Author's response to reviews

Title: Carotid artery intima-media thickness is closely related to impaired left ventricular function in patients with coronary artery disease: a single-centre, blinded, non-randomized study.

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Author's response to reviews: see over
Response Letter

Dear Professor Picano and Professor Sicari,

We re-submit our manuscript entitled: “Carotid artery intima-media thickness is closely related to impaired left ventricular function in patients with coronary artery disease: a single-centre, blinded, non-randomized study.” Manuscript number: MS 2042258560130611 for publication in Cardiovascular Ultrasound.

In this resubmission, all issues raised by the reviewers have been addressed in detail and changed in the text accordingly (outlined in the following pages).

We would like to thank the reviewers and the editors of Cardiovascular Ultrasound for the detailed and rapid peer-review process of our article. There is no doubt that the comments made by the reviewers have greatly improved the quality of our manuscript.

Yours sincerely, on behalf of the co-authors,

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Reviewer # 1:

We thank the reviewer for the very important and helpful comments to our manuscript. We have addressed the specific comments as described below.

Major Compulsory Revisions:

It is not clear if the paper is about the correlation between IMT and LV function measured with strain echo, or about the correlation between strain and extent of CAD. A proper working hypothesis is not clear. The clinical meaning of the investigation is not clear.

Reply: We agree with the reviewer that the aim of the study was somewhat unclearly described in our original manuscript. The main aim of this study was to investigate a possible correlation between IMT and left ventricular function in patients with coronary artery disease. This is now clearly stated in the Background section, page 3, lines 20-22: “The aim of this study was to investigate a possible correlation between IMT and LV function, assessed using strain echo, in patients with CAD”.

The paper adds little to the well known subject of atherosclerosis being a systemic disease, i.e. presence of atherosclerosis in one district is correlated to presence of atherosclerosis in another, and to the well known subject of carotid IMT being a predictor of CVD.

Reply: We agree completely that it is well known that atherosclerosis is a systemic disease. However, there is very limited data regarding a possible correlation between IMT and LV strain in patients with CAD which was the main aim of our study.

No references or sources for a validation of 2D-STE and layer-specific analysis are provided.

Reply: This is a very important comment and we have now added references for validation of 2D-STE and layer specific analyses: page 3, lines 8-10 and in the references section. Reference numbers: (6;7).

References which have been added:

(7) Validation of in vivo myocardial strain measurement by magnetic resonance tagging with sonomicrometry.
Yeon SB, Reichek N, Tallant BA, Lima JA, Calhoun LP, Clark NR, Hoffman EA, Ho KK, Axel L.

**Poor physiopathological explanation are provided for a correlation of IMT with LV function (and why it has been investigated).**

Reply: We agree that the physiopathological explanation should be improved in the manuscript and have therefore added the following information in the Background section, page 3, lines 18-22:

“Carotid IMT may be used to assess the risk for CAD (1; 2). Ischemia due to CAD is one of the causes of decreased LV function and there is therefore a possibility that carotid IMT may be used to assess LV function in these patients. The aim of this study was to investigate a possible correlation between IMT and LV function, assessed using strain echo, in patients with CAD.”

"LV function" is more than just strain. Strain measures a component only of LV function. This should be clearly stated.

Reply: We agree with the reviewer that “LV function" is more than just strain and have therefore clearly stated this point in the Discussion section, page 8, lines 21-24.

“The assessment of LV function is challenging due to its very complex deformation pattern. All imaging modalities have shortcomings in this regard. However, although myocardial strain measures only a component only of LV function, it has been demonstrated to be an accurate and reproducible measure in several studies (6; 7).”
References added:


How is IMT measured? With the standard caliper? It has poor resolution and poor reproducibility, especially if plaques are included and the maximum value is considered. Moreover, simple intima-media thickening and atherosclerotic plaques are not interchangeable neither from a physiopathological, clinical or anatomo-pathological point of view. A thickness of 2.88 mm is definitely a plaque.

Reply: In this study, IMT was measured using the automatic software program of the GE ultrasound machine (Vivid 7). The IMT values were automatically calculated over an area of 1 cm in the common carotid arteries 1cm proximal to the bifurcation, bifurcations and the proximal internal carotid arteries on both sides. Plaques were included in the IMT measurements if present in the areas of interest. This is clearly described in the Methods section, page 4, lines 19-24 and page 5, lines 1-5. We agree with the reviewer that carotid intima-media thickness and plaques have different pathophysiological mechanisms. However, the assessment of both carotid IMT and plaques are well-known methods which can be used to assess the risk for cerebro- and cardiovascular disease (20; 21). We therefore included the diameter of the small number of plaques which were detected in the areas of interest. This information is now included in our Discussion, page 9, lines 5-7.

