Pancreatology 20 (2020) 25–34

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

A clinically feasible method for the assessment and characterization of pain in patients with chronic pancreatitis

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ARTICLE INFO

Article history:
Received 24 September 2019
Received in revised form
14 November 2019
Accepted 18 November 2019
Available online 20 November 2019

Keywords:
Chronic pancreatitis
Pain
Nociception
Central sensitization

ABSTRACT

Background and aims: Pain is the primary symptom of chronic pancreatitis (CP), but methods for sensory testing and pain characterization have not previously been validated for clinical use. We present a clinically feasible method for the assessment and characterization of pain mechanisms in patients with CP based on quantitative sensory testing (QST).

Methods: This was a cross-sectional, multicenter study of 122 control subjects without pancreatic disease and another 60 patients with painful CP. All subjects underwent standardized QST assessments including a cold pressor test, a conditioned pain modulation paradigm, repetitive pin-prick stimuli (temporal summation) and pressure stimulation of the upper abdominal (pancreatic) and control dermatomes. The effects of age and gender on QST assessment parameters were investigated and normative reference values based on quartile regression were derived and implemented in algorithms to categorize patients according to their patterns of central pain processing (normal vs. segmental sensitization vs. widespread sensitization).

Results: Absolute pressure thresholds were subject to clinically relevant gender effects (all $p < 0.001$), while the remainder of QST parameters were unaffected by age and gender. The algorithm with the best discriminatory capacity showed good separation between patients and controls ($p < 0.001$); 50% of patients had normal central pain processing, 23% had evidence of segmental sensitization and 27% had evidence of widespread sensitization.

Conclusion: We show normative reference values for a clinically feasible method for assessment and characterization of pain mechanisms in patients with CP. Application of this method streamlines the evaluation of pancreatic pain and may be used to inform treatment.

Clinicaltrials.gov id: NCT03434392.

Introduction

Chronic pancreatitis (CP) is a debilitating fibro-inflammatory disease of the pancreas which manifests with a primary symptom of abdominal pain that affects over 80% of patients during the course of their disease [1]. Abdominal pain in CP is often debilitating, and patients who have constant pain as opposed to intermittent pain have been found to have lower quality of life, greater rates of disability, and higher resource utilization regardless of the intensity of their pain [1,2]. The presence, severity and temporal nature of pain correlate poorly with imaging findings, making assessment and treatment of pain in CP particularly challenging [3].

There are few disease-specific or personalized approaches to CP-related pain at this time: treatment of pain in CP is guided by

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https://doi.org/10.1016/j.pan.2019.11.007
1424-3903/

assessment with universal questionnaire instruments that have yet to be validated in CP, and step-up analgesic therapy is based on the World Health Organization's treatment for chronic pain [4–7]. Medical therapies for pain remain limited and clinical practice varies widely among gastroenterologists and primary providers who care for patients with CP. Patients are often prescribed opioid analgesics, which are associated with side effects (e.g, constipation) as well as risks of harm (e.g., falls, fractures, misuse, addiction, overdose) [8]. Invasive treatments such as endoscopic therapy for ductal abnormalities, extracorporeal shock wave lithotripsy for stone dissolution, or surgery to remove diseased portions of the organ are effective in achieving pain relief by themselves or in combination in only a subset of patients [9–11].

The common approach of assessing presence, temporal nature, and severity does not capture the complexity of visceral pain in CP and its dynamic nature, and additional methods for assessing and treating pain have been identified as an important and unmet need in the field [12,13]. Quantitative Sensory Testing (QST) can be used to characterize sensory processing in peripheral and central pain pathways and provides a means for phenotyping each individual patient's nociceptive profile. The rationale for QST is that different nerve pathways and networks are explored with standardized stimulation of somatic or visceral tissue. The response is then quantified with psychophysical and/or objective methods that reflect the state of the nociceptive system in a standardized and reproducible way [14]. In patients with painful gastrointestinal diseases, including CP, QST with stimulation of the upper or lower gastrointestinal tract has been used to characterize the visceral nociceptive system and corresponding neuroplastic changes in central pain pathways [15–17]. However, in a clinical setting, testing of the skin is easier to perform and more acceptable to patients than the more cumbersome and unpleasant visceral testing techniques [18,19]. Due to convergence between visceral afferents from the pancreas and somatic afferents from the upper abdominal area (T10 dermatome) at the same neuronal structures in the spinal cord, QST of the skin and underlying somatic structures can be used to assess whether or not the central pain pathways are sensitized by nociceptive input from the pancreas [20]. Furthermore, testing with specific paradigms (temporal summation (TS)) and assessment of descending inhibition from brainstem centers on the spinal cord reflects abnormal pain processing in central pain pathways. By combining these different QST assessment parameters it is possible to confer a specific pain phenotype to patients. Hence, QST offers a personalized biomarker through which individual patient pain phenotypes can be categorized [21]. Identification of such phenotypes can potentially allow for individualized treatment approaches that will possibly lead to more effective pain management and improved patient outcomes.

The *Nijmegen Aalborg Screening QST Paradigm (NASQ)* is a specialized QST protocol that has been developed in collaboration between groups in the Netherlands and Denmark. It provides a means of obtaining information on central pain processing specifically developed for pancreatic pain [22,23]. In an effort to simplify the NASQ, a new protocol has been created that streamlines the testing for practical use in a clinical setting amenable to patient testing and research. Prior to evaluation of a cohort of CP patients, this newly revised NASQ method (heretofore simply entitled "P-QST" when referring to the overall method specifically) was tested in a control population to define the normal parameters of these tests. In this study, we first aim to determine the age and gender effects on P-QST assessment parameters. We then propose parameters for obtaining information on central pain processing, and subsequently derived diagnostic thresholds for the specific P-QST assessment parameters. Finally, in a random selection of CP patients, we show feasibility of this method through a demonstration of the distribution of P-QST derived phenotypes.

