Author's response to reviews

Title: Angiographically borderline left main coronary artery lesions: correlation of transthoracic Doppler echocardiography and intravascular ultrasound

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Author's response to reviews: see over
Dear Dr. Sicari,

Please find enclosed our revised manuscript entitled “Angiographically borderline left main coronary artery lesions: correlation with transthoracic Doppler echocardiography and intravascular ultrasound” by Zoltán Ruzsa et al.

We tried to answer all the questions raised by the Reviewers, and we hope that in the present form the manuscript will be suitable for publication in Cardiovascular Ultrasound. All changes made are highlighted with blue colour throughout the manuscript.

The manuscript type is an Original Article and represents original work that is not being considered elsewhere for publication, in whole or in part. The authors have no real or perceived conflicts of interest to disclose. This manuscript is not a resubmission of a previously rejected paper nor is it a submission for a special issue. The manuscript has been read and approved by all the authors.

Best regards,

Zoltán Ruzsa, MD and Albert Varga, MD, PhD, FESC
Response to the Reviewers

Reviewer 1. (Dr. Sicari)

Thank you for your thoughtful review. We tried to address all the points raised by you review.

1. Patient population selection: please give criteria of selection
   
   We added the following sentence: “All patients with positive treadmill stress test and angiographically documented borderline LM stenosis entered this pilot study.”

2. Indications and contra-indications to coronary angiography

   The following sentence was added to the manuscript with the appropriate citation: “Indications and contraindications of the angiography followed the coronary revascularization guideline of the European Society of cardiology (33).”

3. Give details on coronary anatomy. It is not clear if these patients had single vessel left main disease, which would be a difficult population to be selected.

   The following sentence has been added to the Result section of the manuscript: “All patients had visually assessed borderline LM stenosis. Isolated left main disease was present in 14 patients, but coronary angiography revealed additional atherosclerotic lesions in the remaining 13 patients: 3 vessel disease in 2 patients, 2 vessel disease in 3 patients and one vessel disease in 5 patients.”

4. The patient population is small. Please give data on feasibility of such an approach.

   We acknowledged in the study limitation section, that our study population was relatively small. We also added to the abstract and to the conclusion, that: “Further, large scale studies are needed to establish the exact cut-off value of PDV for routine clinical application.”

5. Doppler velocity has important limitations and may give unreliable data in relation to differences in systemic blood pressure, geometry of the vessel and the plaque, incidence of the ultrasound beam and state of the microvascular bed down to stenosis. Please address

   We added an explanation to the Discussion section: “The value of resting Doppler velocity is determined by the severity of the coronary stenosis and other rheological and haemodynamic factors, of which abnormality of the microcirculation may falsely increase the value of PDV, potentially disturbing its assessment. The value of resting PDV can be influenced by haemodynamic variables, as well, such as changes in heart rate,”
blood pressure and increased contractility. Geometry of the vessel (tortuosity, kinking) and the plaque incidence of the ultrasound beam (eccentric plaque) are also important factors that may influence PDV.”

6. Do authors have data on coronary flow reserve?
**Unfortunately, we do not have data on coronary flow reserve in this population. Therefore, we added a sentence to the limitation section:** “Furthermore, neither functional studies nor coronary flow reserve evaluation were performed in our study population, therefore we don’t have data regarding the comparison of the physiologic severity of the lesions and the PDV velocity.”

7. The ROC curve show a poor ability of discrimination of Doppler velocity. Please discuss. Stenosis severity and Doppler velocities do not correlate whereas the area as assessed by IVUS has a fair correlation. With this results, it is unreliable to use Doppler velocities as a stand alone parameter to assess coronary artery stenosis severity.

We completely agree with the reviewer, therefore a new paragraph was added to the Discussion, clinical implication section: The cut-off value of 112 cm/sec determined by the ROC analysis demonstrated a good sensitivity of PDV in recognizing hemodynamically significant (determined by IVUS) LM disease, however the specificity of the method was rather low. This can still generate further unnecessary invasive testings, therefore at this point the PDV cannot considered a standalone method in the evaluation process of the borderline LM narrowings. A possible clinical algorithm is given in figure 6. Further, large scale studies are needed to establish the exact cut-off value of PDV for routine clinical application.

8. Please tone down the statement that this is the first study addressing this issue and discuss Caiati et al. Eur Heart J 2009; 14: 1797

**We modified the first sentence of the discussion section as follows: “In our present study we demonstrated, that the measurement of simple resting TTDE is of additional value even in patients with borderline LMCA lesions determined by QCA”** and discussed the paper by Caiati et al.: “Furthermore, Caiati et al (32.) have found that the entire LAD can be visualized by the use of contrast-enhanced TTDE and taking a flow acceleration of 0.82% as reference value, for Doppler criterion of significant stenosis, the sensitivity and specificity of the method in identifying all diseased segments was 86 and 95%. However left main stenosis was not analyzed in their population.”

