A randomized, prospective trial to assess the safety and efficacy of hilotherapy in patients after orthognathic surgery

Lars Bonitz 1,2 · Adrian El-Karmi 1,2 · Johannes Linssen 1,2 · Dietmar Abel 1,2 · Stefan Hassfeld 1,2 · Ákos Bicsák 1,2

Received: 1 October 2020 / Accepted: 28 January 2021 © The Author(s) 2021

Abstract
Purpose A post-operative cooling method in oral and maxillofacial surgery is the cooling with hilotherapy. The aim of this study was the post-operative comparison of cooling temperatures of 18°C and 22°C. The parameters of this trial were swelling and the post-operative pain levels.

Methods This study included 156 patients, divided into two groups among whom a mono-one, bignathic osteotomy or genioplasty was indicated. The post-operative assessment of swelling was performed using a 3D optical scanner. This examination was repeated on post-operative days 1, 2, 3, 7, 14, 30, and 90. The examination on day 90 served as a reference value in respect of swelling and pain.

Results Group 1 (18°C, 78 patients) showed an increase in post-operative swelling on the 1st post-OP day of 52.06 ± 35.41ml. The maximum was reached on the 2nd post-OP day with 75.82 ± 38.97ml. On the 30th post-OP day, residual swelling measured 11.60 ± 12.62ml. Group 2 (22°C, 78 patients) showed an increase in postoperative swelling on the 1st post-OP day of 76.07 ± 63.15ml. The maximum was reached on the 2nd post-OP day with 106.97 ± 69.63ml. On the 30th post-OP day, residual swelling measured 14.36 ± 32.26ml. The differences between the two groups and between different visits were statistically significant.

Conclusion The study results indicate less residual swelling in group 1 on the 30th post-OP day, possible based on the lower cooling temperature. The post-operative pain exhibits a comparable level of pain intensity between the two groups. In overall terms, a subjectively more agreeable treatment was observed in group 1.

Keywords Orthognathic surgery · Hilotherapy · Cooling temperature · 3D optical scanner · Swelling · Pain

Introduction
Local swelling, hyperemia, hyperthermia, pain, and altered function are well-known consequences of tissue injuries [1]. Reduction of all of these leads to the enhanced healing process, decreasing of pain, and improved post-injury or postoperative quality of life [2–7]. The swelling reaches its maximum after approximately 48 to 72 h after the operation [7, 8]. In this period, it is essential to provide adequate pain medication (non-steroidal antirheumatic drugs—NSAIDs [9], corticosteroids [10], or enzymatic drugs [11]) and is highly suggested to provide supportive local therapy, like manual lymph drainage [12], cooling with wet tissues or cryotherapy [2, 7, 13, 14].

Results have shown that nerve conduction speed drops with decreasing temperature [15, 16] that decreases the sensitivity of the nociception until a total blockade and thus analgesia at approximately 15°C are reached [17]. At temperatures below 10°C, the risk of tissue damage increases [18–20]. Between 20 and 23°C, this drop of the excitability is linear; below this temperature, the raise of this threshold is rapid [21]; and at 4°C, it reaches a complete blockade [16]. By reducing the impulse frequency generated in the axons by influencing membrane properties, it is possible to modify the pain sensation [22]. Cryotherapy reduces the release of inflammatory mediators and enzymatic activity in the local tissue; thus, it leads to a decrease of hematoma and edema formation, too [23]. In oral and maxillofacial surgery, cryotherapy has become a proven supportive therapy after the removal of third molars [3, 8, 10, 14, 23, 24], traumas [25, 26], or after orthognathic surgery [5, 7, 25].
The Hilotherm Clinic device (Hilotherm® GmbH, Argenbühl-Eisenharz, Germany) provides a dry, easy-to-use, continuous cold therapy in a controlled manner that allows in clinical setup even patient-controlled cooling effect. This is reached by anatomically shaped sleeves for many body regions, including the face, in which tempered water is circulated. The setup allows temperature ranges from +10 to +35°C [7]. Hilotherapy is the term used in the literature for cryotherapy by using Hilotherm® devices [7, 25, 27–29].