Methods

Subjects

A total of 122 control subjects were recruited through advertisements and invitation at three international pancreas centers: The University of Pittsburgh Medical Center (Pittsburgh, PA, USA), The Johns Hopkins University Medical Center (Baltimore, MD, USA), and Aalborg University Hospital (Aalborg, Denmark). Institutional Review Board approval was obtained at each of these sites individually (University of Pittsburgh IRB Protocol PRO17060648, Johns Hopkins IRB 00143375, Aalborg University Hospital N-20090008). The study was registered with Clinicaltrials.gov (NCT03434392). Individuals were eligible for this study who were 18 years of age or older, had no pancreatic disease and no abdominal pain. Subjects were excluded from the study if they had abdominal pain more than six times within the past one year, had evidence of medical or surgical disease of importance as judged by the principal investigator and co-investigators of each site, were maintained on chronic opioid analgesics for any reason, or if they were known to be pregnant at the time of screening. Age and gender distribution were targeted to include an approximately equal number of participants in each of six categories: females age <40 ($n = 20$), females age 40 to 59 ($n = 21$), females age ≥ 60 ($n = 20$), males < 40 ($n = 21$), males 40 to 59 ($n = 20$), males age ≥ 60 ($n = 20$). When a category was filled, recruitment stopped for additional participants in that category.

A total of 60 patients with painful CP were included for evaluation in the feasibility sub-study. Patients with CP were enrolled at all three centers during the period of control enrollment. CP patients who were eligible were $\geq$18 years of age, met Cambridge III or IV criteria for CP on cross-sectional imaging or had calcifications as described in the definite M-ANNHEIM criteria [24], and had an average pain score $\geq$3 on a 0–10 numeric pain rating scale (NRS) during the last 24 h. Patients were excluded if they had previously undergone pancreatic surgery or any organ transplantation, if they had a painful abdominal condition whose effect they were unable to distinguish from pancreatitis pain, and if they were having an attack of acute pancreatitis at the time of enrollment. At the time of enrollment, patients completed a questionnaire with the help of the enrolling physician regarding their medical history related to pancreatitis including CP etiology. Of the 91 CP patients enrolled at the time of control data analysis, 60 were chosen at random from the pooled data for inclusion in the feasibility sub-study. Randomization of patients for inclusion was conducted via a random number generator (Stata 16.0, College Station, Texas, USA). This generates a set of pseudorandom numbers from a uniform distribution and we then selected the first 60 random individuals from the pool of 91 potentials with painful CP. Because this portion of our study was not designed for any more than demonstrating feasibility of phenotyping, additional analyses were not performed for evaluation of association with any disease or patient-related factors.

Study procedures

All P-QST procedures were performed by trained study personnel using the same equipment and standardized instructions to the subjects. An instructional video was created by the investigators in Aalborg which was then used for training of study personnel at the other sites. A 4-hr in-person training course for all participating centers was additionally held with technical

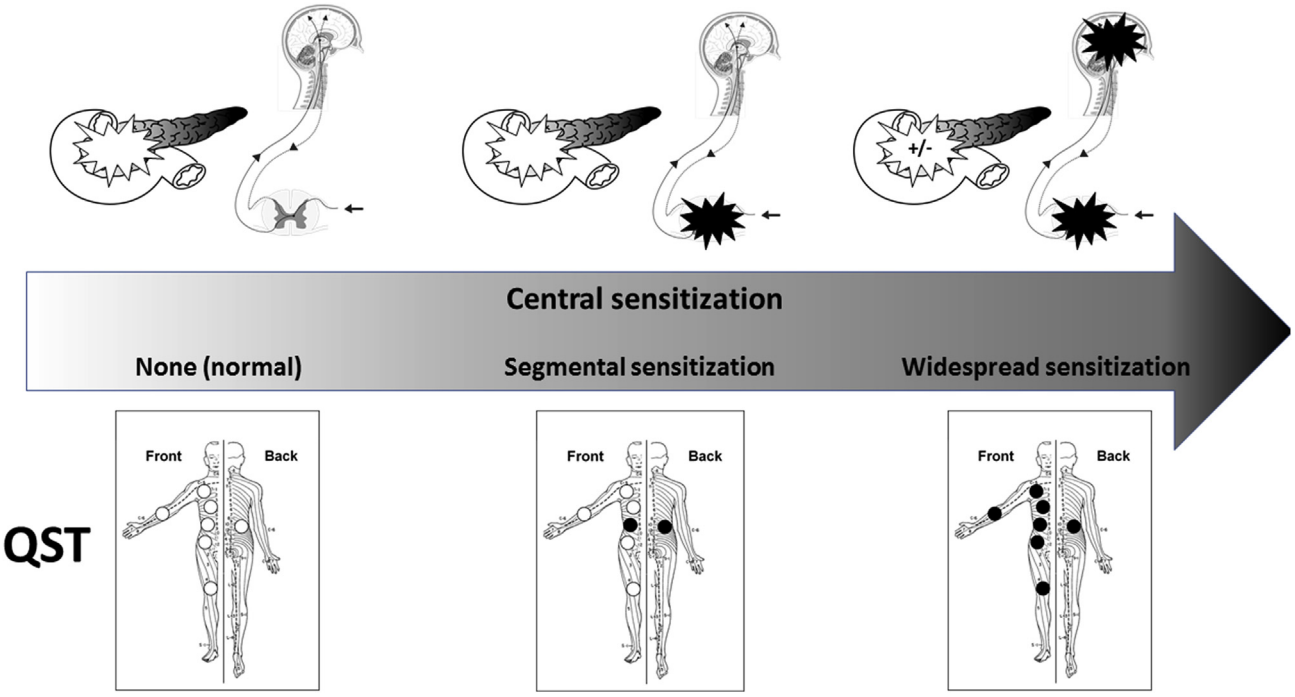

Fig. 1. Spectrum of pain responses, ranging from normal through segmental sensitization to widespread sensitization. Segmental sensitization is associated with increased excitability of second-order neurons in the spinal cord sharing spinal innervation with the pancreatic gland but without further changes in central pain pathways. Widespread sensitization is associated with generalised changes in central pain pathways. Dermatomal distribution of hypersensitivity as tested by the pancreatic quantitative sensory testing (P-QST) study protocol is indicated by the black circles; white circles indicate normal P-QST responses.

