

Response Letter to the Reviewers

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We have read with great interest the comments by the reviewers, and addressed each issue raised by such comments. We have introduced most of the changes suggested, and consider that the article has benefited from these changes, for which we are very grateful. Below we address each comment specifically.

Response to Reviewer number 1

Comment 1: Are the conclusions logically valid and justified by the evidence adduced? Yes, however, most data in conclusion should be shifted to discussion and conclusion should be shortened.

We thank the reviewer for this comment, and agree that most of our conclusion would fit better in the discussion section. Accordingly, we have introduced a discussion section, and considerably shortened our conclusion. See the changes below and in page 24 of the manuscript:

“DISCUSSION

Myocardial ischemia should not be considered to happen exclusively in the presence of critical coronary epicardial stenoses. The physiological significance of intermediate lesions cannot be properly assessed by angiography, and in this case a pressure wire should always be used to decide intervention or deferral. In the absence of significant coronary stenoses, a complete evaluation of the microcirculation and the endothelial function can help identify the fundamental problem, or at the very least reassure the patient and the physician.

When studying a patient with stable angina or acute coronary syndrome, the interventional cardiologist should not be content with an angiography showing non-significant epicardial disease. If there are intermediate lesions (30-70%), FFR should be performed to rule out ischemic lesions; if the arteries are clearly non-stenotic, or if FFR is normal, we propose that microvascular endothelium-independent (CFR and microvascular resistance), and macro and microvascular endothelium-dependent function should be assessed. This thorough protocol can be performed in a matter of minutes, and with a very low risk[10]. Recent studies[9, 10] show that, in most patients with angina who are extensively evaluated, an alteration can be found that explains the symptoms. Figure 4 shows an example from our centre following this protocol in a complex patient. Figure 5 summarizes this diagnostic algorithm.

In other clinical settings, such as stenting, myocardial infarction and heart transplant, vascular function affects clinical outcomes, and can serve as a prognostic marker. Also, coronary physiological parameters can be of

interest as surrogate markers of safety and efficacy in clinical trials for new devices, such as drug eluting stents[66, 74] and bioabsorbable scaffolds[75]. The interventional cardiologist should be acquainted with the methods used to perform these measurements and their interpretation. Table 2 summarizes the main parameters available to date.

CONCLUSION

Coronary physiology assessment in the catheterization laboratory is essential to help decision making in patients with coronary artery disease, providing functional and prognostic information. Physicians, especially interventional cardiologists should implement its use in daily clinical practise."

Comment 2: Is the reference section adequate or is it too long and should it be cut down? References are inconsistent. Some lack year (Ref 7) , others contain a lot of co-authors , Please see journal style , usually after 6th author should be et al.

We have updated our reference section according to the journal style (Ref 7 changed, first author bold-faced, square brackets added, DOI and PMID). We have included all authors in the references, as specified in the "Instructions for authors" document of the Journal.

Response to Reviewer number 2

Comment 1: There are neither formulas nor equations in the text.

We are not sure about the exact meaning of this comment.

If the reviewer meant that the text of the manuscript should not be interrupted by formulas or equations, we accept that this is generally right for a medical article. However, since the aim of our manuscript is to provide a clear and practical guide to the performance and interpretation of physiological measurements, these equations are essential to the article's main objective. We could have set them apart in a table, but we decided against it because we think this may be more distracting, forcing the reader to shift their attention too often. For this reason, we think the best approach is to leave the equations in the text, although we acknowledge that it is uncommon in cardiology journals.

If, on the other hand, the reviewer meant that the formulas were absent from the text, we can only interpret that there has been some problem with the document formatting.

In any case, we appreciate the comment, have reviewed all the equations, and think it is best in this article to maintain them within the text.

Comment 2: Authors should describe clearly contraindications of each examination.

We thank the reviewer for this important comment, and agree that it is important to point out contraindication and/or pitfalls of the different examinations described. In this regard, we have added a “pitfalls and contraindications” section to the main techniques described in the manuscript, giving therefore focus to the limitations sometimes associated.

See for example, page 11:

“Pitfalls and contraindications

Since both thermodilution and Doppler techniques require the use of adenosine, the most common side effects associated are those described to this substance: bradycardia, hypotension, flushing, dyspnea and chest discomfort; however, the effects of adenosine disappear in seconds after the infusion is stopped or the bolus is administered, so concerning side effects are exceptional. Probably the only truly serious complication of adenosine administration is persistent bronchospasm, which is why it should be avoided in asthmatic patients[20]. If bronchospasm occurs, adenosine may be antagonized with theophylline[21]

The procedure is safe in experienced hands. However, physicians must be aware of the generic potential complications related to the insertion of guiding catheters and wires in the coronary arteries, such as coronary thrombosis, dissection, and spasm.”

And page 15:

“Pitfalls and contraindications

FFR is a feasible and reproducible technique, minimally modified by the baseline characteristics and hemodynamic status of the patient. Despite its reproducibility, some pitfalls and limitations have been reported.

Pharmacological side effects of adenosine are the same as those described in CFR. Accordingly, the patient must be in a stable hemodynamic condition, and adenosine should be avoided in patients with bronchospasm, severe hypotension, bradycardia or conduction disturbances.”

Comment 3 Bibliography” is not suitable. Authors should use “references”.

Answer: we have changed "Bibliography" to "References",

We sincerely thank both reviewers for their comments and corrections, and hope to have addressed every issue to their full satisfaction.

Kind Regards.

Felipe Diez del Hoyo.