Rationale for and Development of the Pancreatic Quantitative Sensory Testing Consortium to Study Pain in Chronic Pancreatitis

Anna Evans Phillips, MD, MS, Mahya Faghih, MD,† Vikesh K. Singh, MD, MSc,†*
Søren Schou Olesen, MD, PhD,‡§ Louise Kuhlmann, MD, PhD,§|| Srdan Novovic, MD, PhD,¶
*Benjamin Bick, MD,# Philip A. Hart, MD,** Mitchell L. Ramsey, MD,** Rupjyoti Talukdar, MD,††*
Pramod K. Garg, MD,‡‡ Dhiraj Yadav, MD, MPH, and Asbjørn Mohr Drewes, MD, PhD‡§*
on behalf of the Pancreatic Quantitative Sensory Testing (P-QST) Consortium

Objectives: Abdominal pain is the primary symptom of chronic pancreatitis (CP), but pain is difficult to assess, and objective methods for pain assessment are lacking. The characterization of the sensory component of pain as a surrogate for nociception can be achieved by sensory testing using standardized stimuli. Herein, we describe the rationale for and development of an international consortium to better understand and characterize CP pain.

Methods: A collaboration was initially formed between the University of Aalborg, Johns Hopkins University, and the University of Pittsburgh. This group refined the protocol for pancreatic quantitative sensory testing (P-QST) and then expanded the collaboration with plans for incorporating P-QST into prospective studies.

Results: The collaboration has successfully developed a P-QST nomogram. Chronic pancreatitis patients identified with P-QST as having widespread hyperalgesia had higher pain intensity scores, higher prevalence of constant pain, and decreased quality of life. Psychiatric comorbidities were independent of pain phenotypes. Multiple studies are underway to validate these findings and evaluate their utility in clinical trials.

Conclusions: Development of the P-QST Consortium will facilitate collaborative efforts to use P-QST as a means for evaluation and characterization of pain in CP patients, and optimize methods to guide individualized pain management approaches.

Key Words: chronic pancreatitis, pain, abdominal pain, quantitative sensory testing, nociception, pain management

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From the *Division of Gastroenterology, Hepatology, and Nutrition, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA; †Division of Gastroenterology and Hepatology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD; ‡Centre for Pancreatic Diseases and Mech-Sense, Departments of Gastroenterology and Hepatology and §Clinical Medicine, Aalborg University, Aalborg; ||Department of Medicine, Randers Regional Hospital, Randers; ¶Pancreatitis Centre Copenhagen, Gastrounit, Hvidovre Hospital, Copenhagen, Denmark; #Division of Gastroenterology and Hepatology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN; **Division of Gastroenterology, Hepatology, and Nutrition, Department of Medicine, The Ohio State University Wexner Medical Center, Columbus, OH; ††Department of Gastroenterology, Asian Institute of Gastroenterology, Hyderabad; and ‡‡Department of Gastroenterology, All India Institute of Medical Sciences, New Delhi, India.

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Address correspondence to: Anna Evans Phillips, MD, MS, UPMC Presbyterian Hospital, 200 Lothrop St, Mezzanine Level M-2, Pittsburgh, PA 15213 (e-mail: evansac3@upmc.edu).

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Chronic pancreatitis (CP) is a fibroinflammatory disease that manifests with a primary symptom of abdominal pain affecting 60% to 80% of patients.[1] Painful CP has been associated with lower quality of life, greater rates of disability, and higher resource utilization when comparing with CP patients without pain.[1–4] The presence, severity, and temporal nature of pain correlate poorly with imaging findings or assessment of pancreatic function, making assessment and treatment of pain in CP particularly challenging.[5] The pathophysiology of pain in CP results from the complex interplay between chronic local inflammation, pancreatic nerve damage, and central pain processing alterations including neuronal sensitization and reorganization as well as impaired pain modulatory pathways.[5,6] A critical clinical challenge in painful CP is the differentiation of peripherally generated visceral or pancreatic pain from pain associated with alterations of the central nervous system that often is self-perpetuating and independent of the peripheral noxious stimulus.[7,8] Because pain is a complex multifactorial subjective and emotional response to actual or potential tissue damage,[9] it is unlikely that an objective method of assessment is feasible in the clinical setting. However, a proxy of *nociception*—the neural process of encoding noxious stimuli or the neural signaling that leads to the experience of pain—can be characterized through quantitative sensory testing (QST). Although the assessment of response to the specific stimulations is typically pain intensity (ie, the subjective response), a detailed evaluation of the sensory system can be approximated with a set of recorded patient responses evoked by QST.

