Quantitative Sensory Testing in Painful Chronic Pancreatitis

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Conflicts of Interest

- No conflicts of interest to disclose.

Support

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Objectives

- Describe derivation of normal thresholds of pancreatic quantitative sensory testing
- Describe the use of pancreatic quantitative sensory testing in a population of CP patients

Pain in Chronic Pancreatitis (CP)

- Most disabling symptom
- Affects ~90% of patients
- Invasive therapy is offered to patients whose pain is thought to be due to obstructive disease (Pancreatic duct stones, strictures)
- Pain response to therapies is unpredictable
- Correlates poorly with morphologic features on imaging

-Wilcox CM et al, Clin Gastro and Hep, March 2015
-Olesen SS et al, Pancreapedia, Feb 2015

Pain Assessment Tools in CP

Aspects of pain included in general multidimensional tools, specific pain assessment tools for chronic pancreatitis (CP), and impact of pain assessment tools (adapted from the criteria for evaluation of pain by the American Gastroenterological Association [14] with 8 additional pain aspects from the literature [4,18–20]).

Aspects of Pain	General multidimensional tools		CP-specific tools				Impact of pain tools			
	MPQ[a]	PDQ[b]	Izbicki[c]	Amman	Type A-E	Group 1-3	BPI[d]	PDI	PCCL	QOL scales
Key reference	[37]	[18]	[48]	[49]	[50]	[51]	[18]	[19]	[19]	[20,28,46,47]
Duration of pain										
Location of pain										
Radiation of pain										
Triggers/exacerbators of pain	F									
Pain pattern (Continuous/Intermittent)	F									
Objective measure of pain intensity[e]	S									
Subjective estimate of intensity of pain	F									
Frequency of pain attacks										
Description of pain	B									
Associated symptoms with pain	B									
Postprandial pain										
Analgesic use										
Relieving factors of pain	F									
Ability to work/occupation status										
Effect on daily activities/function										
Effect on mental health										

Teo et al. Pancreatology 2016;16(6):931-939

Pain versus Nociception

- Tools to date: cannot differentiate pain versus nociception
- Cannot predict outcomes of treatment
- Lack objectivity
- Pain: Subjective and emotional experience associated with actual or potential damage

- Nociception : Response of sensory nervous system to harmful or potential harmful stimuli

- Due to the subjective nature and emotional aspect of pain, it is unlikely that there will ever be a biomarker for pain but it is more likely that there will be biomarker(s) to assess nociceptive activity

Suboptimal Pain Response to Existing Therapies

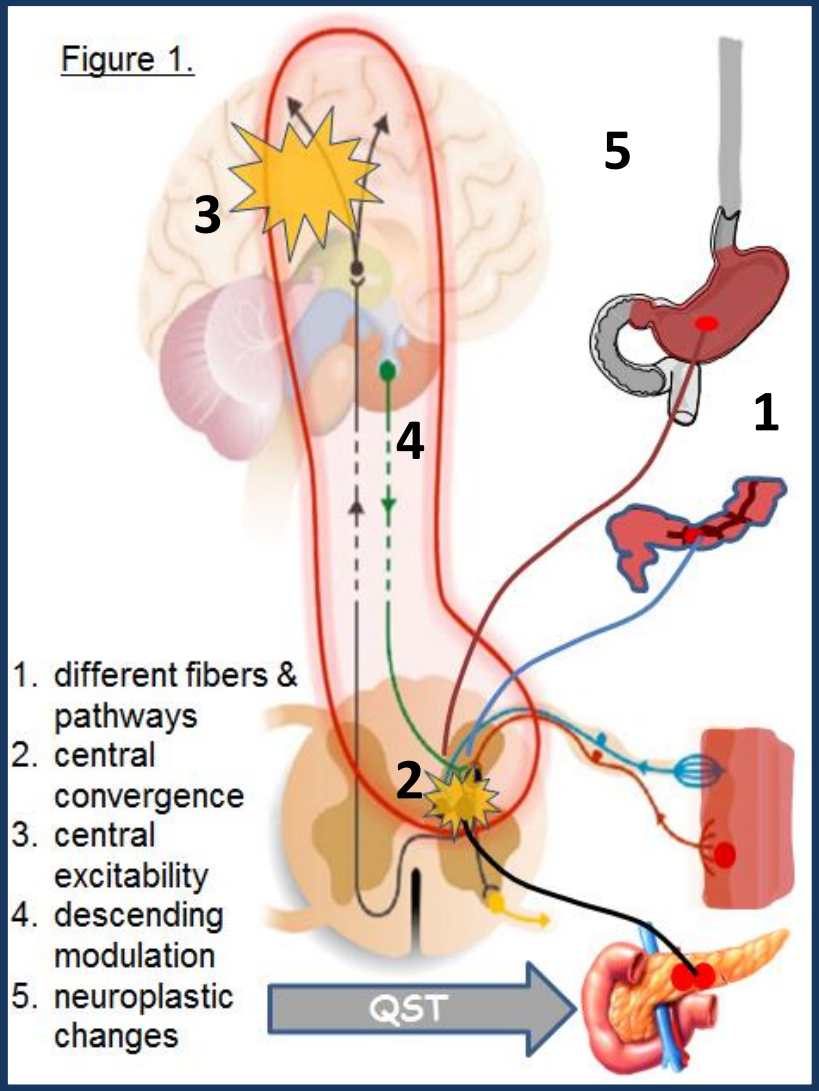
- CP pain results from multiple mechanisms
- Central sensitization: hyper-exitability in the central nervous system
  - functional reorganization of cerebral cortex
  - Neuroplastic and neuropathic changes occur in response to persistent visceral and somatic pain stimuli
  - Incomplete pain response to local CP therapies is thought to be due to central sensitization

