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ORIGINAL ARTICLE

Enhanced pain sensitivity in obese patients with obstructive sleep apnoea syndrome is partially reverted by treatment: An exploratory study

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Abstract

Background: Obesity is frequently associated with obstructive sleep apnoea syndrome (OSA) and chronic pain. OSA as well as continuous positive airway pressure (CPAP) treatment may modulate the pain perception threshold (PT) in patients with obesity.

Methods: In this prospective, longitudinal study, all patients admitted for obesity assessment were screened for OSA by nocturnal polygraphy (SOMNOcheck®, IAH ≥10) and performed mechanical (Von Frey electronic device) and electrical (PainMatcher®) pain tests. Those with severe OSA were retested for PT 1 month after initiation of CPAP therapy. Newly diagnosed patients with severe OSA (hypopnea apnoea index >30) have been offered to start CPAP treatment.

Results: Among 85 patients, there were 27 OSA patients, aged between 40 ± 13.2 years with a BMI of 42 ± 7.2 kg/m^2. Severe OSA patients (N = 11) showed a lower PT than non-OSA patients (N = 58) during mechanical (177 ± 120 vs. 328 ± 136 g, $p < 0.01$) and electrical methods (7.4 ± 6.4 vs. 12.9 ± 6.7 stimulation duration steps; $p = 0.03$). In the severe OSA group (N = 7), an increased PT was observed 1 month after CPAP treatment during mechanical pain testing (298 ± 69 vs. 259 ± 68 g, $p < 0.05$), but not during electrical pain testing (11.5 ± 3.0 vs. 12.4 ± 3.8 stimulation duration steps, $p = 0.50$).

Conclusion: In patients with obesity, this exploratory study showed that the presence of an OSA is associated with a decreased PT, whereas implantation of a CPAP device tends to normalize pain perception.

Significance: Severe obstructive sleep apnoea syndrome in patients with obesity is accompanied by a lower pain perception threshold. In these patients, continuous positive airway pressure therapy may help prevent or reduce chronic pain.

1 | INTRODUCTION

Obesity affects over 650 million people worldwide (World Health Organization) and is associated with a higher incidence of chronic pain compared to the population with a normal body mass index (BMI; Stone and Broderick, 2012). Mechanical weight constraints (Zheng and Chen, 2015), combined with a fragile psychological context in patients with obesity, make the management of these pains particularly difficult.

Many observational and interventional studies have established a link between sleep disorders or sleep deprivation and pain perception thresholds (PT; Finan et al., 2013, Herrero Babiloni et al., 2020). In healthy volunteers, it has been shown that deep slow sleep rebound following sleep deprivation is responsible for a significant increase in mechanical pain thresholds (Onen et al., 2001). Obstructive sleep apnoea syndrome (OSA), defined as at least 10 apnoea and hypopnea events per hour of sleep (apnoea-hypopnoea index or AHI ≥10) (International Classification of Sleep Disorders, 1990), induces major disturbances in stages and cycles of sleep. In obesity, fatty infiltration of the tongue and parapharyngeal spaces increases the risk of airway collapsibility (Lin et al., 2020). OSA is also associated with advancing age (Peppard et al., 2013), OSA is accompanied by cardiovascular mortality and impaired quality of life, including asthenia and disabling daytime sleepiness. Young adults with OSA have greater odds of moderate/severe pain (Athar et al., 2020). OSA has also been associated with altered responsiveness to opioids (Cozowicz et al., 2018).

Continuous positive airway pressure (CPAP) is the gold standard for OSA. Although not necessarily accompanied by an improvement in cardiovascular prognosis (Yu et al., 2017), using a CPAP device is accompanied by a clear improvement in quality of life (Kuhn et al., 2017). This effect could in part be mediated by an elevation of the PT, as has been shown in the elderly (Onen et al., 2010).

This work is based on two hypotheses: (1) OSA may lower PT in a population with obesity, and (2) improvements in sleep afforded by CPAP treatment may 'restore' the PT. We, therefore, studied the link between the presence of OSA and PT, and the effects of CPAP therapy on PT in patients with obesity.

2 | MATERIALS AND METHODS

2.1 | Study design

This prospective, monocentric, longitudinal, controlled study was conducted at the University Hospital of Clermont-Ferrand between February 2010 and February 2017. The University Hospital of Clermont-Ferrand was the promoter of this study and provided funding for an internal tender (AOI 2008 Debouit-Miolanne). Each patient completed an information and consent form. The protocol was approved by the local institutional review board (Comité de Protection des Personnes Sud-Est VI).

This trial involved patients with obesity (BMI ≥30 kg/m^2) of both sexes over the age of 18 under the care of the nutrition and pulmonology departments, and who had undergone sleep recording for OSA. Patients with central sleep apnoea, acute or chronic pain, neuromuscular pathology, chronic analgesic treatment, benzodiazepine, tricyclic or β-blocking therapy, alcohol or illegal drug abuse or dependence (DSM-IV, diagnostic and statistical manual of mental disorders), or those who were not affiliated to the Social Security system were not included. Patients unable to take part due to their involvement in another study, those who received over 4500 euros/year due to their participation in clinical trials, pregnant or breastfeeding women, and individuals subject to a protection measure or deprivation of rights safeguards, were also excluded.