There exists a clear need for a bedside tool to assess and differentiate nociception in painful CP that is clinically feasible.[10] Efforts to develop a QST protocol specific to the pancreas have been in progress since the initial reports of the utility to use visceral QST for characterization of the nociceptive system and corresponding neuroplastic changes in central pain pathways in gastrointestinal disease, including CP.[11–16] Early studies were based on invasive models with endoscopic-guided stimulation of the upper and lower gut segments. These methods were cumbersome, resource demanding, and unpleasant, and therefore, their utility was restricted to experimental settings. To pave the road for large-scale studies, our group has refined and evaluated a simplified and pancreas-specific QST protocol (hereafter referred to as pancreatic quantitative sensory testing, or P-QST) by application in normal subjects and in patients with CP.[17,18] Pancreatic quantitative sensory testing can differentiate 3 separate pain phenotypes in CP characterized by varying degrees of alterations in central pain processing.

The development and use of P-QST is intended to accomplish 3 aims: (1) to characterize the pattern of nociceptive processing in patients with painful CP to understand the pathophysiology underlying the chronic pain state encountered, (2) to evaluate the

ability of P-QST to predict response to pain management, and (3) to facilitate the development and study of targeted treatment plans (medical and surgical) for people with painful CP based on the results of P-QST. The development of the P-QST consortium involves a collaborative group of interdisciplinary experts who are seeking to better understand painful CP and ultimately improve the treatment paradigm for this patient population.

MATERIALS AND METHODS

Study Population

This collaboration was initially begun at 3 tertiary referral hospitals in the United States and Denmark: The University of Pittsburgh Medical Center (Pittsburgh, Pa), Johns Hopkins University Medical Center (Baltimore, Md), and Aalborg University Hospital (Aalborg, Denmark). Institutional review board approval was obtained at each of these sites individually for prospective subject recruitment (University of Pittsburgh IRB Protocol PRO17060648, Johns Hopkins IRB 00143375, Aalborg University Hospital N-20090008). The study was registered with ClinicalTrials.gov (NCT03434392). All subjects provided written informed consent. Eligible controls were 18 years or older and had no pancreatic disease. Exclusion criteria for controls were the following: presence of abdominal pain more than 6 times within the past 1 year, evidence of medical or surgical disease of importance as judged by the study investigator(s) at each site, ongoing scheduled or as-needed opioid analgesic use (irrespective of the indication), or known pregnancy at the time of screening. Eligible CP patients were 18 years or older, met the Cambridge III or IV criteria for CP, or had pancreatic calcifications on cross-sectional imaging (computed tomography or magnetic resonance imaging) as described in the definitive M-ANNHEIM criteria.[19] Patients were excluded if they had previously undergone abdominal organ transplantation, if they had a painful abdominal condition whose effect they were unable to distinguish from pancreatitis pain, and if they were experiencing an episode of acute pancreatitis on top of their CP at the time of consideration for enrollment.

Background

Pancreatic quantitative sensory testing is a method of administering external stimuli of controlled intensities and then recording patient responses to determine nociceptive activity. The P-QST technique has been adapted to evaluate differences between segmental and generalized hyperalgesia by using pressure testing of the T10 dermatome as a proxy for testing visceral nerves predominantly in the pancreatic and peripancreatic regions (ie, the pancreatic viscerotome). This is made possible by the spinal convergence of visceral and somatic nerves (Fig. 1).[20] On the other hand, the dynamic tests (temporal summation [TS] and conditioned pain modulation [CPM]) estimate central sensitization. The P-QST procedures have been demonstrated in the intended sequence in a video format for reference and are additionally described in prior published form (video link can be viewed in the Supplementary Material, http://links.lww.com/MPA/A903).[18] In P-QST, a pressure algometer is used to identify pain thresholds in different dermatomes corresponding with internal segments (viscerotomes). A pin-prick device is used to assess TS (an increase in pain experience due to repeated equal-intensity noxious stimuli delivered at a specific frequency). Conditioned pain modulation—an experimental paradigm used to assess endogenous pain inhibition mechanisms—is performed using a cold pressor test and pain pressure thresholds.