-Drewes AM et al, Pancreatology, Sep 2017

Quantitative Sensory Testing

Central Sensitization

Segmental Sensitization

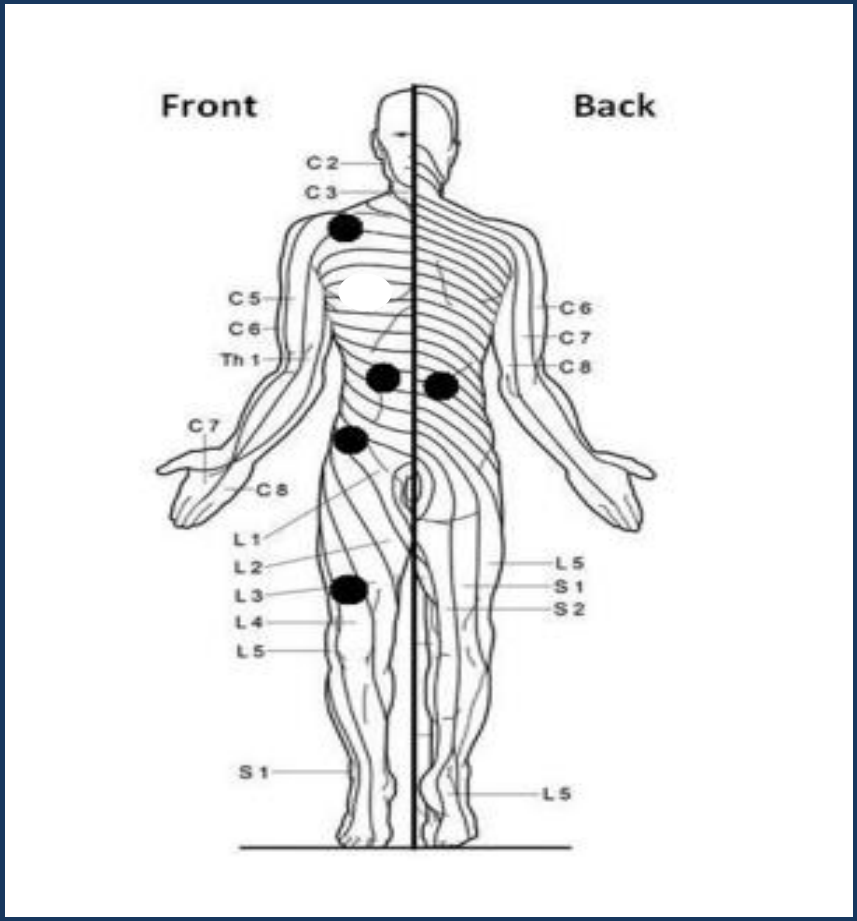


-Drewes et al. , unpublished

Pancreatic QST (P-QST)

- New and simplified testing protocol
- Developed in collaboration with Danish colleagues
- Tailored specifically for use in patients with CP
- Utilizes convergence of visceral nerves and somatic nerves in the spinal cord root
- Facilitates surface testing of the pancreatic viscerotome (T10)

P-QST


Front
Back
C2
C3
C5
C6
Th1
C7
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L3
L4
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S1
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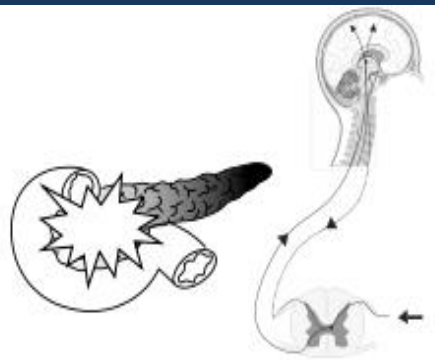
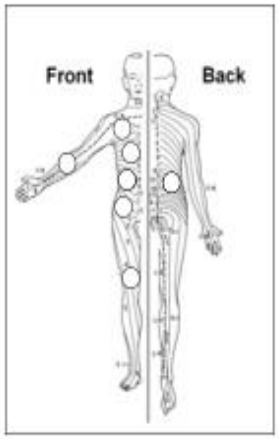
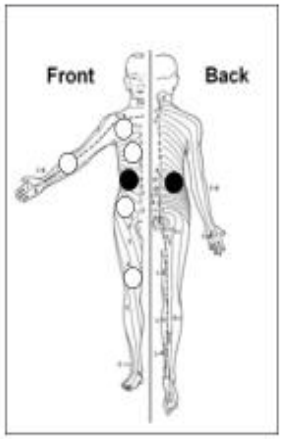