2.2 | Biochemical analyses

The International Diabetes Federation 2005 components of metabolic syndrome were used as follows: (1) abdominal obesity, defined as a waist circumference greater than 94 cm in men or greater than 80 cm in women; (2) fasting plasma glucose greater than 100 mg/dL, or high blood glucose treated with medication; (3) serum triglycerides greater than 150 mg/dL, or high triglycerides treated with medication; (4) serum high-density lipoprotein cholesterol (HDL-C) less than 0.40 mg/dL in men and less than 0.50 mg/dL in women or low HDL-C treated with medication; (5) blood pressure higher than 130/85 mmHg, or high blood pressure treated with medication (Alberti et al., 2005).

2.3 | Sleep measurements

As part of their care, patients with obesity who were hospitalized in the nutrition and pulmonology departments completed a nocturnal polygraphy (measurement of peripheral oxygen saturation, nasal flow, thoracic and abdominal movements, SOMNOcheck® effort, WEINMANN) to confirm or disprove the presence of OSA. Two groups of patients were created: one group without sleep apnoea (<AHI 10) and one group with apnoea (AHI ≥ 10). The latter group included patients with moderate apnoea (AHI between 10 and 30) and severe apnoea (AHI > 30). These thresholds were set from the 1990 definition of the International Classification of Sleep Disorders, a definition that was still widely used when the protocol was designed in 2009.

All patients were subjected to mechanical and electrical pain tests in the week following the polygraphy. Severe OSA (AHI > 30) was an indication for treatment with CPAP and, once they had given consent, patients with severe OSA were admitted to the pulmonology department to have the CPAP device implanted. Patients were then subjected to mechanical and electrical pain tests on the second day after CPAP treatment had begun. One month after beginning CPAP therapy, patients underwent another ambulatory nocturnal polygraphy as well as further mechanical and electrical pain tests.

2.4 | Pain measurements

Two methods for measuring the PT were studied: mechanical and electrical. Mechanical PT was determined through the pressure generated by a Von Frey electronic device (BIOSEB Ltd.). Constantly increasing pressure was applied to the skin using a plastic cone attached to a strain gauge to instantly measure the point pressure exerted and determine the PT. Mechanical PT was determined using the average value of three successive measurements taken on the inside of the forearm (on the non-dominant side). This method has already shown good intraobserver and interobserver reliability (Tena et al., 2012).

Electrical stimulation tests were performed using PainMatcher® (Cefar Medical). This device, with built-in electrodes, was grasped between the thumb and forefinger of the left hand. The device generated single-phase pulses of 15 mA and 10 Hz. The intensity increased with the duration of monophasic pulses in increments of 4 ms (from 4 to 396 ms). The results are expressed in stimulation duration steps (arbitrary unit) between 1 and 99. When they reached their PT, patients let go of the electrodes to interrupt the current, thereby establishing a value between 0 and 99 (Lund et al., 2005). Electrical PT was determined using the average value of three successive measurements with this device.

All these tests were performed on subjects who were comfortably seated in an examination chair in a semi-recumbent position and in a quiet environment. From a baseline level that caused no particular sensation, the mechanical or electrical stimulus was increased at a constant rate of progression. PT, defined as the lowest stimulation intensity that the subject perceived as painful, was used when analysing the primary and secondary endpoints (Tena et al., 2012).

2.5 | Evaluation criteria

The primary outcome of the study was an inter-group comparison of PT in patients with obesity, with or without OSA, in response to electrical or mechanical nociceptive stimuli. The intra-group comparison of the same PT in patients with obesity and severe OSA before and after CPAP therapy was the secondary criterion.

2.6 | Statistical analyses

Calculation of the number of patients required was based on the prior experience of the functional nervous system exploration department in measuring pain thresholds by electrical (PainMatcher®) or mechanical (Von Frey electronics) nociceptive stimulation. We took into account the criteria that offer the greatest variability of measurements, that is, those obtained using the Von Frey electronic device (average values in a population of healthy volunteers = 135 ± 40). A pain threshold difference of 20% (i.e. 27) was considered clinically significant. The sample size estimate was 105 (35 and 70 in each group) for a two-sided type I error of 5%, a 90% statistical power and an unbalanced ratio of 1:2 (OSA: Without OSA). Due to recruitment difficulties, inclusions were closed after 8 years with 85 patients (27 OSA and 58 non-OSA), which corresponds to a statistical power of 80%.

The continuous variables were described according to their statistical distribution by mean ± standard deviation or median deviation [interquartile range]. Normality was studied using the Shapiro–Wilk test. Comparisons between groups (primary comparison: non-apnoeic patients vs. patients with OSA, followed by secondary comparison: non-apnoeic patients vs. patients with severe OSA vs. patients with moderate OSA) considered the following statistical tests: (i) for quantitative variables: the ANOVA (analysis of variance) test, or the Kruskal–Wallis test (KW) when assumptions for the ANOVA test were not met ((1) normality and (2) homoscedasticity studied by the Bartlett test), and (ii) for categorical parameters: chi-squared test or Fisher's exact test for comparisons. When appropriate (omnibus *p*-value less than 0.05 for comparisons between non-apnoeic patients, patients with severe OSA and patients with moderate OSA), post hoc tests for multiple comparisons were conducted in order to take into account the correction of the type I error: Tukey–Kramer post the ANOVA test, and Dunn after the KW test for quantitative variables, and Marascuilo post a chi-squared test procedure.

