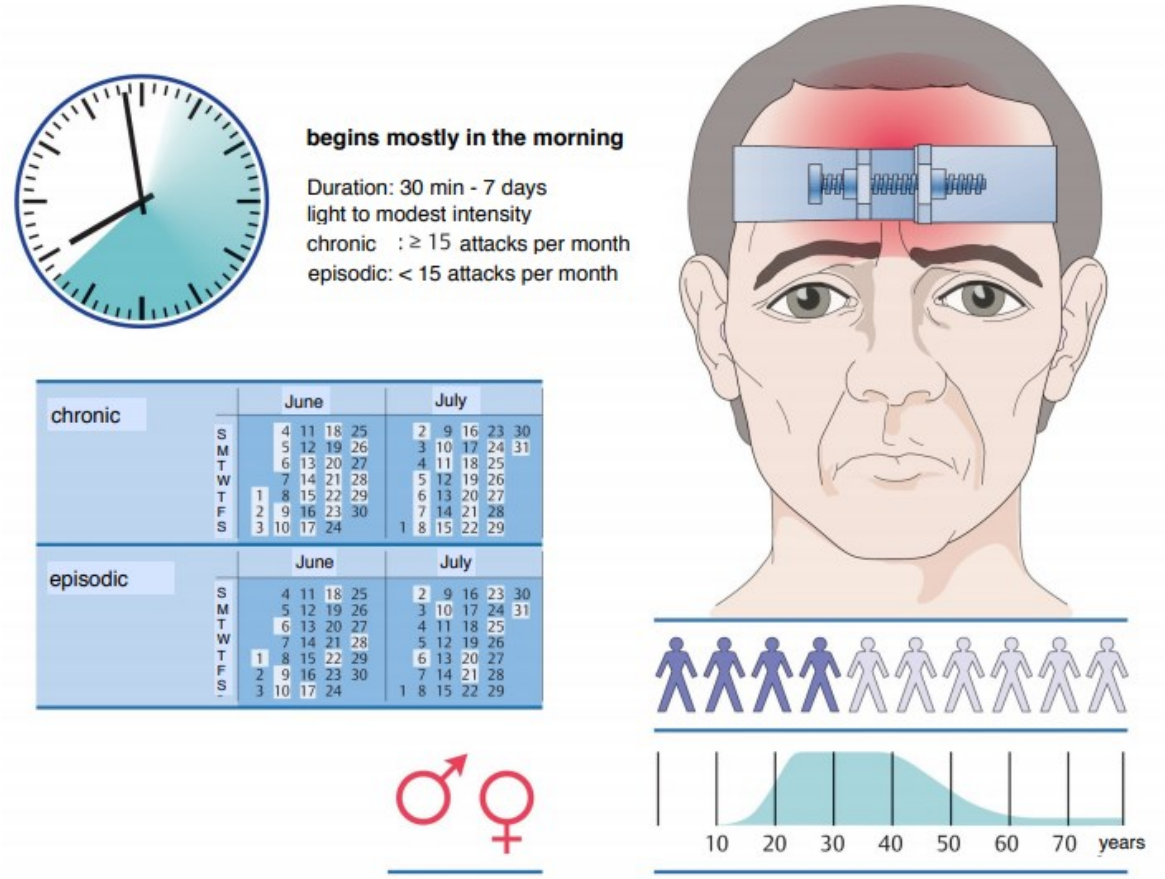

Fig. 1 Symptoms of TTH

Mattle/Mumenthaler, Kurzlehrbuch Neurologie, 4. Auflage, Georg Thieme Verlag, Stuttgart 2015, p.391, translated from german to english (10)

1.2.3.1.3 Pathogenesis of migraine

Essentially, migraine can either be represented by actual pain (migraine without aura), or it can be accompanied by an aura before the pain (migraine with aura). These are two distinct subtypes of migraine that are thought to differ in pathogenesis. However, the actual processes remain unclear (3). The headache period in both subtypes represents a one-sided, pulsating pain. Unlike migraine with aura, no alteration of the bloodstream in cranial vessels has been notified as a trigger mechanism for migraine without aura. Rather a change in neurotransmission was detected. This will be further explained in the following (3).

In contrast to the earlier hypothesis that the pathogenesis was exclusively vascular, research today focuses more on the importance of sensitization of perivascular

nerve endings and neurotransmission in the trigger mechanism of migraine without aura (3).

In case of migraine with aura, pain is a result of activation of the trigeminovascular system leading to a mostly unilateral, pulsating pain. The trigeminal nerve sensitively innervates the dura, the large vessels near to the cranial base, as well as the pial vessels. The trigeminovascular system shields the head from external effects. Nonetheless, according to a faulty activation it causes unnecessary pain (10).

The trigeminovascular system can be activated by intracranial perivascular sensorial axons which mediate an impending or already existing tissue damage. This information is sent by the brain itself, by its supplying blood vessels or the blood vessels' innervating neurons (3).

These sensorial fibers provide information in an efferent and afferent way and thus communicate in both directions. The afferent forwarding of nociceptive information coming from the vessels runs over the nucleus caudalis, whereas the induction of blood vessels happens efferently (3).

Due to the efferent way of communication of these sensorial fibers, it is possible to urge a following reaction to the impending or existing tissue damage, which leads to a sterile neurogenic inflammation. This is further induced by a release of vasodilatory neuropeptides as the Substance P, Neurokinin A, calcitonin-gene-related-peptide (CGRP) and the vasoactive intestinal polypeptide (VIP). By their release, the blood vessel's permeability increases and induces plasma extravasation. The neuropeptides are synthesized in the trigeminal ganglion (3). This electrophysiological phenomenon is described as 'cortical spreading depression' (CSD) and is generally defined by a wave of excitation which is followed by inhibition in cortical neurons and finally results in neurogenic inflammation (14). It explains alteration of the blood flow and increased tenderness. Electrical, mechanical and chemical stimuli are possible trigger mechanisms to set it off (3).

Cortical spreading depression may be the physiological process that underlies the aura whereas CSD's meaning for a migraine without aura is not well understood (14). Although alternations of the bloodstream are provable after the activation of pain in migraine without aura, they are not typical for cortical spreading depression. Thus, there is a high possibility that CSD does not play an important role in the

pathogenesis of migraine without aura (3). However, specific messenger molecules like nitrogen oxide (NO) and calcitonin-gene-related-peptide certainly do. As does the neurotransmitter serotonin which is proved by the high effect of Triptans (5-HT1B/D-receptor antagonists) in acute attacks of migraine without aura. However in this instance the pathophysiological process is still not completely understood (3).

In both cases, cryotherapy is a non-pharmaceutical remedy for pain. The cold temperature is assumed to have a constrictive effect on the dilated vessels and therefore reduces the pain. Although, it is not assumed to be able to interfere or stop the attack of migraine on its own (3).

1.2.3.1.4 Symptoms of migraine

As mentioned above, migraine can be distinguished into many subtypes whereas the main classifications are migraine with and migraine without aura.

Migraine without aura manifests itself by a typical one-sided pulsating pain that comes in attacks lasting 4-72 hours. It shows modest to high intensity and is increased by physical routine activities. The pain is accompanied by nausea and/or phono- and photophobia (3).

Contrarily, migraine with aura is especially characterized by a foregoing aura. It is a phase developing within 15-20 minutes lasting less than 60 minutes. It occurs paroxysmally and contains reversible focal neurological symptoms. The most common neurological symptoms are visual and consist mostly of a flickering and a blurry sight. The actual headache does not have to arise during a migraine with aura. In case that it does, it presents the same characteristics as described for migraine without aura and can also be accompanied by focal neurological symptoms. Several cases also report a prodromal phase which can occur hours to days before the headache and/or a postdrome phase occurring after headache resolution. Both phases include symptoms as hyper- and hypoactivity, depression, food cravings, repetitive yawning, fatigue as well as neck stiffness and/or pain (3).

