BMC Anesthesiology

RESEARCH Open Access

The role of the sympathetic component of the autonomic nervous system on pain before and after third molar extraction– an observational cohort study

Christophe Deschaumes[1], Laurent Devoize[1], Yannick Sudrat[1], Bruno Pereira[2], Radhouane Dallel[1] and Christian Dualé[3,4*]

Abstract

Background Assessing heart rate variability (HRV) before a standardized surgery would help to explore further the relationship between the autonomic nervous system and pain.

Methods A single-center prospective cohort of 117 patients (55% female) scheduled for third molar extraction underwent a preoperative resting measurement of arterial pressure followed by an HRV recording, then potentiated by a Valsalva maneuver and a deep breathing challenge. Finally, pain sensitivity was assessed by hand immersion in hot water. All surgeries were conducted under local anesthesia, with or without sedation. The primary outcome was a composite pain/analgesia score (CPAS) incorporating both pain intensity and analgesic drug intake; it was adjusted to the type of anesthesia by within-subgroup ranking.

Results The increase in heart rate in the Valsalva maneuver, and the low- to high-frequency ratio (LF/HF) in the deep breathing, were inversely correlated to preoperative heat pain, which was correlated itself to the CPAS ($\rho = 0.195$; $p = 0.035$). The only other parameter influencing CPAS was the increase in heart rate in the Valsalva maneuver, with an inverse correlation ($\rho = -0.191$; $p = 0.046$). While age tended to impair HRV, particularly in its parasympathetic component, and while men displayed a stronger parasympathetic response than women, neither age nor sex interacted with these effects. Neither preoperative arterial pressure nor the occurrence of parental hypertension influenced the pain outcomes.

Discussion Although the identified relationships were not particularly strong, they are consistent with an influence of the sympathetic component of the autonomic nervous system. However, they do not support the interest of HRV assessment to predict postoperative pain in current practice.

Trial registration Not applicable.

Keywords Pain, postoperative, Pain perception, Quantitative sensory testing, Autonomic nervous system, Heart rate variability, Hypertension

*Correspondence:
Christian Dualé
cduale@chu-clermontferrand.fr

Full list of author information is available at the end of the article

Introduction

Both nociception and the autonomic nervous system (ANS) participate in the response of the body to a potentially harmful threat, the sympathetic response being an essential element of the behavioral reaction ("fight-or-flight") to threat. Literature data also suggest interactions between those two systems [1]. For example, hypertension in humans is often linked to a reduced sensitivity to pain [2–4], and attempts to increase arterial pressure or sympathetic tone may reduce pain sensitivity [5–8]. However, it is still unknown (i) whether this analgesic effect follows an independent central or descending nervous pathway, or depends on the autonomic response; and (ii), if dependent, whether it results directly from hemodynamic changes, or from a hormonal stress response. In addition, while the stress response is mostly driven by the sympathetic response, there is also a parasympathetic response to threat [9], also possibly interacting with pain sensitivity [10–12].

Heart rate variability (HRV) is considered as a more reliable indicator of the ANS than the sole arterial pressure or heart rate; it has long been used to diagnose autonomic dysfunction [13]. The wide availability of low-cost non-invasive bedside devices has broadened this field of research [14, 15]. HRV outcomes are based either on descriptive statistics of the beat-to-beat intervals, or on fast Fourier transform to determine a frequency spectrum (see Table 1). These analyses help to estimate the balance between the sympathetic and parasympathetic components of the ANS, although their accuracy– especially for the sympathetic– have been challenged [16]. Nevertheless, the accuracy of HRV to assess the ANS function can be enhanced by standardized tests such as the Valsalva maneuver (VM) and the deep breathing (DB) challenge [13].

Relationships between the autonomic response and pain sensitivity have mostly been studied in young healthy volunteers without disturbance to the ANS, and who ethically cannot be subjected to anything worse than transient painful stimuli. Thus, because it involves a tissue damage that, for ethical reasons, does not exist in experimental pain, postsurgical pain appears to be of the best models to study a physiological determinant of pain, as long as the surgical procedure and postoperative analgesia are homogeneous. As it is commonly practiced and often used as a model for testing analgesic drugs [17, 18], we chose to use extraction of the third molar ("wisdom tooth") to study the effects of the preoperative status of the ANS on postoperative pain. As patients are generally young and healthy, pain outcomes are also likely to be less biased by comorbidities and concomitant medications, and this condition therefore more reliable to explore physiological aspects. HRV was tested in a resting condition, then during VM and DB. In addition, to understand the mechanisms underlying a relationship between HRV and postoperative pain (if any), the patients were also preoperatively submitted to an acute pain test by hand immersion in hot water, to assess their natural pain sensitivity [19, 20]. Finally, if we could identify easy-to-record predictors of postoperative pain, they could be used in the future to help devise personalized analgesia [21–23].

Table 1 Selected measures of heart rate variability (HRV)

Time domain statistical measures

Variable	Units	Description	Involved component of the autonomic system
SDNN	ms	Standard deviation of all NN intervals; reflects all the cyclic components during the entire recording; depends on the duration of the recording	both
RMSSD	ms	Square root of the mean of the sum of the squares of differences between adjacent NN intervals	parasympathetic
NN50	count	Number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording	parasympathetic
pNN50	%	NN50 count divided by the total number of all NN intervals	parasympathetic

Frequency domain measures

Variable	*Units*	*Description*	*Frequency range (Hz)*	*Involved component of the autonomic system*
Total power	ms^2	Whole variance of NN intervals	≤ 0.4	both
LF	ms^2	Power in low frequency range; includes the slow oscillations of blood pressure via the baroreflex (Mayer's waves)	0.04 to 0.15	both
HF	ms^2	Power in high frequency range; reflects the HRV evoked by breathing via the stretch receptors ("respiratory arrhythmia")	0.15 to 0.45	parasympathetic
LF/HF	ratio	Surrogate of the relative part of the sympathetic component		sympathetic

Abbreviations: NN, normal-to-normal intervals. References:

