Title: Anginal Symptoms is Related to Symptomology in Underlying Coronary Microvascular and Vasomotor Dysfunction (CMVD) in ANOCA/INOCA Patients

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Introduction: Angina and/or Ischemia with non-obstructive coronary arteries (INOCA/ANOCA) are common conditions associated with chronic angina and poor quality of life. Coronary microvascular and vasomotor dysfunction (CMVD) is the predominant pathophysiological mechanism promoting angina/ischemia in these patients. Prior work in smaller cohorts of ANOCA/INOCA patients has found measures of CMVD to be associated with worse anginal symptoms, but these results are variable. The association between anginal severity and clinical presentation, including CMVD measures in ANOCA/INCOA patients has not been directly determined.

Methods: Using the prospective Women's Heart Center (WHC) Registry, we examined ANOCA/INOCA patients who underwent Invasive Coronary Functional Testing (ICFT) via the doppler or thermodilution method for CMVD diagnosis between October 2020 and December 2024. Anginal symptoms were measured using summary scores from the short version of the Seattle Angina Questionnaire (SAQ-7). Additional validated questionnaires included: University of San Diego Shortness of Breath (UCSD SOB), Rapid Eating Assessment (REAP), Duke Activity Status Index (DASI) and Perceived Stress Scale (PSS). We then compared clinical characteristics and validated questionnaire outcomes by symptom severity. Continuous measures of CMVD were compared including change in Coronary Diameter (Change in CD) and Coronary Flow Reserve (CFR).

Results: A total of 296 patients were included in analysis, 46 had a Low SAQ, 163 had Moderate SAQ scores and 87 had high SAQ scores, results outlined in Table 1. Patients with more severe and moderate angina had a higher prevalence of diabetes. Age significantly differed between groups (Low SAQ=62.38, SD=10.37; Moderate = 56.54, SD=12.60; High SAQ=43.54, SD=21.24; $p<0.001$). Stress as measured by PSS differed among symptom groups, where patients with severe symptoms had lower PSS scores ($p=0.0189$). Functional capacity as measured by DASI differed between groups, where patients with severe symptoms had reduced functional capacity ($p<0.001$). To understand how SAQ related to underlying disease we correlated sores with CFR, however, no significant correlation was observed. SAQ was positively correlated DASI, finding that reduced angina had higher functional capacity (Rho=0.372, 95%CI 0.213 to 0.431, $p<0.001$). There was also a significant correlation between finding an inverse relationship between shortness of breath and anginal symptoms (Rho= -0.617,95% CI -0.689 to -0.532, $p<0.001$).

Conclusions: Our results indicate the relationship between worsening anginal symptoms and other CMVD associated symptoms including worse shortness of breath, reduced exercise capacity and increased perceived stress. We observed no relationship to CFR, though our

investigation was limited. This study emphasizes the burden of anginal symptoms in patients with CMVD. Future work should examine the predictive nature of patient reported symptoms to other risk factors, CMVD phenotypes and clinical comorbidities, such as heart failure.

Table 1. Results	**Severe** (0-23) N=87	**Moderate** (24 to 57) N=163	**Low** (58 to 100) N=46	**P-value**
Demographics				
Sex (%) F	93%	91%	100%	P=0.109
Age (Mean, SD)	**43.54 (21.24)**	**56.54 (12.60)**	**62.38 (10.37)**	**P<0.001**
BMI (Mean, SD)	31.96 (9.07)	31.48 (9.17)	29.47 (6.69)	P=0.289
Hyperlipidemia (%)	76.16	77.91	71.74	P=0.649
HFpEF (%)	8.04	8.58	4.35	P=0.989
Diabetes (%)	**14.94**	**9.20**	**5**	**P=0.032**
Validated Questionnaires				
DASI (Mean, SD)	**26.45 (12.65)**	**35.21 (13.28)**	**36.55 (14.12)**	**P<0.001**
SAQ 7 (Mean, SD)	**10.62 (6.67)**	**38.33 (9.38)**	**70.31 (7.87)**	**P<0.001**
UCSD SOB (Mean, SD)	**61.77 (20.76)**	**33.23 (20.68)**	**21.41 (18.96)**	**P<0.001**
PSS (Mean, SD)	**15.71 (6.44)**	**13.54 (6.24)**	**12.91 (5.40)**	**P=0.0189**
REAP, Median (IQR)	60 (53, 67)	59 (54, 65)	61 (54.25, 66.25)	P=0.6330
Continuous ICFT Measures				
CFR	2.24 (0.758)	2.32 (0.652)	2.24 (0.598)	P=0.688
Change in Coronary Diameter (%)	-0.049 (0.14)	-0.028 (.12)	-0.036 (0.14)	P=0.564

SAQ Scores were categorized as severe (0 to 23), moderate (24 to 57) and low (58 to 100). Group comparisons were made via one-way ANOVAs, Kruskal Wallis (median, IQR) or chi-squares where appropriate. Correlations were conducted with Spearman's Rho.