HERMES Study: Using Cardio-linguistics and Artificial Intelligence to Reframe Typical and Atypical Angina

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Declaration of interest

- I have nothing to declare
- I have nothing to declare

Introduction

Despite coronary artery disease (CAD) being the leading cause of death among men and women, a perception remains that it is predominantly a disease affecting males.

Paradoxically, despite higher prevalence of angina in women, the term “atypical angina” is associated with symptoms common in women, while "typical angina" is used to describe symptoms common in men.

Negative implications→ women receive less medical therapy and fewer invasive procedures compared with men.

Rationale

There are likely nuances with angina symptoms particularly as they relate to sex

Artificial intelligence that uses natural language processing is a sensitive tool able to capture nuances in expression of cardiac symptoms

Study Objectives

Characterize pain symptoms most commonly experienced in men and women with suspected CAD;

Assess the association of symptoms with their respective angiographic findings;

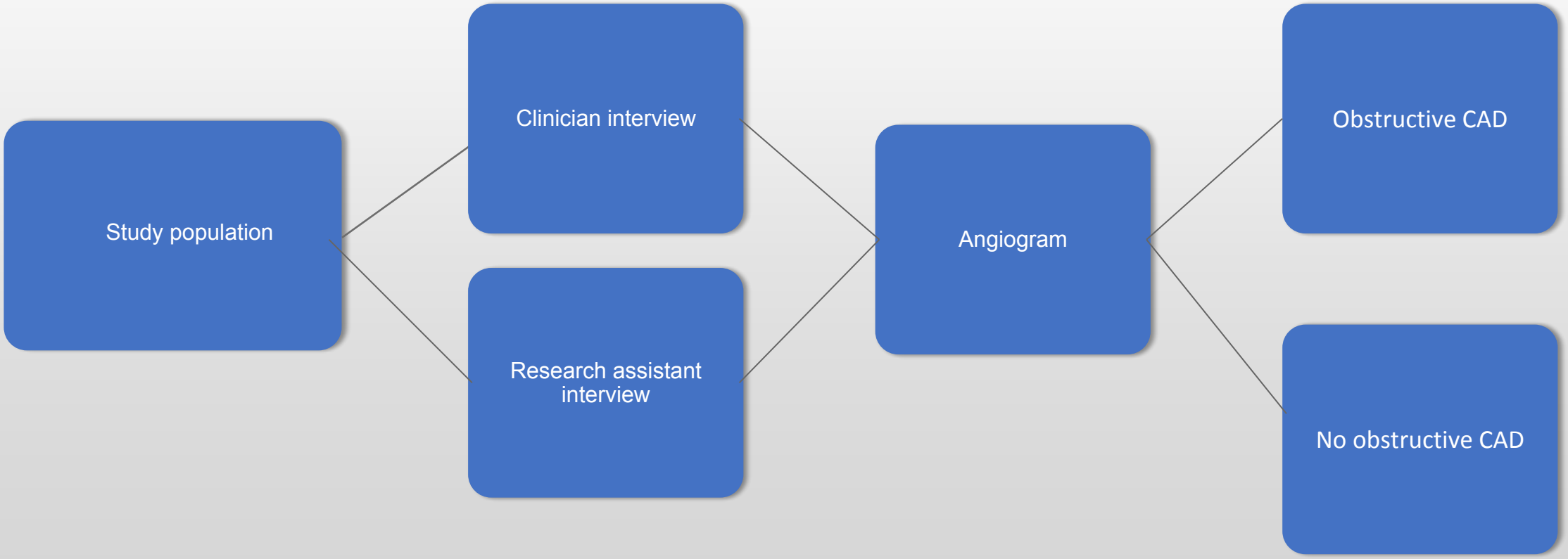
Determine speech patterns and conversation content categories of angina symptoms;

Train machine learning models of symptom patterns to establish a dictionary of symptom expression according to sex, calibrated on coronary angiography.