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Materials and methods

All patients were recruited from the Dental Surgery unit of the University Hospital of Clermont-Ferrand (France). The inclusion criteria for the patients were that they had to be adult, aged 18 or over, ASA I-II, naive from previous 3rd molar extraction, and eligible for outpatient extraction of either two ipsilateral 3rd molars under local anesthesia without sedation ("two wisdom teeth" = 2WT subgroup), or the four 3rd molars under local anesthesia plus intravenous sedation ("four wisdom teeth" = 4WT subgroup). The mandibular tooth/teeth had to be impacted, i.e. completely covered by mucosa and at least partially impacted against bone; the maxillary one(s) had to be either similarly impacted, or impacted in the arch. The exclusion criteria were: weight under 50 kg; difficult access to the teeth to be extracted (e.g. limited mouth opening, temporomandibular joint dysfunction); pregnancy; high gag reflex; need for a regional anaesthesia of the mandibular nerve; contraindication to any of the drugs used in the protocol; any disease likely to impact the surgical outcomes (such as diabetes, renal insufficiency, haemostatic disturbance, autoimmune disease, or immunodeficiency); any ongoing or chronic disease likely to impact the study outcomes such as: orofacial chronic pain (e.g. due to endodontic, periodontal, gingival, osseous, or radiotherapy-induced disease), other invalidating chronic pain, or psychiatric disease; declared risky alcohol drinking (more than 2 standard drinks a day for men and more than 1 for women) or suspected alcohol use disorder; smoking more than 10 cigarettes or equivalent a day; declared or suspected use of recreational drugs; or daily ingestion of more than 4 units of caffeine-containing beverage. In addition, medications likely to impact the study outcomes were exclusion criteria; this included opioid daily intake during the past 3 months, or any intake during the past 7 days of: analgesic drugs (e.g. opioids, NSAIDs or steroids), drugs interacting with the sympathetic system (e.g. alpha/beta agonists or antagonists), drugs interacting with the parasympathetic system (e.g. muscarinic agonists or antagonists, including phenothiazines or antidepressants). Occasional intakes of weak analgesic drugs prior to 7 days before surgery were allowed.

A preoperative visit was conducted 7 to 14 days before surgery. The demographic and morphometric data were collected and the functional explorations were conducted in a quiet room specifically reserved for this purpose. Included in the demographic data noted was a parental hypertension score, based on the number of cases of hypertension amongst the parents and the grandparents, with 0 for no cases, 1 for one case, 2 for two cases, and 3 for more.

Firstly, the arterial pressure was first measured with a semi-automated device (Dinamap ProCare 300, General Electric, Boston, MA, USA) after 5-min rest in a semi-sitting position. Then, HRV was monitored by recording a continuous electrocardiographic signal (sampling frequency: 1000 Hz) transferred to a Powerlab system equipped with a LabChart application (ADInstruments, Colorado Springs, CO, USA), with respective low- and high-pass filters at 1 kHz and 0.3 Hz and a pitch at 60 Hz. The circuit was earthed via an electrode placed on the subject's knee. An initial 5-min recording of HRV at rest was carried out on the patient lying supine. Then further 5-min recordings were conducted during two consecutive challenges with the patients back in a semi-sitting position. Firstly, they underwent a series of ten Valsalva maneuvers (VM), at the rate of one every 30 s; each VM consisted of exhaling forcibly through a manometer against a pressure of 40 mmHg for 15 s. After a resting time of 5 to 10 min (i.e. long enough to return to close to the pre-challenge arterial pressure and heart rate), the patients underwent a series of six deep breathing maneuvers (DB), at the rate of one per minute [13, 24]; each deep breath lasted 10 s, with 5 s of inspiration and 5 s of expiration. A tachogram was obtained with measurements of the normal-to-normal (NN) intervals for these three conditions (baseline, VM and DB). The calculated parameters are listed in Table 1, along with their definitions and interpretations [14, 25]. The HRV measurements were totally machine-dependent, and the data collection and management was made unaware of the postoperative outcomes.

Immediately after the HRV assessment, the patient was subjected to a heat pain challenge, in which he/she had to put the non-dominant hand in a bath of water at 47 °C (SW22, JULABO GmbH, Seelbach, D) for a targeted maximum of 5 min. Every minute, he/she was asked to rate the heat-induced pain on a visual analogue scale (VAS) ranging from 0 (no pain) to 100 (the worst possible pain) and the values were averaged to obtain the heat pain intensity (HPI). In the event of the hand being withdrawn before completion of the 5-min protocol, a value of 100 was attributed to any subsequent observations that were missing.

In both groups, avulsions were conducted under local anesthesia by buccal and lingual infiltration at the operation sites. In addition, patients in the 4WT subgroup received intravenous sedation administered by a senior anesthetist unaware of the protocol. The current sedation protocol included as a first-line a single dose of i.v. remifentanil, to which was added if necessary a single i.v. dose of either midazolam or propofol. All surgeries were performed by one of the three co-authoring surgeons (CDe, LD and YS), all trained in a standardized technique at the same dental school. Immediately after surgery, the surgeon recorded information about the conduction of anesthesia and surgery.

At discharge, the patient was given a typed prescription of analgesia for 5 days, along with an instruction for self-administration. We followed the protocol currently used in in our unit, which differed between subgroups for the molecule of nonsteroidal anti-inflammatory drug (NSAID) only. Acetaminophen was systematically prescribed (1 g first thing in the morning, at midday and last thing at night). In addition, a NSAID could be taken as a first-line rescue treatment, preferentially with food; this was ibuprofen (200 mg per tablet, 1–2 tablets depending on pain intensity, up to a maximum of 8 tablets/24 hrs) in the 2WT subgroup, and ketoprofen (50 mg per tablet, 1–2 tablets depending on pain intensity, up to a maximum of 4 tablets/24 hrs) in the 4WT subgroup. As a second-line rescue treatment, tramadol could be taken (50 mg per tablet, up to a maximum of 3 tablets/24 hrs). All patients were given a booklet to note down postoperative pain and the intake of analgesic drugs. Pain was assessed on the evening of the day of surgery, then every morning (when getting up) and evening (when going to bed) of the 2nd to the 5th postoperative day, by a pen mark on a 10-cm VAS paper with the same scale as described above. The analgesic drugs taken were noted in a table which had a number of rows corresponding to the number of hours from discharge to the end of the 5th postoperative day, and one column per drug, plus one for any other drug than those prescribed. For each intake, the number of tablets had to be noted. The patient was unaware of the results of the HRV and experimental pain challenge, and the investigators had no contact with the patient throughout the postoperative observation period.

