

Case-Control Study

Dynamic Pressure Pain Hypersensitivity as Assessed by Roller Pressure Algometry in Episodic Cluster Headache

María Palacios-Ceña, PT, PhD^{1,2}, Víctor Gómez-Mayordomo, MD³, David García-Azorín, MD⁴, Nuria González-García, MD³, María L. Cuadrado, MD, PhD^{3,5}, César Fernández-de-las-Peñas, PT, PhD, Dr Med Sci², Lars Arendt-Nielsen, PhD, Dr Med Sci², and Ángel L. Guerrero, MD, PhD^{4,6}

From: ¹Department of Physical Therapy, Occupational Therapy, Physical Medicine and Rehabilitation, Universidad Rey Juan Carlos, Alcorcón, Spain; ²Center for Sensory-Motor Interaction (SMI), Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Aalborg, Denmark; ³Department of Neurology, Hospital Clínico San Carlos, Madrid, Spain; ⁴Headache Unit, Hospital Clínico Universitario de Valladolid, Valladolid, Spain; ⁵Department of Medicine, School of Medicine, Universidad Complutense de Madrid, Madrid, Spain; ⁶Institute for Biomedical Research of Salamanca (IBSAL), Salamanca, Spain

Address Correspondence:
César Fernández-de-las-Peñas, PT, PhD, Dr Med Sci
Facultad de Ciencias de la Salud
Universidad Rey Juan Carlos
Avenida de Atenas s/
28922 Alcorcón, Madrid, Spain
E-mail: cesar.fernandez@urjc.es

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Background: A method for assessing dynamic muscle hyperalgesia (dynamic pressure algometry) has been developed and applied in tension-type and migraine headaches.

Objectives: To investigate differences in dynamic pressure pain assessment over the trigeminal area between men with cluster headache (CH) and headache-free controls, and the association between dynamic and static pressure pain sensitivity.

Study Design: A case-control study.

Setting: Tertiary urban hospital.

Methods: Forty men with episodic CH and 40 matched controls participated. Dynamic pressure pain sensitivity was assessed with a dynamic pressure algometry set consisting of 8 rollers with different fixed levels (500, 700, 850, 1,350, 1,550, 2,200, 3,850, and 5,300 g). Each roller was moved at a speed of 0.5 cm/sec over a diagonal line covering the temporalis muscle from an anterior to posterior direction. The dynamic pressure threshold (DPT; load level of the first painful roller) and the pain intensity perceived at the DPT level (roller-evoked pain) were assessed. Static pressure pain thresholds (PPT) were also assessed with a digital pressure algometer applied statically over the mid-muscle belly of the temporalis. Patients were assessed in a remission phase, at least 3 months from the last cluster attack, and without preventive medication.

Results: Side-to-side consistency between DPTs ($r = 0.781$, $P < 0.001$), roller-evoked pain on DPT ($r = 0.586$; $P < 0.001$), and PPTs ($r = 0.874$; $P < 0.001$) were found in men with CH. DPT was moderately, bilaterally, and side-to-side associated with PPTs ($0.663 > r > 0.793$, all $P < 0.001$). Men with CH had bilateral lower DPT and PPT and reported higher levels of roller-evoked pain (all $P < 0.001$) than headache-free controls.

Limitations: Only men with episodic CH were included.

Conclusions: This study supports that a dynamic pressure algometry is as valid as a static pressure algometry for assessing pressure pain sensitivity in patients with CH. Assessing both dynamic and static pain sensitivity may provide new opportunities for differentiated diagnostics.

Key words: Cluster headache, dynamic pressure pain, pressure pain threshold

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Cluster headache (CH) is a primary headache disorder, classified as a trigeminal autonomic cephalalgia with a lifetime prevalence of 124 per 100,000, and a 1-year prevalence of 53 per 100,000 (1). Current underlying theories for CH support a role of the posterior hypothalamus, the activation of the trigeminovascular system, and the presence of sensitization (2). One of the most common manifestations of generalized sensitization is the presence of hyperalgesia and allodynia at different locations. The most common tool for assessing sensitivity to pressure pain is static pressure algometry. There is preliminary evidence suggesting the presence of pressure pain hyperalgesia, by using algometry, in patients with CH (3-5). Nevertheless, these studies included small sample sizes and a mix of men and women with episodic or chronic CH (3-5). Additionally, pressure algometry is statically applied to a localized spot representing a static outcome of nociception in a focal point.

