

## Central Sensitization Drives Symptom Burden in Microvascular Angina: A Cross-Sectional Case-Control Study

### Mikrovasküler Anjinada Semptom Yükünde Santral Duyarlılığın Etkisi: Kesitsel Olgu-Kontrol Çalışması

#### ABSTRACT

**Objective:** Microvascular angina (MVA), a phenotype of ischemia with non obstructive coronary arteries, produces chest pain despite normal epicardial vessels. Central sensitization (CS) may amplify symptoms, but its magnitude in confirmed MVA is unclear.

**Method:** We conducted a single center cross sectional study. Adults with MVA undergoing coronary angiography and age- and sex matched healthy volunteers completed the Central Sensitization Inventory (CSI), Hospital Anxiety and Depression Scale (HADS), and chest pain questionnaires. MVA required documented ischemia with  $\leq 50\%$  epicardial stenosis. The primary outcome was the difference in mean CSI score; secondary outcomes were the proportion with CSI  $\geq 40$  and correlations between CSI, angina measures, and HADS subscores.

**Results:** We enrolled 200 participants; 138 (69%) were male; and the mean age was  $61 \pm 11$  years. Mean CSI-Part A was higher in MVA versus controls ( $43 \pm 15$  vs.  $19 \pm 11$ ;  $P < 0.001$ ), and clinically significant CS was more prevalent (62% vs. 10%). Within MVA, CSI correlated with chest pain intensity ( $r = 0.58$ ), weekly episode frequency ( $r = 0.46$ ), HADS-Anxiety ( $r = 0.51$ ), and HADS-Depression ( $r = 0.44$ ) (all  $P < 0.001$ ). In adjusted models, each 10-point increase in CSI was associated with a 0.47 standard deviation rise in pain score ( $\beta = 0.47$ , 95% confidence interval 0.29-0.64;  $P < 0.001$ ); the model explained 39% of pain-score variance ( $R^2 = 0.39$ ).

**Conclusion:** Central sensitization is highly prevalent and strongly linked to angina burden in MVA, supporting a heart brain contribution to symptom generation. Interventions that reduce central pain amplification may provide meaningful benefit beyond standard anti ischemic therapy.

**Keywords:** Central sensitization, chest pain amplification, coronary microvascular dysfunction, ischemia with non-obstructive coronary arteries, microvascular angina

#### ÖZET

**Amaç:** Obstrüktif olmayan koroner arterlerle seyreden iskeminin bir fenotipi olan mikrovasküler anjina (MVA), epikardiyal damarlar normal görünse bile göğüs ağrısına yol açabilir. Santral duyarlılık (SD) semptomları artırabilir; ancak doğrulanmış MVA'da büyüklüğü net değildir.

**Yöntem:** Tek merkezli, kesitsel bir çalışma yürütüldü. Koroner anjiyografi planlanan MVA'lı yetişkinler ve yaş cinsiyet uyumlu sağlıklı gönüllüler Santral Duyarlılık Envanteri'ni (SDE), Hastane Anksiyete ve Depresyon Ölçeği'ni (HAD) ve göğüs ağrısı anketlerini doldurdu. MVA tanısı,  $\leq 50\%$  epikardiyal darlık ile birlikte objektif iskemi kanıtını gerektirdi. Birincil sonlanım ortalama SDE skoru farkıydı; ikincil sonlanımlar SDE  $\geq 40$  prevalansı ile SDE'nin anjina ölçütleri ve HAD alt skorlarıyla korelasyonlarıydı.

**Bulgular:** Toplam 200 katılımcı dâhil edildi; 138'i (%69) erkekti; ortalama yaş  $61 \pm 11$  yılı. Ortalama SDE A skoru MVA'da kontrollere göre daha yüksekti ( $43 \pm 15$ 'e karşı  $19 \pm 11$ ;  $P < 0,001$ ); klinik olarak anlamlı SD daha sıktı (%62'ye karşı %10). MVA grubunda SDE, göğüs ağrısı şiddeti ( $r = 0,58$ ), haftalık atak sıklığı ( $r = 0,46$ ), HAD Anksiyete ( $r = 0,51$ ) ve HAD Depresyon ( $r = 0,44$ ) ile ilişkiliydi (tümü  $P < 0,001$ ). Ayarlı modellerde SDE'deki her 10 puanlık artış, ağrı puanında 0,47 standart sapma artışla ilişkiliydi ( $\beta = 0,47$ ; %95 güven aralığı 0,29-0,64;  $P < 0,001$ ); model ağrı puanı varyansının %39'unu açıkladı ( $R^2 = 0,39$ ).