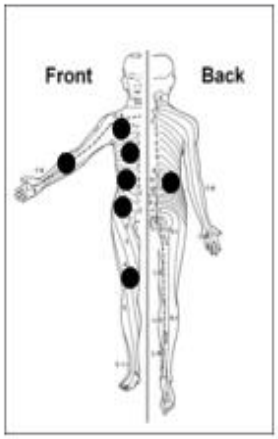
Central sensitization

None (normal) | **Segmental sensitization** | **Widespread sensitization**

QST







Values Used in Diagnostic Thresholds

Central Sensitization

- Temporal Summation Index Forearm (*TS Index Forearm*)
- Pressure Detection Sum (*pPDT sum*)
- Cold Pressor Test Area Under Curve (*AUC*)
- Conditioned Pain Modulation Index (*CPM Index*)

Segmental Sensitization

- Pressure Detection Index (*pPDT Index*)
- Temporal Summation Index Abdomen (TS Index Abdomen)

Temporal Summation

- Wind-up phenomenon from repeated stimuli
- Measured on forearm and abdomen (T10)

Pin-Prick Simulator

$$TS\ Index = 10stim - 1stim$$

Pressure Detection/Tolerance

- Measured in 6 different locations over surface of body
- Pain Detection Threshold: pPDT
- Pain Tolerance Threshold: pPTT

Pressure Algometer

$$pPDT\ or\ pPTT\ Index = \frac{mean(T10^{ABD} + T10^{BACK})}{mean(C5 + L1 + L4)}$$

Conditioned Pain Modulation

- Detection of altered descending inhibition
- Hand is exposed to ice water for 2 minutes
- Patient's discomfort is rated every 10 seconds (scale 1-10)
- If hand is removed, score of 10 is assigned for that timepoint
- Pressure tolerance test before and after

Ice Water Bath

$$CPM = \frac{pPTT^{AFT} - pPTT^{BEF}}{pPTT^{BEF}}$$

Hypothesis

- This protocol will help to identify specific phenotypes in patients with CP.
- These phenotypes will associate with patient and disease characteristics.

Significance

- If QST is able to identify specific phenotypes, it can be used as a predictive tool to identify patients who will respond to specific therapies.

Aims: Normogram Study

1)Use P-QST protocol to develop a normogram

2)Use newly developed normogram to phenotype patients with chronic pancreatitis

Study Sites

- Institutional Review Board approval was obtained at each site individually
  - University of Pittsburgh Medical Center (Pittsburgh, PA, USA)
  - The Johns Hopkins University Medical Center (Baltimore, MD, USA)
  - Aalborg University Hospital (Aalborg, Denmark).

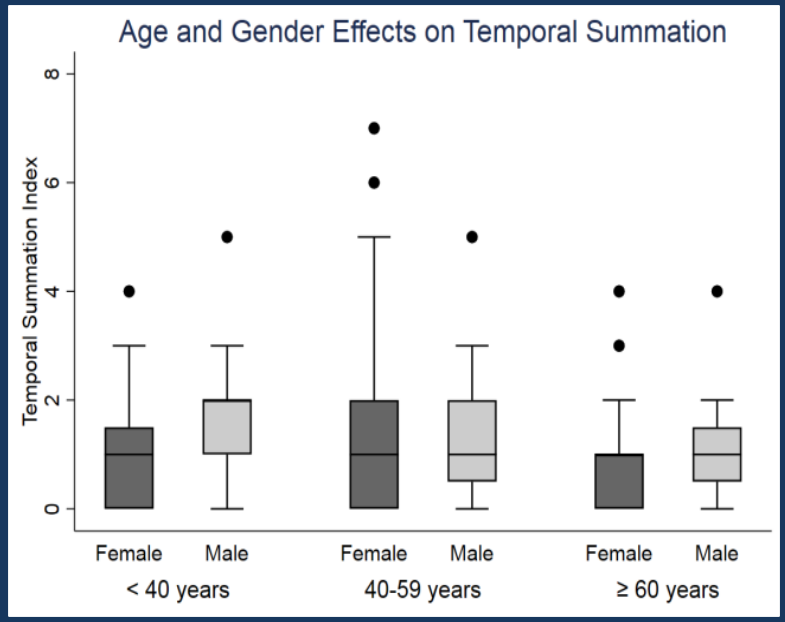
Study Subjects

	Female	Male	Totals
<40 yrs	20	21	41
40-59 yrs	21	20	41
≥ 60	20	20	40
Totals	61	61	122

Exclusion Criteria:
Medical or Surgical disease that would affect QST testing
Chronic Abdominal Pain (daily abdominal pain, or more than 6 episodes of abdominal pain per year)
Chronic Narcotic Use (prescription or otherwise)
Chronic Pain Syndrome
Pregnancy