Another important feature of central sensitization in, for example, neuropathic pain, is the presence of cutaneous allodynia, which can be statically or dynamically assessed. For instance, dynamic stroking over the skin, for example, by a brush, is used to assess dynamic cutaneous allodynia, which cannot be assessed by a static stimulus applied on a specific point. Current data related to the presence of cutaneous allodynia in CH are inconclusive (6). Two studies have reported the presence of mechanical brush allodynia in approximately 40% to 50% of patients with CH (7,8). However, another study has failed to identify the presence of cutaneous allodynia in CH (9). A recent population-based study has identified, by using the Allodynia Symptom Checklist, that 36% of patients with CH reported cutaneous allodynia during attacks (10).

It is important to note that quantitative sensory testing proposed by the German Research Network on Neuropathic Pain usually includes both static hypersensitivity (e.g., pinprick) and dynamic allodynia (brushing the skin) (11). No particular quantitative sensory testing is proposed for assessing deep dynamic pressure pain sensitivity in this protocol. It is possible that dynamic mechanical deep tissue pain sensitivity could provide different information to static pressure pain sensitivity. For that purpose, a novel equipment, the dynamic deep somatic pressure algometer, was developed to apply quantifiable dynamic pressure to deep musculoskeletal structures in a standardized way (12). Finocchietti et al (12) demonstrated that roller pressure algometry was

an easy-to-use and reliable tool for quantitative assessing of spatial muscle hyperalgesia. The roller algometer has been recently used for better understanding of nociceptive processing in primary headaches, such as migraine (13) and tension-type headache (14). Both studies observed that dynamic pressure sensitivity in the temporalis muscle was associated to widespread pressure pain sensitivity (13,14). In addition, roller, but not static, pressure pain sensitivity was able to differentiate between episodic and chronic migraine (13), supporting its potential use in this primary headache.

To our knowledge, no previous study has investigated dynamic pressure algometry in patients with CH. To explore the validity of roller pressure algometry in a trigeminal autonomic cephalalgia, the present study aimed to investigate the presence of dynamic pressure hyperalgesia in CH. The specific aims of this study were to assess (1) differences in dynamic pressure sensitivity over the trigeminal area between patients with episodic CH and headache-free controls; (2) the association between dynamic pressure algometry and the clinical features of headache; and (3) the association between dynamic pressure algometry and static pressure pain algometry, over the trigeminal region in patients with CH. Given that CH shows a clear male predominance (15), and that sensitivity to pressure is gender-dependent with women usually exhibiting lower thresholds than men (16), we decided to include only men with episodic CH.

METHODS

Patients

Consecutive patients suffering from CH who attended a regular neurologist clinic between July 2018 and March 2019 were screened for eligible inclusion criteria. To be eligible, patients had to meet the diagnostic criteria of episodic CH according to the International Classification of Headache Disorders, third edition (17). Patients should have strictly unilateral pain attacks, without attacks on the contralateral side. Clinical data (e.g., time since CH onset, number of cluster periods per year, time from the last cluster period, symptomatic side in the last cluster period and in previous cluster periods, intensity and duration of headache episodes, medication used, and time without medication) were obtained through a standardized interview. All patients had normal neurologic and ophthalmologic examinations, as well as normal brain magnetic resonance imaging. They were excluded if they presented (1) age younger

than 18 or older than 65 years; (2) concomitant diagnosis of another primary or secondary headache; (3) chronic CH at the time of the study; (4) any peripheral neuropathy or another neurologic disease; (5) diagnosis of medical systemic disease (e.g., systemic lupus erythematosus or rheumatoid arthritis); (6) previous head or neck trauma (whiplash); (7) previous head or neck surgery; or (8) any concomitant painful disorder needing regular medication intake. To be part of the control group, age- and gender-matched patients without history of headache and without pain symptoms during the previous 6 months were recruited from volunteers who responded to local announcements.