instruction and correction of methods prior to the enrollment of subjects. The centers engaged in monthly communication after the training session to further clarify any remaining technical questions about the testing. P-QST testing was performed in the same order for each individual as is listed below. Each appointment required approximately 30 min total for P-QST testing with an added 5–10 min for questionnaire completion.

P-QST procedures

Repetitive pinprick stimulation (temporal summation): Recordings of temporal summation to repetitive pinprick stimulations in the upper abdominal area (T10 ventral – pancreatic viscerotome) and dominant forearm (control area) were performed using an 8 mN PinPrick device (Pin-Prick Stimulatoren, MRC Systems GmbH, Heidelberg, Germany). Pain ratings using a 0–10 NRS were obtained verbally after a single application, and after the last application in a series of ten repetitive stimuli at the same location with an inter-stimulus interval of 1 s. For accurate timing of the stimuli, the procedure was guided by an auditory signal using a metronome or a visual signal using an analogue clock with a second hand. The difference between the ratings in the last and the first scores of the ten stimuli was recorded as the temporal summation score [25].

Pressure stimulation: The pressure pain detection threshold (pPDT) and pressure pain tolerance threshold (pPTT) were determined for the following skin dermatomes: C5 (clavicula), T10 back (pancreatic viscerotome), T10 ventral (upper abdominal area – pancreatic viscerotome), L1 (anterior superior iliac crest) and L4 (the quadriceps 15 cm above the patella) (Fig. 1). All lateralized pressure stimulations were applied on the subject's dominant side. An electronic pressure algometer (Algometer Type II, SOMEDIC Electronics, Solna, Sweden) with a probe surface area of 1 cm^2 was used for the pressure stimulations. The device was used in previous studies and has proven its reliability and validity [14]. Pressure was steadily increased at a rate of 30 kPa per second. The patient was asked to state when they first detected pain (pPDT). After an interval where the stimulus was allowed to subside, pressure was again applied, and the patient was asked to state when they reached their pain tolerance threshold (pPTT). The assessment parameter was the pressure at the predefined sensory threshold measured in kPa. To obtain a measure of segmental pressure hyperalgesia in the pancreatic dermatomes, the following indices were calculated from these values with specific attention to the T10 ventral ($T10^{VENTRAL}$) and T10 back ($T10^{BACK}$) dermatomes (pancreatic areas):

$$pPDT\ index = \left[mean\left(T10^{VENTRAL} + T10^{BACK}\right)\right] \div [mean(C5 + L1 + L4)]$$

$$pPTT\ index = \left[mean\left(T10^{VENTRAL} + T10^{BACK}\right)\right] \div [mean(C5 + L1 + L4)]$$

The ratios, by creating a relative measure, bypass interindividual differences in the absolute pressure thresholds. To obtain a measure of widespread pressure hyperalgesia the sum of pPDTs (pPDT sum) and pPTTs (pPTT sum) across the different stimulation sites (dermatomes) were calculated.

Cold pressor test: The dominant hand was immersed in an ice-chilled water bucket. The subject was told to remove the hand from the water after 120 seconds of immersion or sooner if the pain was intolerable. The subjects rated the pain intensity for every 10 seconds during the cold pressor test using a 0–10 NRS rating scale. The cold pressor endurance time in seconds was registered as a measure of cold pressor pain sensitivity [26].

Conditioned pain modulation (CPM): CPM, a clinically measurable form of descending pain modulation, was induced experimentally by a conditioning stimulus (the cold pressor test) and quantified by applying a "test-pain" (pPTT assessed on the non-dominant quadriceps musculature 15 cm above the patella) before ($pPTT^{BEF}$) and immediate after ($pPTT^{AFT}$) the conditioning stimulus [18]. The difference in pressure stimulus intensity before and after the cold pressor test provided a quantitative index of the CPM capacity in the individual subject [18]. The techniques used for pressure stimulation and cold pressor test described above were combined to assess CPM. This was done by subtracting the PTT on the non-dominant L4 dermatome after the cold pressor test (PTT^{AFT}) from the PTT reached in the same dermatome beforehand (PTT^{BEF}), and dividing the result by the PTT^{BEF} to obtain a ratio of how much the subject's pain tolerance had changed as a result of the cold pressor test [27]. The calculation was performed as follows:

$$CPM = \left(pPTT^{AFT} - pPTT^{BEF}\right) \div pPTT^{BEF}$$

Evaluation of central pain processing: Evaluation of central pain processing was based on documentation of the presence of segmental or widespread sensitization as illustrated in Fig. 1.

Segmental sensitization: Decreased pPDT or pPTT indices or enhanced TS at the upper abdominal area served as proxies for segmental sensitization (in the absence of widespread sensitization). The understanding of the pressure indices (pPDT index and pPTT index) are that pressure thresholds out of proportion in the pancreatic dermatome compared to the control areas indicates sensitivity specific to the pancreatic area. Likewise, the TS measured in the upper abdomen (pancreatic area) is a proxy of central integration of sensory information applied in this dermatome and thus provide information on spinal sensory integration at the spinal level receiving visceral afferents from the pancreatic gland (segmental sensitization).