**Sonuç:** SD, MVA'da yüksek prevalanslıdır ve anjina yüküyle güçlü biçimde ilişkilidir; bu durum semptom oluşumunda kalp beyin ekseninin katkısını destekler. Santral ağrı amplifikasyonunu azaltan müdahaleler, standart anti iskemik tedavinin ötesinde anlamlı yarar sağlayabilir.

**Anahtar Kelimeler:** Santral duyarlılık, göğüs ağrısı amplifikasyonu, koroner mikrovasküler disfonksiyon, obstrüktif olmayan koroner arterlerle iskemi, mikrovasküler anjina

#### ORIGINAL ARTICLE

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Microvascular angina (MVA) is now recognized as a major subgroup of ischemia with non obstructive coronary arteries (INOCA). Although epicardial coronaries appear normal, patients experience exertional or rest angina attributable to coronary microvascular dysfunction and have an elevated risk of myocardial infarction, stroke, and heart failure hospitalization.<sup>1,2</sup> Abnormalities in coronary flow reserve, microvascular spasm, and enhanced vasoconstrictor tone only partially explain the symptom burden; accumulating evidence implicates altered pain perception that may arise within the central nervous system.<sup>3</sup> Early studies in women with "cardiac syndrome X" (the historical term for MVA) demonstrated lower pain thresholds to peripheral stimuli compared with controls, suggesting a component of central pain amplification.<sup>4</sup>

Central sensitization (CS) is defined as an activity dependent increase in the excitability and synaptic efficacy of neurons in central nociceptive pathways, leading to amplified responses to peripheral inputs and the generation of pain hypersensitivity.<sup>5</sup> Originally characterized in experimental models, CS has since been shown to contribute to numerous chronic pain conditions, including visceral pain disorders that share clinical overlap with MVA (e.g., irritable bowel syndrome and fibromyalgia).<sup>6</sup> The Central Sensitization Inventory (CSI) is a 25 item self report questionnaire developed to screen for symptoms associated with CS; a score  $\geq 40/100$  is commonly used to indicate clinically significant central sensitization.<sup>7</sup> In a cohort of midlife women with INOCA, higher CSI scores were independently associated with greater angina burden and limited functional capacity, underscoring the relevance of CS in coronary microvascular disease.<sup>8</sup>

Despite these observations, the prevalence and magnitude of CS in patients with objectively confirmed microvascular angina remain poorly characterized. Understanding whether CS is heightened in MVA—and how it relates to chest pain severity, attack frequency, and psychosocial comorbidities—could reveal therapeutic targets beyond conventional anti ischemic therapy. Accordingly, this study aimed (i) to quantify central sensitization in patients with MVA using the CSI, comparing results with an age and sex matched healthy cohort, and (ii) to explore associations between CSI scores, chest pain characteristics, and anxiety–depression measures.

## Materials and Methods

This single center, cross sectional study was conducted in the Cardiology Department of Selçuk University Faculty of Medicine over a six month period. Approval was obtained from the Selçuk University Faculty of Medicine Local Ethics Committee (Approval Number: 2025/177, Date: 26.03.2025), and all procedures conformed to the ethical standards of the Declaration of Helsinki. Written informed consent was secured from each participant before any study procedures were undertaken.

### Participant Recruitment

Patient (Microvascular Angina) Group: Adults ( $\geq 18$  years) presenting with chest pain or equivalent symptoms were screened consecutively at the time they were scheduled for diagnostic coronary angiography. To be included, patients had to show objective evidence of myocardial ischemia on prior non

## ABBREVIATIONS

CSI	Central Sensitization Inventory
HADS	Hospital Anxiety and Depression Scale
INOCA	Ischemia with non-obstructive coronary arteries
MVA	Microvascular angina
ROC-derived	Receiver operating characteristic-derived
WISE	Women's Ischemia Syndrome Evaluation

invasive testing (exercise treadmill, stress echocardiography, or myocardial perfusion scintigraphy) or invasive physiological assessment (coronary flow reserve or index of microcirculatory resistance) and demonstrate no epicardial coronary stenosis  $> 50\%$  on angiography.

