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Abstract

Objective: To investigate differences in clinical, psychological and psychophysical outcomes according to use of prophylactic medication (amitriptyline) in tension type headache (TTH). **Methods**: One hundred and seventy-three (n=173) individuals with TTH participated. Headache features and symptomatic medication intake were collected with a 4-weeks headache diary at baseline and at 6-months. Burden of headache (Headache Disability Inventory-HDI), sleep quality (Pittsburgh Sleep Quality Index-PSQI), anxiety/depression (Hospital Anxiety and Depression Scale-HADS), and trait/state anxiety levels (State-Trait Anxiety Inventory-STAI) were also assessed at baseline. Pressure pain thresholds (PPT) were assessed over the temporalis, C5-C6 joint, second metacarpal, and tibialis anterior at baseline. Differences between subjects taking or not taking prophylactic medication based on self-perceived effectiveness of the medication on headache characteristics were assessed. **Results**: Forty-nine (28%) reported taking prophylactic medication for the headaches (amitriptyline: 100%). From these, eleven (23%) reported no effect, 25 (51%) reported moderate effect and 13 (26%) reported positive effect with medication. Patients taking prophylactic medication had longer headache history, higher frequency of headaches (61% CTTH), higher headache burden, worse quality of sleep, and higher depression than those not taking medication. Prophylactic medication was less effective in patients with generalized pressure pain hyperalgesia. No other significant differences were found. **Conclusions:** Prophylactic medication is used by TTH patients with higher headache frequency, higher headache burden, worse sleep quality, and higher depression. Lower effectiveness of prophylactic amitriptyline was associated with widespread pain hyperalgesia.

Keywords: tension type headache; medication intake; amitriptyline, pressure pain.

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Introduction

Tension type headache (TTH) is a pain disorder with a prevalence of 42% in the general population.[1] In the last Global Burden of Disease Study, headache (mostly TTH and migraine) was found to be the second most prevalent chronic pain condition in the world.[2] Tension type headache has an important socio-economic impact for the society with a reported cost of $21 billion annually, from which 92% were indirect costs.[3]

Pharmacological treatment of patients with TTH includes symptomatic (acute) and prophylactic medication. Symptomatic (acute) medication refers to treatment of a single headache and it is usually considered as over-the counted drug medication. Prophylactic medication refers to treatment used, and generally maintained for several weeks/months, for preventing headache attacks. The clinical practice guideline of European Federation of Neurological Societies recommends amitriptyline as the first-line prophylactic drug for patients with TTH exhibiting high frequency of headaches, i.e., chronic tension type headache (CTTH), but also in individuals with episodic tension type headache with high frequency of headaches, i.e., frequent episodic tension type headache (FETTH).[4] In fact, this recommendation is supported by available data. For instance, a recent meta-analysis has found high-quality evidence suggesting that tricyclic antidepressants (amitriptyline dose 50 to 150 mg) are superior to placebo for reducing headache frequency and the number of analgesic tablets consumed in patients with CTTH;[5] nevertheless, showing greater adverse effects.[6]

Although the mechanisms underlying TTH are not completely understood, current evidence supports that a hyper-excitability of the central nervous system may be one factor involved in the development of TTH.[7] In fact, current theories include associated factors such as anxiety/depression,[8] sleep disturbances,[9] and emotional stress[10] in this

process of central sensitization. No study has previously investigated if these variables are associated to prophylactic medication intake in subjects TTH with high frequency of headaches. Interestingly, practice guidelines suggest a patient-centered approach when deciding whether to start prophylactic medication;[11] however, many patients who could benefit from prophylactic treatment are not receiving it.[12] A recent systematic review found moderate-quality evidence indicating that depression, anxiety, poor sleep, stress, and poor self-efficacy for managing pain were potential prognostic factors for unfavorable outcomes from prophylactic treatment in chronic headaches.[13] Therefore, better understanding of those variables associated to prophylactic medication intake could help to better identify critical areas for medication treatment of TTH. The aim of this longitudinal study was to investigate differences in clinical, psychological and pain sensitivity outcomes related to prophylactic medication intake in patients with TTH. We hypothesized that individuals with TTH: 1) taking prophylactic amitriptyline medication will exhibit better clinical, psychological and psychophysical outcomes at 6 months follow-up than those not taking prophylactic medication; and, 2) in whom prophylactic medication was more effective exhibit better clinical, psychological and psychophysical outcomes than those in whom prophylactic medication was not effective.