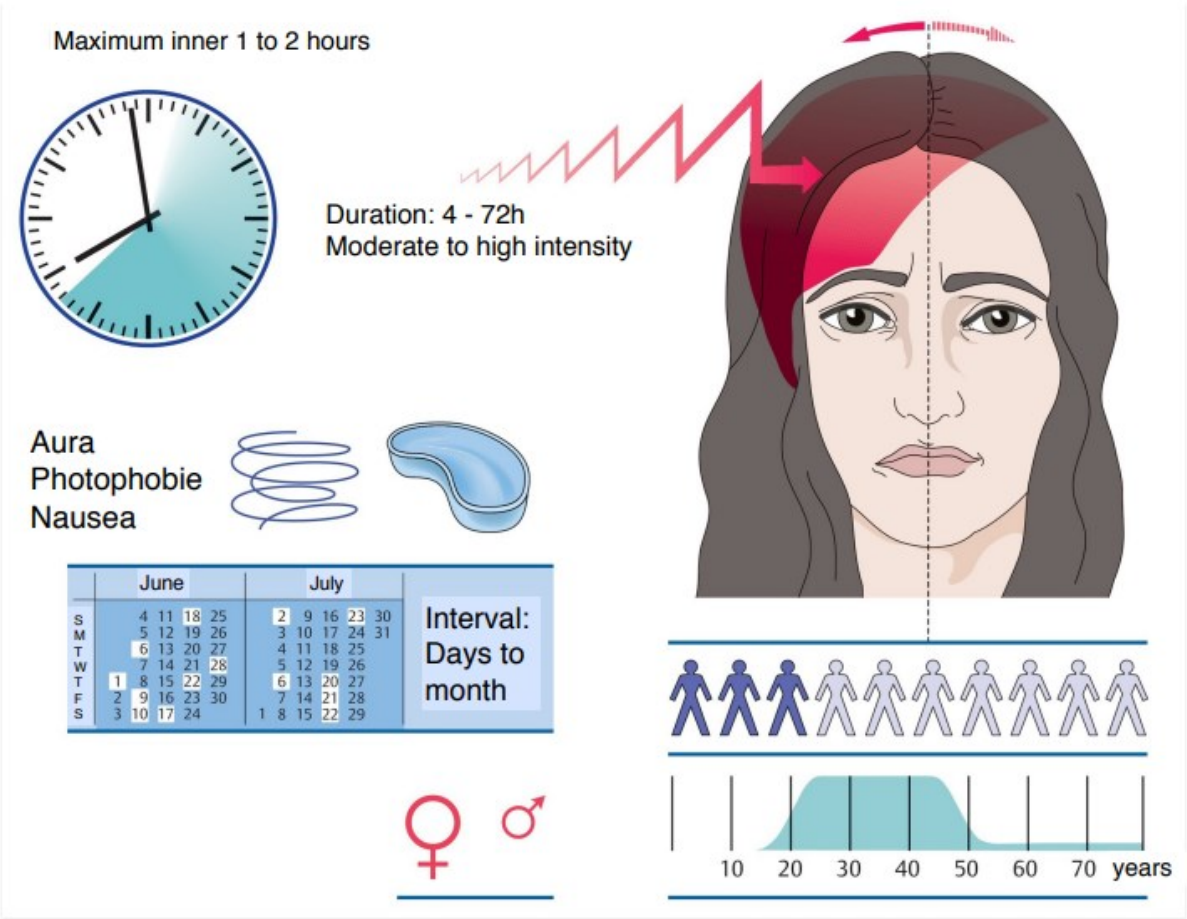

Fig. 2 Symptoms of migraine

Mattle/Mumenthaler, Kurzlehrbuch Neurologie, 4. Auflage, Georg Thieme Verlag, Stuttgart 2015, p. 393, translated from german in english (10)

1.2.3.2 Pathogenesis and symptoms of secondary headache

Secondary headaches indicate more of a symptom of another disease than an independent disorder. This is why there is no specific pathogenesis (10,11). In the International Classification of Headache Disorders a total of 196 secondary headaches are referenced. This does not include other less serious conditions that can cause headaches as they have not all been officially classified. However, the 196 classified secondary headache causes only constitutes 8% of all headaches in general (11).

In the following, a few examples will be given.

A headache attributed to trauma or injury of the head and/or neck is one of the most common secondary headaches. Although its pathogenesis is not exactly known, it

is thought to be linked to axonal injury, neuroinflammation, alterations in cerebral metabolism or haemodynamics, as well as to the simple expectation of patients to develop a headache after trauma (15).

Moreover, in case of a headache attributed to cranial or cervical vascular disorders which include disorders such as cerebral ischaemic events, non-traumatic intracranial haemorrhage, unruptured vascular malformations and cranial venous disorders amongst others, there is no specific pathogenesis either. In most of the cases, however, the actual pain is induced by mechanical compression which again is caused by space requirements as bleedings or vasodilatation, local compressions, a direct and/or indirect activation and irritation of the nociceptive system as well as the increase of intracranial pressure (16).

For headaches that come with non-vascular intracranial disorders such as increased cerebrospinal fluid, intracranial neoplasia etc., the main factor of their pathogenesis is increased intracranial pressure. It causes compression of brain tissue and in later stages also increased pressure on the skull by extension of interior space requirement (17).

Furthermore, headaches often occur as a result of infections, as e.g. intracranial infections, as meningitis, encephalitis or a brain abscess. It occurs as well in case of systemic viral or bacterial infection. In general, intracranial infections lead to pain because they directly stimulate sensory afferents. They also often cause intracranial hypertension by a reactive brain edema and accumulation of pus. At the same time, nociceptive structures can be more sensitive due to release of inflammatory neuropeptides, which promotes the process (17).
There are several theories on the pathogenesis of headaches being attributed to systemic infection. One of them suggests that due to coexisting fever, pyrogens and toxins of infectious agents are released, which stimulate endogenous pyrogens, which thus lead to a sensitization of nociceptive structures. This cascade is responsible for arthralgia, myalgia and particularly headaches. Another hypothesis is that through induction of the release of prostaglandins, prostacyclin and thromboxane, a sensitization of nociceptive structures and vasodilation happen that lead into an excitation of perivascular nociceptors. This excitation results in the typical throbbing pulsating headache, which often relates to a viral or bacterial infection (17).

Moreover, other common causes for secondary headaches can stem from disorders of the skull, neck, eyes, ears, nose, sinuses, teeth, mouth and other facial or cervical structures. In these cases some strict criteria have to be present in order to set a diagnosis. Not every disorder, even if it is known that it can lead to headaches, is validated as an actual diagnosis. For example, although cervical osteochondrosis, spondylosis and chronic sinusitis are often accompanied by a headache, they exist equally often without it and thus cannot be validated as a proper diagnosis (18).

In order to provide examples, some pathogenesis of validated diagnosis will be presented in the following.

Secondary headaches attributed to craniocervical dystonia are caused by pathogenic muscle contractions, which can appear in several craniocervical muscle groups, and secondarily lead to a change in sensitization. In a headache assigned to disorders of the eyes, like an acute angle-closure glaucoma, the pain is caused by hypertension of the posterior chamber of the eye. Furthermore, in case of headaches triggered by heterophorias, the headache is due to a constant dysregulation and muscular overstrain of the concerning eye muscles (18). In terms of occurrence of headaches in ENT, there are several disorders in this field which represent validated diagnoses. As for disorders of the ears, headaches that accompany, e.g. otitis media, petrositis or traumatic as well as neoplastic disorders of the petrous bone can be explained by convergence and overlap of nociceptive pathways in the area of the trigeminal nerve. Thereby, it is inflammation or neoplasia that directly triggers the activation of the trigeminal nerve (18,19). This process is also assumed to be the cause of headache attributed to acute rhinosinusitis. Through inflammation of the particular sinus and increasing pressure, which is explained by its obstruction, the trigeminal pathways are triggered and a following excitation leads to headache (18,20). It is certain that headache is induced by trauma and therefore also trauma in terms of ENT surgery. Thus, a lot of patients have a headache after ENT surgeries, e.g. a septum correction or removal of adenoids (18,21).

There are various etiologies for secondary headaches. To mention all of them is beyond the scope of this thesis, (e.g. secondary headache attributed to a certain substance or its withdrawal, to a disorder of homoeostasis or as well assigned to

psychiatric disorders), thus the focus was put on headaches potentially relieved by cryotherapy (22-24).

1.2.3.2.1 Symptoms of secondary headache

Since secondary headaches are not induced by one specific cause, it can be represented in several different ways. However, its symptoms will mainly resemble those of primary headaches including migraine, TTH and cluster headache. Although, depending on the secondary headache's cause, it is of course possible that pain can be locally enhanced. It usually disappears after a maximum of three months (11,18).

1.2.4 Epidemiology

1.2.4.1 Epidemiology of primary headache

As explained above, due to a wide ranging manifestation and no biological markers, it can be difficult to diagnose headaches. In order to measure or identify it correctly, the International Classification of Headache Disorders (ICHD) was firstly published in 2004 and its third edition (ICHD-III) is now used worldwide (25). It differentiates every kind of headache, such as migraine, TTH or secondary caused headaches into specific subsections and codes them by numbers. These numbers correspond to the actual diagnosis (5).

In general, 47% of the adult human population worldwide suffer from a headache. Primary headaches such as migraine, TTH or cluster headaches are more common than secondarily caused ones (5). This underlines the importance of introducing a standard of a widely accessible, non-pharmaceutical device as cryotherapy in order to readily offer more people pain relief.

The global prevalence of migraine is 10%, of TTH 38%. Nevertheless, it remains a higher lifetime prevalence: for headache in general 66%, for migraine 14%, and for TTH 46%.

There is a regional prevalence to different headache disorders. For example, migraine has a higher prevalence in Europe and North America than in Africa

(Europe: 15%, North America: 12%, Africa: 8%), whereas TTH is more prevalent in Europe than in Africa or America (Europe: 80%; Africa and America: 20-30%) (5).

Furthermore, sex and age also play a role in the prevalence of headache, while there are no remarkable differences in prepubertal children for migraine. There are some distinctions between the occurrences in men and women. The male to female ratio for migraine varies from 1:2 to 1:3. Migraine is most frequently first diagnosed in the second and third decade of life. Generally, its prevalence steadily rises until a peak during the fourth decade. Afterwards it slightly decreases (5). In case of TTH a male to female ratio of 4:5 persists. Contrarily to migraine, the prevalence of TTH increases with advanced age, while it has its peak between the age of 30 to 39. Like many chronic headache diseases, TTH's prevalence increases until the fifth decade of life with only a slight increase afterwards (5).

1.2.4.2 Epidemiology of secondary headache

In general, secondary headache contributes only around 8% to all types of headache (11).