Healthy Control Group: Volunteers of similar age and sex distribution were recruited from staff and community advertisements. Controls had no history of cardiovascular disease, chronic pain syndromes, or regular analgesic use, and met the same consent and language requirements as patients.

### Inclusion and Exclusion Criteria

Participants were eligible if they were aged 18 years or older, capable of reading Turkish, and able to understand and complete self report questionnaires. Exclusion criteria for both groups comprised: (i) significant structural heart disease (e.g., severe valvular pathology or left ventricular ejection fraction  $< 40\%$ ), (ii) previously diagnosed widespread chronic pain conditions such as fibromyalgia, (iii) major uncontrolled psychiatric disorders (e.g., bipolar disorder) that could compromise data reliability or informed consent, (iv) cognitive or communication impairment precluding questionnaire completion, (v) age under 18 or legal incapacity to consent, and (vi) any clinical circumstance judged by the investigators to pose safety or ethical concerns (such as recent major trauma or the immediate postoperative period). For the patient group specifically, detection of  $> 50\%$  epicardial stenosis on angiography excluded the diagnosis of microvascular angina and hence study participation.

### Data Collection

After consent, each participant completed the following instruments under investigator supervision in a quiet room:

1. Central Sensitization Inventory (CSI, Parts A and B): The Turkish validated version, which has proven reliability and internal consistency in chronic pain populations, was used.<sup>9</sup> Consistent with the original validation, we defined clinically significant central sensitization as CSI Part A  $\geq 40/100$ —the receiver operating characteristic-derived (ROC-derived) threshold that best discriminated central sensitivity syndromes from non-patient controls (area under the curve [AUC]: 0.86; sensitivity: 81%; specificity: 75%) and which also performed well in the Turkish validation (sensitivity: 87%, specificity: 90%).<sup>9,10</sup> For reader convenience, open access links to the Turkish CSI instrument and the validation paper are provided in the references.<sup>11</sup>
2. Chest Pain Assessments: Patients reported average chest pain severity during the preceding four weeks on an eleven point numeric rating scale (0 = no pain, 10 = worst imaginable) and the mean number of pain episodes per week.

**Table 1. Baseline characteristics and laboratory findings**

Variable	MVA (n = 100)	Controls (n = 100)	P†
Age, years	61.4 ± 11.0	60.8 ± 10.5	0.56
Male sex, n (%)	70 (70)	68 (68)	0.74
BMI, kg m <sup>-2</sup>	27.8 ± 3.8	27.5 ± 3.6	0.48
SBP, mmHg	114 ± 10	113 ± 11	0.44
DBP, mmHg	69 ± 7	69 ± 7	0.95
HR, min <sup>-1</sup>	75 ± 14	74 ± 13	0.63
HTN, n (%)	35 (35)	32 (32)	0.66
DM, n (%)	21 (21)	19 (19)	0.72
Dyslip., n (%)	38 (38)	36 (36)	0.78
Smoking, n (%)	25 (25)	23 (23)	0.73
Obesity, n (%)	18 (18)	17 (17)	0.85
Anxiety/Dep., n (%)	15 (15)	13 (13)	0.68
Urea, mg dL <sup>-1</sup>	35.0 ± 15.2	34.3 ± 14.7	0.72
Cr, mg dL <sup>-1</sup>	0.90 ± 0.26	0.88 ± 0.24	0.59
Na, mmol L <sup>-1</sup>	137.7 ± 3.1	137.9 ± 3.0	0.68
K, mmol L <sup>-1</sup>	4.40 ± 0.39	4.38 ± 0.37	0.77
Hb, g dL <sup>-1</sup>	14.0 ± 1.7	14.1 ± 1.6	0.65
WBC, 10 <sup>3</sup> µL <sup>-1</sup>	7.9 ± 2.3	7.8 ± 2.2	0.83
TC, mg dL <sup>-1</sup>	189 ± 38	185 ± 35	0.47
LDL C, mg dL <sup>-1</sup>	118 ± 31	116 ± 29	0.66
HDL C, mg dL <sup>-1</sup>	46 ± 11	47 ± 10	0.53
TG, mg dL <sup>-1</sup>	150 ± 60	148 ± 58	0.82