Multivariable analysis was conducted using a multiple linear regression model. The covariates were selected based on the results of univariate analysis and their clinical relevance: age, sex, BMI and tobacco consumption. The normal distribution of residuals was studied using the Shapiro–Wilk test. The results were expressed using effect-sizes and 95% confidence intervals and were interpreted

according to effect-size bounds recommended by Cohen (Cohen, 1988): small (ES: 0.2), medium (ES: 0.5) and large (ES: 0.8, 'grossly perceptible and therefore large').

Finally, paired comparisons were analysed using the Stuart–Maxwell paired test for categorical data, and paired Student or Wilcoxon tests for quantitative variables. All statistical analyses were performed using Stata software (version 13, StataCorp). The type I error was two-sided at 5%.

3 | RESULTS

3.1 | Participants and clinic-biological characteristics

Most of the 1455 patients hospitalized between 2010 and 2017 had exclusion criteria such as chronic pain or interfering treatments (Figure 1). Although only 6% of patients were included, the demographic characteristics of the 91 patients included were comparable in terms of age, BMI and sex to all patients with obesity admitted to the nutrition department over that period. Six patients were excluded secondarily, and 85 were included in the analysis, including 27 patients who had been diagnosed as apnoeic (AHI ≥ 10). Only 11 patients with severe OSA (AHI > 30) who agreed to undergo CPAP could be analysed.

The clinic-biological characteristics of the 91 patients included are shown in Table 1. Most of our patients had grade 3 obesity (90%) and metabolic syndrome (66%). Apnoeic patients were older (45.7 ± 12.3 vs 37.5 ± 12.9, $p < 0.01$) and had a lower female predominance (78 vs. 52%, $p = 0.02$) compared to the non-apnoeic patients. The Epworth score (threshold at 10/24) was in no way discriminatory towards our population in terms of screening of apnoeic subjects Cumulative time spent with Peripheral blood oxygen saturation below 90% (CT90) was higher among apnoeic patients (19.44 ± 23.7 vs 3.9 ± 6.3, $p < 0.001$).

3.2 | Pain PTs

To take into account possible confounders, a multivariable analysis was performed to adjust PT for age, gender, BMI and smoking status. With respect to inter-group analyses, apnoeic patients had a lower PT according to the mechanical method (ES = -0.46 [−0.85;-0.08] $t = 2.40$, $p = 0.019$)

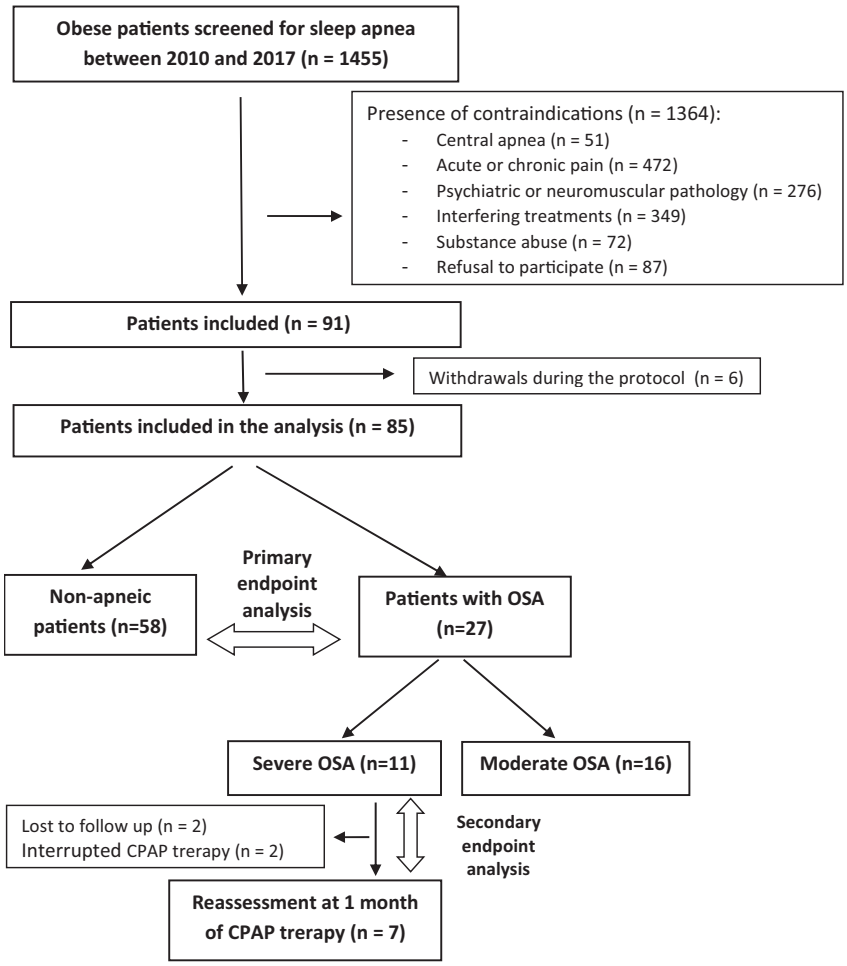

FIGURE 1 Flow diagram of patients participating in the study and major analyses performed. CPAP, continuous positive airway pressure; OSA, obstructive sleep aponea syndrome.