Patients read and signed a written consent form prior to their participation. The ethics committees of Hospital Clínico San Carlos of Madrid (code 17/513-E) and Hospital Clínico Universitario of Valladolid (code PI 17-875) approved the study.

Patients attended a preliminary session for familiarization with the test procedure. In patients with CH, the evaluation was held in a remission phase, defined when no attack had occurred for at least 3 months, to avoid headache-related allodynia. Preventive medication or abortive drugs were discontinued at least 1 month before the assessment. No analgesic or muscle relaxation drugs were allowed in any patient at least 48 hours before testing. Outcomes were evaluated by an assessor blinded to the patient's condition.

Dynamic Pressure Pain Algometry

A roller pressure algometer (Aalborg University, Aalborg, Denmark) was used to evaluate dynamic pressure sensitivity. The roller pressure algometer consists of a wheel through which the clinician could apply 11 different rollers, each with a fixed load level of 500, 700, 850, 1,350, 1,550, 2,200, 2,500, 3,100, 3,500, 3,850, and 5,300 g controlled by springs. The wheel has a diameter of 35 mm and a width of 10 mm made of hard plastic. The assessor maintains a constant pressure while the roller is moving at a speed of approximately 0.5 cm/sec. The track of

the roller was approximately 60 mm crossing over the temporalis muscle from anterior to posterior, with a total dynamically stimulated area of 10*60 mm (Fig. 1), as previously described (13,14). Two repetitions were conducted on each side of the head, and the mean was calculated for the analysis. The second stimulation on the same side was applied when the pain provoked by the first stimulation disappeared.

The load level of the roller in which the dynamic pressure stimuli was first perceived as painful was defined as the dynamic pressure threshold (DPT). Patients were asked to rate the pain intensity perceived at the DPT level (roller-evoked pain) while the roller was moving over the temporalis muscle on a 10-point numerical pain rate scale (NPRS; 0: no pain, 10: maximum pain). These outcomes have shown good reliability in both DPT and pain ratings with intraclass correlation coefficients (ICC) ranging from 0.75 to 0.88 (12).

Static Pressure Pain Algometry

Static pressure pain thresholds (PPTs), that is, the pressure in which a sensation of static pressure changes to pain, were bilaterally assessed with a handheld electronic pressure algometer (Somedic AB, Farsta, Sweden) over the center of the temporalis muscle belly. Patients were instructed to press the algometer "stop-button" as soon as the pressure resulted in the first sensation of pain. Pressure was approximately increased at a rate of 30 kPa/s. The order of assessment was randomized between patients. The mean of 2 trials on each side, with a 30-second resting period for avoiding temporal summation of pain (18), was calculated and used for the analyses. The reliability of pressure algometry has previously been found to be high (19,20).

Sample Size Calculation

The sample size was calculated with an appropriate software

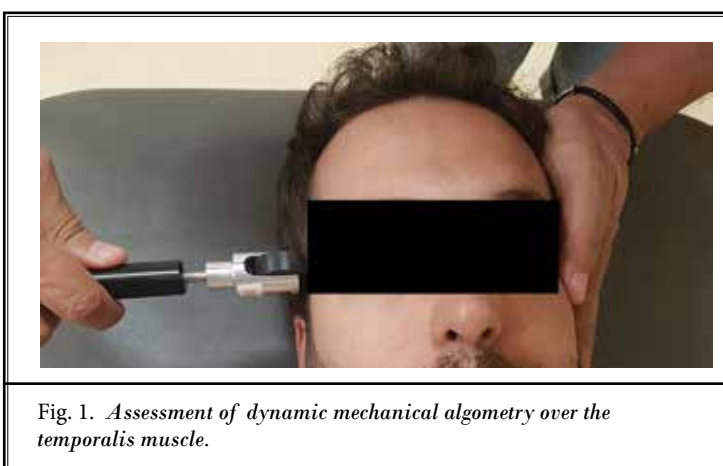


Fig. 1. Assessment of dynamic mechanical algometry over the temporalis muscle.

(Tamaño de la Muestra 1.1, Barcelona, Spain). Sample size determination and calculations were based on detecting a moderate-large effect size of 0.75 between patients and controls, a 2-tailed test, with an alpha level (α) of 0.05, and a desired power (β) of 90%. This generated a sample size of at least 30 patients per group.