Since the various causes that lead to secondary headaches are partly unknown or not well understood, very few documentations of its epidemiology exist. As a result of this field lacking research, the existing data is mainly not usable for epidemiological studies (26).

1.3 SINUSITIS AS POTENTIAL REASON FOR HEADACHE

1.3.1 ANATOMIC BACKGROUND

1.3.1.1 Anatomy of the nose

The nasal cavity is part of the upper respiratory tract and includes the olfactory organ. The nasal cavity is composed of two components, the nasal vestibulum and the common nasal cavity. The nasal septum separates both parts into a right and a left cavity. Through the choanae the nasal cavity is connected to the naso-pharynx. The nasal cavities are lined by respiratory and olfactory mucosa. While the olfactory mucosa is located in the upper part of the cavity (superior septum and superior turbinate), the respiratory mucosa comprises most of the nasal mucosa and extends into the paranasal sinuses. Its function is to warm, humidify and filter inhaled air (27).

Sensory innervation is provided by the trigeminal nerve (27,28).

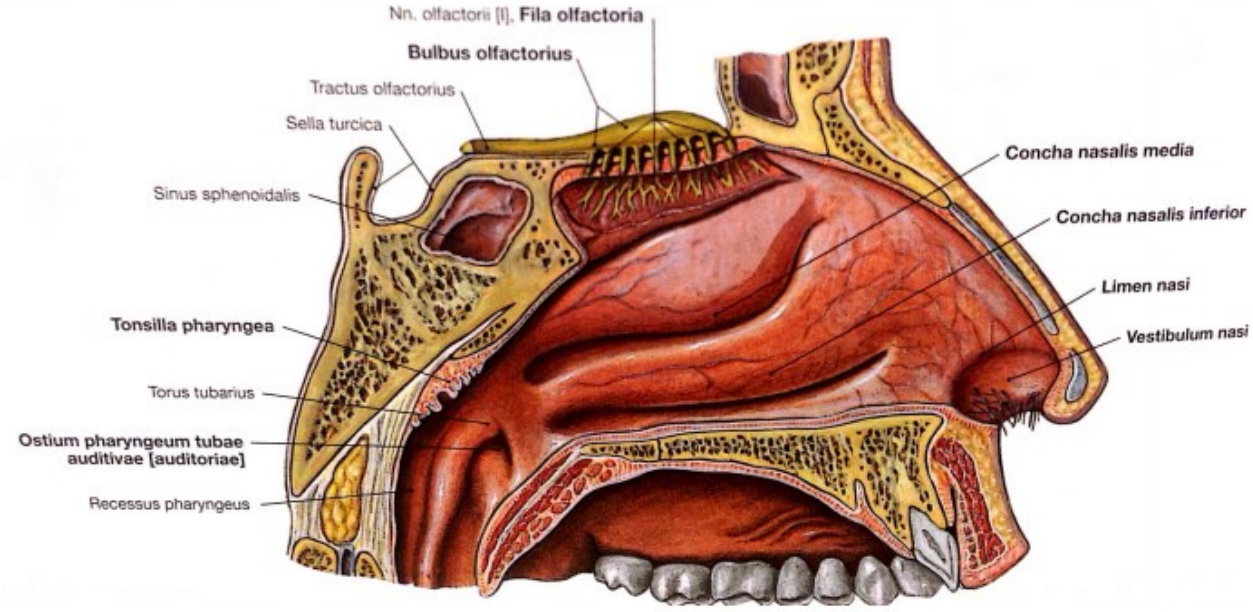

Fig. 3 Lateral nasal septum

Paulsen, F., Waschke, J. (Hrsg.), 2010. Sobotta Atlas der Anatomie des Menschen. Kopf, Hals und Neuroanatomie, 23. Auflage, Urban & Fischer Verlag, München, p. 60 (29)

1.3.1.2 Anatomy of the paranasal sinuses

The paranasal sinuses and the adjoining rooms of the middle ear together form the pneumatized rooms of the cranium. There are four paired paranasal sinuses. As well as reducing the weight of the cranium, the paranasal sinuses act as a resonating cavity and protect important structures in case of trauma. The mucosa is similar to the respiratory mucosa in the nasal cavity but it contains less goblet cells (27).

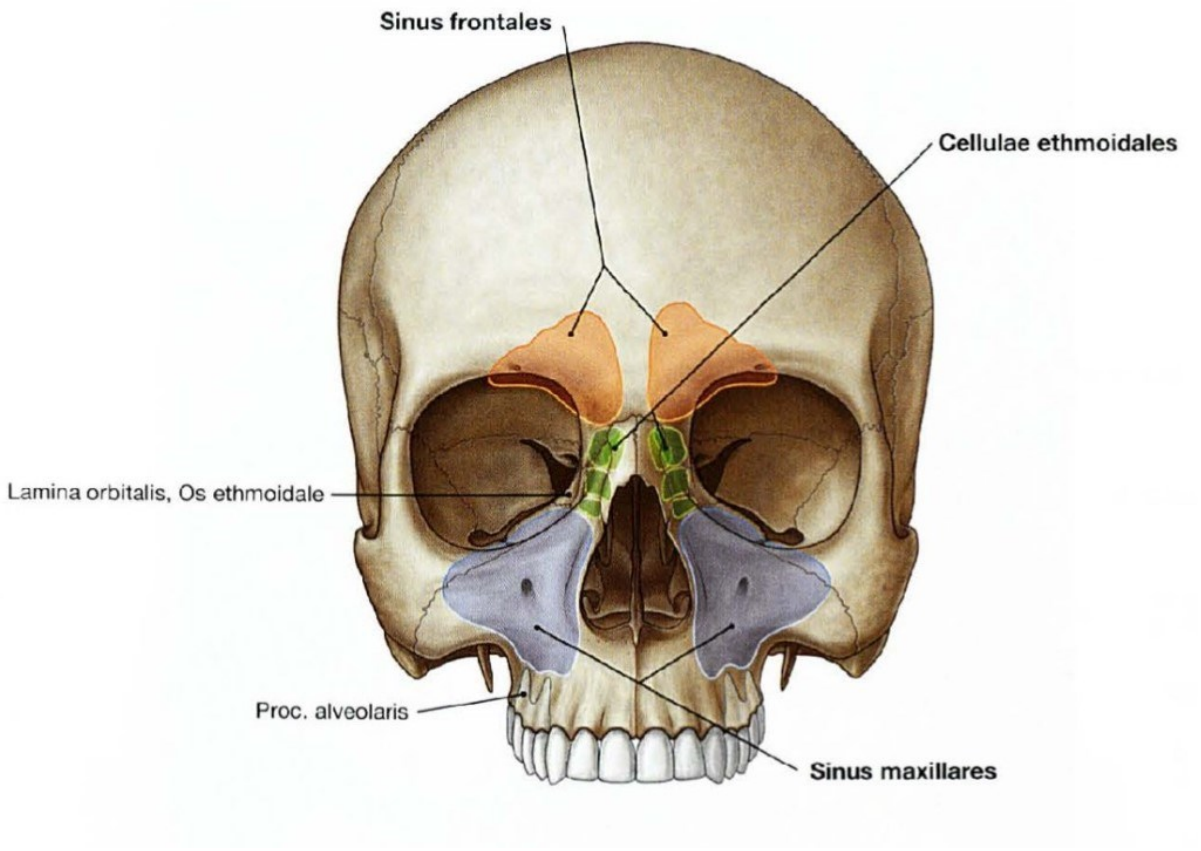

Fig. 4 Paranasal Sinuses

Paulsen, F., Waschke, J. (Hrsg.), 2010. Sobotta Atlas der Anatomie des Menschen. Kopf, Hals und Neuroanatomie, 23. Auflage, Urban & Fischer Verlag, München, p.61 (29)

1.3.1.3 Maxillary sinus

The quadrangular pyramidal shaped maxillary sinus is the largest one (11cm³ ± 4cm³) of the paranasal sinuses in the full-grown state. Its base correlates to the lateral nasal wall while its tip is positioned centrally to the zygomatic bone.

The thin roof of the maxillary sinus is the orbital base while the base of the maxillary sinus is situated over the alveolar process of the maxilla. There is close contact to the roots of the premolar and molar teeth (27).

1.3.1.4 Frontal sinus

The paired frontal sinuses are located in the single frontal bone divided by an asymmetric septum. There are many varieties of asymmetric septums. In the European population, they can be distinguished by four different types of shapes in the European population (after Szilvássy): bean shape, leaf shape, mitral shape, pyramidal shape.
The frontal sinus expands into the squama of the frontal bones. In general, the sinus leads over a recess in the ethmoidal infundibulum and further into the medial meatus (27).

1.3.1.5 Ethmoidal cells

The ethmoid bone contains a labyrinth of up to 16 ethmoidal cells. They spread out between the medial orbital wall and the nasal septum within close proximity to the maxilla and the frontal bone.
Not all of the ethmoidal cells have to be surrounded by bone. These are the so-called extramural ethmoidal cells.
According to the Nomina Anatomica (30), the cells are classified into anterior, medial and posterior ethmoidal cells.

The largest of the anterior ethmoidal cells is called ethmoidal bulla. It reaches, together with other anterior cells, into the ethmoidal infundibulum. Meanwhile the medial cells reach into the medial nasal meatus and the posterior ones into the superior nasal meatus (27).

