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Ahmed AlBadri, *Cedars Sinai Heart Institute*
Derek Leong, *Cedars Sinai Heart Institute*
C. Noel Bairey Merz, *Cedars Sinai Heart Institute*
Janet Wei, *Cedars Sinai Heart Institute*
Eileen M. Handberg, *University of Florida*
Chrisandra L. Shufelt, *Cedars Sinai Heart Institute*
[Puja Mehta](#), *Emory University*
Michael D. Nelson, *Cedars Sinai Heart Institute*
Louise E. Thomson, *Cedars Sinai Medical Center*
Daniel S. Berman, *Cedars Sinai Medical Center*

Only first 10 authors above; see publication for full author list.

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Typical Angina is Associated with Greater Coronary Endothelial Dysfunction but not Abnormal Vasodilatory Reserve

Ahmed AlBadri¹, Derek Leong¹, C. Noel Bairey Merz¹, Janet Wei¹, Eileen M. Handberg², Chrisandra L. Shufelt¹, Puja K. Mehta⁴, Michael D. Nelson¹, Louise E. Thomson³, Daniel S. Berman³, Leslee J. Shaw⁴, Galen Cook-Wiens⁵, and Carl J. Pepine²

¹Barbra Streisand Women's Heart Center, Cedars-Sinai Heart Institute, Los Angeles, CA, USA

²Division of Cardiology, University of Florida, Gainesville, FL, USA

³S. Mark Taper Foundation Imaging Center, Cedars-Sinai Medical Center, Los Angeles, CA, USA

⁴Program in Cardiovascular Outcomes Research and Epidemiology, Emory University, Atlanta, GA, USA

⁵Biostatistics and Bioinformatics Research Center, Cedars-Sinai Medical Center, Los Angeles, CA, USA

Abstract

Background—Typical angina (TA) pectoris is defined as sub-sternal chest pain precipitated by physical exertion or emotional stress and relieved with rest or nitroglycerin. However, many angina patients have atypical symptoms including at rest and during stress, particularly in women and the elderly, often in the setting of non-obstructive coronary artery disease (CAD). To further understand this, we performed subgroup analysis comparing subjects who presented with TA vs non-typical angina (NTA) using baseline data of patients with non-obstructive CAD and coronary microvascular dysfunction (CMD) enrolled in a clinical trial.

Correspondence: C. Noel Bairey Merz, MD, FAHA, FACC, 127 S. San Vicente Blvd, Suite A3600, Los Angeles, CA 90048, Phone: 310-423-9680, Fax: 310-423-9681, Noel.BaireyMerz@cshs.org.

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Methods—In a secondary analysis, the 155 subjects from RWISE study were divided into two groups based upon characteristics of their angina: TA (defined as sub-sternal chest pain, precipitated by physical exertion or emotional stress, and relieved with rest or nitroglycerin) and NTA (defined as angina that does not meet criteria for TA). Coronary reactivity testing (responses to adenosine, acetylcholine, and nitroglycerin), cardiac magnetic resonance determined myocardial perfusion reserve index (MPRI), baseline Seattle Angina Questionnaire (SAQ) and Duke Activity Status Index (DASI) Scores were evaluated.

Results—The mean age was 55 ± 10 years, ethnicity, sex, traditional risk factors and cardiac medications did not differ between the TA and NTA groups. Overall, 30% of the subjects had TA. Compared to NTA, baseline shortness of breath, invasively assessed acetylcholine-mediated coronary endothelial function and SAQ score were worse in the TA group (all $p<0.05$), while adenosine-mediated CFR, MPRI and DASI score were similar to the NTA group.

Conclusions—Among subjects with CMD and no obstructive CAD, those with TA had more angina pectoris, shortness of breath, and worse quality of life, as well as more severe coronary endothelial dysfunction. Typical angina in the setting of CMD is associated with worse symptom burden and coronary endothelial dysfunction. These results indicate that TA CMD subjects represent a relatively new CAD phenotype of focus for future study and treatment trials.

