Evaluation of the scientific literature on Neuroreflex Stimulation Therapy using hyperbaric CO₂ gas (CRYOTHERAPY)

by

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1. Foreword and aim of the scientific evaluation.
Cryotherapy using hyperbaric CO\textsubscript{2} gas is an accepted method of medical
treatment for reducing pain and relieving inflammation and swelling.
Compared with treatment with ice or other cooling procedures, the essential
difference is that a so-called thermo–shock is delivered, which cools the skin
to 2–4 degrees Celsius within approx. 30 seconds. In combination with
pressure and vibration, there is a potentiating action on the neuroreflex
effect. Pain and temperature are conducted through the skin sensors via the
lateral spinothalamic tract to the thalamus and cerebral cortex whereas
pressure and touch are conducted via the anterior spinothalamic tract. The
centrally triggered reflex produces superficial vasoconstriction initially (as
with ice treatment) and then deep vasodilatation (which is not possible with
ice treatment), which produces removal of the inflammatory mediators such
as prostaglandin, histamine, serotonin and kinins, leading to very rapid relief
of oedema and haematomas. Vascular permeability, which is disturbed by
inflammation (semipermeability is abolished), is rapidly normalised again
within a few minutes so that reabsorption of the inflammatory mediators and
their removal via the venous system functions physiologically again. The
success of this special method of treatment is confirmed by the experience
of many users and scientific investigation by a series of authors.
The aim of this scientific evaluation is to examine at least a few scientific articles and expert assessments critically and discuss their contents in order to obtain a standardised use of this innovative treatment method.

2. Discussion and critical evaluation of the individual publications:

Re a) Gas cryotherapy in the treatment of algoneurodystrophy
(Alain CORNC Marc BOULEAU)

This article or statement deals with the treatment of Sudeck’s disease of the hand. The neuroreflex property due to stimulation of the three layers of the skin with conduction of the stimulus to the brain is pointed out. Moreover, lymphatic drainage is considerably accelerated by the stimulation of the lymph drainage channels, which leads to a rapid reduction of swelling and especially to better “perfusion”. The authors explain the positive effect in the treatment of Sudeck’s disease on the basis of their long experience as physiotherapists.

Critical discussion:
This article is based on experiences that the author of this evaluation can confirm on the basis of his many years of experience with this treatment method. It is not based on a study with a stated patient pool.

Re b) The influence of cryotherapy (Cryotron®) on pain and inflammation following arthroscopy of the shoulder.
(Prof. Dr. Romain Meeusen, Dr. Frank Handelberg, Laurence Framhout, Stephanie Daems, Vrije Universiteit Brussel Belgium)

The influence of cryotherapy on postoperative pain and inflammation following arthroscopic surgery of the shoulder was investigated at the Free University Brussels using a placebo–controlled study. The placebo treatment consisted of application but without cooling. Following several studies of postoperative cryotherapy in knee surgery, especially ligament repair operations, this scientific study was intended not only to investigate the effect of treatment of the shoulder but at the same time to establish the correlation between the reduction of skin temperature and the intra–articular
temperature. This was successful in that a significant reduction of the intra-articular temperature was confirmed along with the reduction in skin temperature. It was also found that, after use of cryotherapy, the inflammatory parameter CRP in the plasma was significantly lower 6 hours and 24 hours after operation in the experimental group of patients than in the control group. The recognised VAS (visual analogue scale) was used as an objective measure of the pain. Here, too, a significant reduction of pain was found compared with the control group.

Critical discussion:
This experimental scientific study confirms the positive effect on inflammation, pain and use of medication. The objective findings, particularly measurement of the plasma CRP, demonstrated the rapid postoperative effect of inflammation reduction. It was also confirmed for the first time that a temperature reduction occurs not only on the skin surface but also in the operated joint. This study showed objectively what was described and confirmed in other scientific experimental studies indirectly, such as faster rehabilitation (e.g. in the knee) after cruciate ligament repair or knee arthroplasty, better mobility, faster mobilisation, reduction in analgesic use and earlier hospital discharge. Further investigations to objectively confirm the positive effect of cryotherapy in this area of surgery should be conducted with bigger numbers in the experimental and control groups. Our own experiences in the use of cryotherapy pre- and postoperatively confirm these results.