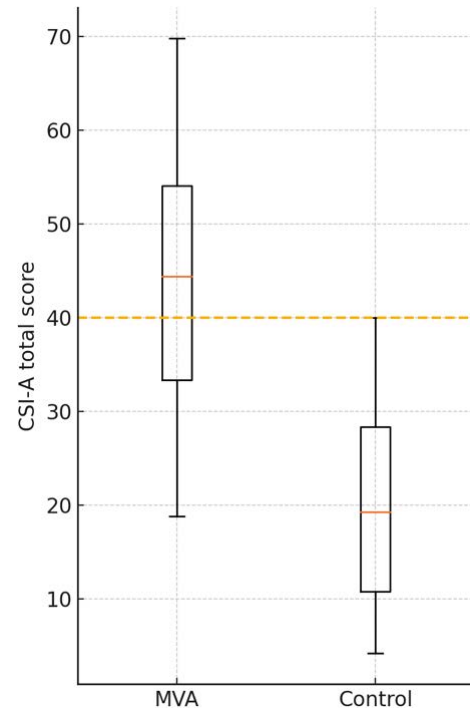
†: Independent t test for continuous variables;  $\chi^2$  test for categorical variables. Anxiety/Dep., History of anxiety or depression; BMI, Body mass index; Cr, Creatinine; DBP, Diastolic blood pressure; DM, Diabetes mellitus; Dyslip., Dyslipidemia; Hb, Hemoglobin; HR, Heart rate; HTN, Hypertension; K, Potassium; MVA, Microvascular angina; Na, Sodium; SBP, Systolic blood pressure; TC, Total cholesterol; TG, Triglycerides; WBC, White blood cell count.

- Hospital Anxiety and Depression Scale (HADS): Separate subscores for anxiety (HADS A) and depression (HADS D) were recorded. We used the Turkish validated version; open access links to the validation citation and a publicly available Turkish HADS form are provided in the references.<sup>12,13</sup>
- Clinical and Demographic Variables: Age, sex, body mass index, cardiovascular risk factors, and current medications were extracted from medical charts.

Questionnaire booklets carried only study codes; no identifying information was recorded on research forms. Completed forms were stored in a locked filing cabinet, and electronic data were entered into a password protected database accessible only to the research team. Participants were free to withdraw at any stage without consequences for clinical care.

### Outcomes

The primary outcome was the difference in mean CSI score between the microvascular angina and healthy control groups. Secondary outcomes included (i) the proportion of individuals in each group with a CSI score  $\geq 40$  (threshold suggestive of clinically relevant central sensitization) and (ii) correlations between CSI scores and chest pain severity, pain episode frequency, and HADS subscores within the patient cohort.

**Figure 1. Markedly higher CSI A scores in microvascular angina.**

Median CSI A was 44 (IQR 33–54) in the MVA group versus 19 (IQR 11–28) in controls ( $P < 0.001$ ); 62 % of patients, but only 10 % of controls, scored  $\geq 40$  (dashed line), indicating clinically significant central sensitization.

### Statistical Analysis

Continuous variables were tested for normality using the Shapiro–Wilk statistic. Between group comparisons employed independent samples t tests for normally distributed data and Mann–Whitney U tests when distributions were non normal. Categorical variables were compared with the  $\chi^2$  test. Pearson or Spearman correlation coefficients, as appropriate, quantified associations between CSI scores and clinical or psychosocial measures. Multivariable linear regression, adjusted for age, sex, and body mass index, assessed the independent relationship between CSI score and chest pain severity. A two sided P value  $< 0.05$  denoted statistical significance. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 29.0 (IBM Corp., Armonk, NY, USA).

### Results

Baseline demographic, clinical, and laboratory features were similar in the two study groups (Table 1). The mean age was  $61 \pm 11$  years, and 69% of participants were male. The prevalence of traditional cardiovascular risk factors—including hypertension (35% in the microvascular angina [MVA] group vs. 32% in controls), diabetes mellitus (21% vs. 19%), dyslipidemia (38% vs. 36%), and current or former smoking (25% vs. 23%)—did not differ significantly (all  $P > 0.05$ ). Body mass index, blood pressure values, heart rate, renal indices, electrolytes, full blood count, and lipid profile were likewise comparable, indicating that the two cohorts were well matched at baseline.