Statistical Analysis

Data were analyzed with the SPSS statistical package Version 22.0 (IBM Corporation, Armonk, NY). The Kolmogorov-Smirnov test revealed that all quantitative data had a normal distribution ($P > 0.05$). Descriptive data are expressed as means with their 95% confidence intervals. Inferential statistics included several types of analysis. First, several Pearson correlation tests (r) were used to determine side-to-side consistency of PPTs, DPTs, and evoked pain during DPTs. Correlations were conducted separately for patients with CH and controls. Correlations were considered weak when $r < 0.3$, moderate when $0.3 < r < 0.7$, and strong when $r > 0.7$ (21). Second, Pearson correlation tests (r) were also used to evaluate the associations between clinical variables relating to CH with DPTs, roller-evoked pain DPT, and PPTs. Third, differences in DPTs, roller-evoked pain during DPT and PPTs between patients with CH and headache-free controls were assessed with a 2-way analysis of variance (ANOVA). In general, a P value < 0.05 was considered significant for the main correlational analysis, but for multiple between-groups comparisons a Bonferroni adjustment of 0.017 (3 comparisons) was applied.

RESULTS

Clinical Data of the Sample

Fifty patients with CH were screened for eligible criteria. Ten (20%) patients were excluded for the following reasons: chronic CH ($n = 4$), concomitant migraine ($n = 3$), and active cluster period ($n = 3$). Finally, 40 men with episodic CH (mean age, 42 ± 5 years) and 40 age-matched men without history of headache as controls (mean age, 41 ± 4 years) were included. Table 1 shows the demographic and clinical features of both groups.

Consistency of Roller Pressure Algometer

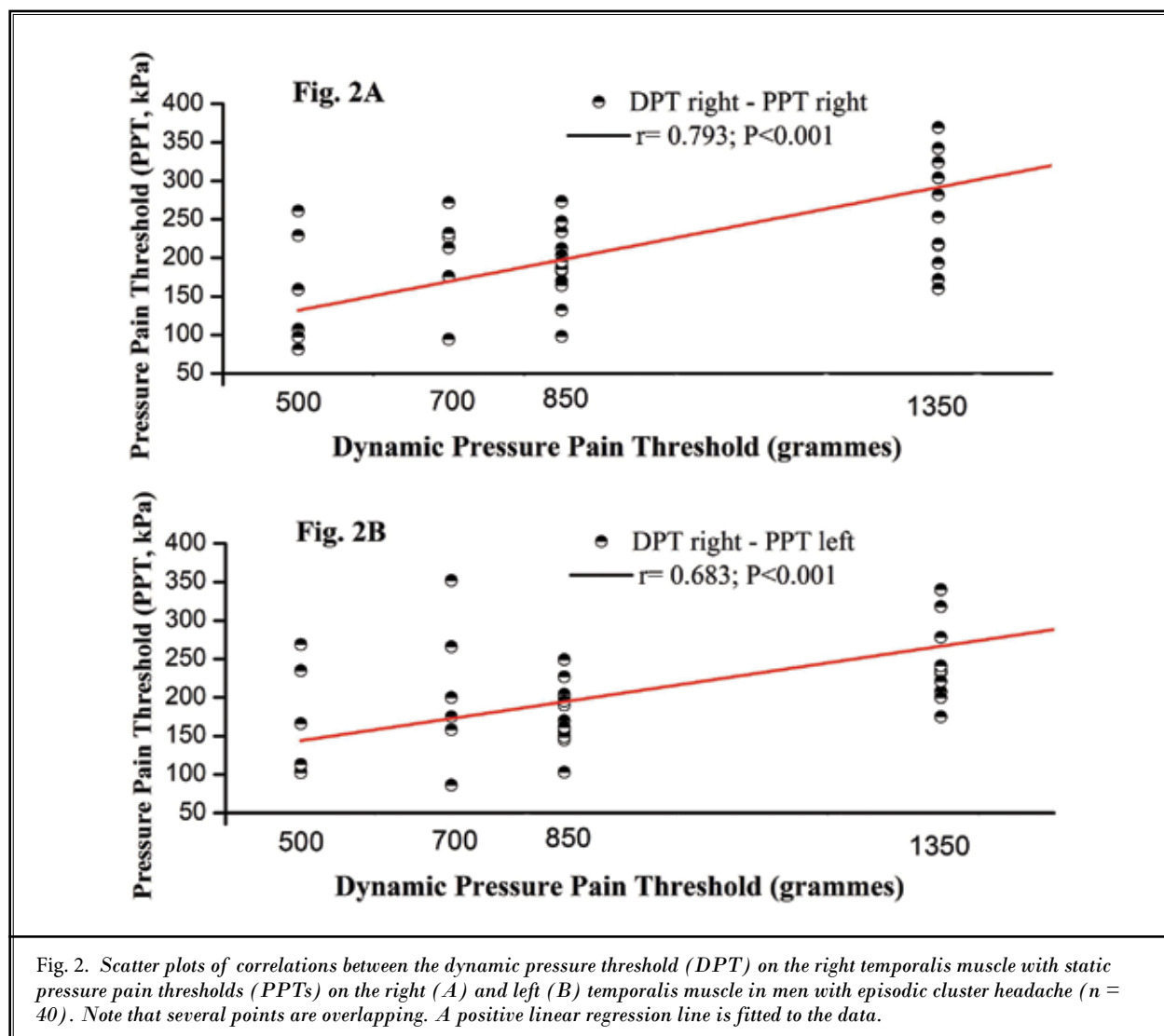
Strong significant side-to-side associations between DPTs were observed in both patients with CH ($r = 0.781$; $P < 0.001$) and headache-free controls ($r = 0.721$; $P < 0.001$) supporting side-to-side consistency of DPTs. Additionally, moderate side-to-side associations were found for evoked pain during DPT in patients with CH ($r = 0.586$; $P < 0.001$) and controls ($r = 0.453$; $P < 0.01$). Finally, DPT was negatively associated with roller-evoked pain during DPT in headache-free controls (dominant side: $r = -0.322$, $P = 0.040$; nondominant side: $r = -0.361$; $P = 0.035$), but not in patients with CH (both $P > 0.65$).