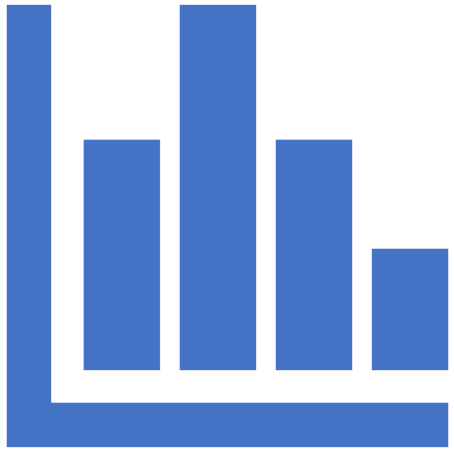
Hermes: Inclusion/ Exclusion Criteria

- Referred for first coronary angiogram for primary diagnosis of suspected CAD, angina and/or cardiac ischemia
- Must have one prior abnormal test
- Excluded if referred for valvular disease, arrhythmia, pre-operation, had prior history of myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention, or were unable to communicate in English.
- Patients and physicians must agree to be audio-recorded
- Patients and physicians provided written informed consent

Overview of Study Design



Statistical Analysis



- Examined baseline characteristics and symptoms as frequencies and means; continuous and dichotomous variables were evaluated using 2-tailed t-tests/ ANOVA and chi-square tests.

- Univariate models examined the association of individual symptoms within sex according to obstructive CAD status.

Machine Learning Analysis

- Patient interviews with RA and physician represent a computational discourse about a shared set of symptom topics
- Interviews were transcribed verbatim and transcriptions were validated against angiographic findings
- Nuances in the natural language expression of symptoms in the transcript were extracted using techniques from NLP
- Probabilistic generative topic models were trained on the distribution of words across symptom clusters according to sex

Table 1: Distribution and Univariate Analysis of Symptoms According to Sex					
Symptoms	**Total Women**		**Total Men**		**Women vs. Men**
	N	**%**	**N**	**%**	**P-value**
Chest pain/ sensation	231	89.9	330	86.8	0.80
Breathing affected	171	66.5	241	63.4	0.42
Faint/ dizzy/ lightheaded	103	40.1	124	32.6	0.05
Pressure	96	37.4	126	33.2	0.95
Fatigue	93	36.2	111	29.2	0.06
Arms	90	35.0	118	31.1	0.30
Tightness	88	34.2	109	28.7	0.33
Hot/ sweating	86	33.5	109	28.7	0.20
Nausea/ vomiting	82	31.9	54	14.2	<0.01
Heaviness	72	28.0	70	18.4	0.04
Burning/ GI sensation	64	24.9	100	26.3	0.33
Discomfort	63	24.5	104	27.4	0.06
Shoulders	71	27.6	65	17.1	<0.01
Back	65	25.3	39	10.3	<0.01
Neck	57	22.2	43	11.3	<0.01
Jaw	49	19.1	30	7.9	<0.01
Ache	11	4.3	25	6.6	0.24
Sitting on chest	21	8.2	18	4.7	0.30
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Table 2: Univariate Analysis of Symptoms According to Disease Status Among Women