Keywords

Typical angina; atypical angina; coronary microvascular dysfunction; coronary endothelial dysfunction; Quality of life

Background

Angina is a common presentation of myocardial ischemia in patients with obstructive coronary artery disease (CAD). Classically, typical angina (TA) is defined as substernal chest discomfort with a characteristic quality and duration, provoked by exertion or emotional stress, and relieved by rest or nitroglycerin¹. In contrast, non-typical angina (NTA) may be defined as symptoms ascribed as angina that do not meet criteria for TA. Older studies have shown that patients with TA have a high pre-test probability of obstructive CAD, especially in men and older patients²⁻⁴, however, current study shows no association between TA and obstructive CAD⁵ or inducible myocardial ischemia⁶. Patients who present with NTA can be misdiagnosed and have worse outcomes than TA patients⁷⁻¹⁰. Atypical symptoms are commonly observed in women, the elderly, and among those with a history of diabetes and/or congestive heart failure, and no obstructive CAD¹¹⁻¹³. Prior contemporary work indicates that patients with signs and symptoms of ischemia but no obstructive CAD have a relatively high prevalence of coronary microvascular dysfunction (CMD)^{14,15}, and elevated adverse cardiac events rate and healthcare resource utilization¹⁶⁻¹⁸.

Patients with non-obstructive CAD and CMD can present with either TA or NTA^{19,20}, however prior reports have not provided sufficient phenotypical data, to better understand risk assessment and treatment response. Specifically, our prior study suggested that patients with TA had a similar response in a randomized, controlled trial of late sodium channel

inhibition (ranolazine) compared to NTA patients²¹. We performed a secondary analysis of these trial subjects to further explore TA vs NTA differences.

Methods

Patient Population

Subjects were recruited from the RWISE trial at Cedars-Sinai Medical Center and the University of Florida. Per the study protocol²¹, we enrolled subjects with signs and symptoms of ischemia and no obstructive CAD (<50% epicardial coronary stenosis in all epicardial coronary arteries), and preserved left ventricular ejection fraction, who had CMD defined as abnormal invasive coronary reactivity testing [coronary flow reserve (CFR) <2.5, and/or no dilation (0% change) with acetylcholine (Ach)], or abnormal noninvasive stress cardiac magnetic resonance imaging (CMRI) myocardial perfusion reserve imaging (MPRI) <2.0. All enrolled trial subjects were included in the current analysis, including subjects with incomplete study visits, missing outcome data, or follow-up that excluded them from the primary study (20) analysis. Institutional Review Boards approved the study at Cedars Sinai Medical Center-Los Angeles and University of Florida-Gainesville. All subjects gave written informed consent.

Study Design

The RWISE design was a double-blind, placebo controlled, cross-over trial, with short-term (2 week) exposure to treatment (ranolazine/placebo) with a 2 week washout period between. Patients in this secondary analysis were classified based upon the predominate characteristics of their chest discomfort as either TA or NTA upon screening and enrollment, and only screening or enrollment information was used to avoid confounding with effects of treatment. Patients who were randomized but did not complete RWISE per protocol were included in this analysis resulting in a larger sample size than for RWISE. The resulting design was a two group comparison using baseline or screening measurements. TA was defined as sub-sternal chest pain precipitated by physical exertion or emotional stress and relieved with rest or nitroglycerin. NTA was defined as symptoms that did not meet criteria for TA. Subjects also completed demographic and health history questionnaires, including the Seattle Angina Questionnaire (SAQ)²² and Duke Activity Status Index (DASI)²³.

Further Testing and Analysis

All subjects then underwent entry and exit CMRI, as previously published²⁴ while a subgroup (62%) qualified by invasive coronary reactivity testing (CRT), as previously published²⁵.

Statistical Analysis

This analysis between angina types at baseline had not been planned as part of the larger crossover trial, so a power calculation was not performed. Only qualifying and baseline measures were compared between the TA and NTA groups, so the analytic approach for CRT and baseline characteristics was a two group comparison. Categorical variables were summarized using counts and percentages and compared using Fisher's Exact test. Continuous variables are summarized with mean and standard deviation. Randomization for

RWISE was not designed to balance these two groups, so baseline demographic and clinical characteristics were compared. The main tests for comparison were two sample Wilcoxon Rank Sum tests due to the presence of outliers or non-normal distributions for SAQ scales. Where this was not the case two sample t tests were used. The significance level of 5% was used for statistical tests. Analyses were performed using SAS v9.3 (SAS Institute Inc, Cary, NC).