Widespread sensitization: Decreased pPDT or pPTT sum scores, enhanced TS at the forearm, increased cold pressor pain sensitivity and impaired CPM served as proxies for widespread hyperalgesia. The understanding of these parameters is that an abnormal response to stimulation remote to the "pancreatic area" reflect that central nociceptive pathways outside the spinal segment receiving afferents from the pancreatic gland have become sensitized and malfunctioning.

The obtained P-QST profiles can be used to characterize three states of central pain processing:

(i) normal central processing, ii) segmental sensitization and iii) widespread sensitization (Fig. 1).

Timeline of experimental setup

The subjects were welcomed into the examination room, and informed consent was obtained. Additional clinical information as described also above was obtained by the principal investigator or co-investigator at each site. The subject was then prepared for P-QST testing by removing any clothing that prohibited direct testing on the skin at the above sites. The subject was re-dressed in a hospital gown or equivalent for performance of testing.

Each subject's P-QST testing was then performed in the following order: temporal summation, followed by pressure stimulation to determine the pPDT and pPTT at C5 (clavicula), T10 back (pancreatic viscerotome), T10 ventral (upper abdominal area – pancreatic viscerotome), L1 (anterior superior iliac crest) and L4 (the quadriceps 15 cm above the patella) on the patient's dominant side. This was followed by CPM testing (which includes cold pressor testing).

Statistical analysis

Data are presented as means ± standard deviations (SD) unless otherwise indicated. Effects of stimulation site (dermatome), age and gender were analyzed using non-parametric regression models. Association between pressure parameters were analyzed using Spearman's correlation coefficient. Derivation of normative thresholds for the P-QST assessment parameters was based on quantile regression analysis. The 5/95, 10/90 and 25/75 percentiles for each P-QST parameter was estimated for the whole control subject sample [28]. For parameters influenced by age or gender effects (pPDT sum scores) percentiles were stratified for relevant subgroups. To facilitate interpretation of pressure profiles across dermatomes in individual CP patients, absolute reference data from the control population were used to normalize test results using the z-transform: $Z = (\text{absolute value}_{\text{patient}} - \text{mean}_{\text{controls}})/\text{SD}_{\text{controls}}$). Absolute values were ln-transformed prior to Z-transformation to obtain a (secondary) normal distribution. The retrieved z-values were projected to maps of dermatomes to illustrate the distribution of pressure sensitivity in individual patients [29]. The proportionate distributions of control subjects and CP patients across P-QST phenotypes were analyzed using Fisher's exact test. All statistical analysis was performed via Stata 16.0 (College Station, Texas, USA).

Results

All control subjects underwent diagnostic testing for all of the P-QST parameters with the exception of one subject who was missing pPTT data.

Age and gender effects on P-QST parameters

The absolute pressure thresholds (pPDT and pPTT) stratified by stimulation site, age and gender groups are reported in Supplementary Table 1. Pressure thresholds were site (dermatome) specific and females were significantly more sensitive to pressure stimulation than males (all $p < 0.001$) – Table 1. In addition, subjects of older age were less sensitive to pressure stimulation than their younger counterparts, although these differences were generally of limited effect size – Table 1. In keeping with the findings for site specific pressure thresholds, the pressure sum scores across all stimulation sites (dermatomes) were also influenced by gender with lower thresholds observed for females (both $p < 0.001$). The effect size (male vs female) was 690 kPa for the pPDT sum score and 1194 kPa for the pPTT sum score. In contrast to the pressure thresholds, no age or gender modifications were evident for the remaining P-QST assessment parameters (pPDT ratio, pPTT ratio, CPM, cold pressor endurance time and pin-prick stimulations) – Table 1.

Taken together, the absolute pressure thresholds were site (dermatome), gender and age-specific, which make them difficult

Table 1
Age and gender effects on QST assessment parameters.

QST parameter	Age		Gender	
	P	Effect size (95% CI)[a]	*P*	Effect size (95% CI)[b]
CPM (%)	0.16	−0.003 (−0.02–0.01)	0.63	−0.02 (−0.08–0.07)
Cold pressor endurance time (sec)	0.16	−2.9 (−6.8–1.1)	0.29	7.7 (−4.5–22.1)
Pressure pain thresholds (kPa)				
Pancreatic areas:				
-T10 dorsum	0.92	−1 (-18–17)	**<0.001**	214 (127–299)
-T10 abdomen	0.04	14 (0–27)	**<0.001**	106 (68–152)
Control areas:				
-C5	0.92	1 (-16–18)	**<0.001**	113 (65–157)
-L1	0.03	18 (2–35)	**<0.001**	86 (37–127)
-L4	0.96	0 (-18–17)	**<0.001**	165 (97–224)
Indices:				
-PDT sum	0.22	50 (-30–130)	**<0.001**	690 (462–915)
-PDT ratio	0.65	0.01 (−0.02–0.03)	0.04	0.09 (0.01–0.16)
Pressure tolerance thresholds (kPa)				
Pancreatic areas:				
-T10 dorsum	0.82	5 (-40–51)	**<0.001**	357 (182–462)
-T10 abdomen	0.61	7 (-19–33)	**<0.001**	189 (122–263)
Control areas:				
-C5	0.85	−5 (-51–42)	**<0.001**	235 (136–331)
-L1	0.08	22 (-3–47)	**<0.001**	156 (62–213)
-L4	0.82	−5 (-47–37)	**<0.001**	278 (173–352)
Indices:				
-PTT sum	0.66	31 (-107–169)	**<0.001**	1194 (733–1556)
-PTT ratio	0.26	0.01 (−0.009–0.03)	0.07	0.07 (0.01–0.18)
Pin-prick (VAS)				
-Forearm	0.96	0.004 (−0.15–0.15)	0.8	−0.07 (−0.5–0.4)
-Upper abdomen	0.50	−0.04 (−0.17–0.08)	0.5	0.2 (−0.4–0.7)

[a] Change in pressure thresholds per 10 years.
[b] Men vs. Women.

to use in clinical practice. Consequently, these parameters were not considered for diagnostic threshold derivation. In contrast, the remaining P-QST assessment parameters based on composite measures appeared to be largely unaffected by age effects and only pressure sum scores differed clinical significantly between genders. This facilitates the clinical utility of these parameters and consequently they were considered further for derivation of diagnostic thresholds.

