Author's response to reviews

Title: The Importance of Achieving a Target Heart Rate to Determine the Normal Limit Value of Coronary Flow Reserve in the Territory of the Left Anterior Descending Coronary Artery During Dobutamine Stress Echocardiography

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Author's response to reviews: see over
Answer to the reviewer Dr. Rosa Sicari:

We appreciate your valuable comments and provide the following explanations:

1) In order to assess a pathophysiologic pattern of normality authors should have studied healthy volunteers. It is not clear which patients have been selected for the study. Please clarify what was the indication to stress echocardiography, and if you selected only subjects with normal function at rest and negative dobutamine stress echo.

   1) We included patients without history of cardiovascular diseases, with normal wall motion and preserved systolic function. Our patients were at low risk for coronary artery disease, with negative tests results for myocardial ischemia and normal coronary flow reserve. Actually, we did not perform coronary angiography to evaluate whether coronary arteries were normal; yet, we mentioned that this was one of the limitations of our study in the corresponding section. On the other hand, we think that the likelihood of coronary artery disease in these patients is low due to the fact that low pretest value followed by negative test results. The indications to choose stress echocardiography are detailed in Table 1 (preoperative, chest pain, diagnosis of coronary artery disease). Patients with history of coronary artery disease or typical angina were excluded from the study.

2) To assess the feasibility of such a method the patient sample studied is too small. This feasibility is built inside ideal conditions that may hard to reproduce on consecutive patients.

   2) We agree with Dr. Sicari about the fact that the sample size is small to evaluate the feasibility of the test, as we have already mentioned in the section “Study Limitations”. However, our study was not focused on evaluating the feasibility of the test; our goal was to give complementary information of the test.

3) Authors mention to medical therapy only in the discussion section of the manuscript but they should inform us on how many were an medical therapy, which therapy and if it was withheld before testing.

   3) In the section “Material and Methods” we mentioned that beta blockers were withheld 48 hours before the study. Some patients were on ARBs, statins or metformin. We did not mention these drugs as we think that they do not have any effect on coronary flow reserve and thus will not alter the results.

4) Authors excluded 1 patient because he did not show a normal CFR: please explain why.

   4) We did not include one patient with reduced coronary flow reserve and normal contractility due to the fact that this abnormality was one of the exclusion criteria for the purpose of this analysis. In this patient, reduced coronary flow reserve was unspecific and due to multiple causes, even technical reasons, which might produce false results.
5) In dobutamine as well as in exercise stress echocardiography the lack of achieving target heart rate may identify patients with worse prognosis as demonstrated by several groups, provided that medical therapy may influence it. Please comment.

5) We agree with the reviewer that it is essential to achieve target HR in dobutamine stress test. In this sense, only 7 out of 31 patients did not reach 85% of the maximum predicted heart rate. We also used atropine and even 50 mcg of dobutamine according to the protocol. As we have previously mentioned, beta blockers had been withheld and patients were not receiving other negative chronotropes that might have influenced the study. Anyway, the essence of the study is precisely that there is no need to achieve very high HR to determine an adequate value of CFR, regardless of the final result of the test.

6) The need to achieve target heart rate or at least a delta of 50 bpm is reasonable but authors should explain the pathophysiologic basis. The correlation between HR and CFR is strong but we do not know how it works in positive tests or in patients with impairment of microcirculation. Please address. In line with the previous comment the way results are presented is confusing.

6) In the section “Discussion” we analyzed the physiopathologic basis of the effect of dobutamine on the coronary arteries (references18-19). By stimulating beta 1 receptors, dobutamine increases contractility and heart rate, with subsequent increase in oxygen demands. In turn, vasodilation occurs and coronary blood flow and velocity increase. By direct activation of beta 2 and alpha receptors, dobutamine produces a minor effect on coronary artery tone. Reference 20. Dobutamine hyperemia is equivalent to adenosine-induced vasodilation in patients with ischemic response to dobutamine, but lower than in non-ischemic patients (in normal patients, the effect of dobutamine on CFR is lower than that of adenosine. Reference 21,22.

Patients with a positive test result usually present microcirculation abnormalities. In this sense, reduced coronary flow reserve might be related to multiple factors, such as stenosis of the epicardial vessels, microcirculation abnormalities, ventricular hypertrophy, valvular hear disease, etc. We know it is unspecific and that it should be evaluated in the individual patient.

