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CLINICAL INVESTIGATIONS

Typical angina is associated with greater coronary endothelial dysfunction but not abnormal vasodilatory reserve

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Background: Typical angina (TA) is defined as substernal chest pain precipitated by physical exertion or emotional stress and relieved with rest or nitroglycerin. Women and elderly patients are usually have atypical symptoms both at rest and during stress, often in the setting of nonobstructive coronary artery disease (CAD).

Hypothesis: To further understand this, we performed subgroup analysis comparing subjects who presented with TA vs nontypical angina (NTA) using baseline data of patients with nonobstructive CAD and coronary microvascular dysfunction (CMD) enrolled in a clinical trial.

Methods: 155 subjects from the RWISE study were divided into 2 groups based on angina characteristics: TA (defined as above) and NTA (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 $\pm$ 10 years; Overall, 30% of subjects had TA. Baseline shortness of breath, invasively assessed acetylcholine-mediated coronary endothelial function, and SAQ score were worse in the TA group (all $P < 0.05$), whereas adenosine-mediated coronary flow reserve, 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 for future study and treatment trials.

KEYWORDS

Typical Angina, Atypical Angina, Coronary Microvascular Dysfunction, Coronary Endothelial Dysfunction, Quality of Life

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1 | INTRODUCTION

Angina pectoris is a common presentation of myocardial ischemia in patients with obstructive coronary artery disease (CAD). Classically, typical angina pectoris (TA) is defined as substernal chest discomfort with a characteristic quality and duration, provoked by exertion or emotional stress, and relieved by rest or nitroglycerin.[1] In contrast, nontypical 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 pretest probability of obstructive CAD, especially in males and older patients[2–4]; however, current study shows no association between TA and obstructive CAD[5] or inducible myocardial ischemia.[6] Patients who present with NTA can be misdiagnosed and have worse outcomes than TA patients.[7–10] Atypical symptoms are commonly observed in females, the elderly, and among those with a history of diabetes mellitus and/or congestive heart failure, and no obstructive CAD.[11–13] 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] an elevated adverse cardiac events rate, and increased healthcare resource utilization.[16–18]

Patients with nonobstructive 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, compared with NTA patients, patients with TA had a similar response in a randomized controlled trial of late sodium channel inhibition (ranolazine).[21] We performed a secondary analysis of these trial subjects to further explore TA-vs-NTA differences.

2 | METHODS

2.1 | Patient population

Subjects were recruited from the Treatment With Ranolazine in Microvascular Coronary Dysfunction (MCD): Impact on Angina Myocardial Ischemia (RWISE) trial at Cedars-Sinai Medical Center and the University of Florida. Per the study protocol,[21] 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 (CMR) 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, California, and the University of Florida, Gainesville. All subjects gave written informed consent.

2.2 | Study design

The RWISE trial was a double-blind, placebo-controlled crossover 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 as either TA or NTA based on the predominant characteristics of their chest discomfort 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 2-group comparison using baseline or screening measurements. TA was defined as substernal 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]

2.3 | Further testing and analysis

All subjects then underwent entry and exit CMR, as previously published,[24] whereas a subgroup (62%) qualified by invasive coronary reactivity testing, as previously published.[25]

2.4 | 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 coronary reactivity testing and baseline characteristics was a 2-group

TABLE 1 Characteristics of subjects in the 2 groups

	TA Group, n = 46	NTA Group, n = 109	*P* Value
Mean age, y	54.1 ± 8.9	55.4 ± 10.8	NS
Female sex	43 (96)	100 (93)	NS
BMI, kg/m^2	30 ± 7.2	28.6 ± 7.7	NS
Non-Caucasian race	17 (37)	31 (28)	NS
Current smoking	1 (2.2)	1 (0.9)	NS
History of HTN	29 (63)	55 (51)	NS
History of DM	8 (17)	18 (17)	NS
History of hyperlipidemia	26 (56)	55 (51)	NS
Family history of premature CAD	30 (65)	67 (64)	NS
Postmenopausal	37 (86)	80 (80)	NS
Prior MI	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
Medications			
β-Blockers	17 (37)	46 (44)	NS
CCBs	15 (33)	22 (21)	NS
ACEIs	12 (26)	17 (16)	NS
ARBs	6 (13)	11 (11)	NS
Nitrates	25 (54)	33 (31)	0.011
Statins	22 (48)	61 (58)	NS
HRT	6 (14)	13 (13)	NS

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blocker; DM, diabetes mellitus; HRT, hormone replacement therapy; HTN, hypertension; MI, myocardial infarction; NS, not significant; NTA, nontypical angina; SD, standard deviation; TA, typical angina.

Data are presented as n (%) or mean ± SD.

comparison. Categorical variables were summarized using counts and percentages and compared using the Fisher exact test. Continuous variables are summarized with mean and SD. Randomization for RWISE was not designed to balance these 2 groups, so baseline demographic and clinical characteristics were compared. The main tests for comparison were 2-sample Wilcoxon rank-sum tests due to the presence of outliers or non-normal distributions for SAQ scales. Where this was not the case, 2-sample *t* tests were used. The significance level of 5% was used for statistical tests. Analyses were performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC).