1.3.1.6 Sphenoidal sinus

The sphenoidal sinus is separated into two chambers by an osseous septum, which is most commonly perforated. It differs a lot in size and can also be separated by other septa. The ostium of the sphenoid septum leads into the spheno-ethmoidal recess (27).

1.3.2 Definition of Sinusitis /Rhinosinusitis

Rhinosinusitis is defined as an inflammation of the nose and paranasal sinuses (31). Usually rhinitis and sinusitis co-exist and influence each other (32), therefore it should always be referred to as 'rhinosinusitis' (33). Rhinosinusitis has many different causes and can generally be divided into acute and chronic rhinosinusitis (31).

It can further be categorized by its localization. If all sinuses are inflamed simultaneously, this is referred to as pansinusitis. When only one sinus is inflamed, this would most commonly be the ethmoidal or the maxillary sinuses. Inflammation of the frontal sinus is less common, inflammation of the sphenoid sinus is very rare (31). Specific symptoms will be further described in *1.3.3,* however it must be highlighted, depending on which sinuses are affected, acute and chronic rhinosinusitis can also induce different types of headache (31). Consequently, cryotherapy represents an important supportive therapy in the treatment of rhinosinusitis, and therefore this study aims to define a standard treatment regimen for its application.

1.3.2.1 Definition of Acute Rhinosinusitis (ARS)

Acute rhinosinusitis is defined by a sudden appearance of symptoms like nasal blockage, nasal discharge and facial pain or pressure, which disappear in less than 12 weeks. The exact description of symptoms follows in *1.3.3.* Moreover, it is necessary to differentiate between an acute viral, a post-viral and an acute bacterial rhinosinusitis (2).

Acute viral rhinosinusitis, also called common cold, suggests a viral infection, as e.g. caused by a rhinovirus, and should not last longer than ten days. A post-viral rhinosinusitis lasts longer than ten days but less than two weeks with a persistence of symptoms or an increase in symptoms after five days. An acute bacterial rhinosinusitis must present at least three symptoms of the following: discolored mucus, severe local pain (often unilateral), fever > 38°C, raised C-reactive protein (CRP)/erythrocyte sedimentation rate (ESR), double sickening (2).

In the case of a bacterial infection, it is most likely caused by Pneumococci, Haemophilus influenzae or, less commonly, by Moraxella catarrhalis, Staphylococci and Streptococci (31).

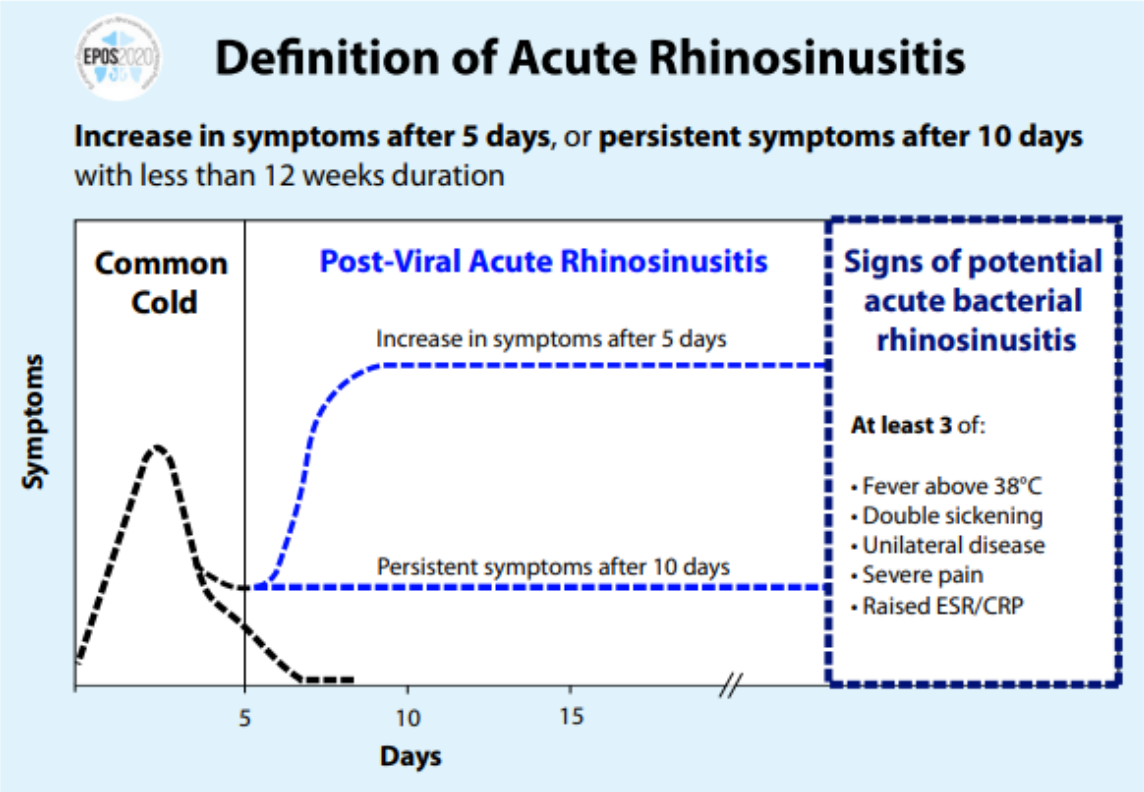

Fig. 5 Definition of acute Rhinosinusitis by symptoms

Fokkens W.J., Lund V.J. , Hopkins C., Hellings P.W., Kern R., Reitsma S., et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020 Rhinology. 2020 Suppl. 29: 1-464 (2).

1.3.2.2 Definition of Chronic Rhinosinusitis (CRS)

CRS is diagnosed in case of persistence of at least one symptom for more than 12 weeks (2).

A subdivision is made by differentiating between a chronic rhinosinusitis with nasal polyps (CRSwNP) and a chronic rhinosinusitis without nasal polyps (CRSsNP) (2).

Etiology as well as pathogenesis of CRS is a current topic of research and within the last decade an eminent amount of progress has been made (2).

1.3.3 Pathogenesis and symptoms of Rhinosinusitis

1.3.3.1 Pathogenesis of ARS

The pathogenesis of ARS depends on the reaction of the innate and the adaptive immune system.

In order to affect the host, bacteria as well as viruses have to invade into the host's body. This process is facilitated in case of anatomical anomalies or any histological or functional aberrations (33).

The human body has many physical barriers against microorganisms like bacteria and viruses in store. The skin represents one of the most important ones. Airway mucosa including a ciliary function incorporates the primal defense against microorganisms. Therefore, it is very important for the conservation of a human's health (33).

Once bacteria or viruses invade the body, several defence mechanisms are activated. Firstly, as during a usual immunological reaction, local cells as lysozymes and C-reactive proteins, as well as the complement system, are mobilized. The cellular reaction belongs to the innate immune system, whereas the complement system belongs to the adaptive one. In this way, the first response appears including homeostasis, phagocytosis, inflammation and apoptosis (33).

After that a cell-mediated immune response is initiated. With the help of neutrophils, monocytes and macrophages the process of phagocytosis takes over (33). Meanwhile, dendritic cells as well as other antigen-presenting cells such as monocytes, macrophages and B-lymphocytes present the antigens to T lymphocytes. They recognize bacteria and viruses amongst others by pattern recognition. Besides the first signal that consists of stimulation of T-cell receptors by the human leukocyte antigen (HLA) complex, the adaptive immune system needs this second signal. It is formed by the system of pattern recognition receptors (PRR) such as Toll-like receptors, which detect molecules on bacteria and viruses. They are called pathogen-associated molecular patterns (PAMPs) (34).

As such, the adaptive immune system is stimulated and ready to react (33).

The goal of the immune reaction is to eliminate microorganisms performed by the processes of discharge, expulsion and destruction (34).

1.3.3.2 Symptoms of ARS

In order to diagnose rhinosinusitis two or more symptoms of which one must be either nasal blockage, an obstruction, a congestion or nasal discharge have to be verifiable. The second component includes facial pain or pressure and/or reduction or even loss of smell (2).

In continuative diagnostics, such as endoscopic examination or imaging techniques such as a computer tomography (CT), verifying signs can be seen as well. Endoscopic signs for rhinosinusitis can be the appearance of nasal polyps and/or a mucopurulent discharge, primarily from the middle meatus. Furthermore, an edema or mucosal obstructions can develop, especially in the middle meatus. A CT can reveal mucosal changes within the ostiomeatal complex and/or the sinuses (2). As mentioned above, bacterial rhinosinusitis has to present at least three symptoms of the following: discolored mucus, severe local pain (often unilateral), fever > 38°C, raised C-reactive protein (CRP)/erythrocyte sedimentation rate (ESR), double sickening (2).

1.3.3.3 Pathogenesis of Chronic Rhinosinusitis

Pathogenesis as well as etiology of CRS are not as easy to identify as for ARS. Since the first publication of the European Proposition Paper on Rhinosinusitis and Nasal Polyps in 2012 (EPOS 2012) (33), numerous new studies have been initialized and some important findings have arisen. They are presented in the current European Proposition Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS 2020) (2). As imagined, there is the strong assumption that not one specific pathogen is responsible for CRS, but that there is rather a polyclonal immune response influenced by multiple factors which leads to the phenotype of CRS (2).

It is known that the immune response in CRS is steadily dynamic and not self-limited, as it does not always relate to the causing pathogen and is often linked to tissue remodeling (2).