Results

Overall, 46/155 (30%) of the subjects had TA. A majority of subjects were female, and most had traditional cardiac risk factors. Baseline variables did not differ between the TA and NTA subjects with the exception of the symptom of shortness of breath, and nitroglycerin use which were more prevalent in the TA subjects (Table 1). Notably, TA subjects had worse physical activity, angina frequency, and quality of life as measured by the Seattle Angina Questionnaire (SAQ) score, and had similar Duke Activity Status Index (DASI) in comparison to patients with NTA (Table 2).

Among the subset who underwent coronary reactivity testing, TA was associated with worse coronary macro and micro-endothelial dysfunction measured by acetylcholine-mediated change in coronary diameter and coronary blood flow (CBF) [defined as <50% increase from baseline CBF in response to Ach] (Table 3). There was no significant difference to NTG response between the two groups. Furthermore, the average noninvasive MPRI in the subset with pre-enrollment CMRI was not significantly different between the two groups (P=0.7) (Table 3).

Discussion

This secondary analysis of subjects with no obstructive CAD and CMD enrolled in a clinical trial of late sodium channel inhibition indicates that TA is associated with relatively worse angina, shortness of breath, quality of life, and coronary endothelial function compared to subjects with NTA. Importantly, we have previously demonstrated that coronary endothelial dysfunction in the setting of CMD and no obstructive CAD is associated with an adverse prognosis¹⁶.

Our findings that coronary endothelial function is relatively more impaired in TA subjects with CMD differ in part from those of Egashira et al.²⁶ who found similar dose-dependent vasoconstriction in both typical and atypical angina patients. The reason for the difference may be related to the difference in population (they included only 36% women compared to 92% in the current study) and/or the difference in the dose of IC-Ach used (they used up to 30 mcg/min compared to 36.4 mcg/min in the current study). Many other factors that modify the response of the vessels to IC-Ach such as age, atherosclerosis and other coronary artery disease risk factors may have also differed²⁶⁻²⁸.

Our coronary endothelial dependent microvascular dysfunction group mean, assessed by CBF response to IC-Ach, was lower in our TA vs NTA subjects. These findings may reflect the importance of symptoms as an indicator of macro- vs micro- coronary endothelial dysfunction in patients with no obstructive CAD²⁹. Interestingly, CFR, which is used to

assess the non-endothelial dependent microvascular dysfunction, was not different between the two groups. These findings are consistent with prior publication that did not show an association between TA and CFR³⁰. Furthermore, myocardial perfusion reserve index (MPRI), a relatively new tool to assess microvascular dysfunction using CMRI, was also not different between the groups. This may be explained by a non-uniform fashion in the left ventricle of coronary microcirculation dysfunction^{31–33}. If this is the case, uneven dilatation of the microcirculation could result in in-homogeneous myocardial perfusion during infusion of adenosine. In one study, patients with angina and “normal” coronary arteries, the increase in myocardial perfusion after administration of vasodilator was not uniform, although it was uniform in the control subjects³⁴. Like patients with obstructive CAD³⁵, this suggests that the quality and/or degree of symptoms may not correlate with the degree of CMD as assessed by adenosine-mediated CFR or MPRI, while relating to the coronary endothelial response.

While older studies linked TA with a high pre-test probability of obstructive CAD, especially in men and older patients^{2–4}, new studies demonstrate no association between TA and obstructive CAD⁵ or inducible myocardial ischemia⁶. These data suggest the concept of phenotypic shift in CAD over time. Specifically, the deployment of statins and other preventive measures³⁶ which have served to lower the incidence of obstructive CAD in populations being evaluated for signs and symptoms of ischemic heart disease³⁷, and rates of ST-segment elevation MI (STEMI) incidence and death³⁸, may have also created new angina phenotypes which need to be characterized and understood.

The strengths of our study are two-centers with expertise in the area, a relatively large sample size, inclusion criteria of CMD, and had rigorous control of angiography interpretation, coronary reactivity testing, and CMRI by core labs. Our study has some limitations that should be noted. The cohort is biased as all subjects were screened and met inclusion criteria for a clinical trial, and may not be generalizable to a more heterogeneous population. Also the cohort included 92% women. While this is important as women often present with CMD compared to men. Prior studies which have included predominantly TA subjects inadvertently excluded NTA subjects, resulting in few enrolled women and a lower evidence-based for treatment of women. Finally, the SAQ was designed for and validated in predominantly obstructive CAD, subjects and may be less relevant to our non-obstructive population.