7) In line with the previous comment the way results are presented is confusing. Please state that CFR was assessed at each stage and that the correlation were created on the overall sampling (as it appears from figures).

7) The values represented in each figure correspond to those measured in each stage of the test. Indeed, there is a typo in Figure 3; the correct legend is “Correlation between delta HR (Max HR - Baseline HR) and CFR”.

8) Due to authors' experience with vasodilator stress testing what is the potential advantage of using dobutamine stress echo when it appears that it is less feasible and more demanding. Please comment.
8) The importance of measuring coronary flow reserve with dobutamine is that dobutamine is more frequently used than dipyridamole. Most dipyridamole tests in the country are performed in our laboratory, where 80% of patients are referred for dobutamine versus 20% for dipyridamole stress testing. Adding the determination of coronary flow reserve to wall motion analysis improves the diagnostic sensitivity and specially the prognostic value of the test (personal unpublished results, presented as abstract in the 2010 Euroecho) as it has been previously demonstrated with dipyridamole. We agree with the reviewer that estimation of coronary flow reserve is more demanding and less feasible compared to the test with vasodilators; however, it adds important and useful information that should be considered.

9) The conclusion in the abstract are not clear and should be rephrased

9) We have modified the abstract as requested by the reviewer.

10) The title is too long

10) We have shortened the title, as follows:

Target Heart Rate to Determine the Normal Value of Coronary Flow Reserve during Dobutamine Stress Echocardiography

11) The references are incomplete and should be extensively revised. Please note that Pellikka et al. Published on the use of CFR during dobutamine stress echo. You may be interested in replacing ref.# 20 with a more recent one by F. Rigo: tricks and pitfalls of CFR. Cardiovascularultrasound 2008

11) We have changed the reference as requested by the reviewer.
We have added the paper by P. Pellika as reference 25..

WE ARE THANKFUL TO THE REVIEWER FOR HER VALUABLE COMMENTS AND WE HAVE CONSIDERED ALL HER SUGGESTIONS.
Answer to the reviewer Dr Patrick Meimoun:

We appreciate your valuable comments and provide the following explanations:

1) Concerning the second point, which is indeed the main objective of the study, the authors should define in the same section of the manuscript that they want to determine the NORMAL limit VALUE of CFR during DSE (which is clearly defined in the title). For this purpose they should define the population studied: without ischemic response during DSE.

1) We focused on determining the difference in heart rate necessary to achieve a normal value of CFR rather than on determining the “normal” value of CFR. In our study, the main factor was HR and not the absolute value of CFR. The study population was prospectively selected from a population with a low pretest risk for coronary artery disease, normal wall motion, normal coronary flow reserve and normal test results, as we have mentioned in the section of the population studied.

2) Concerning the methods: Again, it is important to define more accurately the population studied: is normal DSE test required to be included, or by chance the 33 patients were included because DSE was normal? In an unselected population, even at low risk of CAD, the frequency of normal test is not 100%.

2) We agree with the reviewer with the fact that we should provide more details about the population studied, and have already done so. Patients with abnormal wall motion or reduced coronary flow reserve were not included. We also agree that in an unselected population, the frequency of normal test is not 100%, and we know that DSE has a precision of about 90%; yet all tests were negative in our study, probably due to the small sample size with low risk patients.

3) Furthermore, in the section methodology, it is unclear if 1 or 2 equipment were used (page6). About the Nyquist limit set at about 19cms/s, it is not stated if it was changed during DSE. With increasing heart rate, the LAD flow velocity increased, and keeping the same low scale at high heart rates renders the visualization of the artery more difficult. For the reader, the authors should define if they changed gradually the scale of the color Doppler flow mapping during the test in order to better visualize the LAD. Furthermore, they should precise that they measured the flow velocity at the same position at each stage of DSE.

3) We used two ultrasound systems: an ATL HDI-5000 Ultrasound System (Philips) and a Vivid system (GE). Nyquist limit was set in 19 cm/s, and was gradually increased when the flow velocity in the LAD was higher.

