Peer Review File

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Reviewer A

Methods:
Comment 1: Have you used atropine?
Reply 1: Yes, when indicated.
Changes in the text: We have added the following text "Atropine was used to attain target heart rate when indicated." Page 7/line 103-104.

Comment 2: Have you used target HR?
Reply 2: Yes, please see methods (Page 7, Line 109-111) for how target heart rate was used.
Changes in the text: We have added the following text to methods "Atropine was used to attain target heart rate when indicated." (Page 7, Line 103- 104)

Comment 3: What did you do with patients that did not reach target HR?
Reply 3: Out of the 82 subjects included, 75 reached target HR (91.5%). Studies were deemed indeterminate if no abnormality was observed at baseline or peak stress and target heart rate was not reached. Please see methods (Page 7, Line 109-111)
Changes in the text: We added the following to our text "Of the 82 patients included 75 (91.5%) achieved target HR." (Page 9, line 155-156)

Comment 4: How many patients underwent revascularization initially (those with >=50% narrowing).? For example, those with >=50% LM.
Reply 4: The analysis only included those without prior revascularization and no obstructive CAD. Therefore, none of the study subjects had undergone revascularization.
Changes in the text: None

Table 1:
Comment 5: Severity of CAD is not only 10% stenosis; it is also number of vessels with disease.
Reply 5: Thank you for this clarification. The CAD severity was meant to show the level of stenosis. We will modify the text to make it clearer.
Changes in the text: We made the following changes:
1.We have added the following to the text with citation. "Angiographic coronary disease severity was assessed by the WISE coronary severity score as previously described(11)" Page 8, Line 125-126.
2. CAD Severity has been re-labelled as "CAD (% Stenosis)" and added Sharaf-Gensini Severity Score to table 1

Comment 6: Do you have data for the peak HR and BP in the two groups?
Reply 6: Yes
Changes in the text: We added Peak Heart Rate and BP to Table 1.

Comment 7. Maximum dobutamine dose used?
Reply 7: We do not have this information in our data set
Changes in the text: None

Comment 8: Please quote: "J Electrocardiol. 2020 Nov-Dec;63:164-166. doi: 10.1016/j.jelectrocard.2019.04.008."
Reply 8: Thank you for providing another example of why ECG changes with a normal DSE should not be ignored.
Changes in the text: None

Comment 9: Do you have data on baseline ECG findings: Voltage criteria for LVH? IVCD, BBB? Repolarization changes? LVH can cause ST depression with exercise.
Reply 9: Thank you for the comment. None of the 82 subjects had LVH at baseline.
Changes in the text: None

Reviewer B

The authors provide further evidence that positive ECG despite absence of WMA on DSE is prognostically significant, and particularly in woman. This is believed to reflect INOCA leading to future cardiac events.

The study adds to the body of literature that ECG findings of ischemia remain prognostically significant in the absence of imaging findings of ischemia or obstructive lesions at the time of invasive angiography.

This study has the following limitations:

Comment 1: The authors acknowledge the small sample size of women undergoing DSE.
Reply 1: None
Changes in the text: None

Comment 2: A single experienced cardiologist interpreted the DSE studies, but it may be possible that a wall motion abnormality was missed (false negative) and the stress test was mislabeled as negative WMA. This is particularly important in a small sample size, and so it would be more convincing to have at least 2 reviewers agree that the wall motion analysis was indeed negative. Further of the 9 women with positive ECG findings but negative for WMA, 3 had at least 50% stenosis on invasive angiography (perhaps a mild WMA was missed on those 3 patients).

Reply 2: Thank you for insightful comments. We will add to our limitations.
Changes in the text: We have added the following to the text. “The DSE studies were interpreted by a single experienced cardiologist, and it may be possible that wall motional abnormalities were missed.” (Page 13-14 Lines 254-256)

Comment 3: Patients underwent invasive angiography, yet microvascular dysfunction was not reported as part of the invasive angiography testing, rather postulated to be present in patients with abnormal ECG but negative WMA. It would have been better if microvascular dysfunction was assessed for in this study.
Reply 3: Thank you for the comment. As stated in our limitations only small group of the cohort underwent invasive coronary function testing. Please refer to lines 262-263
Changes in the text: None

Comment 4: It is not clear to this reviewer why akinetic to dyskinetic DSE is considered negative DSE. Kindly explain why those 10 patients were included with the 72 with no WMA and treated as one group.
Reply 4: Thank you for this comment. Worsening WMAs is defined as a change from normal wall thickening to hypokinesis, akinesis, or dyskinesis and from hypokinesis to akinesis or dyskinesis but not from akinesis to dyskinesia. We will add a citation that explains the definition of worse WMAs.
Changes in the text: We have added citation 10. (Page 7 Line 107)

Comment 5: Would it be possible to analyze the DSE patients for echo strain?
Reply 5: Thank you for the comment. Strain analysis is not available in the data set and we will add to our limitations.
Changes in the text: We have added the following to the text, “Furthermore, strain analysis was not available in this data set.” (Line 256-257)