Re c) Evaluation of gas cryotherapy with high pressure in the treatment of tendinopathies.
(by Professor BRUNET-GUEDJ in the Sports Medicine Department of the Edouard Herriot University Hospital (UHC), LYON Published in Sport Med – 2002)

In this study, 21 patients were investigated. Both acute and chronic tendon disorders were investigated. The inclusion criteria were leisure or competitive sport, age over 18 years and microtrauma of the tendons at the shoulder, elbow, wrist, knee and Achilles tendon. The exclusion criteria were cold allergy, surgically managed tendon disorders and metabolic causes.
The distinction between “acute” and “chronic” is made according to the time factor of disease duration of less than or more than one month. The treatment took place once a day for six days. Success was assessed according to the degree of pain on the VAS (visual analogue scale), change in the clinical stage of the tendinopathy and the sporting activity 1 month after the end of the treatment. It was shown that 75 per cent of the acute disorders had a good or very good outcome. The group of chronic disorders was too small to allow a statistically significant conclusion. These results showed no difference from the standard treatment.

Critical discussion:
This randomised and comparative study of the treatment of acute tendon disorders shows an outstanding result in line with the experience that this form of cryotherapy is more effective the earlier the treatment begins, that is, at the acute stage. It must be remarked critically that the number of patients with a chronic disorder is insufficient. In the experience of the author of this evaluation, the positive results in chronic disorders not only of tendons are well above the level of other standard treatments.

Re d) Treatment of oedema in maxillo–facial surgery with Gas Cryotherapy
(Surgical wing, University Hospital, STRASBOURG, Dr. A. WILK – Dr. M–R BOLLACK)

In this randomised prospective study, 36 patients with a fracture of the zygomatic bone accompanied by an orbital floor fracture were investigated. 22 patients were treated with cryotherapy four times per day in the swollen area of the face and on the neck (lymph drainage pathways). For objective measurement, the lid opening distance on the one hand and the distance between the tragus of the ear and the base of the nasal ala on the other were measured on both the injured side and on the healthy side for comparison. The measurements were performed on the 1st, 2nd and 6th postoperative days.
73 per cent of the treated group had very good results and 80 percent of those treated did not find the treatment unpleasant; 20 percent perceived the treatment as unpleasant because of the gas pressure. In the control group,
there was no significant difference in the measurement results, whereas there was a significant difference in the treatment group due to the rapid reduction of swelling.

Result: the statistical analysis shows that the reduction in oedema was markedly greater in the group of patients treated with cryotherapy. This led to this patient group not requiring any anti-inflammatory medication.

Critical discussion:
This article confirms that an outstanding effect of the treatment is achieved in the facial region also. The objective investigation criteria meet scientific requirements fully. The author of this evaluation can confirm this by comprehensive experience in the treatment of boxers with considerable trauma in the facial region.

Re e) Gas Cryotherapy in the Treatment of Trauma in Top Athletes
Published in the journal: SPORT MED Sept 1996)

17 athletes between 17 and 24 years were treated with cryotherapy using hyperbaric CO$_2$ gas following an ankle sprain. The investigation was a prospective study. Each athlete received treatment with CO$_2$ immediately after the injury. The treatment took place twice a day on days 1 to 3 and once more on day 4. In all of the patients, the pain disappeared immediately after the treatment and returned lessened after 3–5 hours. In 15 of the 17 patients the pain was fully abolished after 3 days and in 2 patients after 5 days. Within 48 hours, the oedema had been reabsorbed to the extent that there was a difference in circumference of less than 1.7 compared with the healthy opposite side. In the conclusion, the analgesic, anti-inflammatory, vasomotor and neurological effects are listed. The neurological effect lasts 15 minutes and the other effects last up to 3 hours. The long-term results after 3 months yield no difference compared with traditional treatment.

Critical discussion:
Particularly in sports medicine with top athletes, pain can be eliminated immediately by this method of treatment with CO$_2$. However, the effect of a
rapid reduction of oedema is more important, together with faster than average rehabilitation and thus a rapid return to sporting activity. The author made this observation in numerous sports injury treatments of the ankle, as in the present study. The statement that there is no difference from the control group after 3 months is certainly irrelevant as these injuries recover in this period anyway. What is relevant, rather, is the immediate post–traumatic phase, in which the injured person benefits not only from pain relief but also from faster recovery.

**Ref)** Interest of Gas Cryotherapy in the Immediate Post–Operative Care of Hand Surgery
(Toulon Hand Centre, M. Alain Berthe, Dr. Fritch et.al)

In this prospective study, 30 hand surgery patients were treated immediately after operation and especially as a rehabilitation measure. 4 patients had tendovaginitis, 10 had fractures of the 5th metacarpal and 16 had a radius fracture that was treated surgically by internal fixation. All 30 patients tolerated the treatment well. 27 of 30 patients had pain reduction within 1–5 days postoperatively. In 19 of the 30 patients, the postoperative oedema was already abolished on day 0 and in the other cases the oedema disappeared between days 1 and 3. 26 of the 30 patients had nearly complete joint mobility between days 3 and 5. The effect lasted 1 to 6 hours after the treatment. In conclusion, postoperative cryotherapy is considered an essential part of postoperative treatment in hand surgery.