Symptoms	Obstructive disease		Non-obstructive disease		Obstructive vs. Non-obstructive disease
	N	%	N	%	P-value
Chest pain/ sensation	81	88.0	150	90.9	0.45
Breathing affected	62	67.4	109	66.1	0.83
Faint/ dizzy/ lightheaded	33	35.9	70	42.4	0.30
Pressure	31	33.7	65	39.4	0.37
Fatigue	33	35.9	60	36.4	0.94
Arms	35	38.0	55	33.3	0.45
Tightness	31	33.7	57	34.5	0.89
Hot/ sweating	35	38.0	51	30.9	0.25
Nausea/ vomiting	23	25.0	59	35.8	0.08
Heaviness	23	25.0	49	29.7	0.42
Burning/ GI sensation	25	27.2	39	23.6	0.53
Discomfort	19	20.7	44	26.7	0.28
Shoulders	26	28.3	45	27.3	0.87
Back	24	26.1	41	24.8	0.83
Neck	22	23.9	35	21.2	0.62
Jaw	18	19.6	31	18.8	0.88
Ache	5	5.4	6	3.6	0.50
Sitting on chest	6	6.5	15	9.1	0.47
Sharp pain	11	12.0	34	20.6	0.08
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Table 3: Univariate Analysis of Symptoms According to Disease Status Among Men					
Symptoms	Obstructive disease		Non-obstructive disease		Obstructive vs. Non-obstructive disease
	N	%	N	%	P-value
Chest pain/ sensation	187	89.0	143	84.1	0.16
Breathing affected	130	61.9	111	65.3	0.50
Faint/ dizzy/ lightheaded	56	26.7	68	40.0	<0.01
Pressure	70	33.3	56	32.9	0.94
Fatigue	54	25.7	57	33.5	0.10
Arms	70	33.3	48	28.2	0.29
Tightness	59	28.1	50	29.4	0.78
Hot/ sweating	61	29.0	48	28.2	0.86
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Sitting on chest	8	3.8	10	5.9	0.34
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Figure 1: Absolute differences in mean number of symptoms reported between men and women