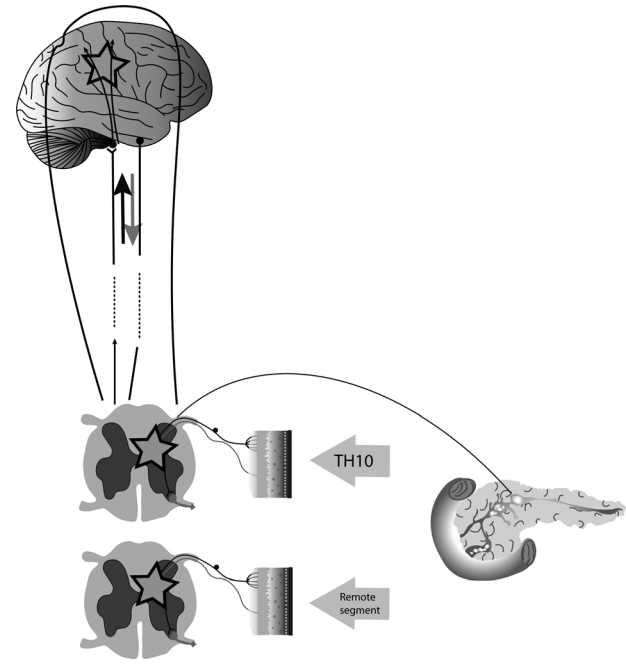

FIGURE 1. Neural pathways that are involved in the proposed nociceptive assessment (P-QST) of the pain system. Convergence between afferents from the pancreas and those of the skin in the T10 dermatome (abdomen and back) facilitates possible central neuronal sensitization secondary to increased afferent barrage from the pancreas (black arrow). This can result in segmental pain threshold lowering to QST of the skin and deep tissue (TH10). If the sensitization spreads along the neuroaxis to remote segments, lowering of pain thresholds can also occur in other areas (remote segment). The efficacy of bulbospinal descending pathways (gray arrow) that attenuate the afferent barrage is also tested indirectly, and the response to repeated pinprick stimuli reflects neuronal sensitization.

P-QST Procedures and Interpretation

The procedures themselves are described in Table 1 and Figure 2. Details of their development were previously described.[18] The P-QST profiles obtained using both static and dynamic tests in combination with pressure thresholds can be used to characterize 3 states of central pain processing: (i) no abnormal sensitization, (ii) segmental sensitization, and (iii) widespread sensitization, which is suggestive of the presence of central sensitization. The evaluation of central pain processing was based on documentation of segmental or widespread sensitization.

Interpretation of Segmental Sensitization

Decreased pressure pain detection threshold (pPDT) or pressure pain tolerance threshold (pPTT) indices, as well as enhanced TS at the abdominal area as compared with control areas served as proxies for segmental sensitization (in the absence of widespread sensitization). The interpretation of the pressure indices (pPDT index and pPTT index) is that pressure thresholds out of proportion in the pancreatic dermatome compared with the control areas indicate sensitivity mainly to the pancreatic area. Likewise, the TS measured in the 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 segments receiving visceral afferents from the pancreatic gland (segmental sensitization).