Despite these similarities, the burden of central sensitization diverged sharply. Mean Central Sensitization Inventory Part A

**Table 2. Central sensitization outcomes**

Outcome	MVA (n = 100)	Controls (n = 100)	P†
CSI A, mean ± SD	<b>43 ± 15</b>	19 ± 11	<0.001
CSI A ≥ 40, n (%)	<b>62 (62)</b>	10 (10)	<0.001
CSI B positive‡, n (%)	<b>46 (46)</b>	15 (15)	<0.001

†: Independent t test or  $\chi^2$  test. ‡: At least one physician diagnosed sensitization related condition. CSI A, Central Sensitization Inventory Part A total score; CSI B, Central Sensitization Inventory Part B.

**Table 3. Correlation of Central Sensitization Inventory Part A scores (CSI A) with pain and psychosocial variables in patients with microvascular angina (MVA)**

Variables	r	P
NRS pain score	0.58	<0.001
Weekly angina episodes	0.46	<0.001
HADS A	0.51	<0.001
HADS D	0.44	<0.001

HADS A, Hospital Anxiety and Depression Scale—Anxiety; HADS D, Hospital Anxiety and Depression Scale—Depression; NRS, Numeric rating scale; r, Pearson (continuous) or Spearman (count) correlation coefficient.

(CSI A) score was  $43 \pm 15$  in the MVA cohort versus  $19 \pm 11$  in controls ( $P < 0.001$ ), and 62% of MVA patients but only 10% of controls scored  $\geq 40$ —the established cut off for clinically relevant sensitization (Table 2). The entire score distribution was visibly shifted upward in MVA, as depicted by the side by side box plot (Figure 1). Consistent with the questionnaire findings, 46% of MVA patients reported at least one physician diagnosed sensitization related condition on CSI Part B, compared with 15% of controls ( $P < 0.001$ ).

Higher CSI A scores were closely associated with symptom burden. Within the MVA group, CSI A correlated strongly with chest pain intensity on the 0–10 numeric rating scale ( $r = 0.58$ ,  $P < 0.001$ ) and with the weekly frequency of angina episodes ( $r = 0.46$ ,  $P < 0.001$ ). Significant positive correlations were also observed with anxiety (HADS A,  $r = 0.51$ ) and depression (HADS D,  $r = 0.44$ ) subscores (all  $P < 0.001$ ) (Table 3). The scatter plot with regression line and 95% confidence band (Figure 2) visually underscores the linear relationship between CSI A and pain severity.

Multivariable linear regression confirmed central sensitization as an independent determinant of angina intensity. After adjusting for age, sex, body mass index, and hypertension, each 10 point increase in CSI A was associated with a 0.47 standard deviation rise in chest pain score ( $\beta = 0.47$ , 95% CI: 0.29–0.64,  $P < 0.001$ ), whereas none of the conventional covariates retained statistical significance (Table 4). The model explained 39% of the variance in pain scores, highlighting the prominent contribution of central pain amplification to the symptomatic burden of microvascular angina.

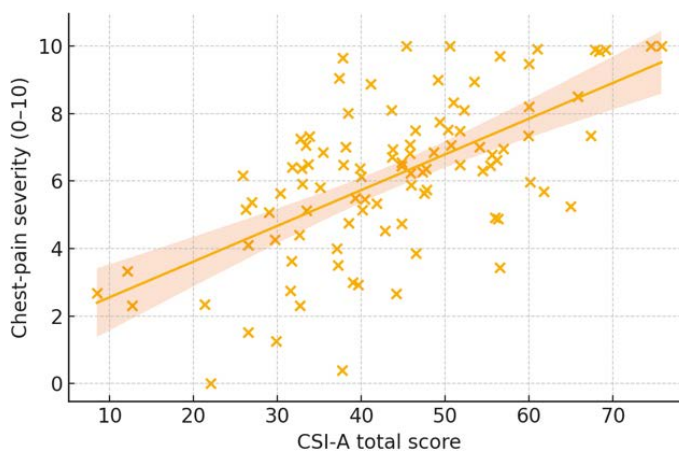
**Discussion**

Microvascular angina is rooted in structural and functional abnormalities of the coronary microcirculation—endothelial nitric oxide dysregulation, small vessel remodeling, impaired coronary