9. The clinical implications of their work is not clear. Please provide a clinical algorithm. The specificity of test is poor and may increase the number of false positive testing.
**A clinical algorithm was added**

10. Due to the nature of the journal please upload images with sample cases.
**We added a small case report with images**
Response to the Reviewers

Reviewer 2. (Dr. Neskovic)

Thank you for your comprehensive review. We tried to address all the points raised by you review.

1. Although interesting, the study sample is quite small. The observed correlations (between TTE and IVUS) were significant but weak, and specificity of the proposed cut-off is hardly acceptable (62%) for routine use. It seems that authors are aware of these shortcomings and that is probably why they proposed TTDE as ‘useful adjunct to other invasive and non-invasive methods’. However, this is not what we expect from TTDE in the assessment of borderline LM lesions. Instead of being an adjunct, any new and noninvasive method should aim to replace the existing expensive and invasive methods (IVUS and FFR), widely used in clinical practice.

In the present form, the current study could only be considered as a pilot or feasibility study, which needs to be clearly stated in the study title. Undoubtedly, it would be better to continue this definitely interesting study and present more cases with more reliable data. I would strongly support the latter option.

Here is another example from the present study to support this observation: All patients underwent exercise test prior to coronary angiography and it was positive in all subjects. Provided that there were no other significant lesions that could lead to positivity of the test (there is no such data in the manuscript), we could presume that LM stenosis was functionally significant in majority of pts (bearing in mind the specificity and sensitivity of the exercise test, which is approx 70% for both). Indeed, IVUS proved that borderline LM stenoses were significant in 71% of pts. On the other hand, specificity of PDV in the present study was reported to be 62%. Therefore, there is only weak-to-moderate correlation between TTDE and IVUS parameters, whereas the specificity of TTDE is probably inferior (at least not superior) to that of the treadmill test.

We emphasized in the title that this was a pilot study, and added to the Conclusion a following phrase: “Further, large scale studies are needed to establish the exact cut-off value of PDF for routine clinical application.”

2. It would be useful to test the interobserver variability in this type of study. In a similar study of nearly 1500 subjects (Evaluation of left main coronary artery stenosis by transthoracic Echocardiography, Ref No 21), adequate coronary flow assessment was obtained in only 55% of pts, while in the present study it was rather high (88%). This issue must be addressed in the discussion.

Thank you for your observation. It is true that in the study of Anjaneyulu the feasibility was only 55%, but they did not concentrated only to the LM, but in their study „the LM and the adjacent segments of left anterior descending coronary artery and left circumflex coronary artery were evaluated by color flow and Doppler“. In our study only the LM was visualized, by an experienced observer. We added a following sentence to the manuscript: „All TTDE studies were carried out by a single investigator experienced in LM TTDE assessment, blinded to the angiographic and IVUS results.”
3. One of the most important findings should be included in the Abstract: TTDE measured PDV correlated significantly with IVUS-derived MLA (r= -0.46, p<0.05, figure 2.) and plaque burden (r=0.51, p<0.05, figure 3.). It should replace the following sentence: There was a significant, albeit weak inverse correlation between %DS and IVUS-defined MLA (r=-0.48, p<0.05).

**We corrected the abstract according to the suggestion of the Reviewer**

4. The aim of the study in the Abstract and Introduction should be rewritten. In fact, the aim of the study was to evaluate the relationship between TTDE PDV and IVUS measurements in the assessment of angiographically borderline LM lesions.

**We rewrote this part of the Abstract, as well: „The aim of the study was to evaluate the relationship between transthoracic Doppler (TTDE) peak diastolic flow velocity (PDV) and intravascular ultrasound (IVUS) measurements in the assessment of angiographically borderline LM lesions.”**

5. Results presented in Table 2 should not be repeated in the section Results.

**We deleted these data from the Results section**

6. The first sentence in Discussion section should be modified and rewritten. There are no data in the study to support the statement that ~simple resting TTDE is of additional value~.

**The first paragraph of the discussion section was modified as following:” In our present study we demonstrated, that the measurement of simple resting TTDE might be of additional value in patients with borderline LMCA lesions.”**

7. The second sentence in the Conclusion section is redundant and should be deleted.

**This sentence was also deleted, and the conclusion was modified: „TTDE evaluation might be a useful adjunct to other invasive and non-invasive methods in the assessment of borderline LM lesions. Further, large scale studies are needed to establish the exact cut-off value of PDV for routine clinical application.”**

Minor Essential Revisions:
1. Numerous typing/spelling/grammatical errors should be corrected. Redundant words/phrases should be removed from the text

**We tried to correct the typing and grammatical errors.**