Similarly, consistent side-to-side associations between PPTs were found in both study groups (patients with CH: $r = 0.874$, $P < 0.001$; headache-free controls: $r = 0.808$, $P < 0.001$).

Table 1. Demographic and clinical variables of patients with episodic cluster headache and healthy controls.

	Cluster Headache (n = 40)	Healthy Controls (n = 40)
Age (years)	42.0 (39.0, 45.0)	41.0 (38.0, 44.0)
Symptomatic side (left/right)	19 (45%) / 21 (55%)	-----
Headache history (years)	13 (9.5, 16.5)	-----
Cluster periods per year	2.0 (1.5, 2.5)	-----
Duration of the cluster period (months)	1.7 (1.2, 2.2)	-----
Number of attacks per day during cluster period	2.0 (1.4, 2.6)	-----
Mean Pain Intensity per attack (NPRS, 0-10)	9.3 (9.0, 9.6)	-----
Duration of each attack (minutes)	65.0 (40.0, 90.0)	-----
Time from the last cluster period (months)	9.9 (7.2, 11.6)	-----
Time without taking medication (months)	9.0 (7.0, 11.0)	-----

Significant differences between patients and controls (ANCOVA test, $P < 0.001$)



DPT and Headache Features

No significant associations were detected between DPT or roller-evoked pain during DPT and the clinical features of headache (all $P > 0.165$).