**Table 4. Multivariable predictors of chest pain severity in microvascular angina (MVA) (linear regression)**

Predictor	$\beta$	95% CI	P
CSI A (per 10 pt)	0.47	0.29–0.64	<0.001
Age (per year)	0.06	–0.03–0.15	0.18
Sex (male)	–0.04	–0.30–0.22	0.75
BMI ( $\text{kg m}^{-2}$ )	0.08	–0.02–0.18	0.11
HTN (yes)	0.03	–0.20–0.27	0.79

Model  $R^2 = 0.39$ ,  $P < 0.001$ .  $\beta$ , Standardized regression coefficient; CI, Confidence interval.



**Figure 2. Central sensitization correlates with angina burden.**

Higher CSI A scores were associated with greater chest pain severity in the MVA cohort ( $r = 0.62$ ,  $P < 0.001$ ); the shaded band denotes the 95% confidence interval for the regression line.

flow reserve, heightened endothelin 1 activity, and microvascular spasm—all of which produce true myocardial ischemia despite angiographically normal epicardial vessels.<sup>14</sup> At the same time, mounting neurobiological evidence shows that repeated ischemic afferent traffic, neuroinflammation, and diminished descending inhibitory control promote central sensitization: an activity dependent amplification of nociceptive signaling in the dorsal horn, thalamus, and cortical pain matrix.<sup>3,15,16</sup> Once established, CS lowers somatic and visceral pain thresholds, recruits “silent” nociceptors, and couples with limbic circuits to magnify the affective dimension of pain, thereby explaining why MVA patients frequently report severe, poorly localized chest discomfort out of proportion to ischemic burden.<sup>10</sup>

Notably, although INOCA/MVA is more prevalent in women, our consecutive, angiography based sampling yielded a male predominant cohort ( $\approx 70\%$ ). This pattern likely reflects referral practices to tertiary invasive testing; however, the under representation of women is a major constraint on generalizability—particularly to Turkish women—who experience documented diagnostic delay and undertreatment.<sup>1,2,14</sup> Accordingly, our estimates of the association between central sensitization and angina should be interpreted with caution for women, and future studies should purposively enrich recruitment of women and be adequately powered for sex stratified analyses.

Unlike obstructive coronary artery disease, MVA offers no stenotic target for percutaneous or surgical revascularization; consequently, patients often remain symptomatic despite guideline directed anti ischemic therapy ( $\beta$  blockers, calcium channel blockers, nitrates).<sup>17</sup> Many cycle through emergency departments, stress laboratories, and catheterization suites with persistently disabling angina, highlighting an unmet need for alternative approaches. Small scale trials with ranolazine, ivabradine, and, more recently, the endothelin A antagonist zibotentan have yielded mixed or modest benefits, underscoring the therapeutic challenge.<sup>1,17-20</sup>

Coronary microvascular dysfunction and CS are not mutually exclusive but mutually reinforcing. Repeated subendocardial ischemia can serve as a persistent peripheral nociceptive driver that maintains central hyperexcitability, whereas CS, by amplifying spinothalamic traffic and heightening interoceptive vigilance, exaggerates the cortical representation of otherwise modest ischemic signals.<sup>21</sup> This interplay raises the therapeutic hypothesis that agents with proven anti sensitizing properties—serotonin–noradrenaline reuptake inhibitors such as duloxetine, gabapentinoids (gabapentin, pregabalin), and tricyclics—as well as non pharmacological modalities like cognitive behavioral therapy or mindfulness based stress reduction, could attenuate chest pain severity in MVA.<sup>9,21-24</sup>

Our findings accord with several recent investigations. In the Women's Ischemia Syndrome Evaluation (WISE) and in an independent INOCA cohort, higher Central Sensitization Inventory scores independently tracked with angina frequency, exercise intolerance, and diminished quality of life, mirroring the strong correlations we observed between CSI, pain intensity, and Hospital Anxiety–Depression Scale scores.<sup>8</sup> Functional neuroimaging studies demonstrate heightened insular and anterior cingulate activation during adenosine induced chest pain in MVA, consistent with central amplification.<sup>25</sup> Conversely, a large Scandinavian registry linked low pain tolerance to obstructive coronary artery disease rather than INOCA, challenging a unifying CS explanation.<sup>26,27</sup> Methodological heterogeneity (small sample sizes, different pain threshold protocols, female only versus mixed cohorts), and the absence of formal CS metrics in negative studies may underlie these discrepancies.