Methods

Participants

Patients with a diagnosis of TTH were recruited from three different university-based hospitals (University Rey Juan Carlos, Aalborg University, Urbino University) from September 2014 to January 2017. Participants were diagnosed following the last criteria of the International Classification of Headache Disorders, (ICHD3 beta, 2013) by a neurologist expert in headaches.[14] Participants were excluded if presented: 1, other primary and/or secondary headache; 2, medication overuse headache as defined by the

ICHD-III; 3, history of neck or head trauma; 4, any systemic degenerative disease; 5, diagnosis of fibromyalgia syndrome; 6, received anesthetic blocks or botulinum toxin the previous 6 months; 7, received physical treatment in the neck or head the previous 6 months; or, 8, pregnancy. All participants read and signed a consent form prior to their participation. The local Ethics Committee approved the study desing (URJC 23/2014, HUFA 14/104, Aalborg N20140063, CESU 5/2015).

Headache Diary

A headache diary for 4 weeks was used to record the headache clinical features and to monitor preventive medication intake.[15] This diary was recorded at baseline and at 6-months follow-up. Patients registered the frequency of headaches (days per week), the intensity of the headache attacks on an 11-points numerical pain rate scale[16] (NPRS; 0: no pain, 10: the maximum pain), and the duration of each attack (hours per day). All patients registered in the diary any change in their preventive medication under their neurologist supervision and self-perceived effectiveness of prophylactic medication (no effect, moderate, or positive) based on a decrease of 30% on headache frequency.[17]

Sleep Quality

The Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality over the previous month by including 19 self-reported questions and 5 questions answered by bed- or room-mates.[18] The total score ranges from 0 to 21 where higher score indicates worse sleep quality. This questionnaire has shown good internal consistency and test-retest reliability.[19] Sleep quality was assessed at baseline.

Anxiety and Depressive Symptoms

The Hospital Anxiety and Depression Scale (HADS) is a 14-items self-report screening scale indicating the presence of anxiety (7 items, HADS-A) and depression (7

items, HADS-D).[20] Each item scores on a Likert scale (0-3) giving a maximum score of 21 points for each scale.[21] The HADS has shown good validity and internal consistency in patients with headache.[22] Anxiety and depression were assessed at baseline.

Burden of Headache

The Headache Disability Inventory (HDI) was used to evaluate the self-perceived burden. This questionnaire consists of 25-items inquiring about the impact of headache on emotional (13 items, HDI-E) and physical (12 items, HDI-P) functioning.[23] A higher score suggests a greater emotional or physical headache burden. The HDI has shown good stability in patients with headache.[24] The HDI was assessed at baseline.

Trait and State Anxiety Levels

The State-Trait Anxiety Inventory (STAI) is a 40-items self-report scale assessing state (items l-20, STAI-S) and trait (items 21-40, STAI-T) level of anxiety.[25] The STAI-S assesses relatively enduring symptoms of anxiety, and the STAI-T measures a stable propensity to experience anxiety, and tendencies to perceive stressful situations as threatening. Both subscales showed good internal consistency.[26] Higher scores indicate greater state or trait anxiety levels. Both scales were assessed at baseline.

Sensitivity to Pressure Pain

An electronic pressure algometer (Somedic®, Sollentuna, Sweden) was used to bilaterally assess pressure pain thresholds (PPT, the minimal amount of pressure where a sense of pressure changes to pain) over the temporalis, the cervical spine, the second metacarpal, and the tibialis anterior. Pressure was increased at a rate of approximately 30 kPa/s applied via a 1 cm^2 rubber coated circular tip. The mean of 3 trials on each point, with a 30sec resting period for avoiding temporal summation of pain,[27] was

calculated and used for the analyses. The order of point's assessment was randomized between participants. The reliability of pressure algometry has been found to be high.[28]

Statistical Analysis

Means and confidence intervals were calculated. The Kolmogorov-Smirnov test revealed that all data had a normal distribution (P>.05). Patients were grouped by use or not use of prophylactic medication and by the self-reported effectiveness of medication (no effect, moderate, positive effect). Differences between grouped patients in clinical features, burden of headache (HDI-E, HDI-P), depression (HADS-D), anxiety (HADS-A, STAI-T, STAI-S) and sleep quality (PSQI) were compared using one-way analysis of variance (ANOVA). Also, a two-way ANOVA was used to evaluate the differences in PPT with side as within-subjects factor and group as the between-subjects factor. The normality and homogeneity criteria were checked for the dependent variables with Kurtosis and Skewness for the normality and Levene's test for the homogeneity criteria. Separate ANOVAs were performed for each variable. As multiple comparisons were conducted in the main analysis, a Bonferroni-corrected alpha level of .025 (2 independent-samples t tests) was required to accept the statistically significance.