**Purpose**

This study aims to examine and compare the safety and efficacy of hiloterapy at two different cooling temperatures at 18°C or 22°C in an investigator-initiated, randomized, prospective, monocentric cohort study. The endpoints for the study were patient assessed subjective pain level and postoperative swelling measured by volume changes of the facial tissue at different visits. The parameters of this trial are swelling and the postoperative development of pain levels. Examining the efficacy of two different cooling temperatures can allow a more effective setup of postoperative pain therapy with a reduction of safety issues that include possible frost injuries, allergies against medicines, or other side effects, like gastric pain or ulcer.

**Material and methods**

This study was examined and approved by the Ethics Committee at the Medical Faculty of the Westfalian Wilhelms-University in Münster, Germany (№ 2013-239-F-S). Before conducting any study procedures, written informed consent was obtained from all study subjects.

As baseline values, data from day 90 assessment was used. This is possible, as there were no early relapses diagnosed but all changes in hard and soft tissue configurations are stable.

**Table 1  Summary of study inclusion and exclusion criteria**

| Inclusion criteria                                      | Exclusion criteria                                           |
|--------------------------------------------------------|-------------------------------------------------------------|
| Surgery for dysgnathia: bimaxillary osteotomy or monomaxillary osteotomy | Allergy, intolerance or contraindication of glucocorticoids or NSAID in the medical history |
| Signed study informed consent form                     | Non-compliance with the requested cooling therapy of at least 16 h/day |
|                                                        | Inability to participate                                     |
|                                                        | Known contraindication of cooling therapy (e.g., Raynaud’s syndrome, cryoglobulines) |
Also 90 days post operatively swelling is expected to be completely resolved.

The study was conducted in a semi-blinded manner. Patients were not aware of the cooling temperature (device digital screen showing temperature data was covered with black tape, an unblinding was not detected; therefore, this had no impact on study data). The investigator performing the volume measurements was not aware of cooling temperatures.

**Patients**

We conducted this study at the Department of Cranio-, Maxillofacial Surgery, Regional Plastic Surgery at Dortmund General Hospital. We involved 156 subjects who underwent orthognathic surgery. The patients were divided into two randomized groups receiving hilotherapy at preset temperatures of 18°C or 22°C. The randomization was performed by using an online randomizer (www.randomizer.org). The surgical procedure included monomaxillary or bimaxillary osteotomy with or without genioplasty performed by the same surgeon. The indication of surgery was standard indication and did not influence the study procedure. The maxillary osteotomy was performed at the Le-Fort-I level (Reuther, 2000), whereas the mandibular split was performed as per Obwegeser and Trauner. Demographic data and surgery length were documented.

**Fig. 2** Summary of study procedures

| Procedure                 | Pre-Operative | Day 0 | Day 1 | Day 2 | Day 3 | Day 7 | Day 14 | Day 30 |
|---------------------------|---------------|-------|-------|-------|-------|-------|--------|--------|
| Surgery                   |               |       |       |       |       |       |        |        |
| Hilotherapy               |               |       |       |       |       |       |        |        |
| Face Scan 3D              |               |       |       |       |       |       |        |        |
| Pain assessment           |               |       |       |       |       |       |        |        |
| Pain therapy (600mg ibuprofen TD p.o.) |               |       |       |       |       |       |        |        |

**Fig. 3** Comparison of the excess swelling in both patient groups (average; ml)
Hilotherapy

The hilotherapy was provided by the Hilotherm® Clinic device (Hilotherm® GmbH, Argenbühl Eisenharz, Germany). This enables a temperature-controlled water flow in the anatomically adapted and very lightweight facial sleeve (hypoallergic, latex-free thermoplastic polyurethane sleeve). Through this continuous flow, a stable skin surface temperature was set at 18°C or 22°C (Fig. 1a, b).

