Cluster headache and oxygen

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Chapter 1

Introduction & Scope of this thesis

Introduction

Cluster headache

Cluster headache (CH) is one of the trigeminal autonomic cephalalgias (TACs), a group of primary headaches which share prominent cranial parasympathetic autonomic features. CH is diagnosed by applying its definition of the International Classification of Headache Disorders (ICHD-3 beta).[1] CH attacks most often are very severe, unilateral and (usually) in the distribution of the first branch of the trigeminal nerve. The attacks are accompanied by ipsilateral cranial parasympathetic autonomic features, an ipsilateral partial Horner's syndrome, a sensation of auricular fullness and/or a sense of restlessness or agitation. Untreated attacks usually last for 15-180 minutes (min) and occur from one every other day to eight per day during the episodes when the disorder is active. Headache attacks either occur in one series/cluster period of less than 1 year, or in at least two series/cluster periods of 7 days to 1 year separated by a headache-free period of at least 1 month (*i.e.* Episodic cluster headache (ECH)), or in one series/cluster period of more than 1 year or in at least two series/cluster periods separated by a headache-free period of less than 1 month (*i.e.* Chronic cluster headache (CCH)). CH can be primary or secondary when it occurs for the first time closely related to another disorder which causes headache.[1]

ECH and CCH are reported in at least 80% and 4 to 20% of CH patients, respectively. In the long term, more than 50% of patients will keep the subtype that is present at the time of diagnosis. The lifetime prevalence of CH is 124 per 100,000 and the 1-year prevalence is 53 per 100,000 in population-based studies. 1-Person year incidence ranges from 2.07 (in 1989-1990) to 9.8 per 100,000 (in 1979-1981). A male to female ratio of 4.3:1 has been reported. The mean age of onset is between 29.6 and 35.7 years. CH has a considerable impact on daily living in three quarters of patients,[2] reflected in the name 'suicide headache'. Active suicidal ideation indeed was found in 5.9% in CCH and 6.3% in ECH patients, and even 55% of CH patients have suicidal thoughts during lifetime.[3] Obviously, the enormous impact of CH makes the search for effective treatments of utmost importance. In this search, understanding CH pathophysiology can provide a basis. And in the other way, effective treatments can expand the knowledge of CH pathophysiology.

Cluster headache pathophysiology

Although headaches that we recognise as and mention CH today have been described since the 17th century,[4] extensive study of the pathophysiology and successful treatment had to wait until the second half of the 20th century. In the causation of CH, a centrally driven change in cranial blood vessel diameter is considered to play a role. Pain afferents from the trigeminovascular system traverse the ophthalmic nerve and synapse in the trigeminocervical complex. The second-order neurons project to the thalamus and thalamocortical projections lead to pain awareness. Trigeminal-autonomic reflex

activation of the efferent parasympathetic fibres arising in the superior salivatory nucleus of the facial nerve causes (further) blood vessel dilatation. Dilatation of the carotid artery can result in a third-order sympathetic nerve lesion with a partial Horner's syndrome. Parasympathetic activation also leads to conjunctival injection, lacrimation, rhinorrhoea and nasal congestion.[5] Parasympathetic outflow is also directly activated by the hypothalamus. Moreover, the posterior hypothalamic grey matter region triggers the pain and controls the (typical) circadian rhythm.[6]

Oxygen treatment in the past 60 years and its position

CH treatment comprises of acute/attack treatment and short-term and long-term preventive/ prophylactic treatment. While preventive treatment (not further discussed here) is aimed to reduce the frequency and intensity of CH attacks, the goal of acute treatment is to abort a CH attack within a few min. Nowadays, this can be achieved in most patients by injecting 6 mg of Sumatriptan subcutaneously or inhaling 100% oxygen. Nasal Sumatriptan, nasal(/oral) Zolmitriptan, nasal Lidocaïne, oral/rectal Ergotamine tartrate and nasal/intravenous(/intramuscular) Dihydroergotamine are alternative, but inferior acute treatments, due to a slower effect, unfavourable pharmacologic profile or impractical route of administration.[7]