Derivation of diagnostic thresholds

The pPDT index and pPTT index (rho = 0.64, $p < 0.001$) as well as the pPDT sum and pPTT sum (rho = 0.76, $p < 0.001$) were strongly correlated and therefore reflected information that could be considered redundant (Fig. 2). It was therefore decided to rely on the parameters based on the pPDT to be used moving forward, as these are based on pain thresholds that are more intuitive and easier to explain to patients [30,31].

The normative criteria for P-QST assessment parameters based on the 5/95, 10/90 and 25/75 percentiles are reported in Table 2 and an algorithm for phenotyping of central pain processing based on these criteria are summarized in Fig. 3. According to this algorithm, the combination of P-QST parameters and their corresponding normative reference criteria allow for classification of patients into three mutually exclusive subgroups characterized by (i) widespread sensitization, (ii) segmental sensitization and iii) normal central pain processing.

Patient feasibility study

Sixty patients with painful CP were enrolled in the patient feasibility study. The mean age was 54.6 ± 11.8 years, 39 (65%) were men, and 40 (66%) had a toxic (alcoholic and/or smoking) etiology of CP. Thirty-three (55%) of patients used opioids and 27 (45%) used one or more adjuvant analgesics.

Pressure stimulation profiles of three representative CP patients with (i) normal response to pressure algometry, (ii) signs of pressure hyperalgesia in the pancreatic dermatomes and iii) generalised pressure hyperalgesia are illustrated in Fig. 4.

Based on the proposed algorithm and retrieved normative criteria for P-QST assessment parameters three distinct phenotypes of central pain processing were identified. The algorithm based on the 25/75 percentiles showed significant differences in distributions of P-QST phenotypes between patients and control subjects ($p = 0.001$), but with a high degree of overlap between subgroups, in particular for the subgroup with evidence of segmental sensitization (Fig. 5a). In contrast, the algorithms based on the 10/90 and 5/95 percentiles showed a good separation of patients and control subjects for both the segmental and widespread sensitization subgroups (both $p < 0.001$) - Fig. 5b and c. The proportion of patients with evidence of abnormal central processing (segmental or widespread sensitization) was lower for the algorithm based on the 5/95 percentiles compared to the algorithm based on the 10/90 percentiles (38% vs. 50%, respectively). To obtain a favorable diagnostic performance for clinical use we propose using the algorithm

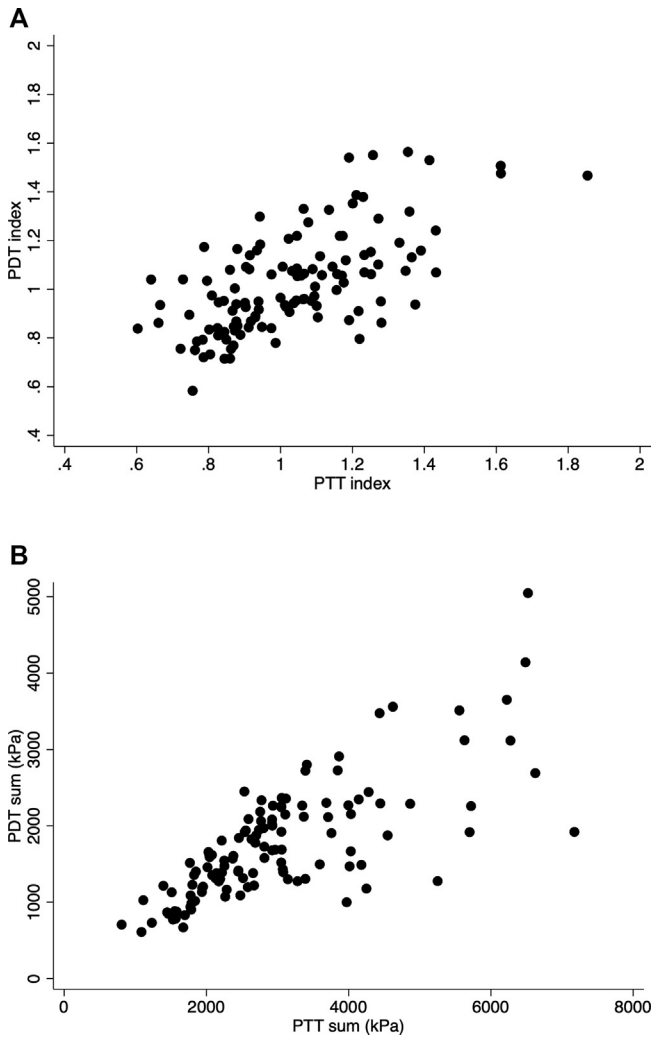

Fig. 2. A. Correlation of pPTT and pPDT indices. B. Correlation of pPDT and pPTT sum scores.

Table 2
Normative criteria for QST assessment parameters.

	N	Mean ± SD	$P^{5/95}$	$P^{10/90}$	$P^{25/75}$
Widespread sensitization					
CPM (%)	122	19.7 ± 17.5	−4	0	9
Cold pressor endurance time (sec)	122	95.2 ± 39.2	20	30	60
pPDT sum					
-Women (kPa)	61	1427 ± 614	730	827	1017
-Men (kPa)	61	2104 ± 759	1303	1381	1571
TS forearm (VAS)	122	1.16 ± 1.26	4	2	2
Segmental sensitization					
pPDT index	122	1.03 ± 0.21	0.75	0.79	0.87
TS abdomen (VAS)	122	1.30 ± 1.35	4	3	2

CPM; conditioned pain modulation, pPDT; pressure pain detection threshold, TS; temporal summation, VAS; visual analogue scale.

based on the 10/90 as the algorithm to be used moving forward.