Inclusion, exclusion, and study parameters

Table 1 provides an overview of the inclusion and exclusion criteria. In accordance with the general perioperative procedure for orthognathic surgery at our department and as per study protocol, all patients received hydrocortisone 500mg i.v. once and antibiotics—3 g ampicillin-sulbactam i.v. (or if not compatible, clindamycin 600 mg i.v.)—was administered starting before the operations and continued every 8 h for 3 days postoperatively. Postoperatively ibuprofen 600mg three times a day p.o. was administered. The postoperative X-rays and lab tests were carried out as per clinic standards. Patients were discharged after 3 days of therapy. The antibiotic therapy was continued with amoxicillin/clavulanic acid 875/125mg (or 600mg clindamycin) p.o. three times a day up to 7 days. For pain therapy, ibuprofen 600 mg was advised up to 3× daily on demand and subject to compatibility. During the entire investigation period, swelling and pain levels were examined and documented based on the 6-point “visual analog scale” (VAS).

Clinical trial procedure

Hilotherapy was introduced as soon as the patients were capable after the general anesthesia. The application of the different cooling temperatures was carried out in a single-blinded manner so that the patients were not informed about their settings. The daily application of hilotherapy lasted for at least 16 h. During the inpatient period, pain medication was administered as per plan.

The swelling assessment was conducted with a 3D optical scanner (FaceSCAN3D®). The pain levels were recorded by using a visual analog scale, VAS. This examination was repeated on post-operative days 1, 2, and 3 during the inpatient stage of this treatment. While being treated as in-patients, as well as a check on progress, a daily mouth and tooth cleaning procedure was followed. During the out-patient stage, the investigation times were post-operative days 7, 14, and 30 (Fig. 2).

Table 2 Summary of the patient group demographics

| Group | 18°C | 22°C |
|-------|------|------|
| Bimax:monomax:genioplasty | 53:25:11 | 48:30:11 |
| Patients (n) | 78 | 78 |
| Gender (W 69.5%/M 30.5%) | 40/38 | 44/34 |
| Age (years) ± SD | 22.84 ± 6.42 | 21.98 ± 5.78 |
| Duration of operation (min) ± SD | 132.3 ± 51.1 | 115.1 ± 42.9 |
| Duration of hospital stay (days) | 4 | 4 |
| Number of surgeries* | 2/15/53/8 | -/14/57/7 |

*The surgeries are listed as follows: LeFort I maxillary osteotomy/mandibular osteotomy/bimaxillary osteotomy/bimaxillary osteotomy and genioplasty

Fig. 4 Comparison of swelling characteristics (boxplot diagrams show the swelling means, maximums, and minimums to different study milestones). The Wilcoxon p-values show a statistically significant difference up to 2 weeks postoperative. After a month time, the swelling is almost gone and there is no significant difference between the two treatment groups.
Assessment of facial swelling

The examination of post-operative swelling was performed with a 3D optical scanner (FaceSCAN3D®). The FaceSCAN3D® sensor was developed to record three-dimensional facial photographs and to perform volume measures based on these recordings. The sensors are based on the principle of strip projection. The distortion of these light strips is used to gain topographic information. This measurement process generates a 3D database and records the texture of the soft tissue surface (FaceSCAN3D®, 3D-Shape GmbH, Erlangen, Germany).

Volumetric assessment

We used MIS (Mimics Innovation Suite) vers. 23 with 3matic vers. 16 to evaluate the three-dimensional datasets and to assess volumetric changes based on this information. As anatomical landmarks, we used the nasion and tragus on both sides, as they remain unchanged throughout all procedures (Fig. 3).

Statistical analysis

The statistical analysis was conducted by an independent statistician using the statistical program R Development Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, Version 3.2.0. Using the non-parametric Wilcoxon-Mann-Whitney test (group comparison), the data were examined for signs of significant differences. A value of $p < 0.05$ was declared as statistically significant.

Results

Study patients and characteristics

This study included 156 patients who underwent orthognathic surgery at the Department of Cranio-, Maxillofacial Surgery, Regional Plastic Surgery at Dortmund General Hospital. The treatment response of both randomized patient groups at 18°C and 22°C was compared. Both randomized groups were treated in a standardized manner by means of hilotherapy. The basic characteristics of the subjects are presented in Table 2. All genioplasties were performed in connection with bimaxillary osteotomies.

