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RESEARCH LETTER

Regional Heterogeneity in the Coronary Vascular Response in Women With Chest Pain and Nonobstructive Coronary Artery Disease

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Women presenting with ischemic chest discomfort without obstructive coronary artery disease (INOCA) are an increasingly recognized group of patients with a heightened risk for adverse cardiovascular events.[1] Symptoms likely reflect abnormal microvascular function,[2] yet the associated pathophysiology is not well understood and represents a clinical challenge. Therefore, accurate noninvasive diagnostic tests for evaluating these patients are needed. Here we report the coronary vascular response to a vasoactive breathing maneuver, assessed by oxygenation-sensitive cardiovascular magnetic resonance imaging (OS-CMR), in female patients with INOCA.

We recruited a cohort of women (40–65 years) with recurrent episodes of INOCA and healthy volunteers. INOCA was defined as a history of chest pain responsive to nitroglycerin in the absence of clinical evidence for nonischemic causes. Documented evidence of ischemia on noninvasive imaging was not an inclusion requirement for our study. All of the women underwent coronary angiography to exclude obstructive coronary artery disease (≥50% stenosis in any epicardial coronary artery) and were excluded if they had evidence for Prinzmetal's angina or a contraindication to magnetic resonance imaging. All of the patients provided written consent, and our study was approved by the institutional committees. The data that support the findings of this study are available from the corresponding author on reasonable request.

Using a clinical 3-T magnetic resonance imaging scanner, OS-CMR image sets were acquired over 4 heartbeats each, applying a T2-prepared, balanced, steady-state free precession cine sequence (echo time/repetition time: 1.70 ms/44.8 ms [3.4 ms], flip angle 35°, voxel size 2.0×2.0×10.0 mm, matrix 192×120, bandwidth 1302 Hz/Px) in 2 short-axis views (basal and mid) before and immediately after paced-cadence monitored hyperventilation, as well as over a subsequent prolonged breath hold.[3] End-systolic OS-CMR signal intensity was measured at baseline and at the time point closest to 30 seconds of breath hold. Changes were expressed as percentage change from baseline (Figure, A).[3]

In this exploratory study, we assessed global and regional variability by measuring intersegmental differences along radial, circumferential, and longitudinal directions (Figure, B). Each short-axis section was divided into 6 segments and then subdivided into endocardial and epicardial subsegments for a total of 12 subsegments per section. Radial differences were defined as the sum of absolute differences between all radially adjacent (endocardial and epicardial) subsegments, circumferential differences as the sum of absolute differences between all circumferentially adjacent subsegments, and longitudinal differences as the sum of absolute differences for all longitudinally adjacent subsegments (Figure, B). All of the OS-CMR images were anonymized and analyzed by 2 readers blinded to the status of case or control subject.

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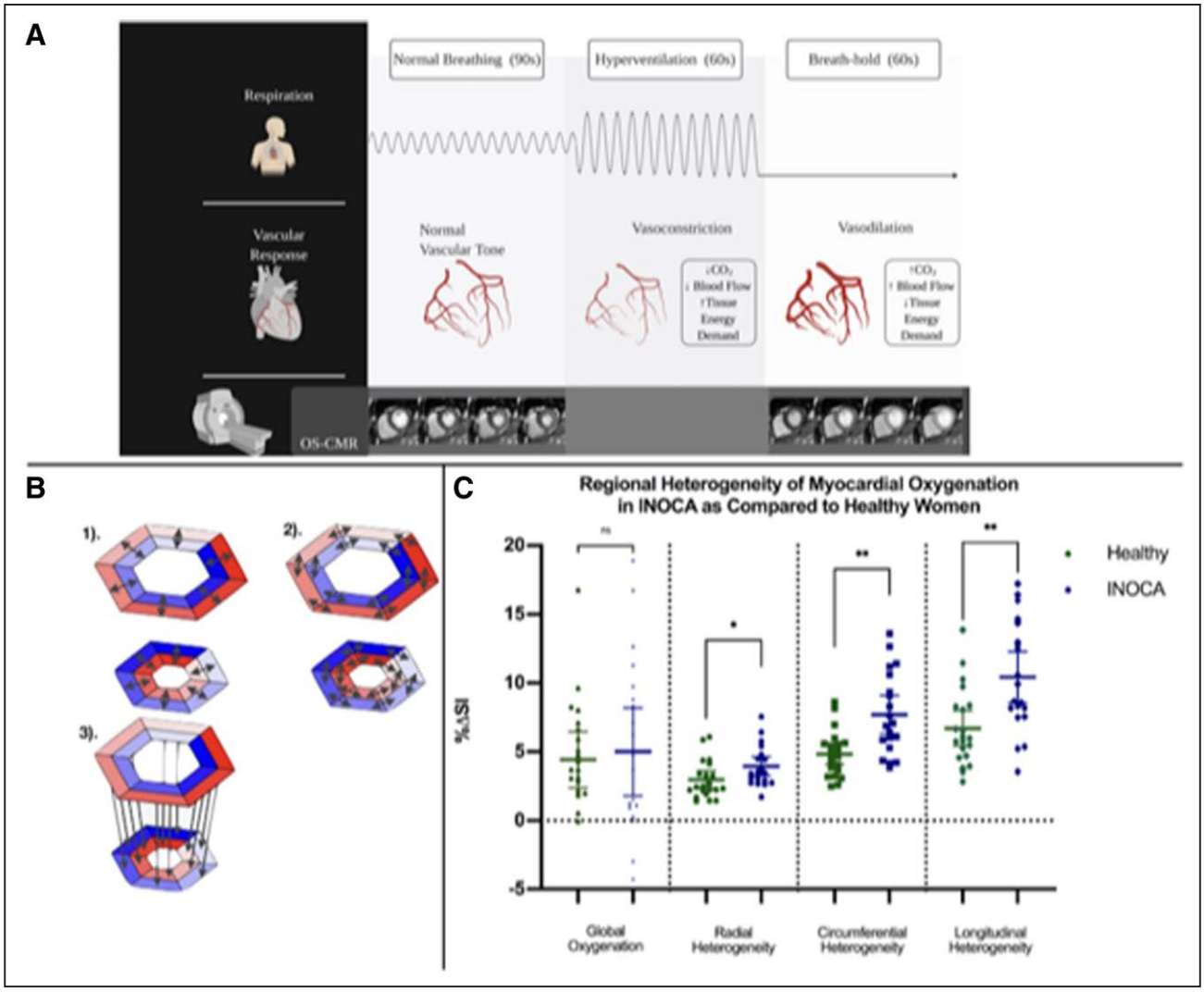