TABLE 1. P-QST Procedures

Test Instrument	Dermatomes Tested	Description of Testing	Measurable Ratios
Pin-prick: 8 mN Stimulatoren, MRC Systems GmbH, Heidelberg, Germany	T10 abdomen C6 forearm	Single stimulation at each site followed by 10 stimulations repeated at 1-s interval. Pain ratings on a 0–10 scale are obtained verbally from patient after single stimulus and series.	TS score abdomen: $10stim^{ABD} - 1stim^{ABD}$ TS score forearm: $10stim^{FOR} - 1stim^{FOR}$
Pressure algometer: Type II, SBMEDIC Electronics, Solna, Sweden	Dominant side: C5 (clavicula) T10 abdomen T10 back L1 (anterior superior iliac crest) L4 (quadriceps)	Pressure will be applied at steadily increasing rate. Patient states when they first detect pain (pPDT). After interval where the stimulus is allowed to subside, pressure will again be applied and the patient is asked to state when they reach pain tolerance threshold (pPTT).	pPDT index: $[mean\ (T10^{ABD} \pm T10^{BACK})] \div [mean\ (C5 + L1 + L4)]$ pPTT Index: $[mean\ (T10^{ABD} + T10^{BACK})] \div [mean\ (C5 + L1 + L4)]$ pPDT sum: $(pPDT^{T10ABD} + pPDT^{T10BACK} + pPDT^{C5} + pPDT^{L1} + pPDT^{L4})$ pPTT sum: $(pPTT^{T10ABD} + pPTT^{T10BACK} + pPTT^{C5} + pPTT^{L1} + pPTT^{L4})$
Cold pressor test: ice-chilled water bucket (2.0°C ± 0.3°C)	Dominant hand	Hand is immersed in ice-chilled water bucket for total 120 s, or less if pain is intolerable to patient. Patient rates intensity of pain every 10 s on 0–10 NRS scale.	Cold pressor endurance time: duration of hand immersion is recorded in seconds
CPM: pressure algometer (same as above)	L4 (quadriceps) on nondominant side	pPTT is assessed at 15 cm above the patella in L4 dermatome before and after cold pressor test is performed.	CPM index: $(pPTT^{(L4)AFT} - pPTT^{(L4)BEF}) \div (pPTT^{(L4)BEF})$

NRS indicates numeric rating scale; $pPTT^{(L4)AFT}$, pPTT at L4 location after cold pressor test; $pPTT^{(L4)BEF}$, pPTT at L4 location before cold pressor test.

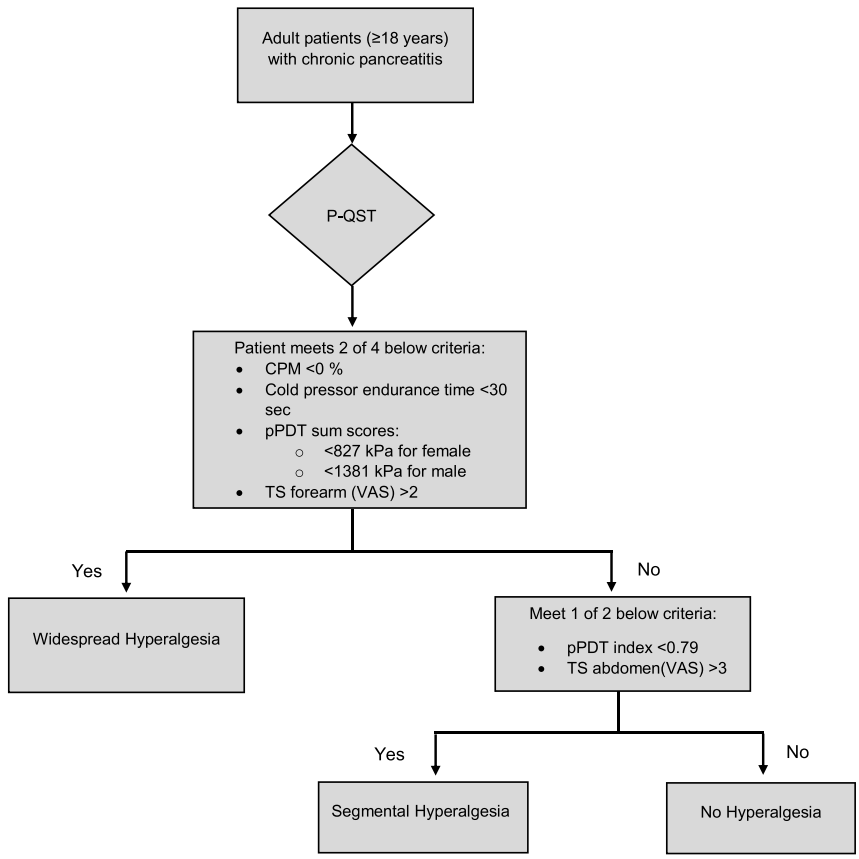

FIGURE 2. Pancreatic quantitative sensory testing algorithm. Adapted with permission from Faghih et al.[21] VAS, visual analog score.