It is suggested that components such as environmental factors, innate and adaptive immune responses, diverse inflammatory mechanisms fostered by imbalance of mucosal barrier and also genetic and epigenetic factors play a key role in pathogenesis of CRS (2).

Environmental factors consist of cigarette smoke, virus infections and their frequency, fungi, pollutants, allergens and bacteria. Staphylococcus aureus seemed to play a more important role than other bacteria in connection with CRS. Nowadays it is generally accepted that a general dysbiosis of sinonasal mucosa leads to chronification. Nevertheless, S. aureus is the most commonly associated microbe with CRS (2,33).

The role of the innate and adaptive immune system has also been researched more intensively over the past few years, and each component has been carefully examined. Overall, the innate immune system aims to maintain homeostasis of the sinonasal mucosa. There is not one certain part of it which is more responsible for susceptibility to CRS than others, it is rather the imbalance of the whole immune system that leads to development of CRS. Equally, there is not enough evidence to support a hypothesis of a certain complement deficiency that leads to CRS, it is rather the long-term excessive complement activation that plays a key role in this (2).

According to the inflammatory mechanisms mentioned above, there are three different physiologic immune responses against viruses, parasites, and bacteria and fungi. All of these three immune responses have different molecular pathways and generate different specific cytokines which then launch a further cascade to eliminate pathogens. They either occur separately or combined (2).

A Type 1 immune response is activated by viruses, the canonical cytokine is IFN-γ. For a Type 2 immune response that is directed against parasites, the canonical cytokines are IL-4, IL-5 and IL-13. Type 3 responds to bacteria and fungi. Its canonical cytokines are IL-17 and IL-22. It has been found that chronic activation of immune response in CRS incorporates one of these three pathways. Type 2 has been identified the most and thus studied more thoroughly. Notwithstanding further

research is required to acquire more knowledge for all of these three types of immune response, surrounding pathways and involved proteins (2).

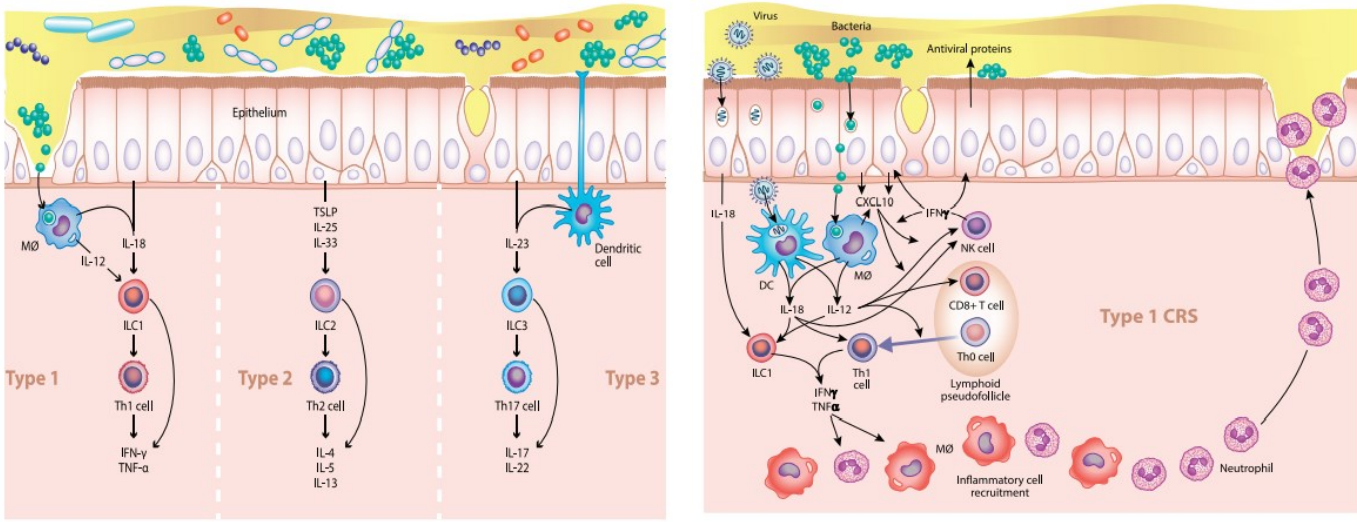

Fig. 6 Inflammatory mechanisms in CRS; left: Type 1-3, right: Type 1

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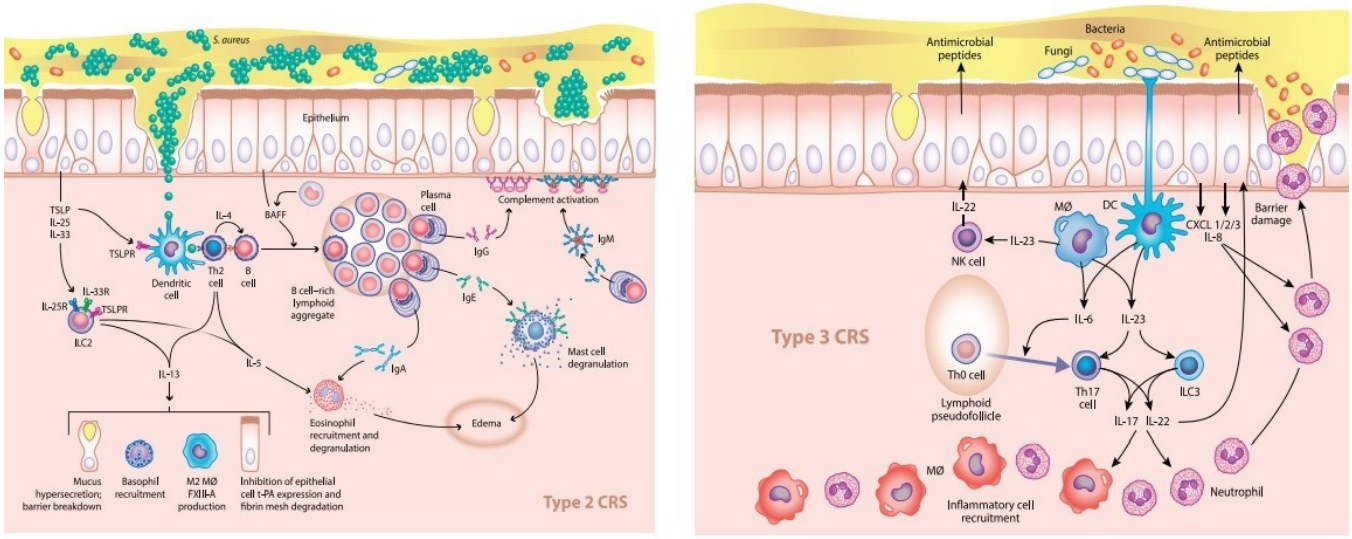

Fig. 7 Inflammatory mechanisms; left: Type 2, right: Type 3

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Since all types of immune responses can either occur separately or together, they often do not match the original inciting pathogen and neither embody unambiguous phenotypes. As such, researchers attempt to subdivide CRS into inflammatory endotypes which can differ individually (2).

In terms of genetic factors, current research has specified some genetic traits that could correlate with CRS and influence its evolution. However, since there is not one specific pathogen it is unlikely to discover that one individual genetic trait causes CRS. Rather, current research aims to identify complex (or individual) genetic traits that cause or influence an individual's susceptibility to CRS in general, the evolution of disease and, in particular, their response to medical treatment. In regard to the developments in biologicals, it is possible that severe cases could be cured more easily in the future (2).

These new findings contribute significantly to progress in the field of Rhinology, but research is still ongoing and necessary in order to further advance the understanding of CRS (2).

1.3.3.4 Symptoms of CRS

CRS is diagnosed in case of persistence of at least one of the symptoms; nasal blockage, obstruction, congestion or nasal discharge with the appearance of facial pain or pressure and/or reduction or even loss of smell for more than 12 weeks (2).

1.3.4 Epidemiology

1.3.4.1 Epidemiology of Acute Rhinosinusitis

The occurrence of ARS is high but differs a lot between individuals. Some individuals are more likely to become unwell with ARS than others. It also alters with the seasons, so meaning that in the colder months the prevalence is higher than in the warmer months (33).

It is also documented that children are more susceptible to ARS than adults, with adults experiencing 2-5 episodes in a year, and children 7-10 episodes (2).

In EPOS 2020 a prevalence of 18% has been pointed out for post-viral ARS (and acute bacterial rhinosinusitis) (2). This, nonetheless, only results out of one single study which was researched in three different cities in the Netherlands (35). Further studies are necessary to achieve better insight (2).

1.3.4.2 Epidemiology of Chronic Rhinosinusitis

Unfortunately, there is a lack of studies that reveal the real prevalence of CRS (2,33,36,37).

The reason why there is so little data on epidemiology is due to the many various factors that cause CRS. As these are not completely understood yet, there is no clear criteria in diagnosing CRS (2). This not only makes it difficult to diagnose, it also makes it complex to obtain the real causes (33,36).

Therefore, a multi-centered study as part of the Global Allergy and Asthma European Network project (GA²LEN) was initiated in 2011. This was the first study to document the prevalence of CRS in Europe (36).
It shows that the average prevalence of CRS in Europe is 10.9% with a variable range from 6.9% in Finland to 27.1% in Portugal (2). As for ARS, geographical location is an underlying factor in CRS (37).