Table 2 Calculation of the analgesic drug score

Treatment	Dose (mg)	NNT	ARR	Classification	Score
Acetaminophen alone	1000	3.5	29%	average	1
Ibuprofen alone	200	2.7	37%	good	2
	400	2.3	43%	good	2
Ibuprofen + acetaminophen	200/500	1.6	63%	very good	3
	400/1000	1.4	71%	very good	3
Ketoprofen alone	50	1.8	56%	good	2
	100	1.6	63%	very good	3
Ketoprofen + acetaminophen	*no data*			*very good*	*3*
Tramadol alone	50	9.1	11%	poor	0,5
	75	8.4	12%	poor	0,5
	100	4.6	22%	average	1
	150	4.2	24%	average	1
Tramadol + acetaminophen	*50/?*	*no data*		*average*	*1*
	75/650	2.6 to 2.9	34 to 38%	good	2
	100/?	*no data*		good	*2*
	150/?	*no data*		*very good*	*3*

The estimated number needed to treat (NNT) for each drug dose or combination has been taken from the literature where the comparison was done vs. placebo in dental surgery (see references in the Methods' section). Comparison with an analgesic drug score has been made by recalculating the absolute risk reduction (ARR = 1/NNT) on the following basis: 0 if no treatment given; 0.5 for poor analgesia (ARR < 20%, NNT > 5); 1 for average analgesia (ARR 20-to-30%, NNT 3.33-to-5); 2 for good analgesia (ARR 30-to-50%, NNT 2-to-3.33); 3 for very good analgesia (ARR > 50%, NNT < 2); 4 when the three analgesic drug families (acetaminophen + NSAID + opiate) were administered

As postoperative analgesia was semi-directed, the primary outcome for representing postoperative pain was a composite score based on both the pain intensity and analgesic drug intake. This followed the Silverman integrated approach, which aims at correcting the bias induced by analgesic treatments on pain by summing pain and analgesia [26]. We therefore called "composite pain/analgesia score" (CPAS) this primary outcome. CPAS is the sum of a total pain score and a total analgesia score, each representing respectively the amount of pain and analgesic drug intake throughout the postoperative observation period. Firstly, to calculate the total pain score, we summed (i) the averaged pain score (i.e. the mean of the nine scores measured over the five postoperative days) and (ii) the maximal pain score reported during this period. This maximal value was considered as equally important than the average pain score because it indicates the patient's preferences of analgesic target [27]; summation was not weighted as both values covered the same range. The relevance of this summation-based outcome had been tested from personal data [4]. Then, this sum obtained for each individual, was centered and reduced by the following transformation: (ranked value within the sample) / [(mean theoretical rank) − 1], with mean theoretical rank = (sample size + 1) / 2. The rank within the sample was calculated in decreasing order. In addition, to control the selection bias as well as the bias induced by the additional sedation or the different NSAID prescribed, the ranking was conducted within each surgery subgroup (2WT/4WT). Secondly, to calculate the total analgesia score, we defined for each individual and each day of observation a parameter of analgesic drug intake. This parameter was devised based on a literature review of the reported number needed to treat (NNT, calculated vs. placebo) for 50% pain relief after a 3rd molar extraction, during the 4th -6th postoperative hours [17, 18, 28–41]. Based on the NNT for each drug dose or combination, an analgesic drug score ranging from 0.5 to 4 was given to each observation of analgesic intake (see Table 2 for details). Then, the sum of the five daily analgesia sub-scores was transformed as done for the total analgesia score. This way, the two components of the CPAS, the total pain score and the total analgesia score, had the same natural range (0 to 2), and CPAS as their sum naturally ranges from 0 to 4. As neither pain nor analgesic drug consumption follow a Gaussian distribution, transforming the data into ranks reduced the

random effects of distribution and harmonized the two components in terms of shape and range. An example of calculation is shown in Fig. 1.

Data analysis was performed using Microsoft Office Excel 2010 (Redmond, WA, USA) and XLStat (Addinsoft, Paris, F). Descriptive statistics were conducted for each variable, and normality was checked by visualization of Q-Q plots. Numerical data were expressed by mean ± SD in the case of a normal distribution, and otherwise as quartiles. Nominal data were expressed by the number of cases and the percentage. The analyses were conducted on full datasets; if the information about HRV, pain or analgesia missed for one patient, then the case was excluded from the analysis. The primary endpoint was to test the influence of a set of hemodynamic and HRV variables on postoperative pain (assessed by the CPAS). The tested variables were the raw systolic, diastolic and mean arterial pressure, the heart rate, and the raw HRV parameters listed in Table 1, for each of the three conditions (baseline, VM and DB), as well as the percentage changes from the baseline for arterial pressure and heart rate during VM and DB. Those percentage changes were calculated by dividing the raw change (difference) by the baseline value. We did not calculate the percentage changes for the HRV parameters because the baseline value was equal to 0 for some of the observations. The main secondary endpoint was to test the influence of these explanatory variables on the intensity of pain induced by the preoperative challenge (HPI). As both the CPAS and heat-induced pain are non-Gaussian numerical variables, we used Spearman's correlation to study the effect of numerical variables; the significance of the correlation was tested by comparing the ρ coefficient to the null value and its strength was expressed by the coefficient of determination, R^2. The same calculation was done to test the relationship between the HPI and the CPAS. In addition, to study the effect of a binary variable on a numerical outcome, comparisons were carried out using either the Student's t-test or the Mann-Whitney test depending on the distribution. To control the quality of the HRV measurement, we also conducted within-measurement principal component analyses (PCA) on Spearman's correlation matrixes, and analyzed the effect of VM and DB for repeated measurements. For this we used either the ANOVA-RM or the Friedman's test depending on the distribution, followed by *post hoc* tests if needed (respectively, the Student's t-test for paired data or the Wilcoxon signed rank test). If multivariable analyses were needed (e.g. to test interactions), a generalized linear model fitted to the type of variables was used. For inferential analyses, the significance threshold was set at 5%. As we wished to know whether either the sympathetic or the parasympathetic, or both, had some influence, and based on the hypothesis is that, although both contributing to a balance, those two components of the ANS act independently [42], the type-I error inflation was not corrected for the separate analyses of these two components. Although there are many different outcomes in HRV analysis, most of them explore a unique domain (especially the parasympathetic one), so the results must be more read by means of internal coherence. Nevertheless, within each domain, depending on the level of multicollinearity between parameters and on the general trends (e.g. whether an effect was observed for several parameters or not), complementary Bonferroni's corrections were conducted to check the reliability of our results. For the analysis of repeatedly measured