Critical discussion:
Particularly in hand surgery, the treatment is very valuable and indispensable for the patient. Postoperative states recover markedly faster and the risk of secondary Sudeck’s disease is considerably reduced. It should be remarked that cryotherapy treatment must naturally not be undertaken if plexus anaesthesia is still working and especially not with a tourniquet as there is a risk of burns. The neuroreflex stimulus response is abolished by the anaesthesia and therefore no effect is to be expected. The close course of the lymph pathways leads to rapid removal of the inflammatory mediators and thus to better perfusion. The number of patients is sufficient at 30 for a statistically significant conclusion.
In this article, the working group of chiropodists, who each have their own chiropody institute, investigated a total of 60 patients. The diseases included conditions such as ingrowing toenails, hallux valgus and corns. Treatment consisted of cryotherapy.

**Ingrowing big toenails:**
88% of the patients had no local skin reaction 48 hours later. There was mild skin erythema to a slight extent. All patients felt well after 48 hours. The assessment of the chiropodists confirms the good effect especially when using the method rapidly is mastered. Healing is hastened.

**Hallux valgus:**
One to four treatment sessions took place in 48 hours. 78% of the patients had local inflammation. 87% complained of pain when wearing shoes. 33% of the patients felt better spontaneously at the first session and the pain was satisfactorily reduced after the second session. Only 8% reported no improvement after 30 days.

**Corns:**
80% of the patients had inflammation. 15% had an infection. 35% were immediately asymptomatic but 60% felt the cold and 15% of the patients also felt pain. After 48 hours, 100% were asymptomatic. It is important that the treatment time is observed strictly in order not to obtain any unwanted skin reactions. High-tech chiropody and foot treatment can no longer be imagined without cryotherapy.

Critical discussion:
The evaluation and conclusion of the authors correspond to general experience. The presentation of the individual patient groups leaves something to be desired with regard to the solidity of a scientific investigation.
This article is not a study with a minimal number of patients but rather individual case descriptions of particular successful treatment cases (3 patients). A 30-year old female patient with knee pain and repeated blocks and nocturnal pain, in whom drug therapy had been unsuccessful, was treated. After one treatment the symptoms were abolished. A 24-year old man with knee symptoms in the lateral part of the joint was unable to play football for 4 months because of the pain. A single treatment with cryotherapy showed freedom from symptoms during the first session so that he was able to play football again the following Sunday. A 40-year old patient who had surgery for a herniated disc in 1995 and had unsuccessful nerve root electrocauterisation in 1996 as a result of persistent radiculopathy had improved so much after 10 treatments with cryotherapy that she had only slight residual symptoms and was able to resume part–time work.

Critical discussion:
This article is a single case description demonstrating in fact unusual treatment success on the basis of great experience. The author of this critical evaluation can also report a number of such treatment successes. These individual cases are what make this treatment method attractive. This article lacks a scientific claim in the sense of a randomised study. Nevertheless, such successes must be taken as an occasion to strive for further meta–analyses.

Re i) Efficacy of Treatment using Gas Cryotherapy in Haemorrhagic Events in Haemophiliacs
(Regional Haemophilia Treatment Centre, Lyon, France, Dr. Anne Lienhart, Nadine Alliaume)

This investigation of the use of CO₂ gas in haemorrhagic events in haemophiliac patients shows the course of 6 haemophilia patients who had bleeding in various regions of the body. After 1 to 5 treatments, all treatments resulted in prompt breakdown of the haematoma in addition to immediate analgesia so that rapid mobility of the affected extremity could be restored. It should be emphasised that one child with a haematoma at the elbow had immediate freedom from pain after one treatment and free
mobility of the elbow joint was achieved after just 24 hours. This form of treatment is tolerated well by children also.

Critical discussion:
The individual case description of the 6 haemophilia patients shows the importance and effectiveness of cryotherapy. There is rapid breakdown of the haematomas without fresh bleeding occurring due to the pressure exerted on the skin. This suggests the conclusion that warfarinised patients can also be treated with this form of therapy. This can also be confirmed as in many individual cases a haematoma of pain can be abolished neuroreflexively without the risk of starting new bleeding.