Post-operative swelling

The assessment of the swelling was performed on post-operative images. Day 90 volume data was taken as baseline. Both groups show similar postoperative swelling development (Figs. 3 and 4). On the 1st post-operative day, group 1 (18°C) exhibits an increase of $52.06 \pm 35.41$ ml. The maximum level of swelling was reached on day 2 with $75.82 \pm 38.97$ ml. Then, the swelling reduced successively over time and there was no significant rest after 30 days postoperatively and measured $11.60 \pm 12.62$ ml ($p=0.045$).

Group 2 (22°C) showed during the whole study period much more swelling reaching $106.97 \pm 69.63$ ml on day 2 and ending with $14.36 \pm 32.26$ ml ($p=0.045$) after 30 days. The differences from day 1 to day 14 were statistically significant, but not on day 30 (Fig. 5).
**Intensity of pain**

Post-operative pain was assessed using the 10-point visual analog scale (VAS) during the study period. Both groups showed the most pain on day 2; however, group 1 had much less pain than group 2 (2.01 vs. 2.44 VAS score respectively). After that, the trend is decreasing and there is no significant difference after finishing the hilotherapy. On the day of the surgery, group 1 showed remarkably less pain, but this difference was not significant (Fig. 6).

**Discussion**

This study examined 156 patients, who received hilotherapy at 18°C and 22°C after the orthognathic surgery procedure. The most important study endpoints were postoperative swelling and pain. Our results have shown that hilotherapy contributes effectively to decrease both postoperative swelling and pain, thus reducing the need for painkillers helping to avoid their side effects. This result corresponds with the literature data [7, 30]. We found further that the hilotherapy at the above temperature levels has an excellent safety profile. We did not register any side effects of hilotherapy. Some authors reported neuropraxia that leads to paresthesia, e.g., paradox vasodilatation, bradycardia, elevated blood pressure, and increased cerebral blood flow through changes of the activation levels and balance between the sympathetic and parasympathetic system [31, 32].

One of the most important findings of this study was the onset and characteristics of the postoperative soft tissue swelling of the face. The patient group with a temperature of 18°C showed a slower onset, the lower peak of swelling, with the maximum level of swelling on day 2. In the group that used 22°C temperature, the peak was higher and the onset accelerated and reached a maximum on day 2 after surgery. The decrease of the postoperative edema showed a similar characteristic: at the lower temperature, the decrease was faster, and the residual swelling was less than in the other group. This result was statistically significant and corresponds with those of Rana et al. [5] and Modabber et al. [6] and El-Karmi et al. [7]. Hilotherapy effectively normalizes local blood flow that regulates fluid extravasation, inflammatory reaction, pain, and the activation of the lymphatic system [17]. Rana et al. confirmed the superiority of hilotherapy over the traditional cooling with wet tissues [5]. The literature states the superiority of hilotherapy over conventional cooling regarding patient satisfaction [7, 29]. There were no inconvenience issues reported by our patients.

The central unit of the device allows a step-by-step adaptation of the cooling temperature, which allows patient-controlled cryotherapy and can lead to further reduction of drug usage and complications. This requires another clinical trial to confirm this.

Limitation of this study is its unblinded nature. However, the volume assessment is digitally performed; thus, the unblinded investigator plays no role in data quality. Patients know in which group they are and VAS is a subjective measure; at this point, there is no more bias seen than in other studies.

![Fig. 6](image-url)
Conclusion

Hilotherapy is a proven method in postoperative pain reduction. It is convenient enough for daily clinical use, clean, dry, and easy to apply. Both 18°C and 22°C are safe temperatures for hilotherapy. Cooling at 18°C provides better pain and swelling control over time.

Funding  Open Access funding enabled and organized by Projekt DEAL.

Declarations

Conflict of interest  The authors declare no competing interests.

Ethical approval  All procedures performed in studies involving human participants were in accordance with the ethical standards of the Declaration of Helsinki. The study has been approved by the Institutional Ethical Committee (No 2013-239-f-S).