Oxygen was actually one of the first successful options for acute treatment. In his 1956 publication on 'Histaminic cephalgia', Bayard T. Horton, a CH investigator of the first hour,[8] stated that breathing of 100% oxygen can alleviate an attack considerably when the attack is mild and oxygen is used immediately.[9] Stimulated by a letter to the editor on this topic by Janks,[10] Kudrow took an interest in oxygen treatment for CH and conducted a trial in 1981, which was positive.[11] Today, inhalation of 100% oxygen via a non-rebreathing mask at a flow rate of at least 7 litre/minute (L/min) is still recommended as an acute treatment,[6] although 12 L/min has also been proven to be effective.[12] However, not all patients are able to use oxygen effectively, and it is this ineffectiveness which necessitates further research into pathophysiology and treatment effects, in order to find a treatment regime which is 100% effective (and has negotiable side effects). Here, I will first present a brief overview of the known degrees and modes of effectiveness of inhalation of 100% oxygen at different flow rates and pressures.

Oxygen response rates at flow rates of 6-8 L/min

A number of studies have investigated the acute treatment success achieved by inhalation of 100% pure oxygen at normal (*i.e.* approximately 7 L/min) flow rates.

In the first part of Kudrow's study fifty-two CH patients were treated with 100% oxygen via a facial mask at a flow rate of 7 L/min for 15 min, starting at the onset of each of ten CH attacks. Prophylactic medication was not withheld in twenty-eight patients. 'Treatment success' was defined as 'complete or almost complete cessation of head pain within 15 min for at least seven of ten attacks'. Seventy-five percent of patients successfully treated their CH attacks. In the second part of the study (a

crossover trial), the effectiveness of oxygen inhalation was compared to that of sublingual ergotamine tartrate administration. An additional fifty patients were treated with 100% oxygen via a facial mask at a flow rate of 7 L/min for 15 min starting at the onset of each of ten CH attacks, and sublingual ergotamine tartrate or *vice versa*. Prophylactic medication was withheld. Eighty-two percent of the oxygen users successfully treated their CH attacks.[11]

In Fogan's double-blind crossover study, treatments of 100% oxygen and compressed room air, both supplied via a non-rebreathing face mask at a flow rate of 6 L/min for up to 15 min, were compared. Nineteen CH patients were treated with each treatment/gas for zero to nine (oxygen) or ten (air) CH attacks. 'CH pain relief' was scored '0 for no relief, 1 for slight relief, 2 for substantial relief and 3 for complete relief'. The 'relief score' was an average of the scores. The average relief score with oxygen was 1.93 and with air was 0.77. The difference between the average relief scores was statistically significant ($p < 0.01$). As a continuation of the Kudrow study, this study ruled out the possible effects of pressurised gas flow itself, the breathing mask and the attention on the person's own breathing.[13]

In Heckl's study, ten patients (eight with CH and two with Chronic paroxysmal hemicrania (CPH)) were treated with oxygen via an oxygen mask at a flow rate of 7 L/min at the onset of a headache attack. All six ECH patients already experienced relief at treatment onset. Mean pain reduction was 60-80%. A primary chronic cluster headache (PCCH) patient had only a temporary mean pain reduction of 60%, with a reduction in attack duration of 67% to circa 20 min. A secondary chronic cluster headache (SCCH) patient had a pain reduction of most 60-70%, without a reduction in attack duration.[14]

