Author's response to reviews

Title: The non-invasive documentation of coronary microcirculation impairment: role of transthoracic echocardiography

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Author's response to reviews:

Reviewer 1:
Very interesting and timely although presentation might be improved. Minor comments:
1 - Title: It is a bit cryptic. I would suggest: The non-invasive documentation of coronary microcirculation impairment by transthoracic echocardiography
2 Table 1 is nice, but a figure showing the resistance drop across the coronary bed would be nicer.
3 On page 4, I would suggest to quote human cardiovascular magnetic resonance studies, clearly showing that subendocardium has lower coronary flow reserve than subepicardium.
4 On page 4, 4 lines before the end, Table 1 should read Table 2.
5 What is the proper stress to recruit coronary flow reserve? Many studies have used pacing, or exercise, or dobutamine, or adenosine, or dipyridamole, with variable doses and rates of infusion. Different stimuli can give different "normal" reference values. Please, specify if the studies you quoted all employed the same stress, to which extent this may contribute to the observed variability of results, and which are your current recommendations.
6 You discuss the sources of biological variability of coronary flow reserve; but which are the sources of methodological variability? In other words, what is the reproducibility of the method as compared to other methods?
7 From the practical point of the clinical implications, what are your suggestions? From the literature that you describe, it seems that chest pain, ST segment depression and perfusion changes are not predictive of "microvascular disease" as documented by coronary flow reserve. Probably you are in a position to recommend criteria for the diagnosis of coronary microvascular disease. In diastolic function, we need a negative criterion (normal ejection fraction) and a positive criterion (evidence of diastolic dysfunction). In a similar fashion, you can suggest the presence of a negative criterion (normal coronary angiography although intracoronary ultrasound would be better) and a positive criterion (reduced coronary flow reserve by TTE). Please comment.
8 What is the role of LVH? Should we exclude the presence of left ventricular hypertrophy to have a positive diagnosis of microvascular disease?
9 The appeal of the paper would greatly benefit from images combining angiographic and coronary flow reserve images/videoclips of a normal, a borderline normal, and a frankly abnormal patient.

Answer (new sections in text are underlined)
1. Title was changed.
2. Figure was added
3. MRI study was added.
4. Number of table was corrected
5. New section was added
6. New section about validity of TTE was added
7. See conclusion
8. The role of LVH was discussed several times. The exclusion of LVH is required only in definition of syndrome X - one of the form of microvascular disease.

Reviewer 2
The authors give a clear explanation of the phenomenon. Microvascular disease can be a common pathway in dilated and hypertrophic cardiomyopathy, and can be useful to detect early alterations in X syndrome (Rigo et al. Am J Cardiol. 2002 May 1;89(9):1141-4) and verify the effects of cardiovascular drugs
The authors should explain the limits of CFR detected by transthoracic echocardiography (i.e., number of vessels and feasibility).
A comparison with MRI might be useful.
The authors might wish to give more information about the drugs and protocol used to measure CFR

Answer:
Information about feasibility is added.
MRI is added
Vasodilators was discussed

Reviewer 3:
The editorial by Dimitrov et al focuses on an interesting aspect of modern cardiovascular physiology, but unfortunately is contradictory and confusing.
The authors start claiming that CFR is a useful index to investigate both severity of coronary epicardial stenosis and dysfunction of coronary microcirculation but they also write that CFR is reduced below 2.0, corresponding to the same cut-off point for severe epicardial artery stenosis in a number of diseases (hypertension, diabetes, hypercholesterolemia, syndrome X, hypertrophic and dilated cardiomyopathies).
How such an index can be useful to detect epicardial stenosis if there is so much overlap with diseases/conditions characterized by microvascular dysfunction?

Answer: The comment of reviewer is appropriate. This paragraph was deleted.

The authors should also recognize that syndrome X is characterized by a supernormal CFR and systolic function at stress, in hypercholesterolemia the reduction of CFR if ever present, is minimal, and that in hypertension and aortic valve disease CFR may be reduced only because part of the reserve is already burned at rest, due to the increased metabolic demand.

Answer: The appropriate paper with clear visualization of subendocardial hypoperfusion in syndrome X was cited., in hypercholesterolemia CFR reduction is not minimal see table 6. As regard hypertension, HCM and aortic stenosis, reviewer propose that increased resting coronary flow (by LV hypertrophy, hypertension) is not be considered as reduced CFR. This statement is contradictory to current definition of CFR (where not only maximal but also baseline coronary flow is used to formula) and negated widely accepted factors limiting CFR (table 3).

The Authors mention with emphasis the work by Hoffman (ref#2) who suggest that CFR of 2.5 or even 3 are potentially damaging to the subendocardium. How is it possible that an increase in flow of up to 3-fold may be damaging? Of note, the great majority of middle-age people have a CFR around 3 (see page 5): are we all at risk of subendocardial damage? In contradiction with this statement is the finding reported in ref 8 and 9 that transplanted hearts have an early CFR of 5.1 despite all what their subendocardium has suffered during agony of the donor, cold-preservation and then transplantation. Of note, 5.1 is the CFR of athletes.

Answer: The suggestion of Hoffman was deleted. The lower limit of normal CFR was discussed.

The authors state on page 5 that Positive exercise myocardial scintigraphy, primarily considered as false positive in relation to angiographically normal coronary vessels, may frequently turn out to be true positive when control intracoronary ultrasound reveals vascular lesions (18); in this setting, CFR is a fairly good predictor of soft lesions, not visualized by coronary angiography. This sentence should be deleted.

Answer: This sentence was deleted
Page 6: in some pediatric patients with hypertrophic cardiomyopathy, CFR was <1 (since non-hypertrophic free wall steals blood flow from hypertrophied septum after vasodilator infusion). However, there are no angiographic collateral to support such a huge steal; in addition, a CFR<1 corresponds to coronary subocclusion, with severe ischemic signs and symptoms.

Answer: This is statement of the authors of paper which we have cited.

The reported experience by Rigo is based on a drug (dipyridamole) which does not necessarily produce maximal microvascular dilatation, and with an inadequate ultrasound equipment.

Answer: The vasodilator effect of dipyridamole was discussed.

In the reference list the Authors failed to mention the most important papers published on coronary flow reserve by other groups mainly in Italy and Japan.

Answer: We do not write manuscript about general CFR (in CAD) but about reduction of CFR in coronary microvascular diseases, thus the list of references is appropriate.