TABLE 1 Clinico-biological characteristics of patients at baseline.

	Total ($n = 85$)	Without OSA ($n = 58$)	OSA	p value[b]	Moderate OSA ($n = 16$)	Severe OSA ($n = 11$)
Age (years)	40.1 ± 13.2	37.5 ± 12.9	45.7 ± 12.3	<0.0011[c]	44.7 ± 13.3	47.3 ± 11.0
Women (%)	69	78	52	0.023[e]	69	27
BMI (kg/m^2)	42.0 ± 7.2	41.1 ± 7.5	43.9 ± 6.3	0.081[c]	43.1 ± 5.6	45.1 ± 7.4
Smoking (%)	24	22	26	0.723[e]	25	27
Metabolic syndrome[a] (%)	66	66	67	0.803[e]	63	73
Increased waist size	100	100	100		100	100
High blood pressure	72	69	78	0.403[e]	75	82
Hypertriglyceridemia	35	36	33	0.803[e]	19	55
Decreased HDL	64	67	56	0.303[e]	56	55
Fasting hyperglycaemia	26	21	37	0.113[e]	44	27
Score de Framingham	7.4 ± 7.5	7.1 ± 7.3	8.0 ± 7.9	0.603[e]	9.2 ± 7.5	6.3 ± 8.7
CRP (mg/L)	6.3 ± 5.5	6.7 ± 5.9	5.4 ± 3.5	0.432[d]	6.2 ± 4.7	4.8 ± 3.1
Epworth score, /24	7.9 ± 4.0	8.3 ± 4.2	6.9 ± 3.0	0.161[c]	9.1 ± 4.3	8.9 ± 6.7
AHI	11.5 ± 20.1	1.8 ± 2.0	32.5 ± 24.9	<0.0012[d]	15.4 ± 4.1	57.5 ± 20.9
CT90	8.5 ± 15.6	1 [0–4]	6 [3–29]	<0.0012[d]	5 [2–23]	11 [5–41]

Note: Values expressed as means ± standard deviation.

Abbreviations: AHI, apnoea–hypopnoea index, CT90, Cumulative time spent with Peripheral blood oxygen saturation below 90%, OSA, obstructive sleep apnoea syndrome.

[a]International Diabetes Federation 2005 criteria.

[b]p value OSA vs. without OSA.

[c]Student or Welch test.

[d]Mann–Whitney.

[e]Chi-squared test.

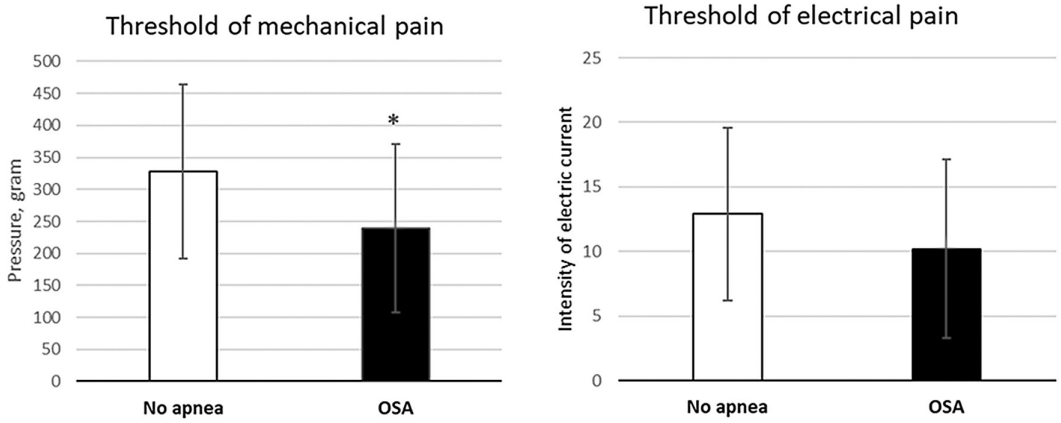

FIGURE 2 Comparison of pain perception thresholds for patients without apnoea ($N = 58$) and patients with OSA ($N = 27$), tested using mechanical and electrical methods. OSA: obstructive sleep aponea syndrome. Values adjusted for age, sex, BMI and smoking status. *$p < 0.05$. Mechanical PT was determined through a constantly increasing pressure generated by a Von Frey electronic on a plastic cone applied on the inside of the non-dominant forearm (average value of three successive measurements). Electrical PT was determined using a PainMatcher®, a built-in electrodes device (grasped between the thumb and forefinger of the left hand) generating single-phase pulses of 15 mA and 10 Hz with gradual increased in duration of monophasic pulses. The intensity of electric current corresponds to the stimulation duration steps (arbitrary unit) between 1 and 99. Electrical and mechanical PT were determined using the average value of three successive measurements. PT was defined as the lowest stimulation intensity that the subject perceived as painful.