In a study conducted by Gallagher *et al.* abortive treatments of analgesics (most commonly 'combination-type medications containing barbiturates or narcotics') and/or 100% oxygen (supplied via a face mask at a flow rate of 8 L/min for 10-15 min) were compared. All sixty patients were offered both treatments. 'Significant (headache) relief' (no definition given) was reported in thirty-nine of fifty-one (*i.e.* 76%) patients, who first chose oxygen inhalation therapy compared to ten of forty-eight (*i.e.* 21%) patients, who first chose analgesics. However, only 31% of patients preferred to continue using oxygen inhalation, compared to 65% of patients who chose to continue using analgesics. The efficacy of oxygen treatment did not outweigh the unpractical use and the occurrence of rebound CH.[15]

Higher oxygen flow rates of 12-15 L/min

Seven L/min has become the standard and minimal oxygen flow rate since Kudrow's study.[11] When I started my studies on CH and oxygen in 2008, there was only one small study with only three CH patients, who were resistant to standard oxygen flow rates of 7-10 L/min, and who inhaled oxygen at flow rates of 14-15 L/min. 'Alleviation', '70-100% relief' and 'full headache relief' were achieved

multiple times using these higher oxygen flow rates. The author suggested that flow rates up to 15 L/min should have been used before CH patients are considered unresponsive to oxygen treatment.[16]

More recently, a trial was published with high flow oxygen, in which 12 L/min was found to be an effective treatment. In Cohen's double-blind crossover trial 100% oxygen and air, both supplied via a non-rebreathing face mask at a flow rate of 12 L/min for 15 min, were compared. Of the seventy-six ECH and CCH patients who completed the study, seventy-three CH patients treated two CH attacks each with each treatment/gas and were included in the primary analysis. A pain free state (or a state of 'adequate relief' (not defined)) after 15 min of inhalation was achieved in 116 out of 150 (*i.e.* 78%) oxygen-treated and 29 out of 148 (*i.e.* 20%) air-treated CH attacks. The difference was statistically significant ($p < 0.001$).[12]

Mechanisms of action of normobaric oxygen

The mechanisms underlying the antinociceptive effect of oxygen are not well understood. Initially a primary vascular target was presumed. Sakai *et al.* suggested at first that inhalation of 100% oxygen during a CH attack reduces the cephalic flow and thereby relieves pain. The *in vitro* evidence for oxygen directly causing vasoconstriction of cerebral blood vessels was discussed.[17] Further endorsement of a direct or indirect vasoconstrictor effect of 100% oxygen came from a reduction in pulsation amplitude of (terminal) branches of the internal and external carotid vasculature, particularly on the symptomatic side, during 10 min of breathing of 100% oxygen in nitroglycerin-induced CH attacks.[18] Moreover, other studies, applying Xenon, visualised a reduction in cerebral blood flow due to oxygen inhalation in spontaneous[19, 20, 21] and nitroglycerin- or alcohol-induced CH attacks.[21] During the conduction phase of our studies on CH and oxygen evidence was published on an indirect vasoconstrictive effect of 100% oxygen, which inhibited a subpopulation of efferent neurons projecting from the superior salivatory nucleus (*i.e.* the aforementioned origin of neurons for the cranial parasympathetic vasodilator pathway), by maximally 33% at 20 min.[22]

Most pain reduction, simultaneously with a reduction in autonomic symptoms, was found in patients with an abnormally high reduction of cerebral blood flow induced by oxygen inhalation during CH attacks. However, some pain relief was also found in patients with a normal cerebral blood flow response, suggesting other factors than vasoconstriction causing pain relief as well as a relation between pain intensity and autonomic symptoms.[19] Schuh-Hofer *et al.* demonstrated that hyperoxia significantly inhibited rat dural protein plasma extravasation and therefore counteracted neurogenic inflammation.[23]

Factors determining normobaric oxygen response

At the start of my research, I specifically assumed that factors determining oxygen response could contribute to our knowledge of CH pathophysiology. At that time, it was not known which characteristics predicted acute treatment response in CH patients completely. Table 1 shows the

factors that had been associated with an unfavourable response to oxygen. Schürks *et al.* identified restlessness (OR 0.09, $p = 0.019$) as a negative predictor of oxygen response. It was hypothesized that restlessness causes intolerance of the oxygen face mask in some.[24] Restlessness during a CH attack was reported by 67.9% of patients.[25]