TS Index

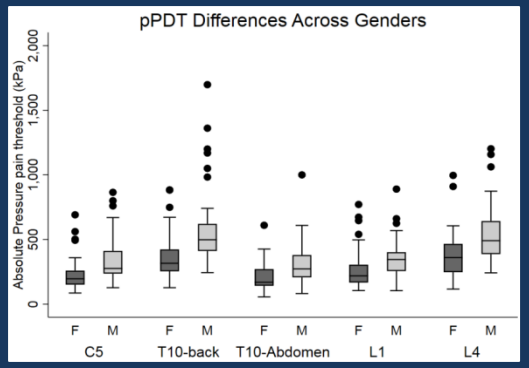
- Non-parametric evaluation
- No age or gender effects were observed
- Median TS Index: 1.0 (IQR 0.0-2.0)
- 75th percentile = 2.0
- Correlation between TS Forearm and TS Abdomen
- TS Forearm: widespread hyperalgesia
- TS Abd: segmental hyperalgesia

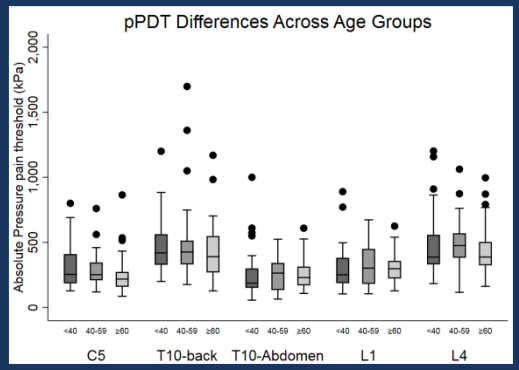


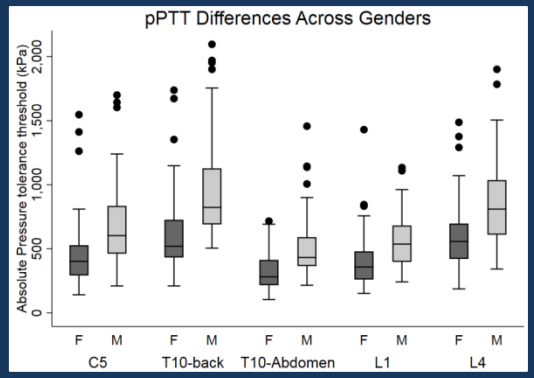
Threshold: TS Index > 2

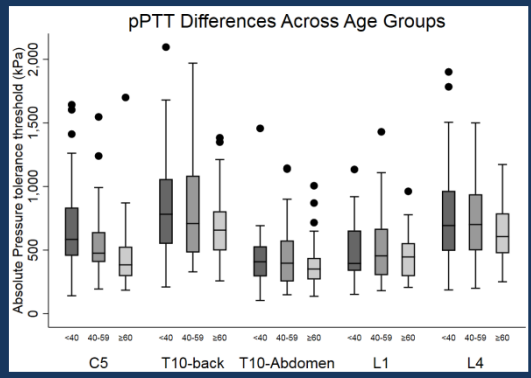
pPDT Index, pPTT Index

- Mixed effects models
- Differences seen in absolute thresholds (lower with increasing age, female)
- pPDT Index: Median 1.0, lower 25th percentile 0.87
- Correlation of pPDT and pPTT Indices (rho 0.66, p<0.001)