Discussion

This study presents a method for standardized characterization of pancreatic pain that has been developed for clinical use. The method is based on a QST protocol specifically designed for evaluation of pancreatic pain (P-QST) and was tested in (a) a multicenter study providing reference values from 122 control subjects distributed evenly across age and gender categories and (b) a feasibility sample of 60 patients with painful CP showing that the method could be used to phenotype patients' patterns of pain processing on an individual patient level. This method has the potential to streamline the evaluation of pancreatic pain and provide a clinically useful means for pain assessment, holding additional promise as a future predictive biomarker for pain treatment in CP.

The P-QST protocol was designed for clinical use and is a simplified version of the NASQ protocol originally designed for research purposes [22,23,32,33]. The simplified protocol takes advantage of the spinal convergence of visceral and somatic nerves, allowing for external testing of second order neuron sensitivity in the central nervous system. By introducing ratios of pancreatic vs. extra pancreatic QST thresholds, interindividual differences in absolute sensory thresholds are bypassed which facilitate clinical implementation. As such, P-QST assessment in the dermatomes of the upper abdomen (sharing spinal segmental innervation with the pancreatic gland) were compared to a number of control dermatomes to assess if segmental central nervous system neuroplasticity had evolved [34,35] In addition, dynamic function of the descending inhibitory and facilitatory regulating systems (at the brainstem and higher cortical levels) and neuronal sensitization was tested using the conditioned pain modulation paradigm and temporal summation, in conjunction with evidence of widespread pressure hyperalgesia, to asses if sensitization of central pain pathways had spread beyond the spinal segments receiving nociceptive inputs from the pancreas [36].

The original NASQ was effective in evaluating CP pain in research settings, and has been used to show that the degree of central sensitization corresponds to worse disease as measured by the M-ANNHEIM severity index and that patients with increased sympathetic drive have increased pain to QST in general [32,33]. In patients with segmental hyperalgesia at the pancreatic dermatome (as compared to widespread hyperalgesia), results of the NASQ have been able to predict the effect of pregabalin [23]. It has also been shown that patients with CP suffer from deficient descending inhibition as reflected in CPM, which raises the possibility of medical treatment for CP patients with medications shown to be effective for enhancing descending pain modulation such as selective serotonin-noradrenaline reuptake inhibitors (SNRIs) [18,25]. Furthermore, it has been shown that CP patients continue to exhibit changes in central pain processing even after pain-relieving pancreatic surgery, suggesting that the degree of persistent post-surgical pain may correlate with the severity of pronociceptive changes experienced by the patient with pancreatic inflammation [37]. The original NASQ, including additional non-pancreatic QST assessment areas, was also successful outside of CP in showing not only that initial post-surgical changes in pain processing can predict who will develop chronic postsurgical pain, but also that early postoperative hyperalgesia to pressure stimulation in the first days after surgery was an independent risk factor for development of chronic pain [22,37]. Taken together, these past studies have shown that QST can be used to phenotype pain in the context of CP and that such phenotyping may be used to predict the outcome of pain treatment.

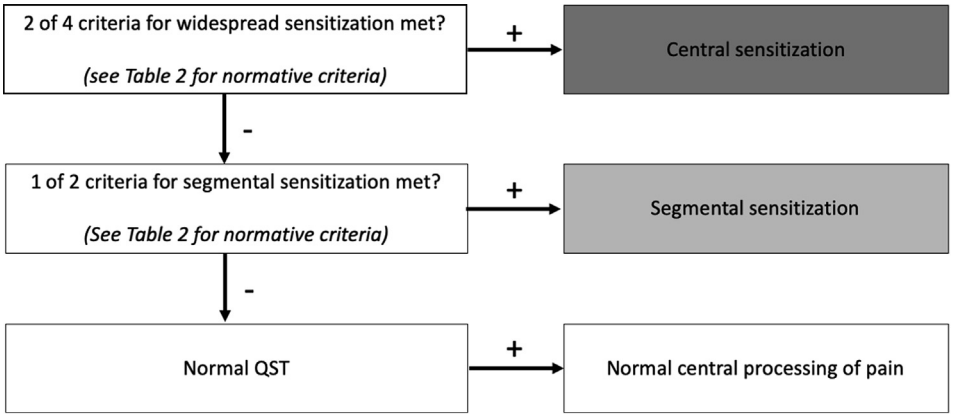

Fig. 3. Proposed diagnostic algorithm to identify patients with segmental sensitization and central sensitization.