Timeline of Experimental Setup

After informed consent, additional clinical information is obtained by the study team at each site, including demographics, pancreatitis history, alcohol and tobacco history, medication use, and ongoing symptoms.[18,21,22] The subject is then prepared for P-QST by removing any clothing that prohibited direct testing on the skin at the aforementioned sites. Testing with P-QST is performed in the following order: TS, followed by 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 is followed by CPM testing (which includes cold pressor testing).

Interpretation of 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" reflects that central nociceptive pathways outside the spinal segment receiving afferents from the pancreatic gland have become sensitized and are malfunctioning: widespread hypersensitization is thought to be suggestive of central sensitization.

Questionnaires

The QST is only measuring sensory response to nociceptive stimuli, whereas the pain process (especially in the chronic state) also includes affective and cognitive components. Therefore, the assessment of pain with P-QST is complemented with questionnaires. Questionnaires are administered in the primary language of the country of the enrolling institution. The European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire is used to evaluate quality of life.[23,24] Pain severity and its interference with daily activities are measured using the modified Brief Pain Inventory Short Form.[25,26] The Hospital Anxiety and Depression Scales are used to assess dimensional and categorical symptoms of anxiety and depression.[27,28] The pain catastrophizing score is used to measure the patients' catastrophizing tendencies.[29]

Statutes

The statutes of the P-QST collaboration (Supplementary Material, http://links.lww.com/MPA/A903) were proposed first by members of the 3 core institutions and subsequently agreed upon by all participating members.

RESULTS

The results from the work of the consortium are forthcoming. Several projects have been completed, which have laid the foundation for future work. Additional projects have been designed and initiated, and work is ongoing to explore the characterization of pain and nociception in painful CP.

CONSORTIUM WORK

The P-QST Consortium has established a nomogram for abnormal P-QST thresholds.[18] In this study, 122 control subjects and 60 patients with painful CP with equal sex and age distribution underwent P-QST (Table 2). An algorithm was developed with optimal capacity to differentiate between groups. In a pilot feasibility study of the 60 CP patients with pain, it was demonstrated that the algorithm was able to differentiate this patient population into 3 distinct pain phenotype groups: 50% were determined to have no abnormal sensitization, 23% had evidence of segmental sensitization, and 27% had evidence of widespread sensitization.

The nomogram thresholds were then applied in a population of 179 CP patients (of which the original 60 were part).[21] In this group, no abnormal sensory processing was seen in 91 (51%), segmental sensitization in 50 (28%), and widespread sensitization in 38 (21%). Subjects with widespread sensitization compared with the other 2 phenotypes had significantly higher pain intensity scores. They also had higher rates of constant pain than did those with no abnormal sensitization (53% vs 32%). On the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, patients with widespread sensitization were noted to have decreased global health and decreased physical functioning in comparison with the other 2 P-QST phenotypes. Psychiatric comorbidities (anxiety and depression) were not associated with pain phenotypes, suggesting that P-QST phenotypes provide an unbiased proxy of the sensory pain component.[21]

We completed a pilot study involving 30 subjects who underwent either endoscopic treatment (endoscopic retrograde cholangiopancreatography [ERCP] ± extracorporeal shock wave lithotripsy [ESWL]) or surgery after P-QST assessment.[30] Response to intervention was defined as a ≥30% reduction in pain at 6 months after intervention compared with baseline. Response to intervention was seen in only (20%) with widespread sensitization as compared with about 60% treatment response in patients with no abnormal sensation or segmental sensitization.

Future Studies

The consortium also plans to work with collaborators in India, evaluating the predictive capability of P-QST as an exploratory outcome for the Combined Extracorporeal Shock Wave Lithotripsy and Endoscopic Treatment for Pain in Chronic Pancreatitis trial.[31] In this randomized, single-blind, parallel-group, sham-controlled trial, 106 patients with painful CP will be randomized to either combined ESWL and ERCP treatment, or sham procedures. The primary outcome of the trial is pain relief at the end of 3 months of postintervention follow-up. Preprocedure P-QST will be performed and analyzed in association with outcomes from the trial to determine its ability to predict outcome to invasive endoscopic treatment. In addition to this, a comparison of P-QST profiles between patients residing in different geographic areas including India, Denmark, and the United States is planned.