Results

Clinical Data of the sample

A total of 220 individuals with headache were screened for possible eligibility criteria. Finally, 180 patients with TTH (72% women) satisfied all eligibility criteria, agreed to participate and signed the informed consent at baseline. Forty patients were excluded: co-morbid migraine (n=20), previous whiplash injury (n=8), medication overuse headache (n=8), or fibromyalgia (n=4). One hundred and seventy-three (n=173, 96%) were assessed at 6-months follow-up and therefore included in the main analysis. Demographic data and outcome measure scores are listed in **Table 1**.

Taking or not taking prophylactic medication

Forty-nine (28%) reported taking prophylactic medication for their headaches (amitriptyline: 100%). Significant difference in the distribution of patients with FETTH and CTTH (P=0.006), years with headache (P=0.01), headache frequency (P=0.003), physical (HDI-P, P=0.024) and emotional (HDI-E, P=0.001) burden of headache, sleep quality (PSQI, P=0.023) and depression (HADS-D, P=0.001) were observed between individuals taking or not taking prophylactic medication. The post hoc analysis revealed a higher proportion of patients with CTTH, those with longer headache history, higher frequency of headaches, higher physical and emotional headache burden, worse quality of sleep and higher depressive levels within the prophylactic medication group (**Table 1**). No significant differences in gender (P=0.929), age (P=0.217), intensity of headache (P=0.144), headache duration (P=0.172), HADS-A (P=0.734), STAI-T (P=0.553), and STAI-S (P=0.482) were found between those patients taking or not taking prophylactic medication (**Table 1**). Similarly, no significant differences in widespread pressure pain sensitivity were either found (temporalis: F=0.374, P=0.542; cervical spine: F=0.133, P=0.716; second metacarpal: F=0.747, P=0.389; or tibialis anterior muscle: F=0.021, P=0.884) (**Table 2**).

Self-reported effectiveness of prophylactic medication

From those taking prophylactic medication, 11 (23%) reported no effect, other 25 (51%) reported moderate effect, and the remaining 13 (26%) experienced positive effect with the medication. No significant differences in the distribution of patients with FETTH and CTTH (P=0.740), gender (P=0.260), age (P=0.843), years with headache (P=0.199), headache intensity (P=0.785), headache frequency (P=0.822), headache duration (P=0.264), HADS-D (P=0.364), HADS-A (P=0.631), HDI-P (P=0.909), HDI-E (P=0.786), STAI-T (P=0.692), STAI-S (P=0.845), PSQI (P=0.619), and PPTs over C5-

C6 joint (F=0.213, P=0.809), temporalis muscle (F=1.401, P=0.257), or second metacarpal (F=0.816, P=0.449) were observed depending on the self-reported effects of preventive medication (**Tables 3-4**). Further, significant differences in PPTs over the tibialis anterior muscle (F=4.103, P=0.022) were found: patients reporting no effect of prophylactic medication exhibited lower PPTs over the tibialis anterior muscle than those reporting moderate or positive effect of the medication (**Table 4**).

Discussion

This longitudinal study investigating the variables associated with the consumption of prophylactic medication intake in individuals with FETTH/CTTH observed that the use of prophylactic medication was associated with a higher frequency of headaches, higher headache burden, worse sleep quality and higher depressive symptoms, but not to other clinical, psychological or pain sensitivity outcomes. Further, no differences in clinical, psychological and sensitivity outcomes, only for PPTs in the tibialis anterior, were reported based on the self-reported effectiveness of prophylactic medication.