TABLE 2 Angina and quality-of-life measures

	TA Group, n = 46	NTA Group, n = 109	*P* Value[a]
Baseline SAQ score			
Physical limitation	57.9 ± 23.7	69.1 ± 22.9	0.016
Angina stability	40.8 ± 24.9	45.9 ± 24.3	0.136
Angina frequency	48.9 ± 28.6	66.3 ± 23.6	<0.001
Treatment satisfaction	68.2 ± 23.3	74.7 ± 22.5	0.091
Quality of life	42.2 ± 22.3	54.0 ± 23.7	0.009
DASI score	5.8 ± 5.2	7.3 ± 5.5	0.112

Abbreviations: DASI, Duke Angina Severity Index; NTA, nontypical angina; SAQ, Seattle Angina Questionnaire; SD, standard deviation; TA, typical angina.

Data are presented as mean ± SD.

[a] Wilcoxon rank sum test *P* values.

3 | RESULTS

Overall, 46 of 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 SAQ score, and had similar DASI in comparison with subjects with NTA (Table 2).

Among the subset who underwent coronary reactivity testing, TA was associated with worse coronary macro- and microvascular endothelial dysfunction measured by ACH-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 nitroglycerin response between the 2 groups. Furthermore, the average noninvasive MPRI in the subset with pre-enrollment CMR was not significantly different between the 2 groups ($P = 0.7$; Table 3).

4 | 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 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 prognosis.[16]

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 TA and NTA patients. The reason for the difference may be related to the difference in population (they included only 36% females, compared with 92% in the current study) and/or the difference in the dose of intracoronary (IC) ACH used (they used up to 30 μg/min, compared with 36.4 μg/min in the current study). Many other factors that modify the response of the vessels to IC ACH, such as age, atherosclerosis, and other CAD risk factors, also may have differed.[26–28]

Our coronary endothelial-dependent microvascular dysfunction group mean, assessed by CBF response to IC ACH, was lower in our TA than in our NTA subjects. These findings may reflect the importance of symptoms as an indicator of macro- vs microcoronary endothelial dysfunction in patients with no obstructive CAD.[29] Interestingly, CFR, which is used to assess the non–endothelial-

TABLE 3 Coronary reactivity testing and MPR parameters

	TA Group		NTA Group		
	%	N	%	N	*P* Value
ACH response, %, n = 82	−8.74 ± 17.92	26	1.4 ± 19.49	56	0.03[a]
CBF, n = 67	37.52 ± 70.86	22	74.88 ± 85.69	45	0.04[a]
CFR, n = 89	2.68 ± 0.56	27	2.64 ± 0.68	62	NS[a]
Baseline MPRI, n = 95	1.78 ± 0.53	29	1.75 ± 0.46	66	NS[a]
NTG response, %, n = 84	3.97 ± 18.24	25	12.9 ± 20.08	59	NS[a]

Abbreviations: ACH, acetylcholine; CBF, coronary blood flow; CFR, coronary flow reserve; MPR, myocardial perfusion reserve; MPRI, myocardial perfusion reserve index; NS, not significant; NTA, nontypical angina; NTG, nitroglycerin; TA, typical angina.

[a] Denotes *P* value from a Wilcoxon rank sum test; otherwise, a 2-sample *t* test.

dependent microvascular dysfunction, was not different between the 2 groups. These findings are consistent with a prior publication that did not show an association between TA and CFR.[30] Furthermore, MPRI, a relatively new tool to assess microvascular dysfunction using CMR, 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 inhomogeneous myocardial perfusion during infusion of adenosine. In one study of 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 subjects.[34] Like patients with obstructive CAD,[35] 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.

Although older studies linked TA with a high pretest probability of obstructive CAD, especially in males and older patients,[2–4] new studies demonstrate no association between TA and obstructive CAD[5] or inducible myocardial ischemia.[6] These data suggest the concept of phenotypic shift in CAD over time. Specifically, the deployment of statins and other preventive measures,[36] which have served to lower the incidence of obstructive CAD in populations being evaluated for signs and symptoms of ischemic heart disease,[37] and rates of ST-segment elevation myocardial infarction incidence and death,[38,39] also may have created new angina phenotypes that need to be characterized and understood.

4.1 | Study limitations

The strengths of our study are 2 centers with expertise in the area, a relatively large sample size, inclusion criteria of CMD, and rigorous control of angiography interpretation, coronary reactivity testing, and CMR by core laboratories. 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 it may not be generalizable to a more heterogeneous population. Also, the cohort included 92% females. This is important, as females often present with CMD, compared with males. Prior studies that have included predominantly TA subjects inadvertently excluded NTA subjects, resulting in few enrolled females and a lower evidence base for treatment of females. Finally, the SAQ was designed for and validated in predominantly obstructive CAD subjects, and thus it may be less relevant to our nonobstructive CAD population.

5 | CONCLUSION

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

Conflicts of interest

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