The consortium plans to work with collaborators throughout Denmark in a multicenter, prospective assessment of patients with different stages of CP.[32] A total of 120 patients with suspected (n = 60) or definitive CP (n = 60) will be enrolled and followed up prospectively for up to 15 years with annual assessment of clinical outcome parameters and blood samples for biobanking, and magnetic resonance imaging obtained every other year. Testing with P-QST will be incorporated with annual assessments in this cohort to assess whether P-QST phenotypes change over time and their association with the clinical course of disease.

DISCUSSION

Quantitative sensory testing provides information on sensory function at the peripheral and central level of the nervous system by recording subjects' responses to different external stimuli of controlled intensity. It can provide an understanding of aspects related to neural transduction, transmission, and pain perception under normal and pathophysiological conditions. The primary advantages of QST are that a pain stimulus can be controlled with a variety of test modalities, delivered repeatedly, and modulated, and that the responses can be assessed qualitatively and quantitatively with psychophysical, neurophysiological, or different

TABLE 2. Publications of the P-QST Consortium to Date

Study	Patient Population	Findings
A clinically feasible method for the assessment and characterization of pain in patients with chronic pancreatitis (Phillips et al, *Pancreatology*, 2020)[18]	Controls 60 patients with painful CP (pilot feasibility study)	An algorithm was developed with optimal capacity to differentiate between 3 separate groups (normal, segmental, and widespread sensitization). In the pilot study of CP patients with pain, it was demonstrated that the distribution of phenotypes among CP patients was as follows: - 50% normal sensitization - 23% segmental sensitization - 27% widespread sensitization
Pancreatic QST differentiates chronic pancreatitis patients into distinct pain phenotypes independent of psychiatric comorbidities (Faghih et al, *Clin Gastroenterol Hepatol*, 2020)[21]	CP patients	Compared with CP patients with segmental or normal sensitization, CP patients with widespread hyperalgesia had significantly - Higher pain intensity scores - Higher rates of constant pain - Decreased quality of life - Decreased physical functioning
Combined Extracorporeal Shock Wave Lithotripsy and Endoscopic Treatment for Pain in Chronic Pancreatitis (SCHOKE trial): study protocol for a randomized, sham-controlled trial (Olesen et al, *Trials*, 2019)[31]	CP patients with pain	- Protocol for a randomized, single-blind, parallel-group, sham-controlled trial - 106 patients with painful CP and pancreatic duct obstruction randomized to ESWL and ERCP, or to sham procedures - Primary outcome: pain response at 3 mo after intervention - Exploratory outcome: P-QST as a predictor of outcome
Pancreatic quantitative sensory testing in painful chronic pancreatitis can predict pain response after intervention: a pilot study (published abstract, Faghih et al, *Pancreatology*, 2020)[30]	CP patients with pain	- Prospective study of 30 patients who underwent ERCP ± ESWL, to test predictive capability of preintervention P-QST - Pain reduction of ≥30% from baseline was seen in 59% of patients with no hyperalgesia, 63% of patients with segmental hyperalgesia, and only 20% of patients with widespread hyperalgesia
Characterisation of the fibroinflammatory process involved in progression from acute to chronic pancreatitis: study protocol for a multicentre, prospective cohort study (Novovic et al, *BMJ Open*, 2019)[32]	Patients in different stages of CP	- Total of 120 patients to be enrolled in different stage of CP - Followed over 15 years, with biological sample collection and imaging follow-up to observe natural history of disease progression

imaging methods.[33] The P-QST protocol was developed specifically for patients with diseases of the pancreas and is noninvasive, is inexpensive, and takes only approximately 20 minutes to perform at bedside. It has the potential to be delivered serially to patients to evaluate for changes in sensory perception related to natural history or other therapies.

