

## BACKGROUND

### Nociplastic pain (formally centralized pain)<sup>1</sup>

- Augmented central nervous system pain and sensory processing
- The hallmark is widespread distribution of pain that co-occurs with mood disturbances, cognitive dysfunction, hypersensitivity to sensory stimuli, sleep disturbances, and fatigue
- Triggered by significant physiological stress such as deployment to war or severe illness
- Development of nociplastic pain after a physiological stressor such as cardiac surgery is not known
- Responds poorly to opioid therapy

### Chronic pain after cardiac surgery<sup>2</sup>

- After open cardiac surgery and intensive care unit (ICU) care, 37% of patients develop chronic pain, and 10% develops chronic opioid use
- Pain can occur in locations unrelated to the site of surgery

### Post-intensive care syndrome (PICS)<sup>3</sup>

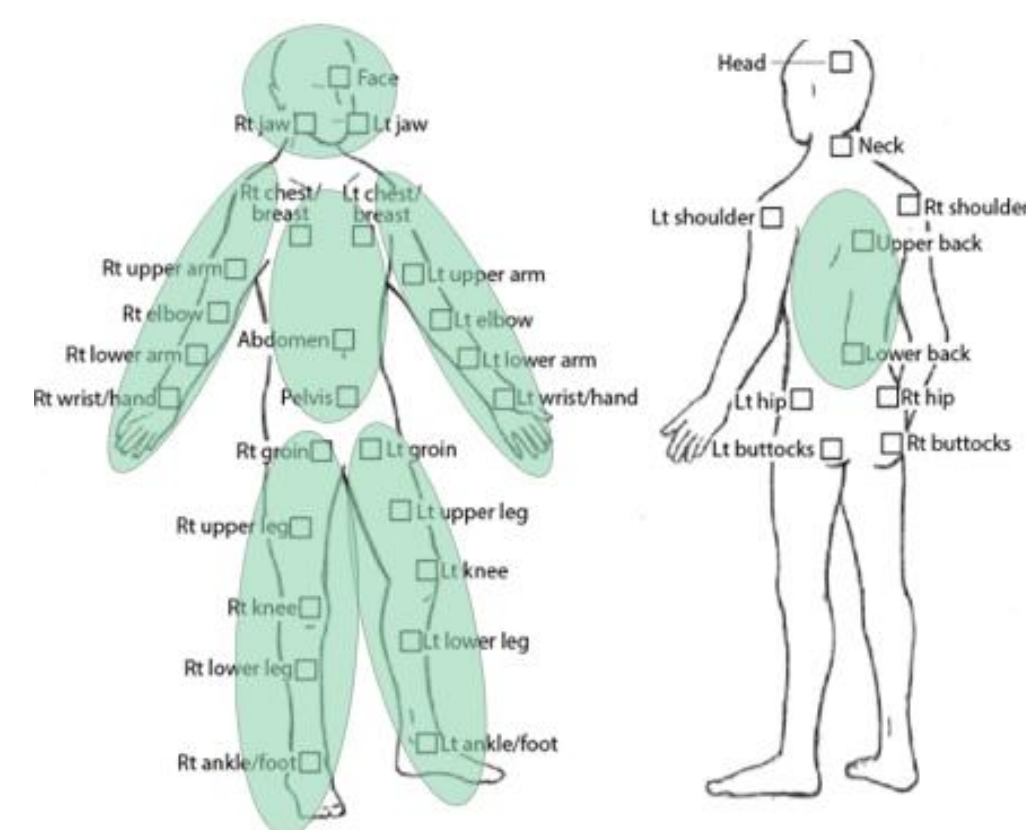
- Over 20% of cardiac surgery patients experience longstanding issues after hospital discharge including physical health, mood and executive dysfunction<sup>4</sup>
- These symptoms have similarities with those seen in nociplastic pain

## PURPOSE

- To determine whether patients after cardiac surgery requiring ICU care experience new widespread pain long term after discharge
- To identify risk factors for new widespread pain and associations between widespread pain and other follow-up symptoms typically seen in nociplastic pain.

## METHODS

- Prospective observational cohort study as part of the Michigan Genomics Initiative at the University of Michigan
- Participants underwent baseline pain and psychological assessments prior to their surgery and postoperative ICU course
- Cohort consisted of cardiac surgery patients who survived the ICU course and responded to a mailed follow-up questionnaire assessing their symptoms.
- Symptoms assessed included the participant's current pain, physical function, mood, cognitive, and somatic symptoms
- **Primary outcome:** New widespread pain at follow-up defined as pain in  $\geq 3$  of 7 body regions (Figure 1).
- Descriptive analysis and logistic regression analyses were conducted to determine the association between baseline and surgical factors with new widespread pain and the association between new widespread pain and other symptoms assessed at the follow-up timepoint.
- Length of time since ICU discharge was controlled for.