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Phillips C, Blakey G, Jaskolka M (2008) Recovery After Orthognathic Surgery: Short-Term Health-Related Quality of Life Outcomes. J Oral Maxillofac Surg 66:2110–2115. https://doi.org/10.1016/j.joms.2008.06.080
2. Belli E, Rendine G, Mazzone N (2009) Cold Therapy in Maxillofacial Surgery. J Craniofac Surg 20:878–880. https://doi.org/10.1097/SCS.0b013e3181ba1a4d3d
3. Rana M, Gelrlich N-C, Ghassemi A, Gerressen M, Riediger D, Modabber A (2011) Three-Dimensional Evaluation of Postoperative Swelling After Third Molar Surgery Using 2 Different Cooling Therapy Methods: A Randomized Observer-Blind Prospective Study. J Oral Maxillofac Surg 69:2092–2098. https://doi.org/10.1016/j.joms.2010.12.038
4. Rana MW, Schröder J, Saygili E et al (2011) Comparative evaluation of the usability of 2 different methods to perform mild hypothermia in patients with out-of-hospital cardiac arrest. Int J Cardiol 152:321–326. https://doi.org/10.1016/j.ijcard.2010.07.026
5. Rana M, Gelrlich N-C, Joos U, Pifikko J, Kater W (2011) 3D evaluation of postoperative swelling using two different cooling methods following orthognathic surgery: a randomised observer blind prospective pilot study. Int J Oral Maxillofac Surg 40:690–696. https://doi.org/10.1016/j.ijoms.2011.02.015
6. Modabber A, Rana M, Ghassemi A, Gerressen M, Gelrlich NC, Hölzlze F, Rana M (2013) Three-dimensional evaluation of postoperative swelling in treatment of zygomatic bone fractures using two different cooling therapy methods: a randomized, observer-blind, prospective study. Trials 14:238. https://doi.org/10.1186/1745-6215-14-238
7. El-Karmi A, Hassfeld S, Bonitz L (2018) Development of swelling following orthognathic surgery at various cooling temperatures by means of hilotherapy--a clinical, prospective, monocentric, single-blinded, randomised study. J Cranio-Maxillofac Surg 46:1401–1407. https://doi.org/10.1016/j.jcms.2018.01.012
8. Seymour RA, Meechan JD, Blair GS (1985) An investigation into post-operative pain after third molar surgery under local analgesia. Br J Oral Maxillofac Surg 23:410–418. https://doi.org/10.1016/0266-4356(85)90025-7
9. Benetello V, Sakamoto FC, Giglio FPM, Sakai VT, Calvo AM, Modena KCS, Colombini BL, Dionisio TJ, Lauris JRP, Faria FAC, Santos CF (2007) The selective and non-selective cyclooxygenase inhibitors valdecoxb and piroxicam induce the same post-operative analgesia and control of trismus and swelling after lower third molar removal. Braz J Med Biol Res 40:1133–1140. https://doi.org/10.1590/S0100-879X20060005000123
10. Grossi GB, Maiorana C, Garramone RA, Borgonovo A, Beretta M, Farronato D, Santoro F (2007) Effect of Submucosal Injection of Dexamethasone on Postoperative Discomfort After Third Molar Surgery: A Prospective Study. J Oral Maxillofac Surg 65:2218–2226. https://doi.org/10.1016/j.joms.2006.11.036
11. Al-Khateeb TH, Nusair Y (2008) Effect of the proteolytic enzyme serrapeptase on swelling, pain and trismus after surgical extraction of mandibular third molars. Int J Oral Maxillofac Surg 37:264–268. https://doi.org/10.1016/j.ijoms.2007.11.011
12. Szolnoky G, Szent-Horváth K, Seres L et al (2007) Manual lymph drainage efficiently reduces postoperative facial swelling and discomfort after removal of impacted third molars. Lymphology 40:138–142
13. Piana LE, Garvey KD, Burns H, Matzkin EG (2018) The Cold, Hard Facts of Cryotherapy in Orthopedics. Am J Orthop 47. https://doi.org/10.12788/ajo.2018.0075
14. Fernandes IA, Armond ACV, Falci SGM (2019) The Effectiveness of the Cold Therapy (cryotherapy) in the Management of Inflammatory Parameters after Removal of Mandibular Third Molars: A Meta-Analysis. Int Arch Otorhinolaryngol 23:221–228. https://doi.org/10.1055/s-0039-1677755
15. Douglas WW, Malcolm JL (1955) The effect of localized cooling on conduction in cat nerves. J Physiol 130:53–71. https://doi.org/10.1113/jphysiol.1955.sp005392
16. Li C-L (1958) Effect of Cooling on Neuromuscular Transmission in the Rat. Am J Physiol-Leg Content 194:200–206. https://doi.org/10.1152/ajplegacy.1958.194.1.200
17. Eyrrich GKH, Haers PL, Sailer HF (1998) Adjuvante Kryotherapie nach maxillofacialen Operationen. Acta Med Dent Helv 93–99
18. Denny-Brown D, Adams RD, Brenner C, Doherty MM (1945) The pathology of injury to nerve induced by COLD1. J Neuropathol Exp Neurol 4:305–325. https://doi.org/10.1097/00000542-194504040-00001
19. Schaumburg H, Byck R, Herman R, Rosengart C (1967) Peripheral Nerve Damage by Cold. Arch Neurol 16:103–109. https://doi.org/10.1001/archneur.1967.00470190107013
20. Zemke JE, Andersen JC, Gyon WK, McMillan J, Joyner AB (1998) Intramuscular Temperature Responses in the Human Leg to Two Forms of Cryotherapy: Ice Massage and Ice Bag. J Orthop Sports Phys Ther 27:301–307. https://doi.org/10.2519/jospt.1998.27.4.301
21. de Jong RH, Henshey WN, Wagman IH (1966) Nerve Conduction Velocity During Hypothermia in Man. Anesthesiology 27:805–810. https://doi.org/10.1097/00000542-196611000-00013
22. Olson JE, Stravino VD (1972) A Review of Cryotherapy. Phys Ther 52:840–853. https://doi.org/10.1093/ptj/52.8.840
23. van der Westhuijzen AJ, Becker PJ, Morkel J, Roelse JA (2005) A randomized observer blind comparison of bilateral facial ice pack therapy with no ice therapy following third molar surgery. Int J Oral Maxillofac Surg 34:281–286. https://doi.org/10.1016/j.ijom.2004.05.006