Dynamic and Static Pressure Algometry

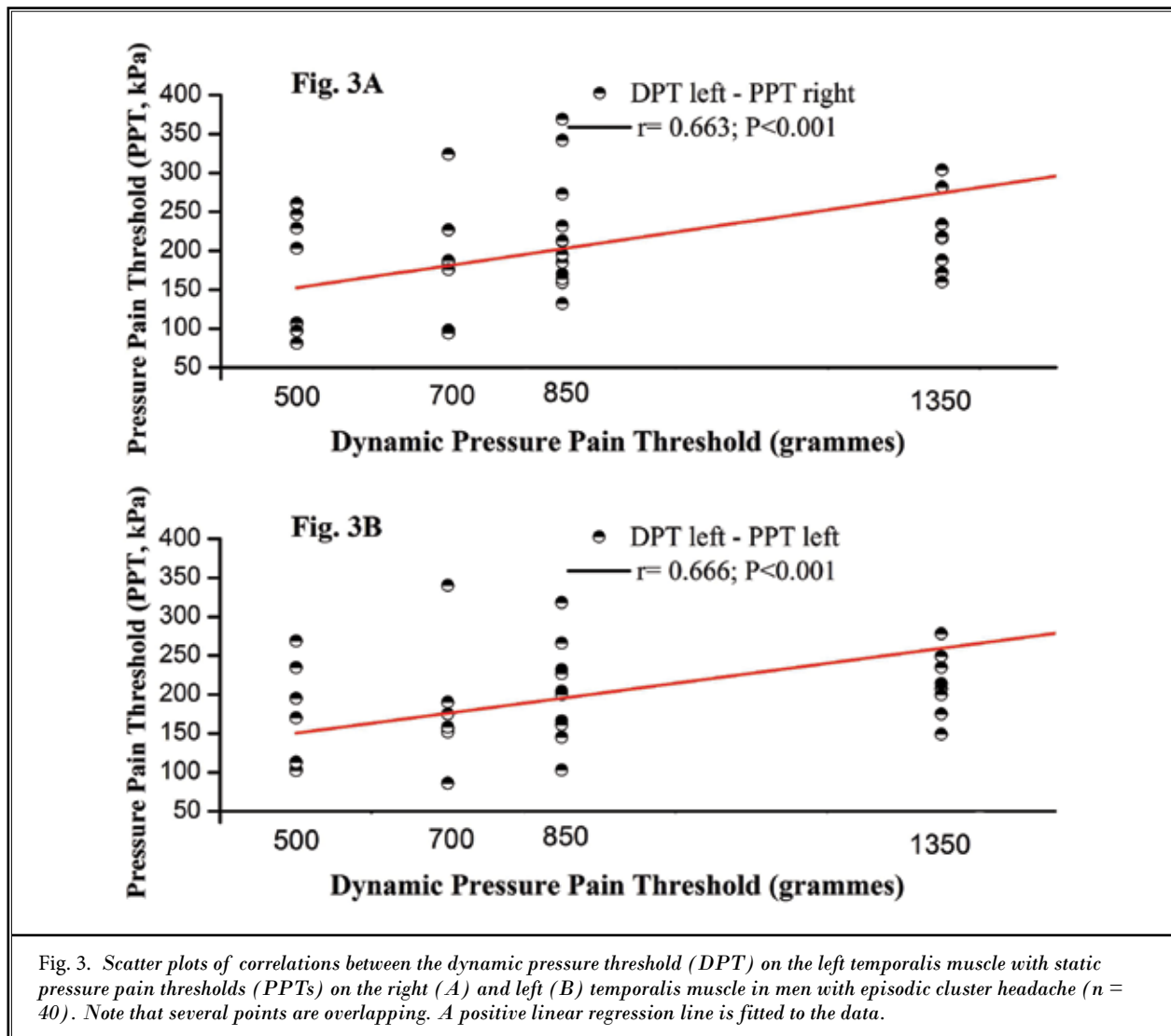
Dynamic and static pressure sensitivity were moderately associated because DPT on each side was associated with PPTs on both sides: DPT right side–PPT right ($r = 0.793$, $P < 0.001$; Fig. 2A) and left ($r = 0.683$, $P < 0.001$; Fig. 2B); DPT left side–PPT right ($r = 0.663$, $P < 0.001$; Fig. 3A) and left ($r = 0.666$, $P < 0.001$; Fig. 3B) sides.

No significant association between roller-evoked

pain during DPT and PPTs on the temporalis muscle were observed (all $P > 0.175$).

Dynamic Pressure Pain Hypersensitivity in CH

The ANOVA revealed significant differences between groups, but not between sides, for DPTs (group: $F = 63.488$, $P < 0.001$; side: $F = 0.003$, $P = 0.957$) and PPTs (group: $F = 37.406$, $P < 0.001$; side: $F = 0.899$, $P = 0.345$) patients with CH exhibited bilateral dynamic and static pressure pain hyperalgesia to a larger extent than headache-free controls. In addition, significant differences between groups, but not between sides, were also found for roller-evoked



pain on DPT (group: $F = 40.209$, $P < 0.001$; side: $F = 0.707$, $P = 0.403$) patients with CH reported higher levels of roller-evoked pain than headache-free controls (Table 5).