N (4WT subgroup)	**70**
Mean theoretical rank (MRT)	**(70+1)/2 = 35.5**

Postoperative day / time	**D1/Ev**	**D2/Mo**	**D2/Ev**	**D3/Mo**	**D3/Ev**	**D3/Mo**	**D4/Ev**	**D5/Mo**	**D5/Ev**	**max**	**mean**	***max+ mean***
Pain intensity (0-100)	**65**	**26**	**54**	**65**	**53**	**65**	**52**	**45**	**65**	**65**	**54**	***119***
(inversed) rank within the 4WD sample →												***50***
Pain composite score (standardized) = rank/(MRT-1) →												***1.45***

Postoperative day	**D1**	**D2**	**D3**	**D4**	**D5**	
Paracetamol (mg)	**2000**	**1000**	**1000**	**1000**	**4000**	
Ketoprofen (mg)	**200**	**100**	**100**	**200**	**100**	***sum ↓***
Ibuprofen (mg)	**0**	**0**	**0**	**0**	**0**	
Tramadol (mg)	**50**	**50**	**50**	**200**	**0**	
Analgesic score	**4**	**4**	**4**	**4**	**3**	***19***
(inversed) rank within the 4WD sample →						***63***
Anagesia composite score (standardized) = rank/(MRT-1) →						***1.83***

Pain composite score (standardized)	**1.45**
Anagesia composite score (standardized)	**1.83**
sum	**↓**
Composite pain/analgesia score	**3.28**

Fig. 1 Example of calculation of the composite pain/analgesia score (CPAS) for one subject of the study sample, who belonged to the "4 wisdom teeth" extraction (4WT) subgroup. How the two components of CPAS are calculated is further detailed in the Methods' chapter

outcomes, the preliminary trend test avoided the type-I error inflation.

We made an initial estimate of the sample size in order to allow for the analysis of 12 putative factors, resulting in an estimation of 104 + 12 = 116 subjects. We based this assumption on a rule for multivariable analysis [43, 44], although the primary endpoint was based on univariate analyses. Our objective was to include 120 patients, considering that this sample size allowed to identify a correlation of 0.3 with 1−β = 90%, and a correlation of 0.25 with 1−β = 80% (with α = 5%) [45, 46].

Results

One hundred and twenty-one patients were included in the study, of which four were unable to undergo the HRV assessment; of the 117 who completed the study, 50 (42.7%) were in the 2WT and 67 (57.2%) in the 4WT subgroup. The characteristics of these patients are presented in Table 3, along with the differences between subgroups. The only noticeable differences are a slightly younger age, a higher maximal Pederson score, and a longer duration of surgery in the 4WT subgroup.

The hemodynamic and HRV data for the whole cohort are presented in Figs. 2 and 3, and Additional file 1 for details. VM increased systolic arterial pressure and heart rate, while DB decreased systolic arterial pressure and increased the heart rate; the increase in heart rate was significantly greater under VM (+11.6%) than under DB (+1.6%). Diastolic arterial pressure was unaffected. Both challenges increased the time-domain parameters of HRV, but these effects were stronger under VM for SDNN, while they were stronger under DB for NN50 and pNN50. Also, both challenges increased the frequency-domain parameters of HRV, but these effects were stronger under VM for total power, while they were stronger under DB for LF and LF/HF. The PCA conducted on all the HRV parameters showed that all the time-domain parameters, along with total power and HF (for the frequency-domain) were collinear and highly represented on the same axis, while LF/HF was highly represented respectively on the second axis. When the challenge-induced change in heart rate was added to the models, it was mostly represented on a third axis, but also on the same axis as LF/HF (Additional file 2). This supports the hypothesis that most of the parameters represent the same domain, theoretically the parasympathetic component of the ANS, while only LF/HF and change in heart rate represent another one, theoretically the sympathetic component.

The two subgroups (2WT/4WT) behaved similarly (Additional file 3), but heart rate was higher at the baseline in the 4WT subgroup ($p = 0.041$), and increased less in this subgroup under both challenges ($p = 0.001$ and 0.003 respectively), in such a way that the raw values became similar to those of the 2WT subgroup. Also, the slight decrease in diastolic arterial pressure under VM was only observed in the 2WT subgroup.

The effects of age on the hemodynamic and HRV parameters are detailed in Additional file 4. Age was positively correlated to both diastolic and mean arterial pressure; it was negatively correlated to the change in systolic arterial pressure during VM (i.e. VM-induced hypertension decreased with age) and positively correlated to the change in mean arterial pressure during DB (i.e. DB-induced hypotension increased with age). Age did not influence heart rate or its changes during VM or DB. In the time-domain, age was negatively correlated to all the baseline parameters for HRV, as well as to all those parameters measured during DB; none of these correlations were observed for measurements during VM. In the frequency-domain, similar trends were observed for total power and HF at baseline and during DB. Conversely, LF/HF tended to increase with age, and this correlation was significant during VM.

The effects of sex on the hemodynamic and HRV parameters are detailed on Additional file 5. For most of the measurements of arterial pressure, higher values were observed in men than in women, and the DB-induced change (i.e. decrease) in mean arterial pressure was greater in men. In the time-domain analysis of HRV, SDNN and RMSSD were higher in male, but this only under VM, and in the frequency-domain, higher values in male under VM were also observed for total power and HF. The LF/HF ratio was unaffected by sex.

The intensity of pain during the hot water challenge (HPI) was similar for the 2WT and 4WT subgroups, and was not influenced by age or sex. Additional file 6 shows the results of the correlation analyses of HPI against the hemodynamic and HRV parameters. Only the increase of heart rate during VM and LF/HF under DB were found to significantly influence HPI, with an inverse correlation. Significance was still present after Bonferroni's correction for two tests. Those effects are displayed in Fig. 4. Neither age nor sex interacted with those two significant correlations.