24. Beech AN, Haworth S, Kneplil GJ (2018) Effect of a domiciliary facial cooling system on generic quality of life after removal of mandibular third molars. Br J Oral Maxillofac Surg 56:315–321. https://doi.org/10.1016/j.bjoms.2018.02.018

25. Lateef TA, AL-Anee AM, Agha MTF (2018) Evaluation the Efficacy of Hilotherm Cooling System in Reducing Postoperative Pain and Edema in Maxillofacial Traumatized Patients and Orthognathic Surgeries. J Craniofac Surg 29:e697–e706. https://doi.org/10.1097/SCS.0000000000004951

26. dos Santos KW, Rech RS, Wendland EMDR, Hilgert JB (2020) Rehabilitation strategies in maxillofacial trauma: systematic review and meta-analysis. Oral Maxillofac Surg 24:1–10. https://doi.org/10.1007/s10006-019-00808-8

27. Hanci D, Üstün O, Yılmazer AB, et al (2020) Evaluation of the Efficacy of Hilotherapy for Postoperative Edema, Ecchymosis, and Pain After Rhinoplasty. J Oral Maxillofac Surg S0278239120303268. https://doi.org/10.1016/j.joms.2020.03.032

28. Moro A, Gasparini G, Marianetti TM, Boniello R, Cervelli D, di Nardo F, Rinaldo F, Alimonti V, Pelo S (2011) Hilotherm Efficacy in Controlling Postoperative Facial Edema in Patients Treated for Maxillomandibular Malformations. J Craniofac Surg 22:2114–2117. https://doi.org/10.1097/SCS.0b013e31822e5e06