### Limitations

Several caveats must be acknowledged when interpreting our findings. First, the cross sectional design precludes any inference of causality—heightened Central Sensitization Inventory scores may contribute to, result from, or simply coexist with microvascular angina; only longitudinal or interventional studies can disentangle directionality. Second, this was a single center study in a tertiary care cardiology clinic that largely serves a referral population. Consequently, disease severity, psychosocial comorbidity, and health seeking behavior may differ from those in primary care or community settings, limiting generalizability. Although INOCA/MVA is more prevalent in women, our sample was predominantly male (~70%). This likely reflects referral patterns to our tertiary, angiography based clinic, where men undergo invasive evaluation more often; however, the under representation of women is a major limitation and reduces the generalizability of our findings to the broader Turkish INOCA

population. Importantly, symptomatic women are frequently diagnosed later and are less likely to receive guideline directed testing and therapy, which may perpetuate symptom burden and healthcare use. If the relationship between central sensitization and angina differs by sex, our effect estimates may also be biased. Future work should purposively enrich recruitment of women, pre specify sex stratified analyses, and be adequately powered to test sex–by–central sensitization interactions.

Third, although we screened consecutively, the sample size was modest and predominantly male ( $\approx$  70%), whereas epidemiological data show that INOCA/MVA is more prevalent in women; sex specific mechanisms could therefore be under represented. Fourth, both central sensitization and chest pain metrics relied on self report instruments (CSI, numeric pain rating, HADS), introducing recall and reporting bias. Objective corroboration—quantitative sensory testing, functional neuroimaging, or ambulatory myocardial ischemia monitoring—was not performed and would strengthen future work.

Fifth, we excluded patients with recognized chronic pain syndromes to isolate the contribution of CS to MVA, yet this may have underestimated the real world prevalence of CS in an unselected INOCA population where fibromyalgia and irritable bowel syndrome are common. Sixth, despite multivariable adjustment, residual confounding remains possible: unmeasured factors such as sleep disturbance, autonomic dysfunction, socioeconomic stress, and antidepressant or opioid use could influence both CSI scores and angina perception.

Seventh, the control group comprised volunteer hospital staff and community respondents, raising the possibility of a “healthy worker” effect and socioeconomic mismatch relative to patients. Eighth, our diagnostic definition of MVA was based on conventional angiography plus prior non invasive or invasive evidence of ischemia; we did not perform systematic coronary flow reserve or acetylcholine testing in every participant, so a degree of physiological heterogeneity is likely. Finally, we lacked longitudinal follow up, preventing assessment of whether elevated CSI predicts downstream outcomes such as emergency department utilization, quality of life trajectories, or incident heart failure. Collectively, these limitations underscore the need for larger, multicenter, prospective studies incorporating objective neurosensory assessments and interventional trials targeting central sensitization in MVA.

### Conclusion

In conclusion, our study is the first to demonstrate—using a validated Turkish version of the CSI—that clinically significant central sensitization is nearly six times more prevalent and markedly more severe in objectively confirmed MVA than in matched healthy controls, and that CS explains almost 40% of the variance in angina intensity beyond traditional cardiovascular covariates.<sup>28</sup> These data shift the therapeutic lens from an exclusively coronary focus to a heart–brain axis, opening avenues for trials of centrally acting analgesic and behavioral interventions in MVA. Clarifying whether attenuating CS translates into fewer emergency visits, better exercise capacity, and improved health related quality of life could substantially enrich future INOCA management guidelines and benefit a patient population that remains undertreated and often misunderstood.

**Ethics Committee Approval:** Ethics committee approval was obtained from Selçuk University Faculty of Medicine Local Ethics Committee (Approval Number: 2025/177, Date: 26.03.2025).

**Informed Consent:** Written informed consent was obtained from the participants.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

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