The CPAS was similar for the 2WT and 4WT subgroups, as expected due to the within-subgroup ranking. Neither age nor sex significantly influenced the CPAS, although it was slightly higher in females (2.4 [1.4–2.9]) than in males (1.8 [1.0–2.6]). There was a significant positive correlation between HPI and CPAS ($\rho = 0.195$; $p = 0.035$; $R^2 = 3.8\%$); correlation was weaker with the total pain score and the analgesia pain score taken separately ($\rho = 0.185$ and 0.165 respectively). Neither age nor sex interacted with this relationship (tested by ANCOVA). Additional file 7 shows the results of the correlation analyses of CPAS against the hemodynamic and HRV parameters. Only the increase of heart rate during

Table 3 Characteristics of the cohort and its two subgroups

	Whole sample (*n* = 117)	2WT (*n* = 50)	4WT (*n* = 67)	*p* value
Demographic data				
Age (years)	23.4 ± 7.1	25.7 ± 8.8	21.6 ± 4.8	0.002
Female gender	64 (54.7)	23 (46.0)	41 (61.2)	0.102
Smoker	37 (31.6)	17 (34.0)	20 (29.9)	NC
Hypertension	1 (0.9)	1 (2.0)	0 (0.0)	NC
Parental hypertension score [a]				NC
0	79 (67.5)	31 (62.0)	48 (71.6)	
1	21 (17.9)	11 (22.0)	10 (14.9)	
2	10 (8.5)	3 (6.0)	7 (10.4)	
3	4 (3.4)	2 (4.0)	2 (3.0)	
not stated	3 (2.6)	3 (6.0)	0 (0.0)	
Preoperative heat pain challenge				
Hand withdrawal before 5 min.	93 (79.5)	35 (70.0)	58 (86.6)	0.050
Duration of immersion (min)	2 [1–4.5]	2.4 [1.1–5]	2 [0.8–3.9]	0.118
Averaged pain intensity (VAS out of 100)	87 [69–95]	85 [58–94]	87 [73–95]	0.260
Surgical characteristics				
Upper jaw, right side	95 (81.2)	31 (62.0)	64 (95.5)	NC
Upper jaw, left side	94 (80.3)	30 (60.0)	64 (95.5)	NC
Lower jaw, right side	94 (80.3)	28 (56.0)	66 (98.5)	NC
Lower jaw, left side	96 (82.1)	30 (60.0)	66 (98.5)	NC
Maximal Pederson score	7 [6–8]	7 [6–8]	7 [7–8]	0.014
Local anesthesia				
Articaine[b]	105 (89.7)	50 (100)	55 (82.1)	NC
Lidocaine[c]	12 (10.3)	0 (0.0)	12 (17.9)	NC
Duration of surgery (min)	31 [15–44]	25 [14–33]	35 [15–53]	0.003
Protocol for sedation[d]				
Remifentanil total dose (µg)	NA	NA	0.25 [0.18–0.3]	NA
Additional midazolam (No. of cases) [e]	NA	NA	21 (31.3)	NA
Additional propofol (No. of cases) [e]	NA	NA	1 (1.5)	NA
Maximal pain score (out of 100)	64 [45–75]	63 [43–75]	65 [54–73]	0.593
Average pain score (out of 100)	30 [21–46]	29 [15–45]	33 [25–48]	0.117
Acetaminophen total dose (g)	13 [10–15]	12 [8–14]	13 [10–16]	NC
Ibuprofen total dose (mg)	NA	1200 [400–2300]	NA	NC
Ketoprofen total dose (mg)	NA	NA	400 [125–700]	NC
Any NSAID intake	105 (89.7)	45 (90.0)	60 (89.6)	1.000
Tramadol (or equivalent) total dose (mg)	50 [0–150]	50 [0–150]	50 [0–150]	NC
Any opioid intake	72 (61.5)	29 (58.0)	43 (64.2)	0.497
Composite pain/analgesia score	1.84 [1.25–2.78]	1.86 [1.25–2.87]	1.80 [1.26–2.62]	0.768
Composite pain/analgesia score > 2	55 (47.0)	23 (46.0)	32 (47.8)	0.850

Characteristics of the patients who completed the study. Numerical data are expressed as mean ± SD in the case of a Gaussian distribution, and otherwise as median [1st quartile– 3rd quartile]. Nominal data are expressed by the number of cases followed by the percentage in rounded brackets. The p values compare the two subgroups. Abbreviations; 2WT and 4WT: "2 wisdom teeth extracted" and "4 wisdom teeth extracted" subgroup, respectively (see Methods' section for details); NA: not applicable; NC: not calculated; NSAID: non-steroidal anti-inflammatory drug. Notes: a, see Methods' section for description; b, articaine was always given as 40 $mg.mL^{-1}$, with 1:200000 adrenaline; c, lidocaine was always given as 20 $mg.mL^{-1}$, with 1:80000 adrenaline; d, see Methods for details of the protocol; e, the percentages are for the 4WT subgroup only

VM influenced the CPAS, with an inverse correlation; however, significance was no longer present after Bonferroni's correction for two tests. This effect is displayed in Fig. 4. Neither age nor sex interacted with this relationship (tested by ANCOVA).

As only one patient in the cohort reported chronic hypertension, we did not take this factor into consideration in our analyses. We did study the influence of parental hypertension score, which was unrelated to either the subgroup, the sex or the age, and was also unrelated to the HPI and to CPAS.

Discussion

In this exploratory study conducted in a healthy young population exposed to a standardized surgical painful condition, we were able to identify a relationship between