DISCUSSION

This study supports the use of dynamic pressure algometry as a tool for assessing somatic tissue pain sensitivity within the trigeminal area in patients with CH. Dynamic algometry outcomes, that is, DPT and roller-evoked pain, showed side-to-side consistency and moderate associations with PPTs. Men with CH exhibited dynamic and static pressure hypersensitivity, that is,

lower DPTs and PPTs, in the trigeminal area compared with headache-free controls.

Current quantitative sensory testing guidelines include the assessment of static and dynamic mechanical allodynia and assessment of mechanical cutaneous sensitivity, which are primarily developed for assessing loss and gain of function in neuropathic pain (11). However, no testing has been proposed for assessing dynamic deep somatic tissue pain sensitivity. The dynamic pressure algometer, as used in the present study, was created to quantify the dynamic sensitivity to deep tissue pain (12). In the current study, DPT (i.e., the lowest roller force felt as first painful) was defined

Dynamic Pain Sensitivity in Cluster Headache

Table 2. Differences in dynamic and static pressure pain sensitivity between men with episodic cluster headache and healthy controls.

	DPT (grams) Temporalis Muscle #	Roller (NPRS, 0-10) evoked pain during DPT#	PPT (kPa) Temporalis Muscle #
Episodic Cluster Headache (n = 40)			
Symptomatic Side	1004.0 (845.0, 1163.0)	3.1 (2.7, 3.5)	217.0 (188.0, 246.0)
Non-Symptomatic Side	1017.0 (860.0, 1174.0)	2.8 (2.3, 3.2)	226.5 (198.0, 255.0)
Healthy Controls (n = 40)			
Dominant side	2039.0 (1880.0, 2198.0)	1.5 (1.1, 1.9)	320.0 (291.0, 349.0)
Non-Dominant side	2033.0 (1875.0, 2191.0)	1.6 (1.2, 2.0)	302.0 (273.0, 331.0)

Values (kPa) are expressed as means (95% confidence intervals)

Significant differences between patients and controls (ANOVA test, $P < 0.001$)

following similar criteria to those established for PPT (i.e., the lowest pressure perceived as first painful). Both definitions are based on the pressure perceived as painful, but it should be considered that PPT is a static measure on a particular point, whereas DPT is a dynamic measure covering a larger stimulated area. It is possible that dynamic pressure sensitivity may provide additional information related to different underlying pain mechanisms, such as the stimulation of different nociceptors or activation of different neural networks. These differences would be analogous to those between static and dynamic assessment of mechanical cutaneous allodynia (22). Moreover, dynamic pressure algometry makes it possible to evaluate pressure pain sensitivity of a large surface in a relatively short time. Topographical pressure sensitivity maps have outlined the spatial heterogeneity of pressure pain sensitivity in different pain conditions. Yet these maps have been created from multiple measurements of static PPTs made at different points (23). Dynamic pressure algometry may help to analyze pain sensitivity in just one examination over a large surface, and not just on a single point, thus being less time-consuming.

Our study showed a clear side-to-side consistency for DPTs and roller-evoked pain during DPT, supporting the consistency of roller pressure algometry. In fact, strong side-to-side consistency usually predicts high reliability for a quantitative sensory outcome (24). In line with this hypothesis, Finocchietti et al (12) reported high reliability (ICC > 0.88) of DPT. Additionally, DPTs were moderately to strongly associated bilaterally with PPTs over the temporalis muscle, supporting that both static and dynamic pressure pain sensitivity outcomes are also consistent between them. Further studies investigating the association between dynamic and static

pressure pain sensitivity in different body areas are needed.