Kudrow found significantly better ($p < 0.05$) effects of oxygen inhalation in ECH patients under 50 years of age ('treatment success' 92.9%) than in CCH patients over 49 years of age ('treatment success' 57.1%). There was no significant response difference between 'young' (*i.e.* under 50 years of age) and 'old' (*i.e.* over 49 years of age) CH patients. Neither was there a significant response difference between ECH and CCH patients in all age groups.[11] Likewise, Schürks *et al.* did not identify age and ECH (%) as statistically significant negative predictors of oxygen response.[24]

Kudrow and Schürks *et al.* both found no significant response difference between male and female patients.[11, 24, 25] However, Rozen *et al.* found an oxygen treatment response in only 59.1% of women, versus 87% of men. This difference was significant ($p = 0.01$).[26]

In another study, Rozen noted that a history of smoking was reported by 75% of women, versus 61% of men.[16] Schürks *et al.* did not identify current smoking (%) as a statistically significant negative predictor of oxygen response.[24] There were statistically significantly more male current smokers than female current smokers.[25]

Rozen *et al.* found significantly more vomiting (46.9% *versus* 17.4%, $p = 0.003$) and more nausea (62.5% *versus* 43.5%, $p = 0.09$) in women.[26] Schürks *et al.* identified nausea/vomiting as a negative predictor of oxygen response (OR 0.41, $p = 0.029$).[24] Nausea and vomiting were reported by 27.8% during CH attacks.[25]

Kudrow noted that in some cases, unresponsive to either oxygen or ergotamine, the acute CH attack treatment had been started late.[11] Schürks *et al.* stated it was less obvious whether the timing of acute treatment influences treatment success, because no data were available to further underpin this issue.[24]

Table 1. Factors associated with an unfavourable response to oxygen in CH attacks

Factors	*p* value
Restlessness [24]	0.019 [a]
CCH and > 49 years of age [11]	< 0.05 [b]
Females [11, 24, 25, 26]	0.01 [c] – 'no significance' [c]
Nausea and vomiting [24, 26]	0.029 [a]

[a] Oxygen responders (defined by the criterion: 'compared to untreated CH attacks, CH pain must have been reduced in at least three CH attacks by at least 50% within 15 min after oxygen application and despite the used flow rate') were compared to non-responders (who should have used therapeutic flow rates).[24]

[b] ECH patients < 50 years of age were compared to CCH patients > 49 years of age.[11]

[c] Females were compared to males.[25, 26]

Hyperbaric oxygen

The rather successful use of oxygen led to experiments with hyperbaric oxygen (HBO). Porta *et al.* stated that a high blood oxygen saturation of 98% during min is required for treatment success, which can be induced by HBO inhalation. After the initial case report by Weiss, Porta *et al.* first confirmed that HBO inhalation could be effective for individual CH attacks.[27] HBO consists of 100% oxygen at a pressure more than 1 atmosphere. Two studies investigated the acute treatment effect achieved by inhalation of HBO.

In the crossover study conducted by Porta *et al.*, abortive treatments of 'normobaric oxygen inhalation' (at a flow rate of 7 L/min for 15 min) and HBO inhalation (administered in a hyperbaric chamber with 100% oxygen with compression up to 2 atmosphere absolute (ATA)) were compared. In contrast to five patients who were 'partially refractory' and three patients who were 'totally refractory' to normobaric oxygen inhalation, all fourteen patients achieved 'complete relief' a few min after starting HBO treatment.[27]

A double-blind study by Di Sabato *et al.* compared the acute treatment effect of HBO (administered in a hyperbaric chamber during 30 min with a pressure up to 2.5 ATA, in seven ECH patients) and of a placebo procedure (normal air administered in a hyperbaric chamber during 30 min at a pressure of 1.0 ATA, in six ECH patients) both to the mean of the duration of the last three CH attacks occurring before the test. HBO interrupted the CH attack in 86% of patients, whereas placebo did not change the duration of CH attacks in 100% of patients (so one can expect there was no interruption).[28] However, the difference was not statistically significant ($p = 0.08$).[29]