Prophylactic medication consumption in TTH

In our study, 28% of our sample of patients with TTH reported taking regularly prophylactic medication, similar to a study conducted in Austria where 38% of their patients with headache, mostly TTH and migraine, also used prophylactic medication.[29] In fact, amitriptyline was the prophylactic medication mostly used by patients with TTH in our study and Zebenholzer et al study.[29] A significant higher proportion (61%) of individuals with CTTH tends to use prophylactic medication as compared to those with FETTH (39%). Our data agree with a previous study reporting that chronic headache sufferers are more likely to use medication than episodic headache sufferers.[30] It seems that medication consumption patterns may be different between patients with chronic or episodic (with low frequency of attacks) headaches. It is interesting to note that 70% of

our sample of patients with TTH did not take prophylactic treatment at the moment of the study. We do not know the reasons for that situation. For instance, it is possible that some patients have never taken prophylactic medication for TTH. It is also possible that others had stopped the medication intake due to absence of effectiveness or because the presence of adverse events. In fact, most of these patients (65%) reported a sporadic use of symptomatic medication intake (100% NSAIDs) when the headache attack is intense.

Patients consuming prophylactic medication exhibited higher headache burden, worse sleep quality and higher depressive symptoms, but not to clinical, pain sensitivity or psychological outcomes, than those not consuming medication. These findings may be related to the fact that higher headache burden, worse sleep quality and depression are outcomes associated with a higher frequency of the headaches;[31,32] therefore, since a higher proportion of patients with CTTH taken prophylactic amitriptyline medication, these features maybe more related to this situation rather than to the medication intake pattern. Since higher frequency of headache attcaks[33] and emotional burden[34] can lead to excitability of central nervous system, it appears that prophylactic medication would be consumed by individuals with central sensitization. Further, the comorbid association between higher frequency of headache attacks and depression in these patients would explain that the prophylactic medication most used was a tricyclic antidepressant such as amitriptyline. Nevertheless, although antidepressants are often prescribed to patients with headache under the assumption that they will be also effective for reducing the comorbid depression, the majority of studies have failed to find a relationship between depression symptoms and headache clinical improvement.[35] It seems that prophylactic medication would lead to a reduction of headache due to anti-nociceptive effects rather than to an antidepressant effect which may be related to the fact that dose recommended for headache is lower than dose used for the management of depression.

Self-perceived effectiveness of prophylactic medication intake

In our study, 27% of our sample taking prophylactic amitriptyline medication reported a positive effect by a reduction on frequency of headache. No differences were observed based on the effectiveness of prophylactic medication, except for the fact that patients reporting no effect of prophylactic medication exhibited lower PPTs over the tibialis anterior muscle than those reporting moderate or positive effect with medication. These results suggest that prophylactic medication would be less effective in individuals with widespread pressure pain hypersensitivity, a manifestation of central sensitization.[7] This hypothesis would be supported by a study showing that amitriptyline was effective for reducing peri-cranial muscle tenderness in those patients who clinically responded to medication (30% reduction in headache).[36] Additionally, it should be noted that patients taking prophylactic medication also took symptomatic medication sporadically, mostly when an attack was intense. Interestingly, no differences in the symptomatic medication based on the effectiveness of prophylactic medication was observed. Nevertheless, due to the small sample of patients in this group, population-based studies are now needed.

A recent meta-analysis reported that depression, poor sleep and emotional stress (burden) were associated with unfavorable outcomes from prophylactic treatment,[13] which disagree with current results. It is probably that the reduced number of patients within the no effect group would lead to lower statistical power.

Strength and limitations

Although strengths of the current study include a large sample size, the inclusion of patients accordingly to the most updated diagnostic criteria, the use of diagnostic diaries and a longitudinal study design, some limitations should be also recognized. First, we included volunteer patients from headache centers; therefore, they may be not representative of the general population. Second, data for depression and sleep quality

were smaller than expected, which could be related to the questionnaires employed in the study. For instance, the HADS is considered a screening rather than a diagnostic instrument for depressive symptoms with a tendency to underestimate its prevalence.[37] We do not know if the use of other outcomes could lead to different results. Third, the effectiveness of prophylactic medication was self-reported by the patients; so, this could have been biased. In fact, we do not know if a lack of effectiveness is a potential reason why most of our sample (70%) did not report prophylactic medication intake at the time of the study. Finally, we do not know if the associations identified in the current study will be maintained with longer follow-up periods since it seems that medication intake patterns change during time in patients with TTH.