Considering "significant" a coronary stenosis of 50 %, and putting the patient in the same category as an occluded artery, irrespective of clinical status, is debatable.

Reply: It is correct that we defined a "significant " a coronary stenosis as a stenosis ≥ 50 % or occlusion of a vessel. However, all patients included in the study had a history of typical or atypical angina or positive ECG stress testing.
Page 7, Discussion, line 2: the investigation does not deal with "ischemic injury".

Reply: We agree with the reviewer and have changed "ischemic injury" to "LV dysfunction" in the Discussion section, page 8, lines 1-2.

Minor Compulsory Revisions.

Page 3, line 5: "minimal cardiovascular resistance" is not clear.

Reply: This refers to one study which showed a possible correlation between carotid artery disease and minimal cardiovascular resistance. We provide a reference for this article (5) where the reader can find detailed information about the authors definition of "minimal cardiovascular resistance" and how it was measured. We do not believe that our text should be expanded to include all of these details. However, we can provide a more detailed description of this article in the text if the reviewer thinks that this is necessary.

A comparison with the behaviour of ejection fraction should be made.

Reply: We agree with the reviewer and have now made a comparison of ejection fraction (EF) and strain values. EF showed normal values for the total group. Comparing EF in the group with normal endocardial values with the group with reduced endocardial values showed no statistically significant difference. This is added in the text in the Results section: page 7, line 7-10:

"Left ventricular Ejection Fraction (LVEF) was: mean ± SD; 61 % ± 6% for the total group of patients. Patients with normal endocardial strain had EF values of: mean ± SD; 62 % ± 6.0 % and patients with reduced endocardial strain mean ± SD; 58 % ± 4.8%. This difference was not significant (p= 0.091)."

Page 4, lines 1-2: patients' characteristics should be in the Results section.
Reply: We agree with the reviewer and have moved patients’ characteristics to the Results section as suggested: page 6, lines 19-22.

Page 4, carotid ultrasound, and figure 1.2: the 45 degrees tilting is mentioned in the text but in the figure the head is vertical.

Reply: This is an important observation. Figure 1.2 has now been changed to a 45 degree tilting of the head as shown below.

Figure 1.2: Probe orientations for the ultrasound examinations are shown for the right common carotid artery

Table 2: columns and rows should be swapped.

Reply: In table 2, columns and rows have been swapped as shown below:

Table 2. Layer-specific global longitudinal strain of the left ventricle compared to coronary angiography findings.
<table>
<thead>
<tr>
<th></th>
<th>&lt; 50% stenosis (n=11)</th>
<th>≥ 50% stenosis (n=18)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocardial LVGLS</td>
<td>-19.5 ± 2.2</td>
<td>-15.0 ± 2.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Mid-myocardial LVGLS</td>
<td>-15.4 ± 1.6</td>
<td>-13.1 ± 2.6</td>
<td>0.011</td>
</tr>
<tr>
<td>Epicardial LVGLS</td>
<td>-12.8 ± 1.9</td>
<td>-11.6 ± 2.2</td>
<td>0.169</td>
</tr>
</tbody>
</table>

Left ventricular global strain (LVGLS) is in mean ± SD
Reviewer # 2:

We thank you for the very important and helpful comments to our manuscript. We have addressed the specific comments as indicated below.

Major Compulsory Revisions:

1. The selection process of patients included in the study group is unclear. The authors state that they assessed 31 consecutive patients between Sept 2010 and Jan 2012 (over 15 months) who met the inclusion criteria (a history of angina and positive ECG exercise test). Does it mean that there were on average only 2 such patients per month in Authors’ institution? The issue of selection process is important because it may potentially be associated with selection bias, which would limit applicability of study results to a larger patient population.

Reply: There are several reasons for the low number of patients included in this time period. This was mainly due to the strict exclusion criteria: “age <18 years, acute coronary syndrome (ST-elevation or non-ST elevation myocardial infarction) in the preceding 3 months, concomitant significant disease or non-cardiological therapy which could affect cardiac remodelling or function, left bundle-branch block, severe valvular dysfunction, atrial fibrillation, sustained severe arrhythmia, or any condition which interfered with the patients’ ability to comply. Another reason was that the echocardiography and the carotid ultrasound examinations had to be performed by the same two researchers who both had to be available on the day patients were included which was not always the case.

2. All patients underwent coronary angiography – my understanding is that the decision to perform this examination was made in each case before the inclusion in the study. Was it also an inclusion criterion? Or was the coronary angiography a part of the study protocol? Again, this issue is associated with potential selection bias and therefore should be clarified.