but not the electrical method (ES = −0.30 [−0.68;0.09], $t = 1.54$, $p = 0.12$) in multivariable analysis adjusted for age, gender, BMI and smoking status (Figure 2). In addition, severe apnoeic subjects had a significantly lower PT than non-apnoeic patients when using the mechanical method (ES = −0.85 [−0.93; −0.16], $t = 2.82$, $p < 0.01$) and

electrical (ES = −0.42 [−0.80; −0.04], $t = 2.19$, $p = 0.03$) stimulations (Figure 3). On the other hand, there was no significant difference in PT between the two severity levels of OSA regardless of the method tested.

Regarding the intragroup analysis of the 11 patients who were treated with CPAP, only seven patients had performed the pain tests at 1 month. An increase in PT was observed following CPAP therapy according to the mechanical method (298 ± 69 vs. 259 ± 68 g, $t = 2.50$, $p < 0.05$) but not with electric stimulation (11.5 ± 3.0 vs. 12.4 ± 3.8, t = 0.72, $p = 0.50$) (Figure 4).

3.3 | Correlation

There was a significant negative correlation between AHI and mechanical PT ($r = -0.239$, $p = 0.03$, Spearman) but not with electrical PT ($r = -0.01$, $p = 0.96$, Spearman) (Figure 5). The two modalities of PT were correlated ($r = 0.5618$, $p < 0.001$, Spearman). As CT90 was not correlated with either electrical ($r = -0.047$, $p = 0.69$, Spearman) or mechanical PT ($r = -0.007$, $p = 0.95$, Spearman), it was not included in the model.

4 | DISCUSSION

The present study suggests that obesity and severe OSA are associated with a decrease in the pain PT and that CPAP therapy could enhance PT in severe OSA. These effects are observed specifically on PT related to mechanical stimulation but not in case of electrical stimulation. This work supports the epidemiological link between sleep pathology and the development of chronic pain as well as the link between sleep deprivation and lowering of the threshold of pain sensitivity (Finan et al., 2013). However, most of these interventional studies involved healthy populations (Onen et al., 2001). On the contrary, our study focused on a poorly studied population with grade 3 obesity. Finally, compared to other studies using painful stimulation via a single modality, we chose to explore mechanical and electrical modalities (Onen et al., 2010).

4.1 | Factors taken into account in the adjustment of PT

Many factors that may influence the frequency of chronic pain have been identified in the literature. High BMI has been associated with an increased frequency of pain whether overall pain (Stone and Broderick, 2012), lower back pain (Heuch et al., 2013), or headaches (Bigal et al., 2007), even once adjustments have been made for age, sex and smoking (Stone and Broderick, 2012). Beyond BMI, percentage of fat mass and central distribution (increased waist circumference) have been associated with back, knee and foot pain intensity and disability (Hussain et al., 2017; Peiris et al., 2021). This high incidence of musculoskeletal pain in obese people has been linked to mechanical joint overload, a source of early osteoarthritis (Kulkarni et al., 2016). In addition, nociceptor hypersensitivity may result from the chronic low-grade inflammatory state associated with obesity (Eichwald & Talbot, 2020). An increasing percentage of body fat has

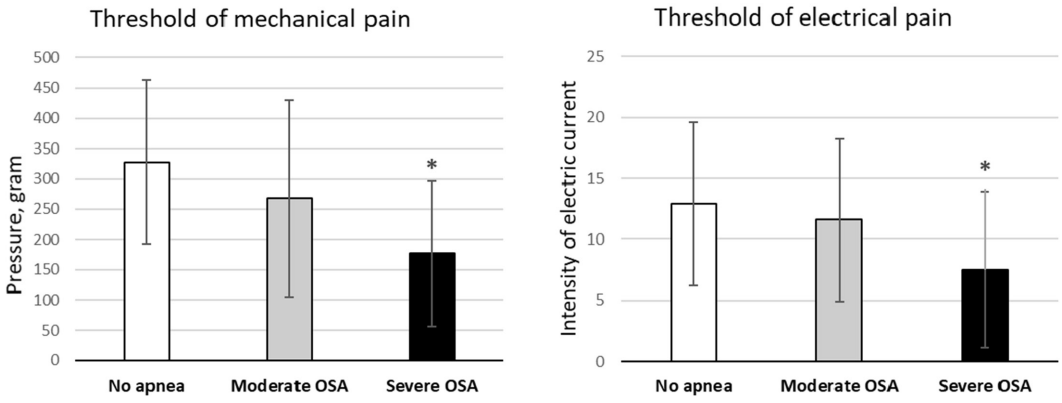

FIGURE 3 Comparison of pain perception thresholds for patients without apnoea ($N = 58$), moderately apnoeic patients ($N = 16$) and severely apnoeic patients ($N = 11$), using mechanical and electrical methods.Values adjusted for age, sex, BMI and smoking status. *$p < 0.05$ between the groups no apnea and severe OSA. Mechanical PT was determined through a constantly increasing pressure generated by a Von Frey electronic on a plastic cone applied on the inside of the non-dominant forearm (average value of three successive measurements). Electrical PT was determined using a PainMatcher®, a built-in electrodes device (grasped between the thumb and forefinger of the left hand) generating single-phase pulses of 15 mA and 10 Hz with gradual increased in duration of monophasic pulses. The intensity of electric current corresponds to the stimulation duration steps (arbitrary unit) between 1 and 99. Electrical and mechanical PT were determined using the average value of three successive measurements. PT was defined as the lowest stimulation intensity that the subject perceived as painful.