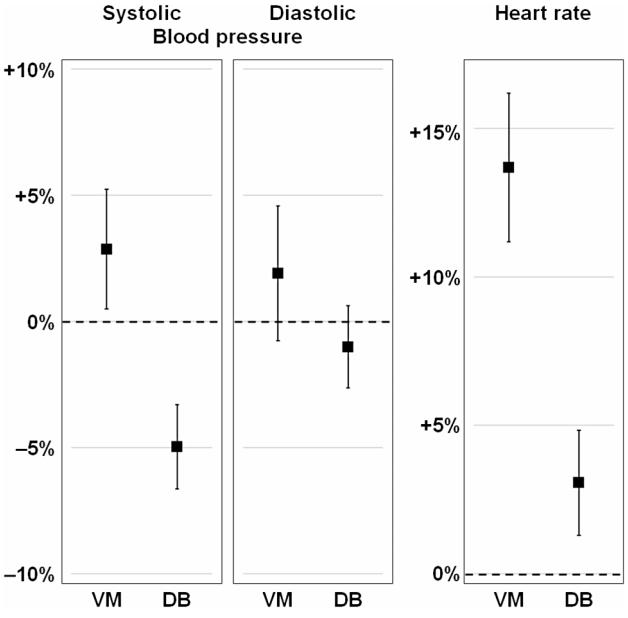

Fig. 2 Summary of the effects of the two challenges, namely the Valsalva maneuver (VM) and the deep breathing challenge (DB) on the hemodynamic parameters of the study sample. The variables displayed on the graph are the percentage of change from the baseline values; the black squares represent the mean value, and the whiskers represent the 95% confidence interval (CI) limits. When the null value is out of CI limits, this corresponds to a significant difference ($p < 0.05$) compared to baseline; when the respective CI limits of the variable for each challenge do not overlap, this corresponds to a significant difference between the two challenges. Those significances are without Bonferroni's correction. The aggregated data are detailed in the Supplementary Table 1

the sympathetic component of the ANS and pain, while no effect of the parasympathetic component could be shown. As the observed effects (inverse correlations, i.e. the sympathetic response may protect form pain) were significant only for the increase in heart rate in the Valsalva maneuver, we must consider that this relationship was mild, compared to the multiple putative determinants of pain. A limitation of the study lies on the existence of two surgery subgroups, including difference in the anesthetic protocol and the NSAID molecule; nevertheless, the other typological differences between those subgroups were mild, and furthermore this bias was corrected as the primary outcome was ranked within each subgroup.

The reliability of the explorations of ANS we performed, as well as the meaning of our observations, must be discussed under the light of the current knowledge. While it is currently admitted that HRV may reflect the ANS [14, 25], its ability to explore its sympathetic component is a matter of debate [16]. Also, the frequency-domain analyses are considered to be a better fit for short recordings [14]. HRV measurements in resting conditions reflect the natural balance between the two components of ANS, and normative data obtained in very similar conditions in young adults fell into similar ranges to those of our observations [47]. However, and probably because the ANS balance was in the physiological range in this healthy population, those resting conditions were not favorable to observe an effect of any of the two components of ANS. The VM and DB challenges have been designed to elicit the ANS activity and therefore to potentiate the putative effects of its components [13]. Firstly, as we observed an increase of all the HRV parameters under the VM and DB challenges, we can consider that ANS was generally functional in our cohort. However, while both VM and DB evoked significant increases of all the HRV parameters– of which most are supposed to be parasympathetic-driven– they acted differently on the main hemodynamic parameters (Fig. 2). According to physiological knowledge, VM induces a multiphase response with an initial direct effect of intrathoracic overpressure eliciting a sympathetic response (with tachycardia), then delayed mixed effects due to both a rebound improvement of circulation and a parasympathetic response [25]. As our recording averaged the events occurring during all the phases and beyond, we could not discriminate the successive responses, but we observed that VM stimulated both components of the ANS, with a lesser sympathetic response (as expressed by tachycardia). Contrary to the orthostatic test (which we did not perform), VM does not increase diastolic arterial pressure, probably because the intrathoracic overpressure stresses the heart cavities and because the sympathetic response is more hormonal that neural [25]. How DB influences ANS is more controversial, although it might stimulate preferentially the cardiac afferent innervation through extracardiac baroreceptors. While a close relationship between the parasympathetic control and DB-induced HRV has been demonstrated [48, 49], a predominantly sympathetic response was suggested by a study on young healthy volunteers, in which DB increased sensibly more LF/HF than HF [50]. Such between-studies discrepancies can be explained by differences in the technique used and in the intrathoracic pressure regimens. As, in our DB test, HF and LF/HF both increased in a similar range (by 150 and 143%, respectively), an activation of both components is possible, but a recent review pointed out that LF/HF may not reflect properly the sympathetic component of ANS, especially if respiratory frequency is out of its physiological range [16]. Finally, we observed that HPI was able to predict CPAS, confirming that preoperative pain sensitivity partly explains postoperative pain [21]. Nevertheless, HPI explained only 4.3% of the whole variance of CPAS, highlighting the multiple other factors influencing postoperative pain (e.g. psychology, surgery), and this may explain why VM-induced tachycardia predicted HPI but not CPAS.