As expected, Di Sabato *et al.* realised that HBO as an acute treatment is not practical, because of the short duration of CH attacks and the costs of HBO treatment.[28] Pascual *et al.* suggested that HBO

could have prophylactic effects.[30] Five studies investigated the prophylactic treatment effect achieved by inhalation of HBO.

In the study by Di Sabato *et al.* described above, of the six patients (*i.e.* 86%) in which HBO interrupted the current CH attack, three patients did not have CH attacks for 4-6 days and another three patients did not have CH attacks during the follow-up period of 2 months. The CH attack pattern remained unchanged in the patients on placebo.[28]

Pascual *et al.* studied the frequency and duration of CH attacks during HBO treatment (ten sessions administered in a hyperbaric chamber for 70 min per session at a pressure of 2.5 ATA), compared to the last (minimum) 2 weeks before treatment start. The four CCH patients continued using preventive treatment (Lithium). One patient did not have any CH attacks until 31 days after his 8 day treatment. In contrast, another patient did not experience any effect in frequency (and duration).[30]

Nilsson Remahl *et al.* conducted a double-blind crossover study in which HBO treatment (composed of 100% oxygen) and hyperbaric normoxic placebo treatment (composed of 10% oxygen), both supplied in a hyperbaric chamber by a mask for 70 min in two sessions 24 hours apart at 2.5 ATA, were compared. Fourteen CH patients breathed HBO, sixteen CH patients breathed hyperbaric normoxic placebo. 'A headache index' (HI) (sum of (number of headache attacks times their degree of severity)) was calculated for 1 week prior to as well as for 1 week following each separate treatment. A treatment was considered effective if the HI decreased by > 50%. HBO treatment was effective in five of fourteen (*i.e.* 36%) patients and hyperbaric normoxic placebo treatment was effective in six of sixteen (*i.e.* 38%) patients.[31] There was no significant ($p = 0.92$) difference in treatment effectiveness between HBO and hyperbaric normoxic placebo treatment.[29] One ECH patient who responded to HBO was free of CH attacks for 6.5 months. However, two ECH patients who responded to hyperbaric normoxic placebo treatment had a remission period (free of CH attacks) for even more than 1 year. The study only found a true preventing effect of (100%) oxygen while the patient was under hyperbaric conditions.[31]

Di Sabato *et al.* placed seven ECH patients in a hyperbaric chamber during 30 min with pressures up to 2.5 ATA. A disappearance or at least a 50% diminution 'of the CH' (unknown frequency, duration or severity) was observed during 3 days after exposure.[32] In another study by Di Sabato *et al.* ten CCH patients were placed in a hyperbaric chamber during fiteen sessions of 30 min with pressure up to 2.5 'atm abs' while breathing 100% oxygen administered through a facial mask. There was a decrease in the weekly number of attacks during the treatment period (*i.e.* 30 days). The 'clinical index' (not defined) remained at 'significantly' lowered numbers during the first 2 weeks of a 4-week follow-up period after HBO treatment.[33]

The authors mentioned several mechanisms that could explain the effect of HBO. It induces vasoconstriction, reduces cerebral hypoxia by increasing oxygen diffusion, acts against oedema of the blood vessel wall and *interstitium* and stimulates the serotonin synthesis in the central nervous system.[28] *In vitro* a normal 5-Hydroxytryptamine (5-HT) turnover was found after HBO.[33]

Furthermore, HBO could act against the sterile inflammation produced by release of neuropeptides from the trigeminal neuron.[32] Finally, HBO has some nonspecific actions such as an influence in the prostaglandin cascade.[30]