**Figure 1:** Body Map for Widespread Pain Assessment. Green areas indicate the 7 body regions

## RESULTS

**Table 1:** Baseline Characteristics and Risk Factors for Widespread Pain at Follow-Up

Variable (Categorical or Continuous)	Frequency (%) or Mean (SD), n=53	Association with new widespread pain OR (95% CI, p value)
<i>Sociodemographic Characteristics</i>		
Age (years)	65 (12)	1.02 (0.96-1.09) p=0.51
Body Mass Index (kg/m <sup>2</sup> )	29.5 (5.1)	0.99 (0.86-1.15) p=0.93
Sex	Female 12 (22.6%)	0.86 (0.15-4.92) p=0.86
	Male (ref) 41 (77.4%)	
Race	White 52 (98.1%)	(p=1.00)
	African American 1 (1.9%)	
	Other (ref)	
Tobacco Use	Current 24 (45.3%)	0.08 (0.004-1.82) p=0.11
	Former 2 (3.8%)	0.26 (0.01-4.99) p=0.37
	Never (ref) 27 (50.9%)	
Alcohol Use	Current 11 (22.0%)	0.66 (0.11-3.99) p=0.65
	Never (ref) 39 (78.0%)	
Drug Use	Current 50 (94.3%)	4.07 (0.35-38.55) p=0.39
	Never (ref) 3 (5.7%)	
<i>Baseline characteristics</i>		
ASA Classification	Class 1 0 (0%)	p=1.00
	Class 2 1 (1.9%)	
	Class 3 19 (35.8%)	
	Class 4 (ref) 33 (62.3%)	
Preoperative Opioid Use	Yes 1 (3.1%)	(p=1.00)
	No (ref) 31 (96.9%)	
At Least Moderate Depression <sup>a</sup>	Yes 6 (11.3%)	1.14 (0.11-11.31) p=0.91
	No (ref) 47 (88.7%)	
At Least Moderate Anxiety <sup>a</sup>	Yes 14 (26.4%)	0.92 (0.16-5.18) p=0.92
	No (ref) 39 (73.6%)	
Neuropathic Pain (Pain Detect Scale)	2.0 (2.7)	1.11 (0.82-1.50) p=0.51
Somatic Symptoms <sup>b</sup>	2.7 (2.3)	1.47 (1.01-2.12) <b>p=0.043</b>
Life Satisfaction Scale	7.9 (2.2)	1.26 (0.79-2.04) p=0.34
Life Stress Scale	4.3 (3.0)	1.16 (0.86-1.57) p=0.33
Physical Function (PROMIS SF 4a)	16.8 (3.8)	0.93 (0.73-1.17) p=0.52
Acute Pain (Brief Pain Inventory)	1.1 (1.5)	1.47 (0.93-2.32) p=0.10
<i>Surgery and ICU characteristics</i>		
Anesthesia Duration (hours)	7.1 (1.8)	1.00 (1.00-1.01) p=0.53
ICU Length of Stay	2.6 (1.9)	0.92 (0.59-1.43) p=0.71
Daily Average OME Use in the ICU	38.4 (44.3)	0.99 (0.97-1.02) p=0.53
ICU Mechanical Ventilation	Yes 7 (13.2%)	0.93 (0.10-8.94) p=0.95
	No (ref) 46 (86.8%)	
Major surgery	No (ref) 1 (1.9%)	(p=1.00)
	Yes 52 (98.1%)	

<sup>a</sup> Defined by score >8 on HADS or PROMIS scale

<sup>b</sup> Symptom Severity Scale: Sum of the severity of fatigue, waking unrefreshed, and trouble thinking over the past week (0-3 scale) plus the presence of headaches, lower abdominal pain/cramps, and depression in the previous 6 months.

## RESULTS (CONTINUED)

- 349 patients who underwent cardiac surgery and ICU care were sent a follow-up questionnaire. 109 questionnaire were completed. Response rate 31%.
- Questionnaires were completed on average 3.5 ± 1.2 years after their postoperative ICU admission
- A total of 53 participants were included in the analysis after excluding those with missing data (n=40) and those with preoperative evidence of widespread pain (n=16).
- 8 of 53 (15%) participants developed new widespread pain at the follow-up timepoint
- In univariable analyses, a higher burden of baseline somatic symptoms (through the symptom severity score) was the only variable significantly associated with new widespread pain (Table 1)
- New widespread pain is associated with several symptoms at the follow-up timepoint, including anxiety, cognitive impairment, sleep disturbance (Table 2)

**Table 2:** Associations Between New Widespread Pain and Symptoms at Follow-up

Symptoms at time of follow-up questionnaire	Logistic Regression OR (95% CI)	P value
Anxiety (PROMIS SF 4a)	9.28 (1.37-62.68)	<b>0.022</b>
Depression (PROMIS SF 4a)	4.98 (0.89-27.92)	0.068
Executive function (Multidimensional Inventory of Subjective Cognitive Impairment Scale)	0.89 (0.82-0.97)	<b>0.008</b>
Sleep (Pittsburg Sleep Quality Index)	1.22 (1.00-1.49)	<b>0.047</b>
Life Satisfaction Scale	0.76 (0.57-1.02)	0.070
Life Stress Scale	1.10 (0.79-1.54)	0.566
Somatic Symptoms (Symptom Severity Scale)	2.10 (1.33-3.30)	<b>0.001</b>
Physical Function (PROMIS SF 4a)	0.95 (0.82-1.10)	0.496
Pain Severity (Brief Pain Inventory)	2.39 (1.27-4.51)	<b>0.007</b>
Neuropathic pain (Pain Detect Scale)	1.63 (1.17-2.28)	<b>0.004</b>

## CONCLUSION

- Since widespread pain is the central feature of nociplastic pain, the occurrence of widespread pain after cardiac surgery suggests a possible nociplastic pain syndrome in the cardiac surgery population
- Baseline somatic symptoms were found to be a risk factor for new widespread pain after cardiac surgery. Higher burden of somatic symptoms is also a risk factor in other populations with nociplastic pain<sup>5,6</sup>
- Collectively symptoms of widespread pain with adverse mood and cognitive function, that occur in a subset of patients after cardiac surgery and ICU could represent a nociplastic pain syndrome
- Understanding whether nociplastic pain occurs following cardiac surgery can have implications on pain management in the perioperative period particularly since opioids are a mainstay therapy during the perioperative and ICU period
- Larger prospective studies are needed to further characterize widespread pain after cardiac surgery and its mechanisms

## REFERENCES

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