Previous studies reported that dynamic pressure pain sensitivity was correlated with widespread pressure hypersensitivity in women with migraine and tension-type headache (13,14), but no comparison with a control group was conducted. The current study is the first one, to our knowledge, comparing the presence of dynamic pressure pain hypersensitivity in patients with headache suffering from a primary headache and headache-free controls. We observed that men with episodic CH exhibited both dynamic and static pressure pain hyperalgesia, that is, lower DPT and PPT, over the temporalis area bilaterally as compared with headache-free controls. These findings agree with those of 2 previous studies also reporting bilateral lower PPT in the temporalis area in CH (4,5). However, they are in contrast with another study showing side-to-side differences (3). It is important to note that this last study included patients with CH within the symptomatic phase, so the influence of lateralized pain-related allodynia in the active cluster period cannot be ruled out. In our study, individuals with CH exhibited dynamic and static pressure pain hyperalgesia during a remission phase, suggesting that trigeminal sensitization is present, albeit they did not suffer from any headache attack.

The presence of bilateral pressure pain hypersensitivity in patients with strictly unilateral headache is consistent with generalized trigeminal sensitization and could be attributable to plastic changes in central pain pathways induced by repetitive CH attacks during the active cluster periods. Additionally, current evidence supports a fundamental role of the hypothalamic region in the pathogenesis of CH because of its connections with other regions involved in descending

pain modulation (2). Therefore bilateral decreases in dynamic or static pain thresholds observed in individuals with strictly unilateral CH during remission is in line with a background disturbance of the hypothalamic pain control system. Nevertheless, it should be noted that decreased pain thresholds over the temporalis area is a common finding observed in other primary headaches, for example, migraine or tension-type headache (25). Yet the current study is the first one, to our knowledge, providing evidence of dynamic hypersensitivity to pressure pain in a trigeminal autonomic cephalgia.

Finally, we did not find any association between dynamic and static pressure pain outcomes and the clinical features of the headache. Our findings agree with previous evidence supporting that pain and disability do not exhibit a clear association with PPTs, at least not in spinal pain disorders (25). Therefore it is possible that dynamic and static pressure pain sensitivity assess complementary aspects of the headache spectrum. Because the current study demonstrated the presence of dynamic pressure pain hyperalgesia in patients with CH, it would be interesting to investigate if this dynamic pressure hyperalgesia is associated with a decreased response to treatment, as it has been previously suggested for cutaneous allodynia in patients with migraine (26). Pain threshold measurements cannot be recommended as clinical diagnostic tests in CH or other headaches (27), but they might provide a tool for assessing central sensitization and treatment effects.

Some limitations of the current study should be recognized. First, we only included men with episodic CH during remission; therefore we do not know if women with CH or patients with active or chronic CH would exhibit similar results. Because women exhibit less efficient pain habituation, greater susceptibility to pressure excitability, and less efficient inhibitory pathways than men (16), it is possible that our results would be more pronounced in women with CH. In future studies, it would be interesting to investigate gender differences or differences between the different forms and stages of the disease. Second, the role of psycho-

logical variables, such as anxiety, depression, or sleep disturbances, which may potentially influence pressure pain sensitivity, were not included in our study. Third, the cross-sectional nature of the study design does not permit to determine a cause and effect relationship between dynamic pressure pain hyperalgesia and CH and the clinical relevance of this outcome. Future studies are needed to determine the clinical relevance of dynamic algometry in primary headaches, including CH.

CONCLUSIONS

The current study describes dynamic pressure algometry as a new tool for assessing dynamic pressure pain sensitivity in the trigeminal area in men with CH. Dynamically, roller-evoked pain showed side-to-side consistency and also a moderate association with PPTs. Men with CH exhibited stronger dynamic and static pressure pain hypersensitivity, that is, lower DPTs and PPTs, as compared with headache-free controls. Dynamic deep somatic tissue algometry may provide new opportunities for investigating the pathophysiological mechanisms involved in primary headaches and for assessing treatment effects.

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Author contributions: All authors contributed to the study concept and design. VGM and ALG did the statistical analysis. MLC, CFdIP, LAN, and ALG contributed to analysis and interpretation of data. CFdIP and LAN contributed to drafting of the article. LAN and ALG provided administrative, technical, and material support. LAN, MLC, and ALG supervised the study. All authors revised the text for intellectual content and have read and approved the final version of the manuscript. CFdIP had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses. All data generated or analyzed during this study are included in this published article.

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