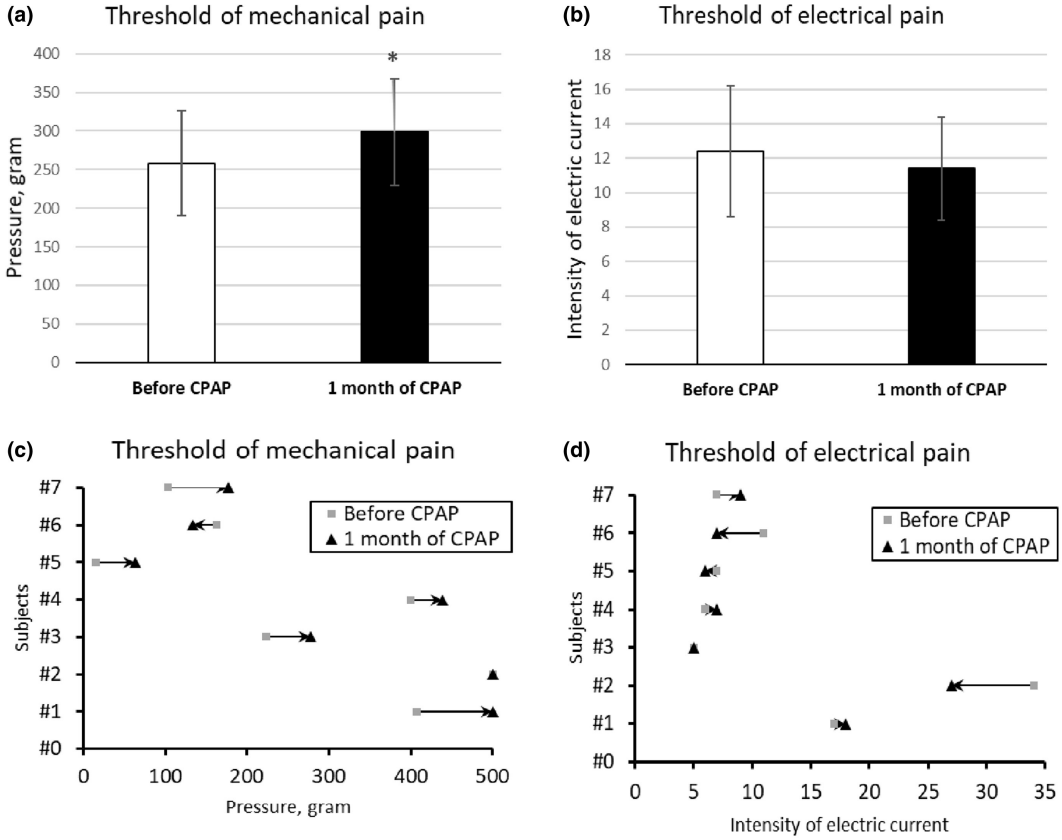

FIGURE 4 Comparison of pain perception thresholds before and after CPAP treatment, using mechanical (a and c) and electrical methods (b and d) in severely apnoeic patients ($N = 7$). (a) and (b) The mean values and standard deviations (values adjusted for age, sex, BMI and smoking status; *p <0.05). (c) and (d) represent individual variations. CPAP, continuous positive airway pressure. Mechanical PT was determined through a constantly increasing pressure generated by a Von Frey electronic on a plastic cone applied on the inside of the non-dominant forearm (average value of 3 successive measurements). Electrical PT was determined using a PainMatcher®, a built-in electrodes device (grasped between the thumb and forefinger of the left hand) generating single-phase pulses of 15 mA and 10 Hz with gradual increased in duration of monophasic pulses. The intensity of electric current corresponds to the stimulation duration steps (arbitrary unit) between 1 and 99. Electrical and mechanical PT were determined using the average value of 3 successive measurements. PT was defined as the lowest stimulation intensity that the subject perceived as painful. CPAP, continuous positive airway pressure.

previously been associated with a decrease in pressure pain threshold (Tashani et al., 2017). However, these differences may be affected by the test site and by the thickness of the subcutaneous fat (waist vs. thenar eminence). Here, we chose a rather classical site on the internal face of the forearm, which is only moderately affected by the increase in subcutaneous fat.