Conclusions

Among subjects with non-obstructive CAD and CMD, TA subjects had relatively worse angina, shortness of breath, quality of life and coronary endothelial dysfunction compared to NTA subjects. These results indicate that TA CMD subjects have a greater symptom burden and adverse prognosis, and represent a new relatively CAD phenotype of focus for future study and treatment trials.

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Table 1

Subjects Characteristics

Mean \pm SD, or absolute frequency (%)	Typical Angina (n=46)	Non-typical Angina (n=109)	p-value
Age (years)	54.1 \pm 8.9	55.4 \pm 10.8	NS
Female, N (%)	43 (96%)	100 (93%)	NS
BMI	30 \pm 7.2	28.6 \pm 7.7	NS
Race (non-Caucasian), N (%)	17 (37%)	31 (28%)	NS
Current smoking, N (%)	1 (2.2%)	1 (0.9%)	NS
History of Hypertension, N (%)	29 (63%)	55 (51%)	NS
History of Diabetes, N (%)	8 (17%)	18 (17%)	NS
History of Hyperlipidemia, N (%)	26 (56%)	55 (51%)	NS
Family History of Premature Coronary Artery Disease, N (%)	30 (65%)	67 (64%)	NS
Postmenopausal, N (%)	37 (86%)	80 (80%)	NS
Prior MI, N (%)	3 (7%)	8 (8%)	NS
Associated symptoms			
•Shortness of breath	37 (80%)	63 (60%)	0.016
•Palpitations	22 (48%)	43 (41%)	NS
•Nausea	17 (37%)	30 (29%)	NS
Beta-Blockers, N (%)	17 (37%)	46 (44%)	NS
Calcium Current Blockers, N (%)	15 (33%)	22 (21%)	NS
Angiotensin Converting Enzyme Inhibitor, N (%)	12 (26%)	17 (16%)	NS
Angiotensin Receptor Blockers, N (%)	6 (13%)	11 (11%)	NS
Nitrates, N (%)	25 (54%)	33 (31%)	0.011
Statins, N (%)	22 (48%)	61 (58%)	NS
Hormone Replacement Therapy, N (%)	6 (14%)	13 (13%)	NS

Table 2

Angina and Quality of Life Measures

Score (mean \pm SD)	Typical angina(N=46)	Non-Typical Angina(N=109)	P-value*
<u>Baseline SAQ</u>			
•Physical Limitation	57.9 \pm 23.7	69.1 \pm 22.9	0.016
•Angina Stability	40.8 \pm 24.9	45.9 \pm 24.3	0.136
•Angina Frequency	48.9 \pm 28.6	66.3 \pm 23.6	<0.001
•Treatment Satisfaction	68.2 \pm 23.3	74.7 \pm 22.5	0.091
- Quality of Life	42.2 \pm 22.3	54.0 \pm 23.7	0.009
<u>DASI</u>			
	5.8 \pm 5.2	7.3 \pm 5.5	0.112

SAQ: Seattle Angina Questionnaire, DASI: Duke Angina Severity Index

* Wilcoxon rank sum test p-values

Table 3

Coronary reactivity testing and myocardial perfusion reserve parameters

	Typical Angina		Atypical Angina		P-value
	%	N	%	N	
ACH response (%) (N=82)	-8.74 ± 17.92	26	1.4 ± 19.49	56	0.03 *
CBF (n=67)	37.52 ± 70.86	22	74.88 ± 85.69	45	0.04 *
CFR (n=89)	2.68 ± 0.56	27	2.64 ± 0.68	62	NS*
Baseline MPRI (n=95)	1.78 ± 0.53	29	1.75 ± 0.46	66	NS*
NTG response (%) (n=84)	3.97 ± 18.24	25	12.9 ± 20.08	59	NS*

ACH: Acetylcholine, CBF: coronary blood flow, CFR: coronary flow reserve, MPRI: myocardial perfusion reserve index, NTG: nitroglycerine.

* Denotes p-value from a Wilcoxon rank sum test, otherwise a two sample t test.