This is also shown by several studies which followed mostly the same method as GA²LEN, e.g. a prevalence of 5.5% in Brazil (38), 8% in China (39), 11% in South Korea (40), 12% in the USA (41), 16% in the Netherlands (35) and 28% in Iran (42).

2 MATERIALS AND METHOD

2.1 DATA COLLECTION

From March 2016 to June 2016 participants suffering from headaches were recruited from the Department of Otorhinolaryngology (ENT) and the Department of Neurology.
The institutional review board of the Medical University of Graz approved the study (approval number: 28200 ex 15/16)

2.2 PARTICIPANTS

15 male and female participants between the age of 19 and 57 years with a mean age of 30 years were included in the study (SD 11.44). They had to be older than 18 years, non-pregnant, fully orientated and free from other diseases.

2.3 MATERIAL AND PROCEDURE

2.3.1 Material

In order to evaluate temperature and comfort, ten cool packs (Veidel Medizin®,Buchendorf, Österreich) constantly stored in a refrigerator at 4° Celsius were used.
Cryotherapy was applied using these cool packs. For temperature documentation of the packs, a temperature probe (OMEGA HH501AJK, Sensotec, Feldkirchen near Graz, Austria) was used. A self-adhesive bandage was applied to keep the cool packs in place.

2.3.2 Procedure

Interval cooling was carried out in one of the examination rooms at the ENT department. Interval cooling was chosen in terms of prevention of cold injury and in order to provide an easier assessment of different temperatures during the procedure.

Four localizations on the head were examined: left and right forehead, at each exit point of the trigeminal nerve and the left and right temples. All four localizations were cooled at the same time following a schedule of a 1 minute cooling to 1 minute without cooling. This was repeated ten times. The temperature was documented throughout the entire time the cooling pack was applied, with special regard to the temperature that was defined as the most comfortable for the participant. Since after the first trials the cool packs were found to be too cold and uncomfortable, the temperature of the first application was then adapted to circa 10°C by letting the cool packs warm up at room temperature.

This study was carried out in the form of a feasibility study in order to find out a suitable standard treatment regimen that can be applied on patients with acute headache episodes in the future.

2.4 PARAMETERS

The analyzed parameters were:

- General effect categorized as very pleasing, pleasing or not pleasing
- Temperature and its comfort range for the participant
- Differences regarding sensitivity between the localizations of the forehead and the temples

2.5 STATISTICAL ANALYSIS

Statistical evaluation was performed with IBM SPSS Statistics®. For plotting the results IBM SPSS Statistics® and Python is used. The Participants' data was anonymized by numeric identities and descriptive statistics were applied. Results are presented by means of percentage distribution, statistical average, median and standard deviation.

3 Results

This prospective study includes 15 participants, who have all previously experienced different types of headaches. It should be noted that during the trial of interval therapy the participants were not supposed to have a headache. This was in order to find out if application of cool generally provides a very pleasing or pleasing effect or not.

The effect of cryotherapy on the head was analyzed with a special regard to the temperature that was felt as most pleasant. Possible differences of sensitivity between the observed localizations on the head where cool packs were applied were also closely observed.

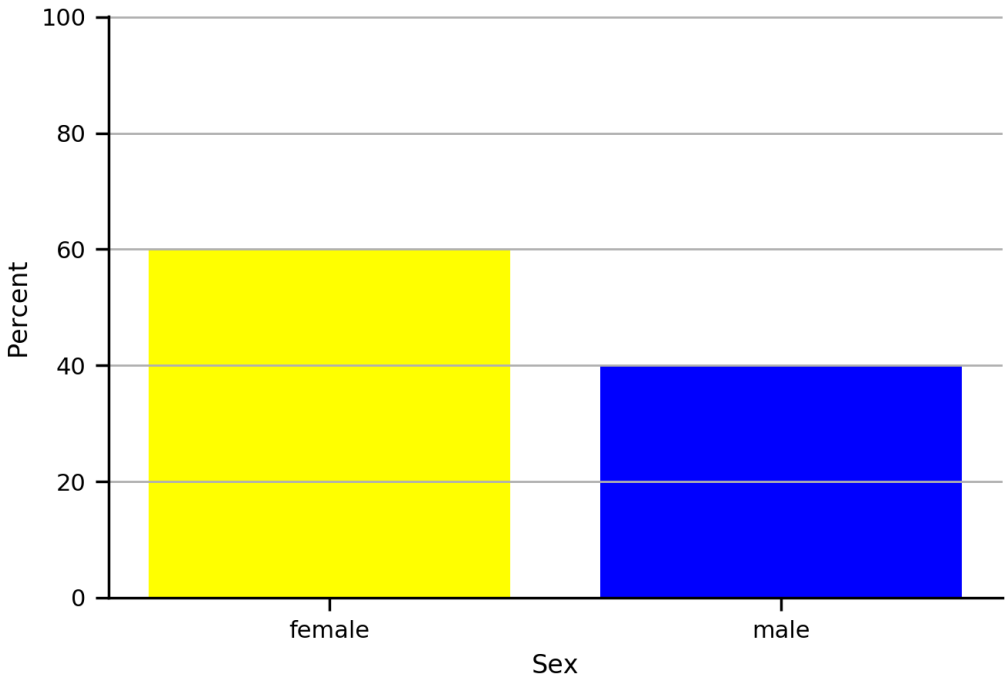

Fig. 8 Distribution of participants by sex

Nine female (60%) and 6 male (40%) participants were included. Their age range was between 19 – 57 years, with a mean age of 30 years.

Amongst them, there were 8 participants (53.3%) that had used cryotherapy in order to reduce and/or to treat a headache before and 7 participants (46.7%) who had not.

		N	Percent
Cryotherapy used	yes	8	53.3
	no	7	46.7
	Total	15	100.0

Table 1 Distribution of application of cryotherapy before the study

All participants carried out the interval cryotherapy seated in a regular patient chair. A calm environment was provided in all cases. None of them had a headache before starting the therapy trial.

Directly after the trial, 14 participants (93.3 %) did not have any kind of headache. Only 1 participant (6.7 %) reported headache. This participant started having a headache after the trial since the temperature of the cool pack was found to be too cold.

		N	Percent
Occurrence of headache after the trial	yes	1	6.7
	no	14	93.3
	Total	15	100.0

Table 2 Distribution of occurrence of a headache after the trial

The participants were asked to define the general effects after having completed the trial. Fourteen participants (93.3%) stated that they have perceived cryotherapy as very pleasing or pleasing. Whereas one participant (6.7%) claimed that it had rather a negative effect.

		N	Percent
Effect after trial	pleasing	14	93.3
	negative	1	6.7
	Total	15	100.0

Table 3 Distribution of impression of the effect of cryotherapy

All participants confirmed that they would use cryotherapy in case of a headache of any kind in the future.

		N	Percent
Usage of cryotherapy in the future	yes	15	100.0

Table 4 Distribution of possible application of cryotherapy in the future

Furthermore, the effect of cryotherapy was analyzed according to the localization of application: Five participants (33.3%) noticed higher sensitivity to cold on the forehead. Two (13.3%) experienced more sensitivity on the temples, and a total of 8 participants (53.3%) felt indifferent about sensitivity on the different cooling sites.

		N	Percent
Sensitivity	forehead	5	33.3
	temple	2	13.3
	equal	8	53.3
	Total	15	100.0

Table 5 Distribution of differences in sensitivity to cold between forehead and temples

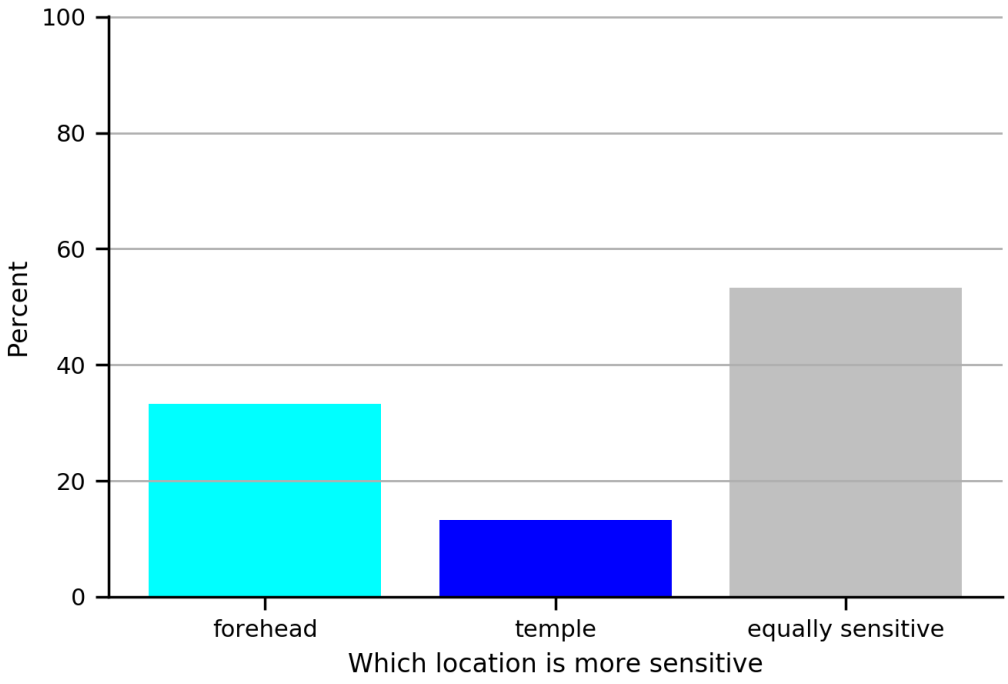

Fig. 9 Distribution of different localizations experienced as most sensitive

In addition, the participants had to define their impression of the one-minute breaks between cooling intervals with regard to their efficacy. They therefore had to identify if the interval breaks provided a cooling, soothing and pleasant effect or not. Nine participants (60%) noted a positive effect during the breaks and six out of them (40%) felt indifferent.