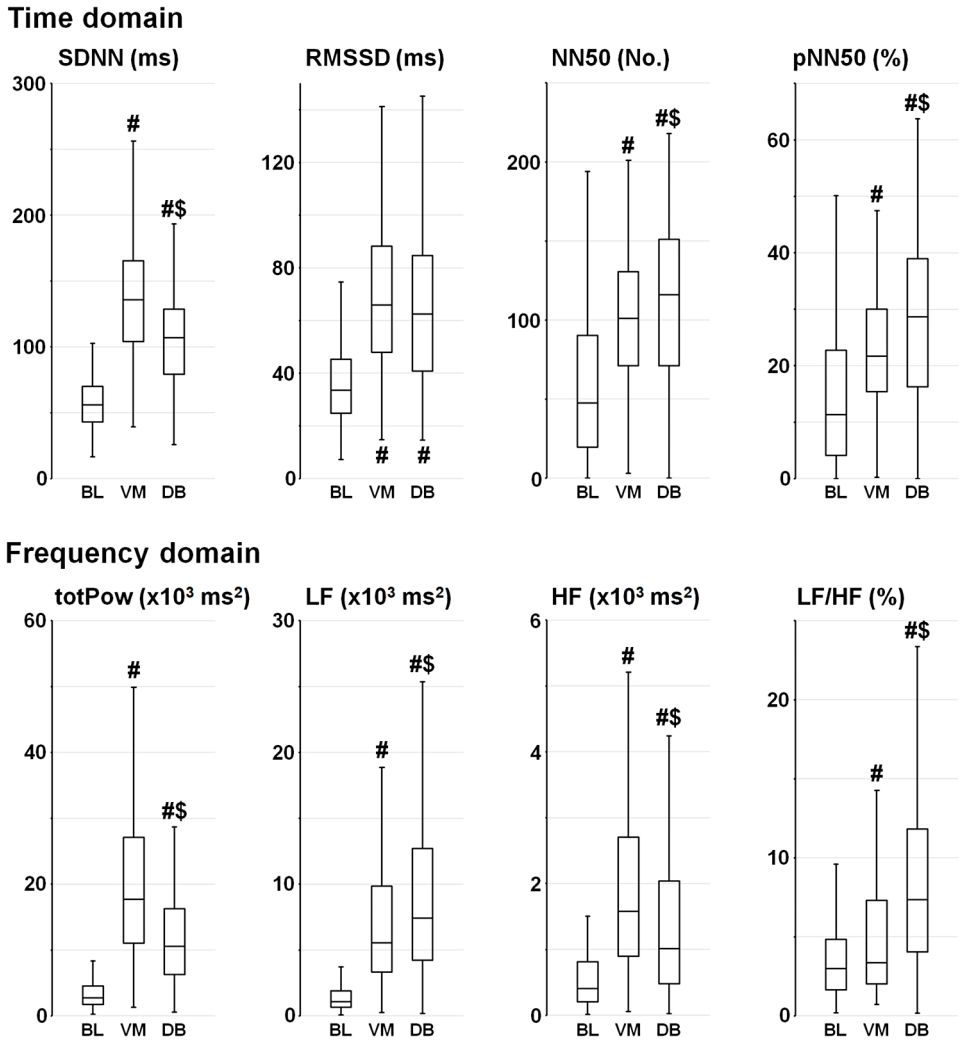

Fig. 3 Summary of the effects of the two challenges, namely the Valsalva maneuver (VM) and the deep breathing challenge (DB) on the heart rate variability (HRV) parameters of the study sample, in comparison to the baseline values (BL). The variables displayed on the graph are box plots of the raw values. The interpretation of the HRV parameters is detailed in Table 1. The symbols '#' and '$' signal a significant difference ($p < 0.05$), respectively with baseline and between VM and DB (see Methods' chapter for detailed description of the statistics). The aggregated data are detailed in the Supplementary Table 1

Our results suggest that pain sensitivity is related to the subject's capacity for a sympathetic response. Nevertheless, a recent systematic review investigated the ability of ECG-derived assessments of ANS function to predict pain in various clinical conditions (i.e. experimental, postoperative, and persistent pain), and highlighted a general trend in showing antinociceptive effects of the parasympathetic, but not of the sympathetic tone [12]. However, while such trend was also noted in predicting surgical acute pain– which we consider as particularly relevant to study pain mechanisms– the results of those studies were not so strongly conclusive. One study conducted in 30 patients undergoing open carpal surgery (moderate postoperative pain) reported that the parasympathetic component (HF at rest) predicted a lesser pain [10]; LF/HF was not tested. A British team worked on a HRV-based polynomial model to predict postoperative pain in small samples of patients (respectively 17 and 29) undergoing varicose vein surgery, and concluded that most of the autonomic contribution in the model was parasympathetic; nevertheless, the role of LF (nonspecific) seemed to overcome this of HF [51, 52]. In 30 patients undergoing surgery for epilepsy, postoperative pain was also negatively correlated with HF, but positively correlated with LF/HF [53]; of note, HRV was recorded in patients entering the operating room, i.e. in stressful conditions. A study conducted in neonates reported a predictive value of a marker of parasympathetic activity in postoperative pain, but here again, the sympathetic component was not explored [54]. Finally, the preoperative (not HRV-based) cardiovagal baroreflex sensitivity has been studied in 55 patients before cardiothoracic