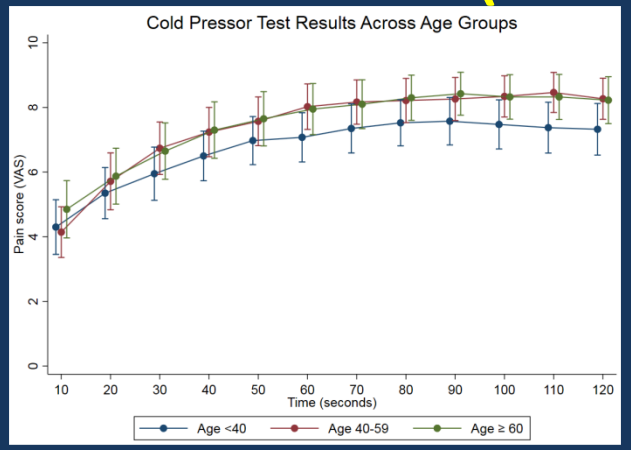
Threshold pPDT Index ≤ 0.85

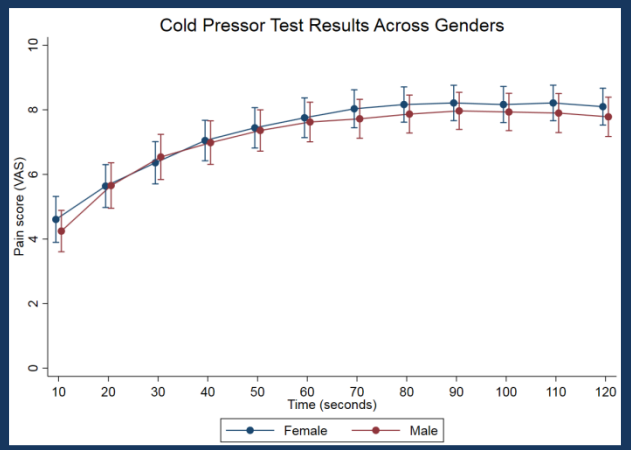
pPDT Sum Scores

- Sum of pPDT and pPTT absolute thresholds across all dermatomes (C5 + T10 back + T10 abd+ L1 + L4)
- Gender differences seen
- Correlation of pPDT and pPTT sum scores (rho 0.75, $p<0.001$)
- pPDT Sum score female: Median 520 kPa (lower 25th percentile 403kPa)
  - Threshold pPDT Sum (female) = <400kPa
- pPDT Sum score male: Median 786 kPa (lower 25th percentile626kPa)
  - Threshold pPDT Sum (male) = <600kPa

Cold Pressor Test: Area Under Curve (AUC)

- No age or gender effects seen
- Median: 7.3 VAS per sec
- Upper 75th percentile 8.8 VAS per sec





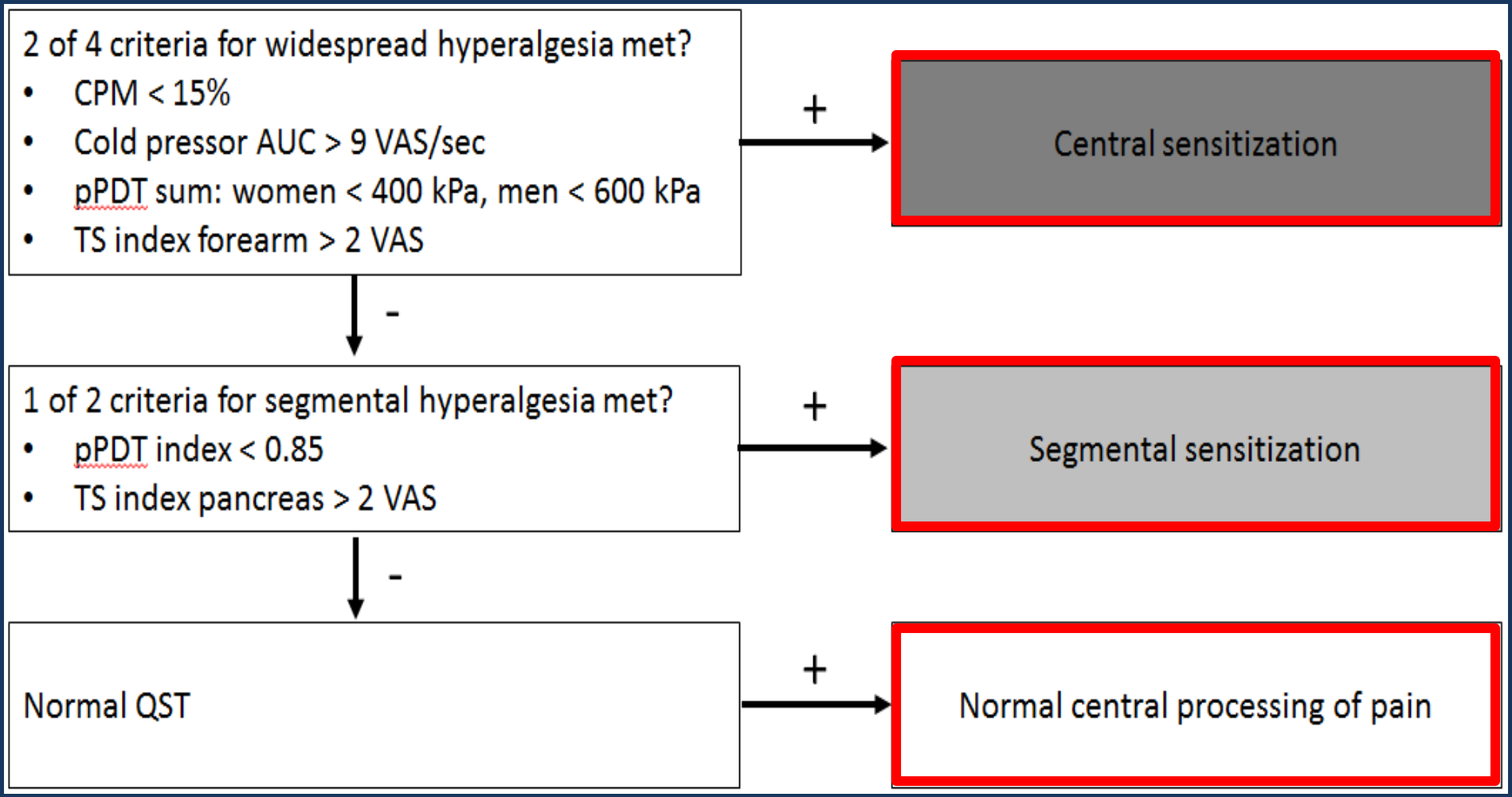
Threshold AUC >9 VAS per sec

CPM Index

- Suboptimal increase in pain tolerance threshold after ice water exposure
- Normality: based on within-subject coefficient of variation in CPM test stimulus (pPTT non-dominant L4 dermatome)
- Impaired: CPM response ≤ normal within-subject variation in CPM test stimulus between two repeated assessments without the conditioning stimulus
- Percentage variation in reference population: 13.0% (95% CI 10.9% - 15.2%)