29. Bates AS, Kneplil GJ (2016) Systematic review and meta-analysis of the efficacy of hilotherapy following oral and maxillofacial surgery. Int J Oral Maxillofac Surg 45:110–117. https://doi.org/10.1016/j.ijom.2015.08.983

30. Pergola PE, Johnson JM, Kellogg DL, Kosiba WA (1996) Control of skin blood flow by whole body and local skin cooling in exercising humans. Am J Physiol-Heart Circ Physiol 270:H208–H215. https://doi.org/10.1152/ajpheart.1996.270.1.H208

31. Brown CM, Sanyo EO, Hilz MJ (2003) Effect of cold face stimulation on cerebral blood flow in humans. Brain Res Bull 61:81–86. https://doi.org/10.1016/S0361-9230(03)00065-0

32. Hall JE, Guyton AC (2016) Guyton and Hall textbook of medical physiology, 13th edn. Elsevier, Philadelphia

**Publisher's note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.
Terms and Conditions

Springer Nature journal content, brought to you courtesy of Springer Nature Customer Service Center GmbH (“Springer Nature”). Springer Nature supports a reasonable amount of sharing of research papers by authors, subscribers and authorised users (“Users”), for small-scale personal, non-commercial use provided that all copyright, trade and service marks and other proprietary notices are maintained. By accessing, sharing, receiving or otherwise using the Springer Nature journal content you agree to these terms of use (“Terms”). For these purposes, Springer Nature considers academic use (by researchers and students) to be non-commercial. These Terms are supplementary and will apply in addition to any applicable website terms and conditions, a relevant site licence or a personal subscription. These Terms will prevail over any conflict or ambiguity with regards to the relevant terms, a site licence or a personal subscription (to the extent of the conflict or ambiguity only). For Creative Commons-licensed articles, the terms of the Creative Commons license used will apply.

We collect and use personal data to provide access to the Springer Nature journal content. We may also use these personal data internally within ResearchGate and Springer Nature and as agreed share it, in an anonymised way, for purposes of tracking, analysis and reporting. We will not otherwise disclose your personal data outside the ResearchGate or the Springer Nature group of companies unless we have your permission as detailed in the Privacy Policy.

While Users may use the Springer Nature journal content for small scale, personal non-commercial use, it is important to note that Users may not:

1. use such content for the purpose of providing other users with access on a regular or large scale basis or as a means to circumvent access control;
2. use such content where to do so would be considered a criminal or statutory offence in any jurisdiction, or gives rise to civil liability, or is otherwise unlawful;
3. falsely or misleadingly imply or suggest endorsement, approval, sponsorship, or association unless explicitly agreed to by Springer Nature in writing;
4. use bots or other automated methods to access the content or redirect messages
5. override any security feature or exclusionary protocol; or
6. share the content in order to create substitute for Springer Nature products or services or a systematic database of Springer Nature journal content.

In line with the restriction against commercial use, Springer Nature does not permit the creation of a product or service that creates revenue, royalties, rent or income from our content or its inclusion as part of a paid for service or for other commercial gain. Springer Nature journal content cannot be used for inter-library loans and librarians may not upload Springer Nature journal content on a large scale into their, or any other, institutional repository.

These terms of use are reviewed regularly and may be amended at any time. Springer Nature is not obligated to publish any information or content on this website and may remove it or features or functionality at our sole discretion, at any time with or without notice. Springer Nature may revoke this licence to you at any time and remove access to any copies of the Springer Nature journal content which have been saved.

To the fullest extent permitted by law, Springer Nature makes no warranties, representations or guarantees to Users, either express or implied with respect to the Springer nature journal content and all parties disclaim and waive any implied warranties or warranties imposed by law, including merchantability or fitness for any particular purpose.

Please note that these rights do not automatically extend to content, data or other material published by Springer Nature that may be licensed from third parties.

If you would like to use or distribute our Springer Nature journal content to a wider audience or on a regular basis or in any other manner not expressly permitted by these Terms, please contact Springer Nature at

onlineservice@springernature.com