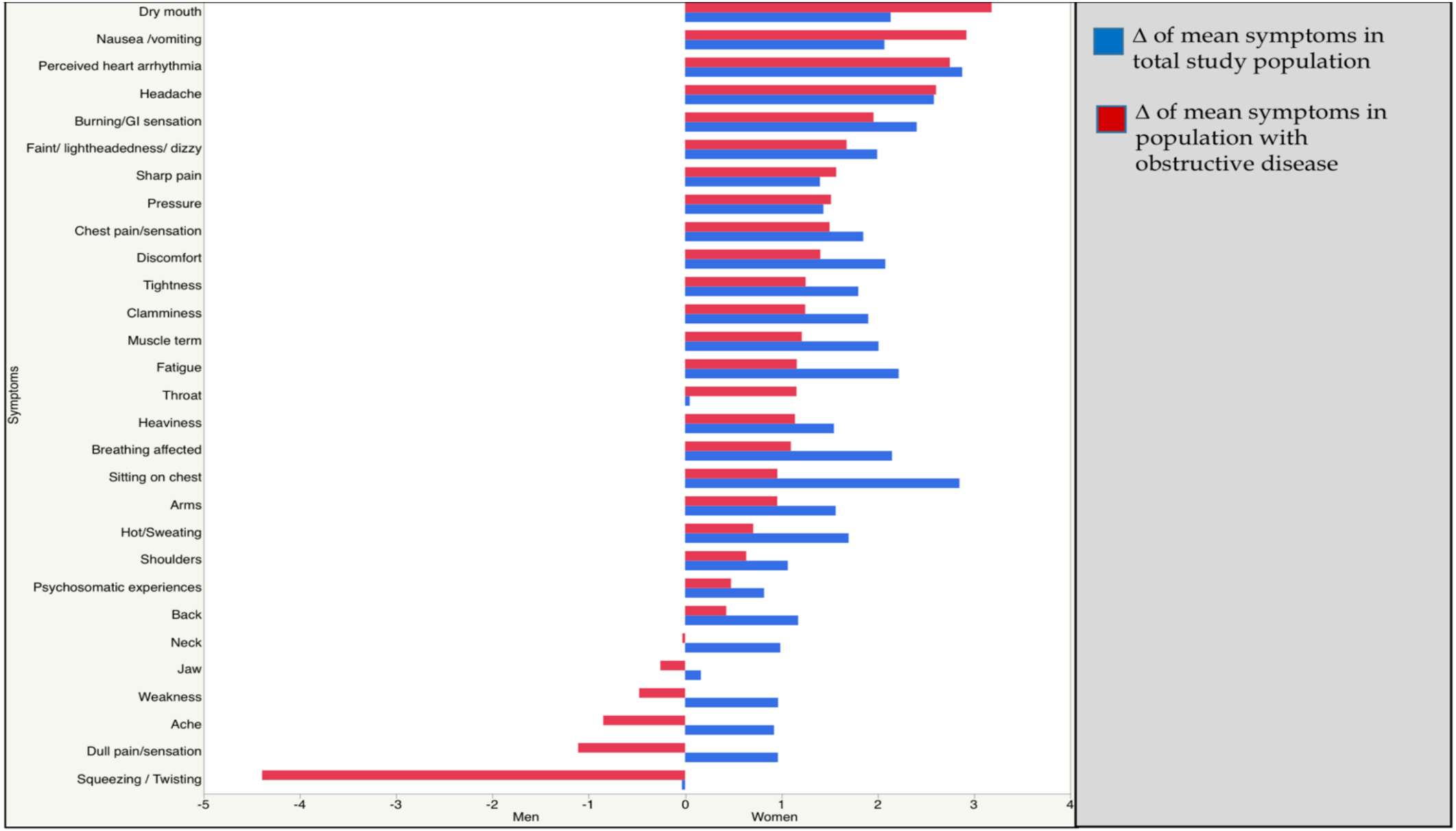

Table 4: Natural language symptom clusters

Cluster	Symptom
Chest sensation and physical limitation	felt, shortness, breath, physically, limited, severity, experiencing, increased, severe, feeling, pain, frequently, tightness, fatigue, heaviness, pressure, weakness, anxiety
Non-chest area & associated symptoms	arm, pain, left, shoulders, neck, jaw, sweating, experiencing, chest, pressure, tightness, heaviness, nausea, burning, throat, arms, severe, discomfort, crushing, soreness
Non-chest weary symptoms	light-headedness, faint, shortness of breath, fatigue, headache, weakness, nausea, sweating, clamminess, vomiting, dizziness, anxiety, confusion, increased, panic
Chest sensation descriptions	pain chest, discomfort, pressure, sharp, pressing, indigestion-type, annoying, dull, breathing, squeezing, stomach, vague, smothered, worse, elephant, sensation, uncomfortable
Duration & severity of symptoms	time, lasted, longer, frequently, severity, increased, feeling, tightness, severe, anxiety, pressure, burning, sweating, air, heavy, center, heard, heart, weren't, exercise
Secondary bothersome symptoms	mouth, dry, women, anxiety, men, experience, confusion, medication, achy, vessels, pinching, face, lung, blurry
Perceived physical yardsticks	stairs, flight, hours, lasts, checked, decided, rest, row, episodes, long, climb, min, tense, suffer, alcohol, drink, smoke, healthier, heartbeat, yards
Perceived gender differences	men, women, heart, attack, pain, strong, differently, slight, attacks, incident, child, smaller, pinching, denial, silent, fluttering, vertigo
Heart rhythm perceptions	heart, beat, palpitations, racing, rapid, side, burn, beats, fast, pounding, feels, curiosity, irregular, palpitations, caused, beating, vomiting, underplay, discovered, circulation

Figure 2: Distribution of Symptom Clusters According to Men and Women with Obstructive Disease

Symptom Cluster	Male %	Female %	Abs Δ
Chest Sensations and Physical Limitations	89.5%	90.2%	0.7%
Non-chest Area & Associated Symptoms	79.0%	75.0%	4.0%
Chest Pain and Associated Symptoms	61.4%	55.4%	6.0%
Duration & Severity of Symptoms	55.7%	47.8%	7.9%
Non-chest Distressing Symptoms	48.1%	39.1%	9.0%
Secondary Bothersome Symptoms	12.4%	13.0%	0.7%
Perceived Gender Differences	9.5%	29.3%	19.8%
Heart Rhythm Perceptions	5.2%	12.0%	6.7%
Perceived Physical Yardsticks	0.0%	0.0%	0.0%