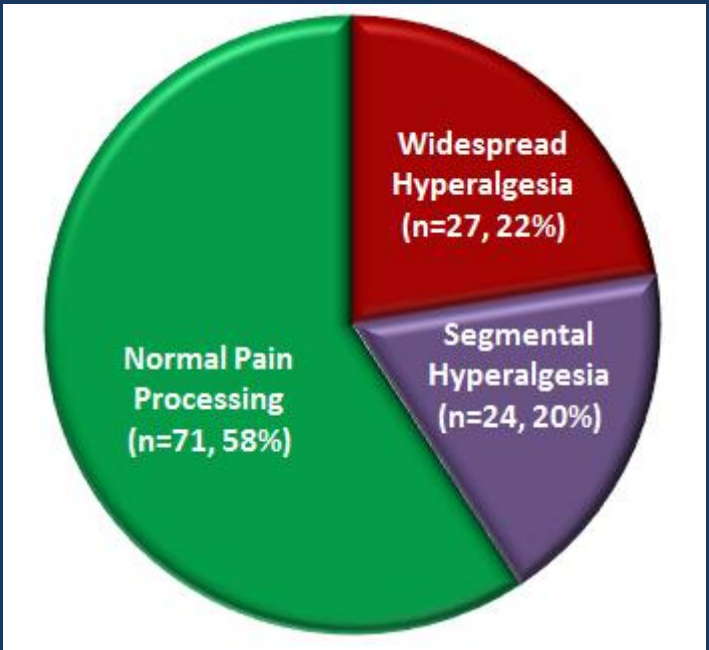
Threshold Impaired CPM: ≤ increase of 15% from baseline pPTT

Diagnostic Thresholds



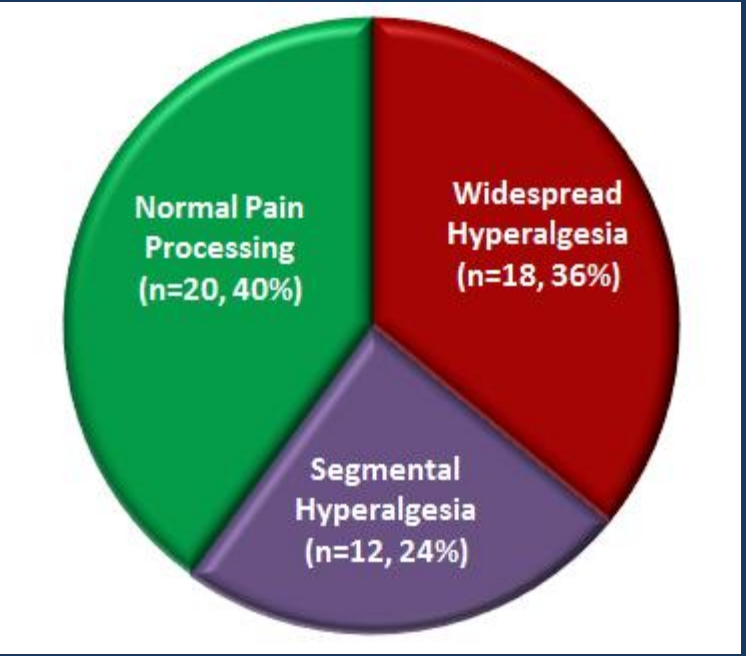
Distribution Across QST Phenotypes

Controls



N=122
M/F Equal gender groups
3 age groups: <40, 40-60, > 60

CP Patients



N=50.
Mean age 54.4±12.3 years. 30 (60%) male.
32 (64%) EtOH etiology.