		N	Percent
Impression	effective	9	60.0
	indifferent	6	40.0
	Total	15	100.0

Table 6 Distribution of the impression of the interval break

	N	Minimum	Maximum	Mean	Std. Deviation
Temperature which is felt as best	15	12.0	19.6	16.447	2.5354
Valid N (listwise)	15				

Table 7 Distribution of the temperature identified as most effective

A mean temperature of 16.48°C (SD: 2.54) was defined as most effective/pleasant by the participants. The temperature distribution had a range of 7.6°C, with a minimal temperature of 12°C and a maximal of 19.6°C.

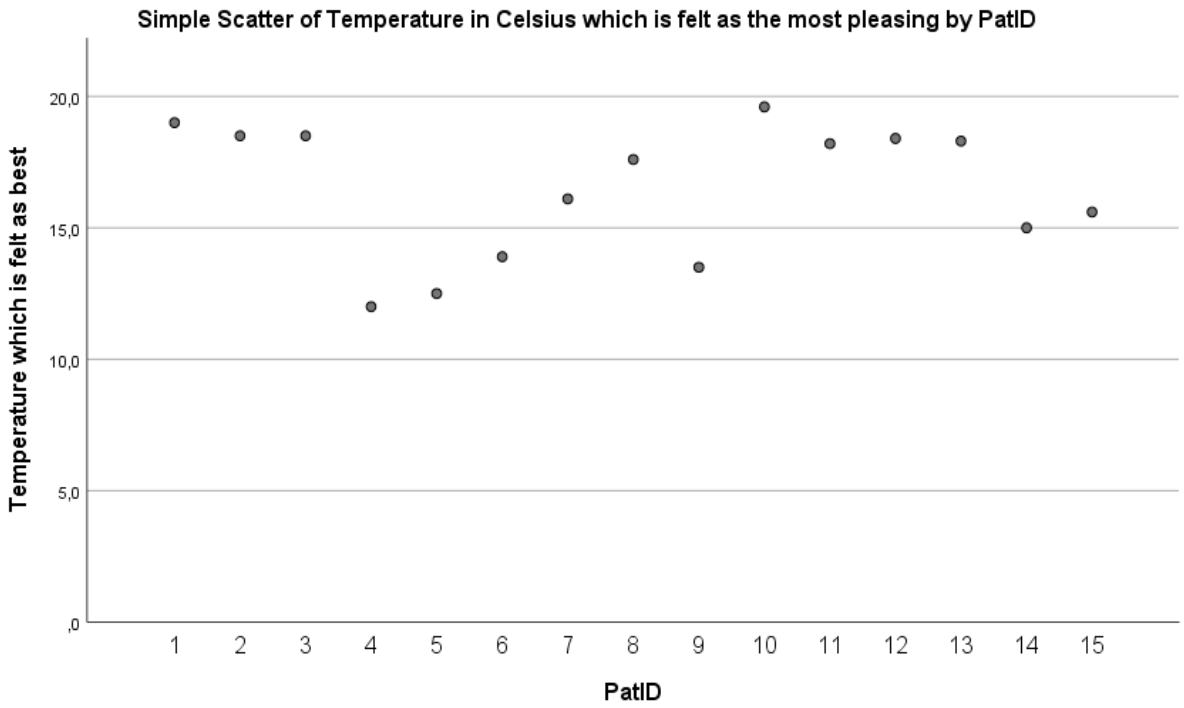

Fig. 10 Distribution of the temperature which was felt as most effective

4 DISCUSSION

Cryotherapy is a commonly used therapy in clinical routine for any kind of headache. Nevertheless, there is no standard treatment regimen for its application or a standard temperature that is advised to be used. In order to provide a standard treatment regimen for the application of cryotherapy for patients with headache, we initialized this feasibility study. As such, cryotherapy was used on healthy participants without a current headache in order to observe its effects regarding the parameters temperature and localization.

A majority (93.3%) defined cryotherapy as very pleasing or pleasing and only 6.7% defined it as not pleasing. In fact, one participant which represents 6.7% on a percentage basis, happened to have a headache right after completing the study. The temperature used was supposedly too low and consequently induced pain. 93.3% did not have a headache afterwards. Nonetheless, 100% were in favor of the application of cryotherapy in case of a headache in the future. It can be assumed that the participant had a single negative effect because of the inconvenient temperature used, but that a general positive effect could be noted, especially in the beginning of the trial when the pain had not yet occurred. Therefore, a general positive effect can be observed and cryotherapy can be identified as a suitable device in order to support an intense attack of e.g. migraine or TTH or even interrupt a light to modest TTH or secondary headache. But the implication of a standard temperature is highly important in terms of providing a pleasant effect and also in order to prevent negative effects.

In this study, 53.3% already used cryotherapy in the occurrence of headaches before their participation in the study, 46.7% did not. The application could be more promoted by doctors in order to provide a simple and effective device to relieve pain.

Concerning the standardization of cryotherapy, a temperature of 16.48°C with a standard deviation of 2.54 was found to be most effective. The standard deviation lies in an acceptable range but it reflects the individual perception of cold. Nevertheless, it shows that in clinical use it is possible to provide a suitable application of cryotherapy. The distribution of the temperature which was defined as most effective had a range of 7.6°C, with a minimum temperature of 12°C and a maximum of 19.6°C. Again, this range shows that this parameter differs greatly

between individuals but still stays in a range less than 8°C which could be helpful in the further development of a standard regimen of cryotherapy for headache patients.

A temperature of 16.48°C was identified as most effective, which highlights the fact that the cool packs which were stored constantly at 4°C were too cold for direct application. This is why after several trials the temperature of the first application was adapted to ca. 10°C. This should be observed for clinical use. Cool packs should be either stored at a higher temperature or warmed up a little before application on patients.

In terms of qualifying differences in sensitivity between the employed localizations of application on the head, a slight tendency towards sensitivity could be noticed for the forehead (33.3%). Only 13.3% defined the temples as more sensitive to cold. Although the majority of 53.3% could not define any difference between forehead and temples at all. In order to simplify the application, it is possible to consider applying cool packs only on one area of the head. Cryotherapy should preferably be applied to the area which the individual finds most sensitive, as well as both areas. As this study used a one-minute interval model of cryotherapy in order to prevent cold injuries, temperatures could also be assessed more easily during the procedure and during the breaks.

Participants were asked to pay close attention to their impressions during the breaks with regard to the efficacy of their cryotherapy. As only a slight majority of 60% identified the breaks as cooling, soothing and pleasant, the interval mode of cryotherapy could be questioned according to its higher efficacy compared to a standard mode without breaks. However, with regard to the prevention of cold injuries, the interval mode might be a safer mode of application, even though it does not have a significant advantage for the outcome of cryotherapy.

4.1 Critical evaluation

This study relies on only 15 participants which does not represent a sufficient number of cases in order to apply the results on the general public.

The low number is explained by difficulties in recruiting participants. Originally it was planned to apply the interval cryotherapy on postoperative ENT patients or migraine patients with an acute episode of headache. However, in terms of clinical routines,

e.g. analgesic therapy after surgery, this was difficult to organize and carry out as an external member of the clinic. Therefore the focus had to be changed on the research of parameters of cryotherapy such as general effects, temperature and localization in order to provide a more standardized treatment regimen which will then need to be studied on patients with actual headache episodes.

Lastly, it is interesting that the temperature of the cool packs was too cold during the first clinical trials. This was quickly noticed and the starting temperature was adapted to ca. 10°C by letting them warm up before starting each trial.

4.2 Conclusion

In this thesis a general positive effect of cryotherapy is identified, which highlights a willingness for future application by participants who experience headaches. The most effective temperature of cryotherapy was observed as 16.48°C. A slightly higher sensitivity to cold of the forehead was noticed compared to the temples. Therefore in clinical routine, the application of cryotherapy should follow a standard treatment regimen aiming to provide patients with the most efficient treatment of cryotherapy whilst preventing cold injuries. This standardized treatment regimen will also prevent the incorrect delivery of cryotherapy. One should also consider including cryotherapy in any headache therapy as a non-medical device in order to reduce intake of analgesics in cases of light to modest headache.

More studies and research in this field are required to identify the effect of the results of this study on cases with an acute headache episode.

References

(1) Vanderpol J, Bishop B, Matharu M, Glencorse M. Therapeutic effect of intranasal evaporative cooling in patients with migraine: a pilot study. J Headache Pain 2015 Jan 26;16:5-2377-16-5.

(2) Fokkens W, Lund V, Hopkins C, Hellings P, Kern R, Reitsma S, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology 2020 2020 Feb;58((Suppl S29)):1-464.