Conclusions

This 6 months longitudinal study found that the use of prophylactic amitriptyline medication was associated with a higher frequency of headaches, higher headache burden, worse sleep quality, and higher depressive symptoms, but not to other clinical, psychological or pain sensitivity outcomes in TTH. Lower effectiveness of prophylactic medication was associated with widespread pressure pain hyperalgesia.

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Conflict of Interest Statement

The Author(s) declare(s) that there is no conflict of interest.

Author contributions

All authors contributed to the study concept and design. MPC and CFdlP did the main analysis and interpretation of data. All authors contributed to draft the report. MC, KW and COB provided administrative, technical, and material support. LAN and CFdlP supervised the study. All authors revised the text for intellectual content and have read and approved the final version of the manuscript.

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Table 1: Clinical features, psychological and related-disability outcomes in patients with tension-type headache in the total sample and with and without prophylactic medication intake (n=173)

	Total sample (n=173)	**Taking medication (n=49)**	**No taking medication (n=124)**
Clinical Pain Features			
Gender (male/female) n (%)	49 (28%) / 124 (72%)	14 (29%) / 35 (71%)	35 (28%) / 89 (72%)
FETTH / CTTH n (%)*	98 (57%) / 75 (43%)	19 (39%) / 30 (61%)	79 (64%) / 45 (36%)
Age (years)	48 (45, 51)	47 (43, 51)	48 (46, 50)
Headache history (years)*	10.6 (8.7, 12.5)	14.5 (11.4, 17.6)	9.3 (7.3, 11.3)
Headache intensity (0-10)	6.1 (5.7, 6.5)	6.3 (6.0, 6.6)	6.0 (5.5, 6.5)
Headache frequency (days/month)*	16.7 (13.3, 20.1)	19.2 (14.7, 23.7)	15.4 (13.8, 17.0)
Headache duration (hours per attack)	7.2 (6.5, 7.9)	8.0 (6.5, 9.5)	7.0 (6.2, 7.8)
Psychological and disability-related outcomes			
HADS-D (0-21)*	8.3 (7.5, 9.1)	9.7 (8.1,11.3)	7.1 (6.3, 7.9)
HADS-A (0-21)	10.0 (9.2, 10.8)	10.1 (8.9, 12.3)	9.8 (8.8, 10.8)
HDI-P (0-48)*	23.2 (21.2, 25.2)	26.2 (23.5, 29.0)	21.3 (19.4, 23.2)
HDI-E (0-52)*	19.7 (17.5, 21.9)	24.1 (19.6, 28.6)	16.7 (14.6, 18.8)
STAI-T (0-60)	23.9 (22.7, 25.1)	23.4 (21.7, 25.1)	24.1 (22.5, 25.7)
STAI-S (0-60)	21.7 (20.7, 22.7)	21.3 (19.7, 22.9)	22.0 (20.6, 23.4)
PSQI (0-21)*	8.3 (7.5, 9.1)	9.3 (7.7, 10.9)	7.7 (7.0, 8.6)

Values are expressed as means (95% confidence interval); * Significant differences between groups (ANOVA, P<0.025)

FETTH: Frequent episodic tension type headache; CTTH: Chronic tension type headache; HADS: Hospital Anxiety and Depression Scale (D: Depression; A: Anxiety), HDI: Headache Disability Inventory (P: Physical; E: Emotional), STAI: State-Trait Anxiety Inventory (T: Trait; S: State); PSQI: Pittsburgh Sleep Quality Index

Table 2: Differences in pressure pain thresholds (PPT, kPa) between individuals with tension-type headache with and without prophylactic medication intake (n=173)

	Temporalis muscle	**Cervical Spine**	**Second metacarpal**	**Tibialis anterior muscle**
Taking medication (n=49)				
Right side	202.5 (181.5, 223.5)	189.9 (157.8, 222.0)	264.5 (238.0, 291.0)	411.6 (371.3, 451.9)
Left side	196.6 (174.3, 218.9)	199.3 (168.7, 229.9)	261.6 (236.3, 286.9)	407.8 (366.2, 449.4)
No taking medication (n=124)				
Right side	216.2 (198.6, 233.8)	212.1 (192.1, 232.1)	248.5 (229.5, 267.5)	406.2 (368.6, 443.8)
Left side	196.0 (180.8, 211.2)	213.0 (193.9, 232.1)	250.8 (232.1, 269.5)	400.6 (363.0, 438.2)