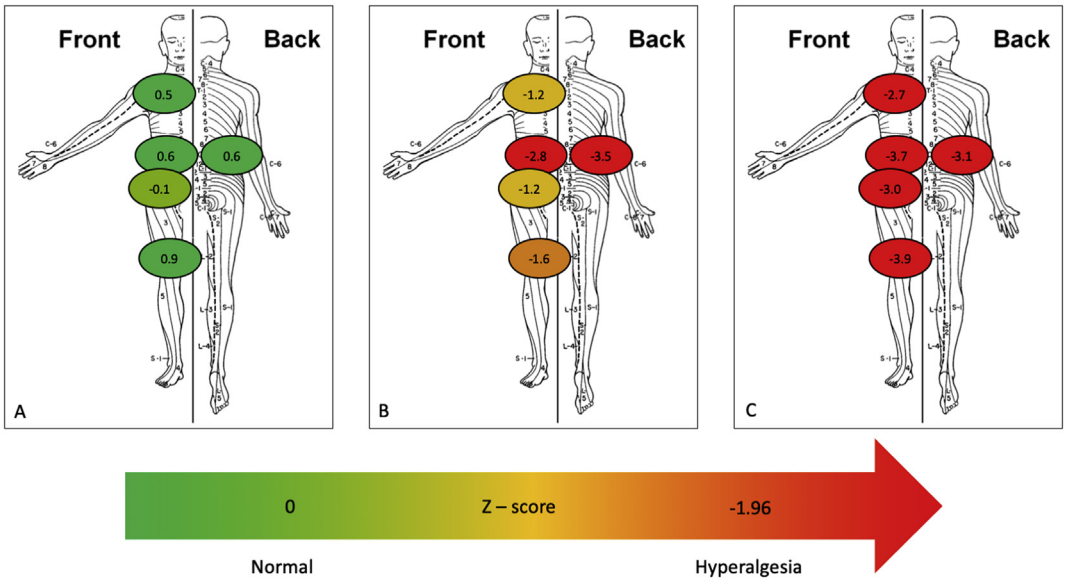

Fig. 4. Pressure pain sensitivity profiles in three individual patients with painful chronic pancreatitis that illustrate the full range of the sensitization spectrum. The z-score is employed here to directly compare sensitivity across dermatomes. Patient A is a 59 year old male patient with chronic pancreatitis secondary to alcohol and smoking misuse. The pressure profile shows normal responses to pressure stimulation in the 5 stimulated dermatomes (all Z-scores > -1.96). Patient B is a 54-year-old female patient with idiopathic chronic pancreatitis. The pressure profile shows evidence of segmental sensitization of the dermatomes sharing spinal segmental innervation with the pancreatic gland (Z-scores < -1.96), while sensory responses are within the normal range for control dermatomes (Z-scores ≥ -1.96). Patient C is a 60-year-old male patient with chronic alcoholic pancreatitis. Pressure profiles show evidence of widespread sensitization with all Z-scores < -1.96. Numbers in circles indicate Z-scores: numbers of standard deviations between patient data and group-specific mean value (absolute reference data; see Supplementary Tables 1 and 2).

There are some drawbacks to the original NASQ including bedside feasibility and patient willingness to participate. In simplifying the NASQ to a more clinically feasible bedside protocol, both advantages and disadvantages of the original protocol were considered. The pressure and electrical stimulations included in the original NASQ protocol were previously shown to be reproducible in patients with CP [14]. However, as many patients are reluctant towards the electrical stimulation and the method also is technically more demanding, we compared pain assessment between electrical and pressure stimulation at different dermatomes in a pilot study [38]. There was limited gain using electrical stimulation as compared with pressure thresholds and consequently the simplified protocol omitted electrical stimulation. In contrast, pinprick stimulation was added to the protocol to address "temporal summation". This is a phenomenon that corresponds to "wind-up" in preclinical studies and is suitable to study central sensitization [39]. When temporal summation is studied in patients with a sensitized pain system they show increased pain response to repeated stimuli delivered with a frequency above 0.3 Hz and at the same intensity. Temporal summation has also been shown to reflect central sensitization in patients with pain due to CP [40] and provides complementary information on central sensitization as compared to the measures of widespread pressure hyperalgesia and cold pressor test.

Absolute thresholds of pressure testing in our study were similar in this study to prior studies and pain pressure thresholds have been shown to be reproducible thus verifying the validity of the method in a multicenter setup [23,33,35,37,41-47]. As is common in QST evaluations, absolute thresholds in this study were seen to be site (dermatome), gender, and age-specific, and; therefore, the decision was made to use composite metrics for evaluation of the different QST assessment parameters [48]. This will allow for a more robust and intuitive implementation of the protocol in a clinical setting without the need to look up age and site specific

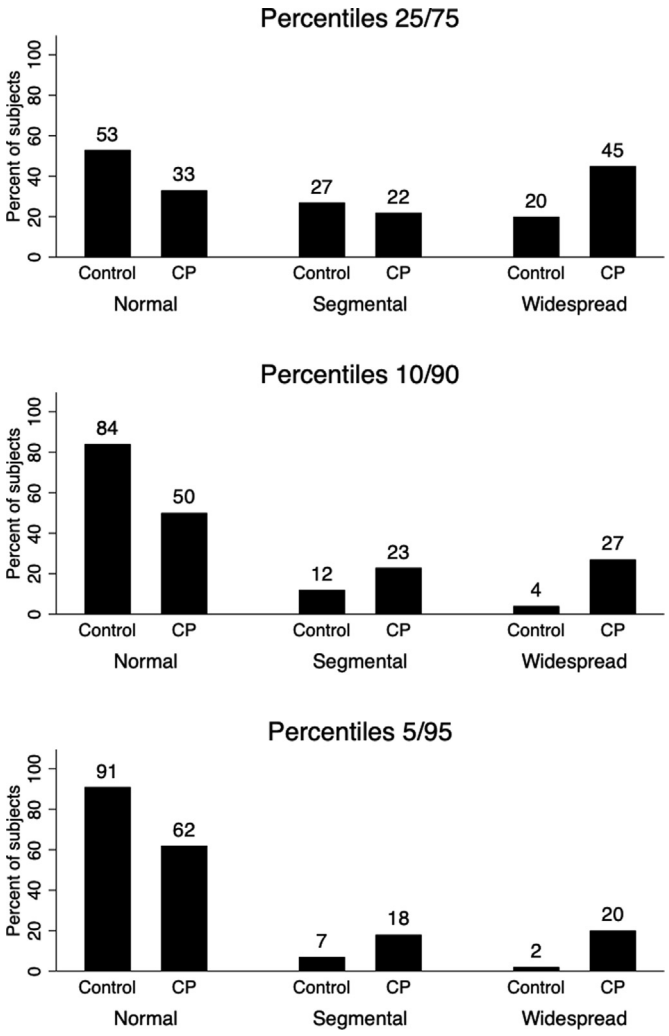

Fig. 5. Distributions of P-QST phenotypes among chronic pancreatitides patients (n = 60) and control subjects (n = 122). A. Normative criteria based on 25/75 percentiles (p = 0.001). B. Normative criteria based on 10/90 percentiles (p < 0.001). C. Normative criteria based on 5/95 percentiles (p < 0.001).

thresholds for the individual assessment parameters.