(3) Göbel H. Migräne. Die Kopfschmerzen Ursachen, Mechanismen, Diagnostik, Therapie. 3. überarbeitete und aktualisierte Auflage ed. Berlin, Heidelberg: Springer-Verlag; 2012. p. 145-381.

(4) Göbel H. Kopfschmerz vom Spannungstyp. Die Kopfschmerzen Ursachen, Mechanismen, Diagnostik, Therapie. 3. überarbeitete und aktualisierte Auflage ed. Berlin, Heidelberg: Springer-Verlag; 2012. p. 383-473.

(5) Jensen R, Stovner LJ. Epidemiology and comorbidity of headache. Lancet Neurol 2008 Apr;7(4):354-361.

(6) Günther R, Jantsch H. Kryotherapie. In: Günther Robert, editor. Physikalische Medizin. 2.th ed. Berlin [u.a.]: Springer; 1986.

(7) Furmanek MP, Slomka K, Juras G. The effects of cryotherapy on proprioception system. Biomed Res Int 2014;2014:696397.

(8) Zhang FR, Zheng Y, Yan LJ, Ma CS, Chen JT, Li W. Cryotherapy Relieves Pain and Edema After Inguinal Hernioplasty in Males With End-Stage Renal Disease: A Prospective Randomized Study. J Pain Symptom Manage 2018 Jul 17.

(9) Danziger N, Alamowitch S. Neurologie. 11th ed.: ÉDITIONS MED-LINE; 2016.

(10) Mattle H, Mumenthaler Marco editors. Kurzlehrbuch Neurologie. 3.th ed. Stuttgart, New York: Georg Thieme verlag; 2011.

(11) Göbel H. Die sekundären Kopfschmerzen. Die Kopfschmerzen Ursachen, Mechanismen, Diagnostik, Therapie. 3. überarbeitete und aktualisierte Auflage ed. Berlin, Heidelberg: Springer-Verlag; 2012. p. 561-566.

(12) Göbel H. Klassifikation von Kopfschmerzen. Die Kopfschmerzen Ursachen, Mechanismen, Diagnostik, Therapie. 3. überarbeitete und aktualisierte Auflage ed. Berlin, Heidelberg: Springer-Verlag; 2012. p. 1-24.

(13) Pschyrembel Redaktion. Spannungskopfschmerz. 2017; Available at: https://www-1pschyrembel-1de-1pschyrembel.han.medunigraz.at/Spannungskopfschmerz/K0L7L/doc;. Accessed 04/19, 2017.

(14) Borsook D, Maleki N, Burstein R. Migraine. In: Zigmon MJ, Rowland LP, Coyle JT, editors. Neurobiology of Brain Disorders. 1st ed. Amsterdam: Elsevier [u.a.]; 2015. p. 693-708.

(15) Göbel H. 5. Headache attributed to trauma or injury to the head and/or neck. IHS Classifications ICHD-3. 2019; Available at: https://ichd-3.org/5-headache-attributed-to-trauma-or-injury-to-the-head-andor-neck/. Accessed 04/11, 2020.

(16) Göbel H. Kopfschmerzen zurückzuführen auf Gefäßstörungen im Bereich des Kopfes oder des Halses. Die Kopfschmerzen Ursachen, Mechanismen, Diagnostik, Therapie . 3. überarbeitete und aktualisierte Auflage ed. Berlin, Heidelberg: Springer-Verlag; 2012. p. 583-611.

(17) Göbel H. Kopfschmerz zurückzuführen auf eine Infektion. Die Kopfschmerzen Ursachen, Mechanismen, Diagnostik, Therapie. 3. überarbeitete und aktualisierte Auflage ed. Berlin, Heidelberg: Springer-Verlag; 2012. p. 669-678.

(18) Göbel H. Kopf- oder Gesichtsschmerz zurückzuführen auf Erkrankungen des Schädels sowie von Hals, Augen, Ohren, Nase, Neben höhlen, Zähnen, Mund oder anderen Gesichts- oder Schädelstrukturen. Die Kopfschmerzen Ursachen, Mechanismen, Diagnostik, Therapie. 3. überarbeitete und aktualisierte Auflage ed. Berlin, Heidelberg: Springer-Verlag; 2012. p. 693-710.

(19) Göbel H. IHS Classification ICHD-3 Headache attributed to the disorder of the ears. 2019; Available at: https://ichd-3.org/11-headache-or-facial-pain-attributed-to-disorder-of-the-cranium-neck-eyes-ears-nose-sinuses-teeth-mouth-or-other-facial-or-cervical-structure/11-4-headache-attributed-to-disorder-of-the-ears/. Accessed 04/14, 2020.

(20) Kaur A, Singh A. Clinical study of headache in relation to sinusitis and its management. J Med Life 2013 Epub 2013 Dec 25;6(4):389-394.

(21) Chen M, Lin T, Huang K, Shih W, Chen H, Tsai M. [A project to improve nasal ice packs]. Hu Li Za Zhi 2008;55(3):61-68.

(22) Göbel H. Kopfschmerzen zurückzuführen auf eine Substanz oder deren Entzug. Die Kopfschmerzen Ursachen, Mechanismen, Diagnostik, Therapie. 3. überarbeitete und aktualisierte Auflage ed. Berlin, Heidelberg: Springer-Verlag; 2012. p. 641-668.

(23) Göbel H. Kopfschmerzen zurückzuführen auf psychische Störungen. Die Kopfschmerzen
Ursachen, Mechanismen, Diagnostik, Therapie. 3. überarbeitete und aktualisierte Auflage ed. Berlin, Heidelberg: Springer-Verlag; 2012. p. 711-719.

(24) Göbel H. Kopfschmerzen zurückzuführen auf eine Störung der Homöostasis. Die Kopfschmerzen Ursachen, Mechanismen, Diagnostik, Therapie. 3. überarbeitete und aktualisierte Auflage ed. Berlin, Heidelberg: Springer-Verlag; 2012. p. 679-692.

(25) Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013 Jul;33(9):629-808.

(26) Stovner LJ, Al Jumah M, Birbeck GL, Gururaj G, Jensen R, Katsarava Z, et al. The methodology of population surveys of headache prevalence, burden and cost: principles and recommendations from the Global Campaign against Headache. J Headache Pain 2014 Jan 27;15:5-2377-15-5.

(27) Waldeyer A, Anderhuber F, Pera F, Streicher Johannes. Waldeyer - Anatomie des Menschen. 19th ed. Berlin; Boston: De Gruyter; 2012.

(28) Lenarz T, Boenninghaus H. Hals-Nasen-Ohren-Heilkunde. 14.th ed. Berlin Heidelberg: Springer; 2012.

(29) Paulsen F, Waschke J. Sobotta - Atlas der Anatomie des Menschen, Kopf, Hals und Neuroanatomie. 23. Auflage ed. München: Elsevier Urban&Fischer; 2010.

(30) Cibis W, Pschyrembel Redaktion. Nomenklatur. 2020; .

(31) Boenninghaus H, Lenarz T. Hals-Nasen-Ohren-Heilkunde. 13th ed. Heidelberg: Springer; 2007.

(32) Iro H. Rhinitis. 2018; Available at: https://www-1pschyrembel-1de-1pschyrembel.han.medunigraz.at/rhinitis/K0JV5/doc/;. Accessed 07/09, 2017.

(33) Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. Rhinology 2012 Mar;50(1):1-12.

(34) Arastéh K. Innere Medizin - Duale Reihe. 3. überarbeitete ed. Stuttgart: Thieme; 2013.

(35) Hoffmans R, Wagemakers A, van Drunen C, Hellings P, Fokkens W. Acute and chronic rhinosinusitis and allergic rhinitis in relation to comorbidity, ethnicity and environment. PLoS One 2018;13:e0192330.

(36) Bachert C, Pawankar R, Zhang L, Bunnag C, Fokkens WJ, Hamilos DL, et al. ICON: chronic rhinosinusitis. World Allergy Organ J 2014 Oct 27;7(1):25-4551-7-25. eCollection 2014.

(37) Hastan D, Fokkens WJ, Bachert C, Newson RB, Bislimovska J, Bockelbrink A, et al. Chronic rhinosinusitis in Europe--an underestimated disease. A GA(2)LEN study. Allergy 2011 Sep;66(9):1216-1223.

(38) Pilan RR, Pinna FR, Bezerra TF, Mori RL, Padua FG, Bento RF, et al. Prevalence of chronic rhinosinusitis in Sao Paulo. Rhinology 2012 Jun;50(2):129-138.

(39) Shi J, Fu Q, Zhang H, et al. Epidemiology of chronic rhinosinusitis: results from a cross-sectional survey in seven Chinese cities Allergy. Allergy 2015;70:533-609.

(40) Kim J, Cho C, Lee E, Suh Y, Choi B, Kim K. Prevalence and risk factors of chronic rhinosinusitis in South Korea according to diagnostic criteria. Rhinology 2016;54:329-335.

(41) Hirsch A, Stewart W, Sundaresan A, et al. Nasal and sinus symptoms and chronic rhinosinusitis in a population-based sample. Allergy 2017;72:274-81. Allergy 2017;72:274-281.

(42) Ostovar A, Fokkens W, Vahdat, K., Raeisi A, Mallahzadeh A, et al. Epidemiology of chronic rhinosinusitis in Bushehr, southwestern region of Iran: a GA2LEN study 2019;57:43-8. Rhinology 2019;57:43-58.