Chronic pain is particularly common with age, affecting almost 50% of the population over 65, and particularly correlates with functional impairment (Patel et al., 2013). This frequency seems to relate to inflammation and dysregulated cytokine production (Cruz-Almeida et al., 2015). Conversely, some experimental studies show an increase in pain thresholds with age, particularly in the lower limbs (Riley et al., 2014). Differences in pain sensitivity and response to analgesics have been found between men and women in relation to genetic, hormonal and psycho-social factors (Bartley & Fillingim, 2013) Although experimentally nicotine may have antalgic properties, epidemiological studies show on the contrary a connection between smoking and painful, chronic pathologies (Shi et al., 2010).

The pathophysiology of these statistical associations is often too uncertain to establish causal links. To compensate for the uneven distribution of some of these factors in our different groups, an age adjustment for sex, BMI and smoking was performed. However, the study's design did not allow for the collection of the data needed to take into account genetic or dietary factors, physical activity or thymic state.

4.2 | Other potential factors influencing pain perception

The link between inflammation, the local production of cytokines, which sensitize nociceptors, and inflammatory pain is well established and explains the analgesic efficacy of

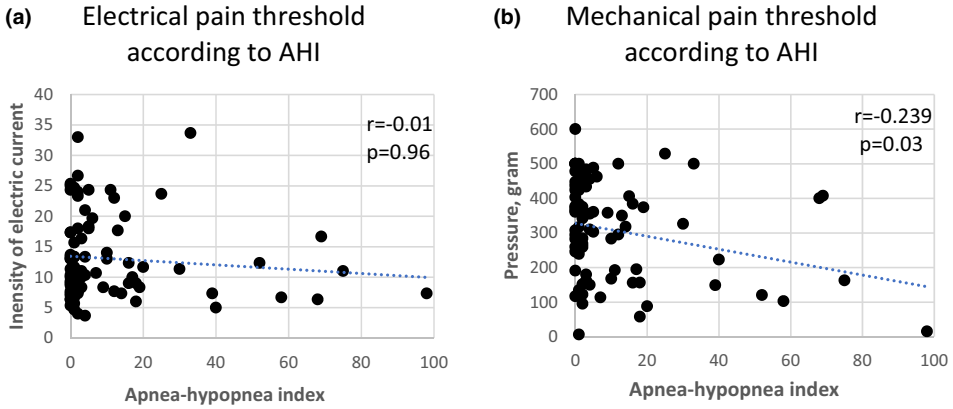

FIGURE 5 Correlations between apnoea–hypopnoea index and electrical pain (a) or mechanical pain threshold (b). AHI, apnoea-hypopnoea index.

anti-inflammatory treatments (Guillot et al., 2012). Adipose tissue releases numerous mediators, named adipokines, with both paracrine and systemic actions. In patients with obesity and visceral fat accumulation, the inflammatory ones (resistin, leptin, chemerin and visfatin-1) tend to be overexpressed, while others with anti-inflammatory effects are reduced (adiponectin and omentin), leading to low-grade systemic inflammation (Azamar-Llamas 2017). Epidemiologically, an inverse relationship between the pain score (pain component of SF36) and the nutritional quality score (Healthy Eating Index 2010) has been reported. This effect seems particularly mediated by foods with anti-inflammatory effects (rich in omega 3) (Emery et al., 2017). However, the effect on pain of low-level systemic inflammation in chronic diseases such as obesity or cancer remains controversial (Paulsen et al., 2017). Thus, the only marker of inflammation measured in our population, the C Reactive Protein level, was not higher in cases of OSA or even severe OSA, while the percentage of body fat was higher than in non-apnoeics.

Chronic pain is a classic symptom in diabetes that takes several years to develop as a result of peripheral neurological involvement. In addition, there appears to be hypersensitivity to nociceptive stimuli as early as the insulin resistance stage (Zhai et al., 2016, Iftikhar et al., 2015).

Depression and other psychological disorders such as anxiety are frequently associated with obesity (Luppino et al. 2010). These psycho-thymic disorders are also linked to pain hypersensitivity due to possible altered central pain mechanics (e.g. altered descending pain modulation or emotional aspect of pain) (Nahman-Averbuch et al., 2016). Depression is associated with an increased incidence of chronic pain, particularly lower back pain (Lopez-Lopez et al., 2017) and headaches (Lampl et al., 2016). Similarly, sedentariness compared to low to moderate physical activity is associated with increased pain frequency, possibly due to the positive effects of physical activity on psychological well-being (Krøll et al., 2017, Naugle et al., 2017). Research involving pairs of twins has highlighted the importance of genetics in many painful pathologies beyond mood state and environmental factors (Dario et al., 2016). Some genetic or environmental factors seem able to influence the frequency of both chronic pain and depression (Pinheiro et al., 2015).