Development of a QST Protocol for CP

A prior QST protocol—the Nijmegen Aalborg Screening QST paradigm—has been effective in research settings to evaluate pain processing in CP.[34] It demonstrated that a subset of CP patients has evidence of widespread hyperalgesia and that the degree of widespread hyperalgesia corresponds to more severe stages of CP as characterized by the M-ANNHEIM classification.[16,35] It has also shown that persistent widespread hyperalgesia is a predictor of poor surgical outcome to thoracoscopic splanchnic denervation in CP.[36] In patients with segmental hyperalgesia at the pancreatic dermatome, QST results have been able to predict improvement in pain with pregabalin.[37]

Evolution of Pancreatic QST

The Nijmegen Aalborg Screening QST protocol involved electrotetanical testing, which some patients were unwilling to do and providers found cumbersome. The sensory thresholds have been shown to be reproducible over time, whereas conditioned pain stimulation was not.[38] This is also seen in other studies in different patient groups where dynamic testing was used to evaluate somatic and visceral pain, and likely reflect diurnal variation and influence of a variety of factors (cognitive, emotional, medication, etc) that interfere with the testing.[39] The protocol has been adapted into P-QST for bedside use with handheld tools, as described previously. The use of the pPTT index and sum score in the P-QST protocol was found to be redundant with pPDT index and sum, and therefore, it was not used in the final protocol (Tables 1, 2).

Different QST protocols have been suggested for profiling patients, and P-QST has now been tested for reliability and validity in many studies.[36,38,40,41] It should be stressed that, although QST has been shown to reliably assess different pain mechanisms, it only assesses part of the sensory process mainly relating to the acute pain response induced by test stimuli. The testing does require active and willing participation on the part of the subject: although

the pressure testing is designed to reach thresholds for pain, no persistent pain or lasting effects of the testing have been reported.

Results of P-QST may therefore only be a piece in the puzzle of the many pathological mechanisms that are involved in the complex neuronal reorganization and sensitization involved in chronification of pain. However, the methods have been shown to mirror the pathological pain processing to a high degree. The P-QST results also do not measure the aspects of chronic pain that are indirectly related to nociception such as emotional, affective, and social consequences to the painful disease. To partly compensate for this, we have added different questionnaires to measure these processes, although their subjective nature contrasts the (semi)objective assessment with P-QST.

The incorporation of P-QST into the existing treatment paradigm for painful CP has the potential to optimize treatment strategies based on underlying pain processing: patients with no abnormal sensitization may benefit most from local invasive therapies, whereas those with widespread sensitization may benefit most from medical therapy. For incorporation of P-QST to occur, the findings from early P-QST consortium studies must be validated in larger populations of CP patients that include patients of differing etiologies and all pancreas morphologies. Clarification of the impact of opioid analgesics on widespread sensitization must be pursued. In addition, performance of P-QST alongside imaging techniques that can elucidate morphologic or physiologic findings of patients' neuroanatomy will help to better understand the phenomena of widespread sensitization witnessed in these patients.

The P-QST Consortium

The P-QST Consortium now consists of members from 7 international pancreatic centers of excellence: Aalborg University Hospital (Aalborg, Denmark), Copenhagen University Hospital Hvidovre (Copenhagen, Denmark), The University of Pittsburgh Medical Center (Pittsburgh, Pa), Johns Hopkins University Medical Center (Baltimore, Md), Indiana University Medical Center (Indianapolis, Ind), The Ohio State University Wexner Medical Center (Columbus, Ohio), and The Asian Institute of Gastroenterology (Hyderabad, India). The All India Institute of Medical Sciences (New Delhi, India) is planned as an eighth center. The consortium is led by a single director, who is decided upon by the members of the Steering Committee. Membership in the Steering Committee is decided annually by a vote from all members of the consortium. To streamline the productivity and collaborative efforts of the consortium, the statutes have been proposed, edited, and agreed upon by all members (Supplementary Material, http://links.lww.com/MPA/A903). New membership criteria in the consortium for sites interested in joining the consortium have also been provided.

CONCLUSIONS

Testing with P-QST has the potential to more accurately characterize an individual patient's pain phenotype, which should help provide an opportunity for a tailored treatment paradigm for painful CP by identifying patients who are at high risk of nonresponse to invasive treatments. Identification of individuals who have a greater chance for response to treatments can optimize patient selection for high-risk procedures and help to improve outcomes in CP. This technique may also have the ability to identify response patterns in other (medical) treatments for CP as well. Collaboration and harmonization of these testing methods and recruitment of large, international, multicenter cohorts of CP patients should also allow for extrapolation and dissemination of findings.

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