Author's response to reviews

Title: Cardiac Functional Stress Imaging: a Sequential Approach with Stress Echo and Cardiovascular Magnetic Resonance

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Version: 2 Date: 2 November 2007

Author's response to reviews: see over
November 2, 2007

Dear Dr. Picano

Attached please find the revised manuscript entitled "Cardiac Functional Stress Imaging: a Sequential Approach with Stress Echo and Cardiovascular Magnetic Resonance." by R. Sicari et al. We tried to address all the issues raised by the reviewers. All the changes made throughout the manuscript are reported in italic. We hope that the manuscript in the present form is suitable for publication. All authors have read and approved submission of the manuscript, and the manuscript has not been published and is not being considered for publication elsewhere in whole or in part in any language except as an abstract. No conflict of interest has to be disclosed for authors acknowledged by name.

Best regards

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Rosa Sicari, MD, PhD, FESC
Reviewer 1: Thank you for your thoughtful and constructive criticism; In **bold** your comments; in italic parts added to the revised manuscript.

A very innovative approach for a well-designed and well written paper showing the feasibility of a totally non-ionizing cardiac stress imaging approach. I have only minor comments:

Page 3, line 14: “its operator-independence” perhaps should be more realistically “its less pronounced operator-independence”
We changed the sentence as suggested (pg. 3 of the revised manuscript)

Page 3, Patients, line 2 and again page 7, line 12: sign ± missing
We inserted the sign ±

Page 4, lines 11-12: please, round-off percentages (6%, 30%; 64%)
We rounded off percentages (pg. 4 of the revised manuscript)

Page 4, 2 lines before the end: delete “electrocardiography” (already specified 2 lines above)
We deleted electrocardiography (pg. 4 of the revised manuscript)

Page 4, 2 lines before the end: ... high dose dipyridamole with the same dose used for stress echo (delete: in accordance with well established protocols)
We deleted in accordance with well established protocols and changed with high dose dipyridamole with the same dose used for stress echo (pg. 4 of the revised manuscript)

Page 9, last line before the conclusion: I would add two lines to make this important concept more explicit: “In this algorithm, CMR replaces cardiac stress scintigraphy which gives a dose exposure corresponding to 500 (with Sestamibi) to 1,600 (with Thallium or dual isotope scan) chest x-rays per each exam (33-36). Since 10 million cardiac stress scintographies are performed each year in US, the positive impact of our proposed algorithm on downstream risks would be remarkable (37-38)”. New ref 35 might be Thompson, J Nucl Cardiol 2006. New ref 36 Einstein, Circulation 2007; new ref 37 Picano E, Am J Med 2003 and new ref 38 Picano E, Cardiovasc Ultrasound 2007.
We added the sentence in order to explicit the concept and changed the references as suggested (pg. 9 of the revised manuscript)

**Table 1:** disease is disease (repeated 3 times)
Thank you for having outlined the typos that we corrected

**References:** please, correct typos on ref 27.

In the discussion, please add a comment on the relatively low sensitivity (63%) due to:

a) Normal baseline function;
b) High number of patients under anti-ischemic therapy (59 out of 152), which reduces sensitivity of wall motion;
c) 50% cut-off
d) High number (31 out of 88) of patients with single vessel disease;
e) Use of regional wall motion for both SE and CMR, without addition of myocardial perfusion or CFR criteria.

The low sensitivity of the test may be due to several factors: All patients had a normal baseline function; a high number of patients were studied under anti-ischemic therapy (59 out of 152), which reduces sensitivity of wall motion; 31 out of 88 patients had a single vessel disease;
Moreover we analysed only regional wall motion for both SE and CMR, without addition of myocardial perfusion or CFR criteria. Nevertheless, the overall performance of the algorithm seemed acceptable in the “real life” context. (pg. 8-9 of the revised manuscript).