Re j) Utilisation simultanee des ondes de choc radiales et de la Cryotherapie Gazeuse hyperbare en Cabinet de Traummatologie sportive.
A propos de 333 cas.
(Marc ROZENBLAT Centre Coralis – 32 ter avenue du Général Leclerc 77330 OZOIR LA FERRIERE – FRANCE)

Over 15 months, 333 patients with musculoskeletal disorders were treated simultaneously with extracorporeal shockwave therapy (ESWT) and hyperbaric CO₂ gas for thermoshock treatment in a sports injury department. ESWT was given first, followed directly by the cryotherapy. In certain diseases, such as calcified bursa of the shoulder, supraspinatus syndrome, epicondylitis, tendinitis of the patellar ligament and Achilles tendon and plantar fasciitis, outstanding results are obtained. In contrast, low back pain and sciatica do not appear to achieve sufficiently good results even though 80 % of these patients reported satisfaction. From April 2002 to June 2003 171 men and 162 women with an average age of 32 years (18–65 years) were treated. 27 % of them take part in competitive sport and 30 % in leisure sport. 31 % practice sport occasionally and 13 % are not athletes but want the same treatment methods that athletes benefit from. The results show that 186 cases, or 56 %, were very successful. 17 % (58 cases) were satisfied, still with intermittent but tolerable symptoms. Unsatisfactory results were reported by 14 %. 11 % suffered recurrence or the treatment had to be discontinued in favour of other treatments. 62 % of the patients reported that they returned to their sport to the same extent as before. The most frequently treated
diseases were at the shoulder, followed by the elbow, the wrist and the hand. Plantar fasciitis (heel spur) demonstrated over 90% patient satisfaction. This summary lists only the most important conditions with the greatest number of patients.

Critical discussion:
This article by Rozenblat is one of the first scientific documentations with a large number of patients (333). This also allows a reliable statement about the positive mode of action. The fact that a combined treatment method with extracorporeal shockwave therapy and hyperbaric CO₂ gas treatment was used to produce thermal shock and the neuroreflex effect is not a compelling individual conclusion for cryotherapy. However, since many investigations with ESWT alone do not yield such outstanding results, it is confirmed that potentiation of the regenerative effect comes about only by the combination of these two treatment methods. This is also plausible. ESWT leads to a local brief inflammatory reaction that increases pain, and cryotherapy leads to rapid removal of the inflammatory mediators and to pain relief, which represents the secret of this treatment combination. The conclusion can be drawn that this form of treatment should receive much more attention in orthopaedic and traumatological treatment. Nevertheless, further clinical studies of cryotherapy in various disease conditions are required.

3. Summary and overall critical evaluation
In the overall view of the publications presented here, a good to very good result of cryotherapy using hyperbaric CO₂ can be demonstrated. The individual studies, some of them randomised, can confirm the enormous benefit for the patient, which is the priority. The studies refer to various disease and treatment areas so that a comprehensive statement can be made about the positive mode of action of this form of treatment. Tendinopathies, shoulder and elbow disorders, facial injuries, haemorrhage in haemophilia, Sudeck’s disease, hand surgery, foot surgery, low back pain, rheumatic myopathies and many other conditions were investigated, covering the entire necessary treatment range. Outstanding results were achieved overall with this form of therapy, confirmed by a rapid regression of oedema, haematomas, inflammation and thus pain. Co-medication for pain and
antibiotic therapy could be reduced or even avoided. This leads ultimately to the goal of earlier mobilisation of individual joints after surgery and to markedly earlier overall mobilisation of the patient. The duration of hospitalisation can therefore be shortened and the patients can be discharged sooner to rehabilitation. There is thus not only a gain for the patient due to the rapid and natural reduction in pain in association with a gain in function and quality of life. There is also a substantial economic gain due to the reduction in overall treatment costs, which is in the interest of the public and not least of the health insurers. Cryotherapy is a recognised form of treatment, which in fact is not therapy with cold, as initially assumed, but rather neuroreflex stimulation therapy using hyperbaric liquid CO$_2$-gas. The stimulus is conducted via the cold, pressure and vibration sensors of the skin and thus makes use of natural reaction mechanisms.

4. Prospects and need for further clinical studies
When the results of research and use hitherto are considered, together with the fact that treatment with hyperbaric CO$_2$ gas is a natural and non-invasive method in humans, it is likely that this therapy has a great future. Due to the great benefit of rapid pain relief, the discriminating patient will start to demand this therapy. The fact that combination forms of this treatment with other measures are possible and effective was confirmed by Rozenblat. Cryotherapy in the hands of a doctor, therapist and nonmedical practitioner is a great gain in the range of possible treatments. It is a version of therapy for nearly all groups of doctors. Already today, a large number of doctors’ surgeries, outpatient clinics, hospitals and rehabilitation clinics and also sports clubs and boxing associations are equipped with this form of treatment. Meta-studies are urgently required to extend the acceptance of cryotherapy in this form; a start has already been made. This should also include the economic component referred to above, in which the shorter hospitalisation and the shorter unfitness for work will be investigated. These are already apparent from experience. There should be further stimulus for clinical studies as part of the accompanying monochromatic colour light therapy with blue light in the 420 to 490 nm spectrum, particularly for ulcers and delayed wound healing. A further combined form of therapy can be seen here due to the antibacterial effect, particularly on anaerobes, and the increased tissue oxygen supply.