4.3 | Pathophysiological hypotheses linking pain and OSA

Sleep disturbance has been previously linked to pain hypersensitivity. Thus, a night of poor sleep quality or difficulty falling asleep has been associated with worsening pain symptoms (Alsaadi et al., 2014). Reciprocally, some authors suggest that pain disturbs sleep continuity/quality and poor sleep further exacerbates pain, generating a vicious circle (Alsaadi et al., 2014; Smith & Haythornthwaite, 2004). Although the underlying mechanisms connecting sleep disturbance and pain hypersensitivity are unclear, some brain areas have been suggested to modulate both sleep stages and pain. Thus, the raphe nuclei are involved in the descending pain control system and the ascending reticular activating system, which is also responsible for the transition between sleep and wakefulness (Lu et al., 2006). This bidirectional relationship between sleep and pain could involve many neurobiological mechanisms, including the opioid, monoaminergic, orexinergic, immune, melatonin and endocannabinoid systems; the hypothalamus–pituitary–adrenal axis and adenosine and nitric oxide signalling (Haack et al. 2020).

Some of the previously mentioned factors explain both the reduced pain thresholds in the population with particularly severe apnoea and the effectiveness of CPAP

treatment on pain PTs. Severe OSA has been implicated in a reduction in functional abilities (Ben Saad et al., 2015), which may itself promote a sedentary lifestyle, combined with fatigue relating to poor quality of sleep. OSA treatment improves sleep quality (Cruz et al., 2012), daytime sleepiness (Giles et al., 2006) and overall levels of physical activity (Jean et al., 2017). Depression contributes to the quality of life in OSA patients (Lee et al., 2016; Stelmach-Mardas et al., 2016). CPAP therapy appears to reduce symptoms of anxiety and depression (Gupta et al., 2016) as well as the quality of life (Kuhn et al., 2017), particularly in severely apnoeic patients (Batool-Anwar et al., 2016). However, it remains difficult to establish whether pain perception benefits from mood improvement, or whether it is a contributing factor. In addition, improvement in depression scores could also, at least in part, be mediated by the attention offered by healthcare teams to an often isolated and frail population (Newton et al., 2017). Finally, treatment with CPAP has been associated with a lasting improvement in insulin resistance (Iftikhar et al., 2015; Martínez-Cerón et al., 2016). However, this improvement is still contested (Zhu et al., 2017).

4.4 | Other considerations

In our study, the effect of OSA on PT, which is observed with the mechanical method, has only been significantly demonstrated with electrical stimulation in severely apnoeic populations. Tashani et al. (2017) have also reported that obese individuals were more sensitive than non-obese individuals to pressure pain but not to thermal pain. The different nervous pathways used by the two stimulations can explain this discrepancy. On the one hand, mechanical or thermal stimulations directly implicate peripheral nociceptive endings. On the other hand, electrical stimulations are not a physiological pain stimulus and activate various types of nerve fibre in a more undifferentiated way (Balogun, 1986; Reddy et al., 2012). Moreover, this difference may be explained by the low statistical power that resulted from the small number of patients who showed greater PT variability with the electrical method.

The link between OSA and hypertension, diabetes and metabolic syndrome potentiates cardiovascular risk (Heinzer et al., 2015). The presence of a metabolic syndrome in 2/3 of our patients is thus consistent with the main data found in the literature. However, our small numbers of patients do not allow us to establish an overrepresentation of metabolic syndrome in apnoeic patients as compared to controls.

The Epworth score assesses the degree of daytime sleepiness and has been used as an OSA test for many years. However, in a population with grade III obesity, this score seems to be a very poor predictor of AHI during sleep recording (Dixon et al., 2007). The presence of obesity hypoventilation syndrome or depression is a common factor influencing the level of daytime sleepiness, regardless of the presence of OSA. In our study, the Epworth score proved to be a very poor screening tool, highlighting the importance of routine sleep recording in a population with obesity.

4.5 | Strengths, limitations and perspectives

Our study was based on a properly phenotyped population with obesity. The evaluation of pain PTs was carried out using two different methods with validated tools and performed by a single trained operator.

This study has several limitations. First, the estimated sample size was not reached. However, our results are based on a small size population, particularly in intervention groups, and should be considered as an exploratory investigation Thus, our findings need to be further confirmed by larger studies in the future. Second, the level of physical activity, as a possible confounding factor, should have been assessed and reassessed 1 month after CPAP treatment. Third, the selected exclusion criteria have ruled out certain populations with obesity, particularly populations with painful, chronic conditions. This subpopulation may have specific PT and it would be interesting to study the impact of CPAP therapy on the consumption of analgesics. Finally, the reduction in the pain PT related to SAOS might modify eating behaviours (eating balance, compulsive eating, etc.). Thus, sleep disorders associated with OSA may be an underestimated factor in eating disturbance that could be the subject of more targeted studies in the future.

5 | CONCLUSION

In patients with obesity, the presence of OSA is associated with a decreased PT, particularly using mechanical stimuli and in severe OSA. This might therefore contribute to the frequency of chronic pain phenomena in this population. CPAP therapy tends to limit this discrepancy. More than ever, screening and management of OSA is therefore a major challenge in terms of quality of life for patients with obesity.

AUTHOR CONTRIBUTIONS

CL: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization;

original draft; review & editing. MM: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; review & editing. NF: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; review & editing. BP: Conceptualization; Data curation; Methodology; Software; Validation; Visualization; review & editing. CD: Methodology; Validation; Visualization; review & editing. PB: Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; review & editing. AG: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; review & editing. YB: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; review & editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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