Values are expressed as means (95% confidence interval)

Table 3: Clinical features, psychological and related-disability outcomes in patients with tension-type headache depending on the self-reported perception of effectiveness of prophylactic medication (n=49)

	No Effect (n=11)	**Moderate Effect (n=25)**	**Positive Effect (n=13)**
Clinical Pain Features			
Gender (male/female) n (%)	3 (27%) / 9 (73%)	7 (28%) / 18 (72%)	4 (31%) / 9 (69%)
FETTH / CTTH n (%)	4 (36%) / 7 (64%)	10 (40%) / 15 (60%)	5 (38%) / 8 (62%)
Age (years)	47 (44, 50)	48 (45, 51)	46 (44, 48)
Headache history (years)	12.5 (10.0, 15.0)	16.9 (13.9, 19.9)	16.3 (12.6, 20.0)
Headache intensity (0-10)	6.0 (5.1, 6.9)	6.5 (5.9, 7.1)	6.7 (6.0, 7.4)
Headache frequency (days/)	18.2 (13.5, 22.9)	20.9 (17.5, 24.3)	19.4 (18.2, 20.6)
Headache duration (hours per attack)	8.2 (6.8, 9.6)	8.1 (7.0, 9.2)	7.8 (6.3, 9.3)
Psychological and disability-related outcomes			
HADS-D (0-21)	11.2 (9.5, 12.9)	9.4 (8.2, 10.6)	9.6 (8.0, 11.2)
HADS-A (0-21)	11.1 (8.5, 12.7)	10.0 (8.2, 11.8)	9.3 (8.3, 10.3)
HDI-P (0-48)	26.9 (24.7, 29.2)	25.9 (23.8, 28.0)	25.7 (24.0, 27.4)
HDI-E (0-52)	23.8 (19.3, 28.3)	24.4 (20.7, 28.1)	23.9 (20.9, 26.9)
STAI-T (0-60)	23.3 (21.6, 25.0)	23.9 (22.1, 24.7)	22.8 (20.0, 25.6)
STAI-S (0-60)	20.5 (18.4, 22.6)	21.3 (19.1, 23.5)	21.7 (20.3, 23.1)
PSQI (0-21)	9.7 (8.4, 11.0)	8.8 (7.6, 10.0)	9.6 (8.5, 10.7)

Values are expressed as means (95% confidence interval)

FETTH: Frequent episodic tension type headache; CTTH: Chronic tension type headache; HADS: Hospital Anxiety and Depression Scale (D: Depression; A: Anxiety), HDI: Headache Disability Inventory (P: Physical; E: Emotional), STAI: State-Trait Anxiety Inventory (T: Trait; S: State); PSQI: Pittsburgh Sleep Quality Index

Table 4: Differences in pressure pain thresholds (PPT, kPa) in individuals with tension-type headache depending on the self-reported perception of effectiveness of prophylactic medication (n=49)

	Temporalis muscle	**Cervical Spine**	**Second metacarpal**	**Tibialis anterior muscle***
No Effect (n=11)				
Right side	186.7 (167.3, 206.1)	189.8 (157.3, 222.4)	260.8 (232.1, 289.5)	357.2 (322.3, 392.1)
Left side	196.3 (168.1, 224.5)	195.0 (682.1, 227.9)	260.5 (237.2, 283.2)	354.0 (321.9, 386.1)
Moderate Effect (n=25)				
Right side	208.9 (185.9, 231.9)	193.2 (159.4, 227.0)	261.2 (236.6, 285.8)	417.3 (367.7, 466.9)
Left side	196.5 (172.5, 220.5)	207.3 (183.6, 231.0)	265.9 (238.1, 293.7)	422.9 (366.7, 479.1)
Positive Effect (n=13)				
Right side	198.7 (170.5, 226.9)	183.0 (153.7, 212.3)	272.1 (247.5, 296.7)	432.5 (390.4, 474.6)
Left side	195.2 (169.4, 221.0)	197.1 (161.5, 232.7)	258.4 (232.2, 284.6)	434.1 (392.9, 475.3)

Values are expressed as means (95% confidence interval); * Significant differences between groups (ANOVA, P<0.025)