Cold air

Mc Leod *et al.* investigated the interesting hypothesis that cooling rather than the oxygen concentration plays the main role in relieving a CH attack as cold temperature causes vasoconstriction. Eight CH patients treated ten CH attacks using a device which delivered room air cooled to 5°C via a non-rebreathing face mask at a flow rate of 6 L/min for 15 min or until the headache was aborted. Of these eight CH patients, six treated the next five CH attacks using 100% oxygen (no details of administration were provided). The level of relief was scored '0 for no or minimal relief, 1 for slight relief, 2 for substantial relief and 3 for complete relief'. 'Significant relief' combined categories 2 and 3. 'Significant relief' was achieved in 85% ($p < 0.0005$) using the cold room air device and in 83% ($p < 0.0005$) using 100% oxygen. The main relief score for the sixty-eight observations in which cold room air provided 'significant relief' was 2.69 and for the twenty-five observations in which 100% oxygen provided 'significant relief' was 2.72. The difference between the main relief scores was not statistically significant. So, contrary to Fogan's and Cohen's results, cold room air can be effective in the acute treatment of CH.[34]

To summarize, 100% oxygen supplied via a facial mask at a flow rate of 7 L/min given at pain onset for 15 min, provides successful headache relief in 75-82%. Patients who have no response to 100% oxygen at a flow rate of 7 L/min should be exposed to flow rates of 12 and possibly even 14-15 L/min, before they are considered refractory. Restlessness, an age > 49 years in CCH, (female gender) and nausea and vomiting are proven factors predicting a negative oxygen response.

HBO of 2.0–2.5 ATA can terminate CH attacks in a few to 30 min in 86% to probably 100%. HBO can terminate CH attacks also in those considered refractory to normobaric oxygen. HBO cannot prevent subsequent CH attacks.

Cold (5°C) room air supplied via a face mask at a flow rate of 6 L/min for 15 min was as effective in relieving pain as 100% oxygen.

Scope of this thesis

When I started my studies in 2008, it was not possible to find clues that provided further insight into CH pathophysiology, based upon the data on proven factors predicting the oxygen response in CH attacks in particular. It led me to believe that it would be worthwhile to set up a systematic search for characteristics that would predict the effect of oxygen in CH.

I referred shortly to the history of oxygen application for CH in the past 60 years. As is true for the rebound phenomenon, which had been noted by Kudrow in 1981 already,[11] I increasingly realised more things could be learned from the past. Being interested in the origin of applying oxygen for CH, which provides a perspective for our studies, I did a more extensive historical review of CH and oxygen therapy (chapter 2).

I carried out a retrospective (chapter 3) and subsequently a prospective (chapter 4) cross-sectional correlation study. Although described in more detail in the prospective study, in both studies I used the same classification in five groups of response to oxygen, which enabled a comparison.

In my retrospective study, six patients spontaneously reported an increase in CH attack frequency when using oxygen as acute treatment. Because this phenomenon implies an important limitation in the use of oxygen, in my prospective study I specifically asked for a change in CH attack frequency after start of oxygen therapy. During the course of my prospective study, 7% of the patients reported the phenomenon. As Kudrow described a rebound phenomenon in even 25% of his patients using oxygen for CH,[11] I decided not to wait until the final patient inclusion in my prospective study, and I studied the phenomenon more closely in my patient series present at that time. To study the rebound phenomenon, first I had to define it. This definition and the results of the study will be presented in chapter 5.

Apart from studying clinical characteristics, during the course of our studies I became interested in clinical neurophysiology as a means for further elucidation of pathophysiological mechanisms in CH. To investigate the (direct or indirect) effect of oxygen on medullary interneurons, I intended to study the nociception specific blink reflex before and during a CH attack, as well as before and during oxygen treatment. This study had unexpected, serendipitous results, that are described in chapter 6. As the remaining data from this study, notably the effect of oxygen on the nociception specific blink reflex may be useful in further research, I described these data in an additional chapter 7.

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