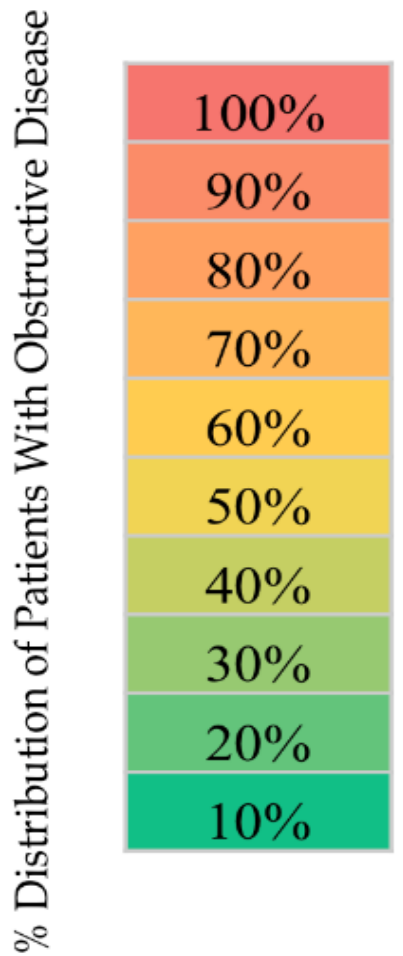

Figure 3: Cluster Plot Analysis of Symptom Groupings by Men and Women with Obstructive Disease

Males with obstructive disease | *Females with obstructive disease*

A cluster plot analysis of symptom groupings shows the density and size of clusters scaled to the proportional representation of symptoms; the distance between clusters are scaled to the proximity of symptom co-occurrence. Each dot in a cluster represents a patient and the darkness of each dot is proportional to the prevalence in the said patient of the respective symptom cluster.

Discussion

- Using the natural language of patients, we found no differences in how men and women describe angina symptoms
- Patients describe a constellation of symptoms and machine learning methods identified nine clusters of symptoms with no differences between men and women, irrespective if they had obstructive disease
- This finding challenges the notion that women experience more “atypical angina” compared to men

More on atypical angina

Atypical symptoms such as pain in non-chest areas and associated symptoms were higher in women compared with men

Men reported atypical symptoms also

The overall prevalence of these symptoms was low (<25%) among women

Atypical symptoms were not associated with obstructive disease in women or men

Why this study is important

- Much controversy associated with atypical angina and interpretation of symptoms particularly among women
- Conventional statistical analyses (i.e. multivariable logistic regression) may in part perpetuate differences
    - Multivariable analysis embed implicit mathematical assumptions on the independence of symptom occurrence
    - Prior clinical biases in the formulization of these relationships
- Machine learning algorithms do not prespecify a set of symptoms, thereby eliminating clinical biases that may play a role in the construction of the machine learning model

Machine learning advantages

- Patients present a constellation of symptoms and physicians consider the entire set of symptoms in their differential analysis
- ML derives clusters of symptoms directly from the natural language of patients
- Each cluster represents a unique fingerprint of symptom clusters for each patient, across the entire study population
- ML algorithms were calibrated against coronary angiograms

Limitations

Study does not address microvascular disease

There may be upstream biases at the point of angiography referral

Future studies are needed to explore symptom presentation among patients' first point of clinical care

Conclusions

- Machine learning methods reveal a more nuanced interpretation of symptoms using the natural language of patients
- Both statistical and machine learning methods reveal that angina symptoms are largely similar in men and women and there are no significant differences in overall symptomatology among patients with obstructive disease
- The terms typical and atypical angina should be abandoned, as they do not correlate with actual disease burden and perpetuate stereotypes based on sex that may interfere with the diagnosis and treatment of patients, especially women

Thank you to my outstanding research team

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Karishma Manji

Claudia Sikorski

Gabriel Kuper

Alexandra Boucouvalas

Malcolm Hartman

Kayli Culig

Elysia Grose

Shangmou Wu

Harvard University/ Brigham and Women's Hospital

Frank Zhou

Andy Dwarakanath

Kaitlyn Stanislawzyk

Sravya Shankara

Samantha Subramanian

In loving memory of Sidharth Ramakrishnana