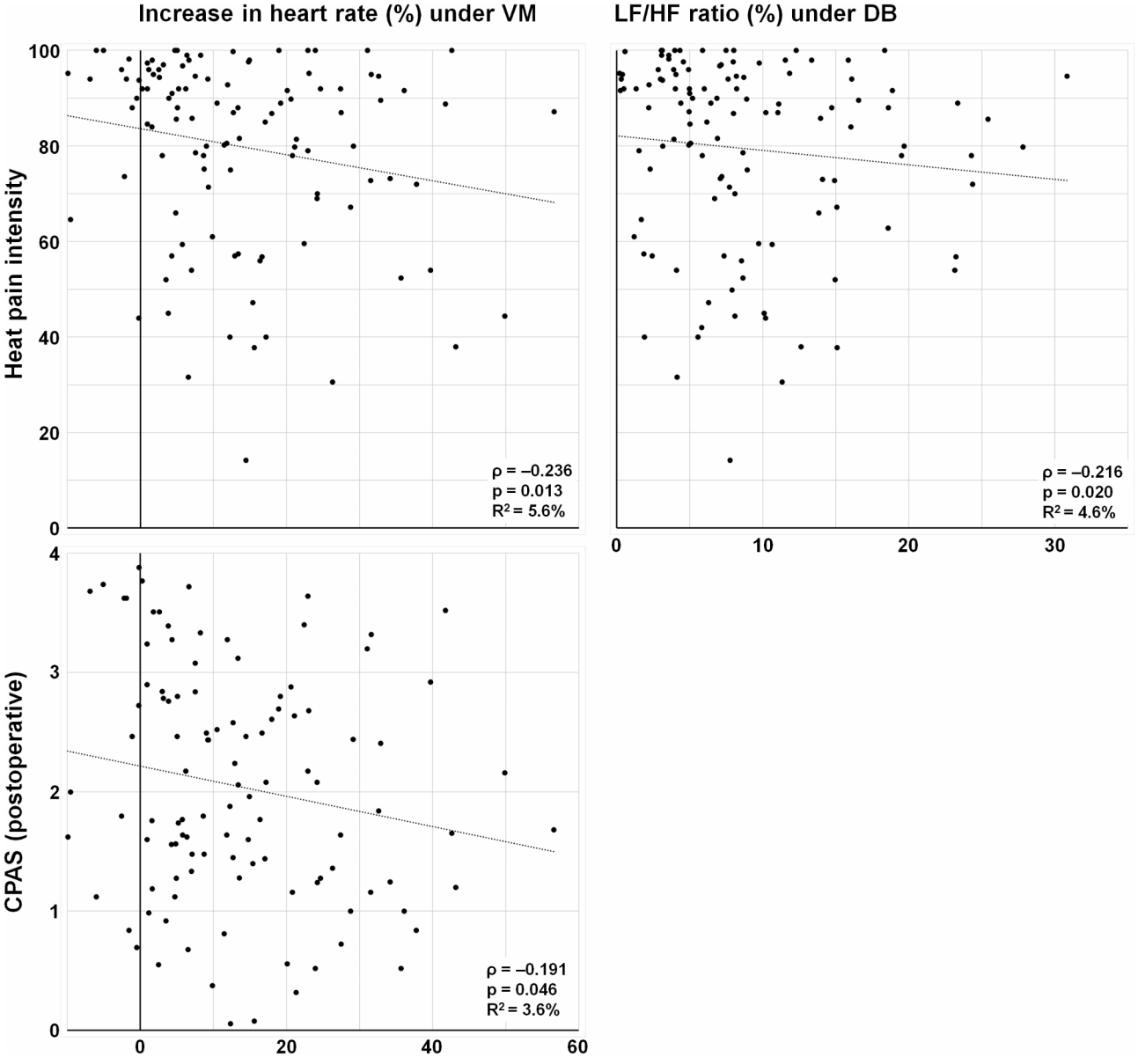

Fig. 4 Scatterplots showing the relationships between hemodynamic or heart rate variability (HRV) parameters that have been found significant ($p < 0.05$) in the correlation analyses without Bonferroni's correction. The dependent variables are either heat pain intensity (experimental pain) or the composite pain/analgesia score (CPAS) (see Methods' chapter for details). The parameters tested are either the increase in heart rate as observed under Valsalva maneuver (VM) or the LF/HF ratio (HRV parameter, see Table 1 for interpretation) under deep breathing challenge (DB). The values shown for each relationship scatterplot are the Spearman's correlation coefficient (ρ), the p value for the comparison of ρ to the null value (without Bonferroni's correction), and the coefficient of determination R^2

surgery, and– contrary to the previous studies– this marker of parasympathetic tone was found as favoring postoperative pain [55]; heterogeneity in surgery, anesthesia and postoperative analgesia could have influenced those results. With a sensibly bigger and homogeneous sample of patients, the results of the current study contradict those previous reports of a parasympathetic influence on pain, as none of the related parameters– even under potentiation of VM and DB and without Bonferroni's correction– was show to be influential.

Neither age nor sex were found to influence the pain outcomes in our cohort (despite a small trend for sex), and none of these biometric factors interacted with the effects of HRV on pain, while both had some influence on the hemodynamic and HRV parameters. While pain sensitivity is known to decrease with age [56, 57], and women are more sensitive to pain than men [58, 59], none of these effects were observed in our cohort. This could be explained by the particularities of our sample or of our pain models, or by insufficient statistical power

(age variation was limited in our sample). On the other hand, we observed that age correlated with arterial pressure (a phenomenon currently explained by vascular stiffness) [60], and tended to impair many HRV parameters, also consistently with published data [47, 49, 61]. Of note, such age-induced impairment was not observed for LF/HF, also consistent with previous reports [47], and suggesting that ageing has a greater effect on the parasympathetic component of HRV. This could also explain why the age effect on HRV was not converted into an effect on pain in our study. In terms of sex, we observed that our male patients had a higher arterial pressure, as well as higher values for several HRV parameters, but this was only during VM and was not observed for LF/HF. This was also in accordance with reports in young resting subjects [47, 60]. Whereas this sex effect we observed on arterial pressure cannot currently be explained [60], this effect on HRV is explained by a higher vagal tone in young males, while the sympathetic response seems unaffected by sex [62, 63]. This could support the hypothesis that sex effects on pain– if any– are not transmitted by the ANS.

Conclusions

Within a standardized model of postoperative pain, we identified a relationship between the sympathetic component of ANS, and pain perception. Although the effects we observed were quite mild, this contradicts previous reports of a preferential predictive role of parasympathetic activity. We also observed a gap between experimental pain– as measured in healthy preoperative conditions– and postoperative pain, probably because the surgery itself adds many other physiological and psychological factors to the strictly neurosensory ones. Furthermore, the expression of pain itself as a relevant marker of the nociceptive processes is also matter of debate, as it is highly dependent from individual prior pain/life experiences. Anyway, a simple preoperative assessment of VM-induced tachycardia could be interesting for prediction of postoperative pain, but probably with a small added value besides the already known psychosocial predictors [64–66]. Finally, attempts at modifying the ANS balance by medical or psychological interventions to prevent pain deserve further attention in future research.

Abbreviations

ANOVA-RM	Analysis-of-variance for repeated measures
ANS	Autonomic nervous system
ASA	American Association of Anesthesiologists
CPAS	Composite pain/analgesia score
DB	Deep breathing (challenge)
HPI	Heat pain intensity
HRV	Heart rate variability
NN	Normal-to-normal (intervals)
NNT	Number-needed-to-treat
NSAID	Nonsteroidal anti-inflammatory drug
PCA	Principal component analysis
VAS	Visual analogue scale
VM	Valsalva maneuver
2WT/4WT	"Two" and "four wisdom teeth" subgroup, respectively

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-025-02949-8.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

Acknowledgements

The authors would thank the staff of the dental surgery unit and the clinical research and innovation office of the university hospital of Clermont-Ferrand (France).

Author contributions

CDe, LD and YS recruited the patients, conducted the explorations, performed the surgeries and collected the data. CDe, LD, BP, RD and CDu designed the study. CDe coordinated the research. BP and CDu conducted the analyses. CDe and CDu drafted the manuscript. All authors read and approved the final manuscript.

Funding

The devices to explore HRV and pain sensitivity were provided by the INSERM U1107 Neuro-Dol research unit (Clermont-Ferrand, France).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study has been approved by the appropriate research ethics committee (*Comité de Protection des Personnes Sud-Est VI*, ref. n° AU841). All participants gave their written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Université Clermont-Auvergne, CHU Clermont-Ferrand, Neuro-Dol, Inserm, Clermont-Ferrand F-63000, France
[2]Direction de la Recherche Clinique et des Innovations, CHU Clermont-Ferrand, Clermont-Ferrand F-63000, France
[3]CHU Clermont-Ferrand, Plateforme d'Investigation Clinique, Inserm, Neuro-Dol, Clermont-Ferrand F- 63000, France
[4]Centre d'Investigation Clinique, CHU de Clermont- Ferrand, 58 Rue Montalembert, Clermont-Ferrand 63000, France

Received: 29 July 2024 / Accepted: 6 February 2025
Published online: 08 March 2025

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