Aims: P-QST in CP Patients

1) Phenotype pain in patients with chronic pancreatitis using P-QST

2) Evaluate whether the QST profiles of these patients correlate with QOL and psychologic variables

Methods

Multicenter study

-University of Pittsburgh Medical Center

-The Johns Hopkins University Medical Center

-Aalborg University Hospital

CP definition

- At least one of the following:
  - Calcification(s) (definitive M-ANNHEIM)
  - Marked/severe ductal changes (Cambridge classification III or IV)

Pain Subset: Clinical phenotype

-Painful: constant or intermittent pain

-Painless: previous pain, no pain at time of enrollment

-Silent: presented with no pain

Methods

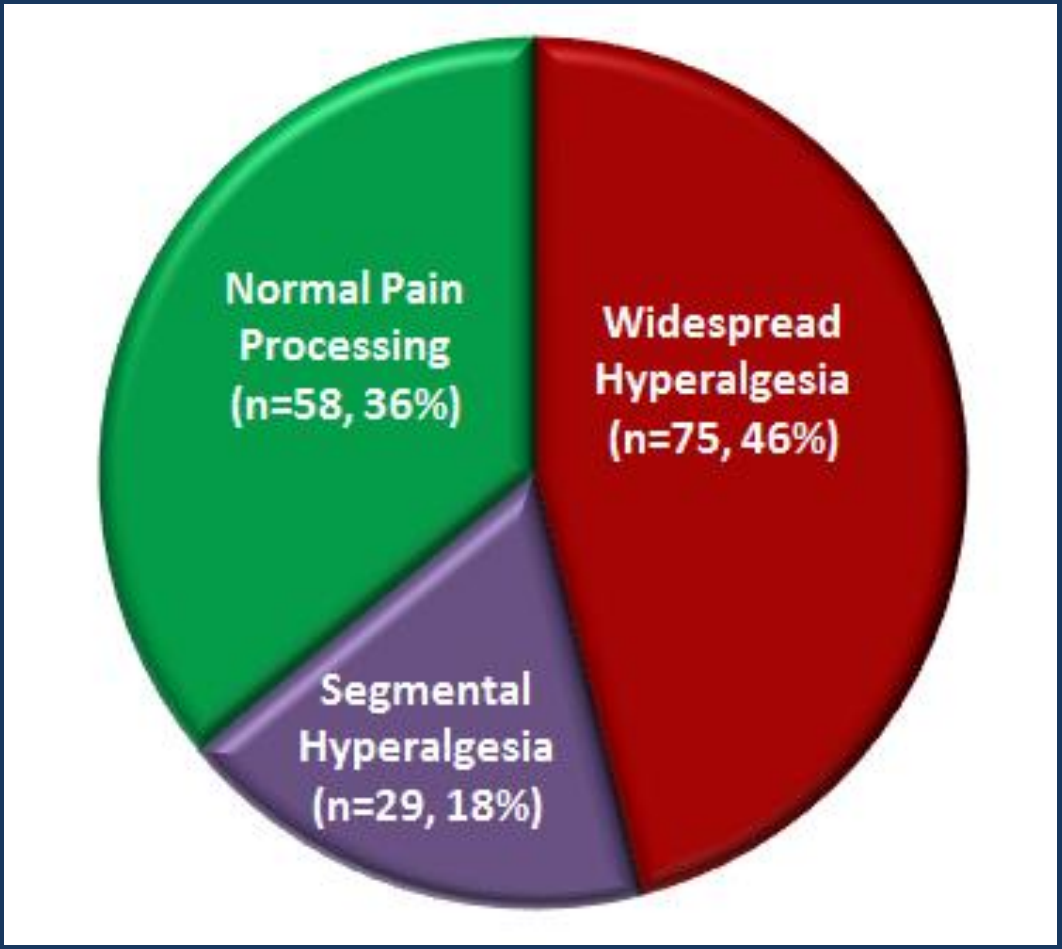
P-QST Testing in all CP Patients

Questionnaire Assessment:

1) Pain: Modified Brief Pain Inventory-short form (mBPI-sf)
2) Quality of life: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30)
3) Psychological impact of pain:
    a. Hospital Anxiety and Depression Scale (HADS)
    b. Patient Catastrophizing Scale (PCS)

Demographic characteristics		Total n=162
Male, n (%)		96 (59)
Age, Mean Yr (SD)		53.8 (13.6)
Race, n (%)	Caucasian	142 (89)
	African American	12 (8)
	Asian	6 (4)
Etiological risk factors, n (%)*	Toxic	121 (75)
	Idiopathic	20 (13)
	Genetic	12 (7)
	Autoimmune	0 (0)
	Recurrent and severe acute pancreatitis	40 (25)
	Obstructive	10 (6)
EPI, n (%)	Yes	101 (62)
	No	52 (32)
	Undetermined	9 (6)
Diabetes mellitus, n (%)	Yes	61 (38)
	No	95 (59)
	Undetermined	6 (4)
Prior endoscopic treatment, n (%)		86 (53)
Pancreatic surgery, n (%)		19 (12)