Figure. Impact of the breathing maneuver on the myocardium (A) and associated heterogenous myocardial oxygenation changes as reflected by a change of signal intensity in OS-CMR images in the 3 spatial dimensions (B), shown for healthy participants and patients with INOCA (C). **A**, OS-CMR using a standardized breathing maneuver. Hyperventilation leads to a coronary vasoconstrictive response through a decrease in arterial carbon dioxide, while the following breath hold increases arterial carbon dioxide and induces coronary artery dilatation. Myocardial signal intensity changes in OS-CMR images are measured at the end of hyperventilation (maximal vasoconstriction) to the end of the breath hold (maximal vasodilatation). **B**, Schema demonstrating the determination of regional variability in signal intensity using radial, circumferential, and longitudinal differences. (**1**) Radial differences were defined as the sum of the absolute differences between the endo- and epicardium in each of the myocardial segments. (**2**) Circumferential differences were the sum of the absolute differences between myocardial segments within the endocardium and epicardium. (**3**) Longitudinal differences were the sum of the absolute differences within the endocardium and epicardium for corresponding segments of each slice. **C**, Regional heterogeneity in myocardial oxygenation in women with INOCA compared with healthy volunteers. INOCA indicates ischemic chest pain with no obstructive coronary artery disease; OS-CMR, oxygenation-sensitive cardiovascular magnetic resonance imaging; and SI, signal intensity. **P*<0.05, ***P*<0.01.

We studied 20 women with INOCA (mean age, 54.2±6.12 years). When compared with 20 age-matched healthy volunteers (mean age, 52.3±3.99 years), there were no differences in any of the CMR parameters of volumes, function, or mass. There was also no difference in the global mean percentage of change in myocardial oxygenation between women with INOCA compared with healthy volunteers (5.00% versus 4.42%, *P*=0.7). Women with INOCA, however, had statistically significantly higher regional variations in myocardial oxygenation in circumferential (7.71% vs 4.83%, *P*<0.001), longitudinal (10.42% vs 6.41%, *P*=0.001), and radial (3.94% vs 2.97%, *P*=0.03) directions (Figure, C).

Overall, our findings suggest that, among women with INOCA, there is heterogeneous coronary vasomotor activity in response to standardized breathing maneuvers, as evidenced by increased regional heterogeneity in the change of myocardial oxygenation.

To date, assessments of patients with INOCA have relied mainly on global measures of coronary perfusion, thereby limiting the evaluation of regional heterogeneity or layer-specific alterations in microvascular dysfunction. This may explain the inconsistency of reported results. In fact, studies of regional coronary flow reserve in patients

with INOCA using positron emission tomography have shown a significant perfusion heterogeneity, likely reflecting endothelial dysfunction.[4] Our observations provide direct and important insights into the physiology of microvascular dysfunction in this poorly characterized population. Heterogeneous myocardial oxygenation may explain the presence of ischemic symptoms in the absence of epicardial coronary artery disease or global perfusion abnormalities. These findings are also consistent with previous reports on heterogeneous flow in microvascular dysfunction associated with regional intramyocardial shunts, induced by endothelial-derived relaxing factors or abnormal neural stimuli.[5] Women with INOCA may also be more prone to an increased coronary vascular tone, mediated through endothelial dysfunction in response to a hyperventilation–breath hold stimulus.

In summary, our data indicate that, in women with INOCA, regional heterogeneity of myocardial oxygenation may explain inducible ischemia in the presence of normal global coronary blood flow. OS-CMR can identify such abnormalities and therefore may serve as an important diagnostic marker in clinical studies of patients with INOCA.

ARTICLE INFORMATION

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