Reply: The patients in our study were recruited from a group of patients with a history of typical or atypical angina or positive ECG stress testing who were all referred to our hospital for coronary angiography. The decision to perform this examination was made in each case before inclusion into the study. The coronary angiography findings were therefore available in all patients.

3. Authors provided results of layer-specific speckle tracking analysis (in 3
separate layers of the myocardium). However, not all vendors offer possibility of layer-specific speckle tracking in their software packages. Therefore, I believe that providing results of longitudinal strain measurement of the whole thickness of the myocardium would increase scientific value of this paper.

Reply: The off-line software (Toshiba Medical Systems Corporation, Tokyo, Japan) did not allow analysis of deformation of the entire wall thickness of the myocardium. We could therefore not carry out longitudinal strain measurements of the whole thickness of the myocardium.

4. This study is composed of three parts: A/ correlation between LV strain measurement and IMT B/ correlation between LV strain measurement and coronary angiography results C/ correlation between IMT and coronary Angiography results. I believe parts A and B are especially interesting. However, the title of the manuscript and Conclusions section of the abstract reflect only part A. Furthermore in the Results section of the manuscript there is no clear division between these three parts. I suggest expanding the Results section and dividing it into two or three parts.

Reply: We agree with the reviewer and have expanded the Results section and divided it into two sections with the correlation between coronary angiography and LV strain first and second the correlation between IMT and LV strain.

Page 7, lines 1-21.

A) “A total of 20 (65%) patients had significant CAD (≥50% stenosis. Eight of these patients had an occlusion of a major coronary artery) and 11 (35%) had a non-significant CAD (<50% stenosis). There was a significant difference in endocardial and mid-myocardial LVGLS between the patients with significant coronary stenosis and the patients with non-significant coronary stenosis. Layer-specific LVGLS compared to the coronary angiography findings are shown in table 2.

Left ventricular Ejection Fraction (LVEF) was: mean ± SD; 61% ± 6% for the total group of patients. Patients with normal endocardial strain had EF values of: mean ± SD; 62%
± 6.0 % and patients with reduced endocardial strain mean± SD; 58 % ± 4.8%. This difference was not significant (p= 0.091).

B) Figures 2 a-d shows ROC analyses of layer specific strain parameters and the ability of IMT measurements to identify patients with significant CAD Maximum carotid IMT ranged between 1 mm and 2.88 mm for the whole group of patients including carotid plaques in the IMT measurements. For the group with normal endocardial strain values, defined by the cut-off strain value of -16.7, carotid IMT was 1.2 mm ± 0.2 (mean ±SD) and for the group with reduced endocardial strain values the carotid IMT value was 1.7 mm ± 0.5 (mean ±SD). Independent samples t-test comparing the two groups was statistically significant (p= 0.006). There was significant correlation between endocardial LVGLS and maximum carotid IMT (p= 0.006). The results of linear regression analyses which incorporated adjustment for known risk factors of atherosclerosis (hypertension, smoking, hyperlipidemia, diabetes and BMI ) were made and showed significant results (p= 0.02).”

Minor essential revisions
1. I could not find the website www.openepi.org Instead I found www.openepi.com

Reply: The website has changed it’s address and is now as you suggested: www.openepi.com. This has been changed on page 6, line 17.

2. I suggest removing the phrase “Adjustments were made for hypertension, smoking, hyperlipidemia, diabetes and BMI.” from the Methods section of the abstract. This information is repeated in the Results section: “ also when adjusted for hypertension, smoking, hyperlipidemia, diabetes and BMI.”. Instead I suggest expanding the Results section of the abstract.
Reply: We agree and have removed this phrase from the Methods section and expanded the Results section.

3. I believe a figure with an example of layer-specific strain analysis would increase the value of the manuscript.

Reply: We agree and have added a figure of layer-specific strain to the article. This has been added on page 6, line 1 and as Figure 2.

**Figure 2:** Endocardial longitudinal strain study of a patient with significant coronary artery disease.

The automatic strain analysis in a patient with angina and significant left anterior descending (LAD) artery stenosis. The apical four-chamber view shows reduced colour coded subendocardial strain values in segments supplied by the left LAD artery. Colour-coding from yellow to green indicates strain from +30% to -30%. Yellow = normal strain. Brown = areas with reduced strain. On the right strain curves for the 6 subendocardial segments are presented. The white arrow shows reduced strain values of – 14% in the curves representing the segments supplied by the LAD artery.

AL = apicolateral; AS = apicoseptal; BL = basolateral; BS = basoseptal; ML = midlateral; MS = midseptal