P-QST Phenotype Distributions in CP



Pain and Psychological Variables

	All patients (n=162)	Normal sensory profile (n=58)	Segmental hyperalgesia (n=29)	Widespread hyperalgesia (n=75)	P-value
Opioid treatment, n (%)	81 (50)	25 (43)	17 (59)	39 (52)	0.37
Adjuvant analgesics, n (%)	67 (41)	25 (43)	14 (48)	28 (37)	0.55
BPI pain score	4.0 (1.5-5.5)	3.8 (0.5-5.3)	3.0 (0-5.6)	4.5 (2.0-5.8)	0.16
BPI interference score	3.5 (0.3-6.0)	3.0 (0-5.9)	2.9 (0-6.1)	4.1 (1.3-6.3)	0.25
Psychological variables					
Pain catastrophizing					
Conditional	20.0 (7.0-31.0)	16.0 (6.0-29.0)	20.0 (7.0-30.0)	23.0 (8.0-33.0)	0.23
Situational	23.0 (12.0-33.0)	22.0 (12.0-32.0)	20.5 (9.5-32.0)	26.0 (12.0-34.0)	0.46
HADS					
Depression score	6.0 (3.-10.0)	5.0 (2.0-9.0)	5.0 (1.0-9.0)	6.5 (4.0-10.0)	0.13
Anxiety score	7.0 (4.0-11.0)	7.0 (4.0-12.0)	7.0 (4.0-9.0)	8.0 (5.0-12.0)	0.25

	All patients (n=162)	Normal sensory profile (n=58)	Segmental hyperalgesia (n=29)	Widespread hyperalgesia (n=75)	P-value
Pain characteristics					
Pancreatic pain phenotype, n (%)					
Painful CP	128 (79)	40 (69)	21 (72)	67 (89)	0.008
Painless and silent CP	34 (21)	18 (31)	8 (28)	8 (11)	
Pain pattern, n (%)*					
Intermittent pain	48 (38)	20 (50)	6 (29)	22 (33)	0.15
Constant pain	80 (63)	20 (50)	15 (71)	45 (67)	

Quality of Life

	All patients (n=162)	Normal sensory profile (n=58)	Segmental hyperalgesia (n=29)	Widespread hyperalgesia (n=75)	P-value
Global health	50.0 (33.3-66.7)	58.3 (33.3-83.3)	58.3 (41.7-83.3)	41.7 (33.3-58.3)*##	0.006
Functional scales					
Physical functioning	73.3 (60.0-93.3)	80.0 (66.7-93.3)	93.3 (66.7-100)	66.7 (46.7-86.7)**##	<0.001
Role functioning	66.7 (33.3-83.3)	66.7 (33.3-91.7)	66.7 (33.3-100)	50.0 (33.3-66.7)	0.11
Emotional functioning	66.7 (50.0-83.3)	75.0 (41.7-91.7)	75.0 (50.0-100)	58.3 (50.0-83.3)	0.08
Cognitive functioning	66.7 (50.0-100)	83.3 (50.0-100)	100 (66.7-100)	66.7 (33.3-83.3)##	<0.001
Social functioning	66.7 (33.3-100)	66.7 (33.3-100)	83.3 (50.0-100)	58.3 (33.3-83.3)	0.08
Symptom scales / items					
Fatigue	55.6 (33.3-66.7)	55.6 (22.2-77.8)	33.3 (22.2-55.6)	55.6 (33.3-77.8)	0.06
Nausea and vomiting	16.7 (0-50.0)	16.7 (0-33.3)	0 (0-33.3)	33.3 (16.7-50.0)**#	0.005
Pain	66.7 (33.3-83.3)	50.0 (16.7-83.3)	50.0 (16.7-66.7)	66.7 (33.3-83.3)#	0.04
Dyspnoea	0 (0-33.3)	0 (0-33.3)	0 (0-33.3)	0 (0-33.3)	0.99
Insomnia	33.3 (0-66.7)	33.3 (0-66.7)	33.3 (33.3-66.7)	33.3 (0-66.7)	0.92
Appetite loss	33.3 (0-66.7)	33.3 (0-66.7)	0 (0-33.3)	33.3 (0-66.7)	0.06
Constipation	0 (0-33.3)	33.3 (0-66.7)	0 (0-33.3)	33.3 (0-66.7)	0.88
Diarrhoea	33.3 (0-33.3)	33.3 (0-33.3)	0 (0-33.3)	0 (0-33.3)	0.77
Financial difficulties	33.3 (0-66.7)	33.3 (0-66.7)	0 (0-66.7)	33.3 (0-66.7)	0.50

Significance of the difference between patients with widespread hyperalgesia and normal sensory profile: *P<0.05, **P<0.01
Significance of the difference between patients with widespread hyperalgesia and segmental hyperalgesia: #P<0.05, ##P<0.01

Conclusions: P-QST

- It is feasible to phenotype CP patients by apparent level of nociception
- CP patients with widespread sensitization (Central Sensitization) have more pain and significantly lower QOL
- P-QST characterizes the sensory profiles independently of psychological status (anxiety, depression, catastrophizing) and thus provides an unbiased proxy of pain processing or nociception

Hypothesis

- Presence of central sensitization renders patients less likely to respond to invasive local therapies indicated for the treatment of pain in CP

Future Directions

- Evaluation of whether P-QST phenotype is predictive of likelihood of response to invasive local therapy
  - Can pre-procedural QST pain phenotypes predict outcomes after intervention in painful chronic pancreatitis?
- Facilitate tailored therapies for CP patients with pain

Thank You

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- Pancreasfest Organizing Committee

Questions?