Clinical implications

Application of this protocol in a clinical setting may be useful for prediction of which patients with painful CP may respond to specific therapies. As seen in our preliminary feasibility sub-study, patients can be phenotyped into one of three categories based on results of P-QST: those with normal pain processing, those with evidence of segmental sensitization and those with evidence of widespread sensitization of central pain pathways. Theoretically, CP patients with normal central pain processing or patients affected with segmental sensitization are likely suffering from pain triggered by an ongoing nociceptive input from the pancreas and may respond to specific pancreas-focused therapies (in the presence of suitable pancreatic pathology) or drugs targeting mechanisms of central sensitization including gabapentinoids (in the absence of suitable pathology for invasive treatment) [17,23,49,50]. Conversely, patients with widespread central sensitization may be suffering from a self-perpetuating pain-state that has become independent from the peripheral nociceptive drive from the pancreas. These patients are hypothesized to have a less favorable outcome to pancreas-focused therapies and may comprise a subgroup of up to 30% of patients according to our feasibility sub-study [4,51]. Interestingly, comparable proportions of patients with CP have previously been reported to have a poor outcome to endoscopic therapy [52,53].

By way of example, consider the 54-year-old female patient with CP in whom the P-QST scores indicates the presence of segmental sensitization (patient B in Fig. 4). In the presence of relevant pancreatic pathology, she is predicted to potentially benefit (as measured by pain relief) from endoscopic treatment with stone extraction and/or stent placement (as appropriate therapy for pancreatic duct obstruction), and potentially derive additional benefit from pregabalin therapy as well [4,20,23,50].

In a contrasting example, consider the 59-year-old male patient in whom the P-QST scores indicate the presence of widespread sensitization (patient C in Fig. 4). In this setting, it is hypothesized that the patient would show benefit from neuromodulatory therapy including medication such as an SNRI that will have direct effect on central pain pathways, while therapies directed at pancreatic sources of pain are predicted to be less effective [4,20,25].

Study limitations

Our study has some limitations that need to be mentioned. First, QST has been used for research purposes to evaluate numerous painful conditions over the past 4 decades. Static tests in QST, including pressure algometry, have shown high levels of standardization and reproducibility [14]. In contrast, dynamic testing in QST, including assessment of CPM, has shown some variability, both between patients (including CP) and in day-to-day variability [14,54]. Expecting this, we have performed our evaluations in a standardized fashion for all patients, and used ratios and composite QST metrics to eliminate as much inter-individual variation as possible. Also, the presence of widespread hyperalgesia (a potential biomarker of poor outcome to pancreas directed therapies) relies on a composite score including more than a single QST parameter, which limits the day-to-day variability concerns previously observed for CPM. Second, the derived normative thresholds were all based on statistical analysis and need to be further validated for clinical use in future prospective studies. As such, the proposed normative criteria and phenotypes are hypothesis-generating and based on information in future analyses in additional controls and accumulation of data in CP patients, these criteria may need to be refined. Of particular importance, the capacity of P-QST assessment for prediction of outcome to pancreas directed (invasive) therapies needs further confirmation and initiatives are currently taken to study this further. Third, the population studied here are controls without abdominal pain or other chronic pain conditions, but they are not necessarily free from other medical conditions. This makes the results more generalizable to a real-life clinical population of patients; however, the effect of any underlying medical condition will need to be studied in the future. Fourth, our cohort size of approximately 20 patients per specific age and gender group is based on previous normograms established in the QST literature [29], but the current study was not powered to investigate the generalizability of our normative data across centers and this will need further investigation. Fifth, we acknowledge that additional disease- and patient -specific factors including (but not limited to) etiology and duration of disease, opioid use, and psychiatric comorbidities may impact P-QST phenotypes. Our feasibility study was designed only to evaluate the ability of P-QST to differentiate patients into separate groups, and was not powered to evaluate these factors. Future studies will be needed to more carefully determine patient and disease characteristics that associate with P-

QST phenotypes. Finally, most of our control subjects and patients were Caucasian, which reflects only a portion of patients who are affected with pancreatitis. Future studies will need to be performed to validate the derived normative criteria in controls without abdominal pain and patients of other ethnic populations.

Conclusion

We have developed a method for standardized assessment and characterization of pancreatic pain that has been designed for clinical use. Normative thresholds were derived, and the presented method showed great promise in its ability to differentiate phenotypes of central pain processing by providing reliable indicators of nociceptive changes including evidence of segmental and widespread sensitization of central nociceptive pathways. These pain phenotypes can be used in the future to attempt prediction of response to treatment in patients with painful CP and thus provides a framework for personalized pain management.

Author contributions

AEP (drafting of manuscript, acquisition of data), MF (acquisition of data), LFK (critical revision of manuscript for important intellectual content), IML (acquisition of data), AMD (study concept and design, critical revision of manuscript for important intellectual content), VKS (study design, critical revision of manuscript), DY (study design, critical revision of manuscript for important intellectual content), SSO (study design, statistical analysis, analysis and interpretation of data, drafting and critical revision of the manuscript for important intellectual content). SSO is guarantor of the article. All authors approved of the final version of the manuscript.

Funding

American Pancreatic Association Young Investigator in Pancreatitis Award (AEP).

Declaration of competing interest

The authors declare that they have no relevant conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2019.11.007.

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