4) The definition of CFR was clearly defined on page 8, but the authors used the term CFR for all ratios of flow velocities at each stage of DSE along the manuscript, which is somewhat confusing. They should use CFR for the final value clearly defined on page 8, and use the term “ratio of flow velocities” for all intermediate values measured during each stage of DSE, in order to improve the reading of the data.
4) We agree with the reviewer that the term CFR cannot be used in intermediate stages of the test. We think that the reviewer refers to Table 2, in which CFR is mentioned in each stage of the test. According to your correction, we have replaced the term CFR with “ratio of flow velocities”.

5) On page 10, the “excellent concordance” is not a synonym of correlation. Furthermore, the p value for each correlation should be clearly defined. We can have a weak but significant correlation and vice-versa.

5) In page 10, we have replaced the word concordance with correlation, as suggested by the reviewer. We have included the p value < 0.001 in both figures following your correction.

6) In the section discussion, the authors mentioned the effects of dobutamina on the coronary circulation which is important for the reader (page 11), but there is another mechanism by which the coronary flow increases during DSE, which his some what less important in this setting: the endothelium dependent flow mediated vasodilation (ref Kernetal, JACC 2003; 42:1602-4, and Ghalehetal Circulation 1995;92:2627-35 for instance).

6) We have added the following phrase according to the reviewer’s suggestion: In addition, dobutamine, by increasing contractility and myocardial oxygen consumption, leads to a release of vasodilatory substances such as adenosine, which acts on epicardial arteries and microvasculature. Finally, dobutamine, by increasing the heart rate, induces flow mediated epicardial vasodilation.

7) The authors mentioned that they “have not found any study analyzing and measuring the relation between heart rate and CFR during DSE”, and they discussed briefly about the results of the reference 9 and 10 by comparison, and surprisingly not of the reference 11. However, the study mentioned in the reference 11 assessed CFR during DSE and compared it to the CFR obtained with adenosine in the same group of patient and found a good correlation and concordance between the tests, in a wide range of LAD disease (normal and abnormal tests were analyzed). Although a clear cut-off of heart rate was not established in that study, it was emphasized along the manuscript that a maximal achievable target heart rate was necessary during DSE to obtain the good correlation and concordance between CFR-DSE and CFR-adenosine (which is a method of reference cited by the authors in introduction to measure CFR). Furthermore, a significant correlation was found in that study between CFR during DSE and change of rate-pressure product in patients with anormal DSE.
In addition, the normal and abnormal values of CFR during DSE were clearly described in that study. A CFR <2 with DSE was found in all patients who had a positive DSE in the LAD territory (n=8) and interestingly the same low CFR<2 was obtained with adenosine in these patients. Consequently, it would be interesting to discuss also briefly the results of the only available study in the literature comparing non invasive CFR with DSE and CFR with adenosine in order to emphasize the results of the current study.

7) We do not discuss the relevance of the study by Dr Meimoun P, which is included in our bibliography as an excellent study and the only available that has validated the method. Yet, and in accordance with the author’s words, we think that the relevance of
the study lies on finding an excellent correlation with the most accurate non-invasive method for the estimation of CFR. We did not find a specific analysis of HR in that study. Actually, the study mentions the necessity of achieving adequate predicted HR value to consider DSE sufficient. On the other hand, in the “Discussion” section we make a brief comment of other studies as we have not found enough information about the relation between HR and CFR during DSE. Anyway, we have added a comment about reference 13 in the “Discussion” section, following the reviewer’s suggestion.

8) Concerning the Table 1, the reasons of ordering the study mentioned “diagnosis”. It should be stated briefly about which diagnosis the authors spoke.

8) In Table 1, “diagnosis” refers to asymptomatic patients with unclear history of coronary artery disease who are referred to the stress echocardiography laboratory to confirm or rule out ischemia. We have specified in the paper: diagnosis of coronary artery disease.

9) Concerning the Figure 3, the legend does not correspond to the graph.

9) We appreciate the reviewer’s correction. Indeed, there is a typo in Figure 3; the correct legend is “Correlation between delta HR (Max HR - Baseline HR) and CFR”. We have already corrected the mistake.

10) Concerning the Figure 4, it is unclear for the reader if we deal with a population with low and normal CFR or if for each patient the ratio of flow velocities was measured at each step of DSE? Furthermore, the final values of flow velocities (the real CFR) should be depicted in a different color (is it the white circle?) and the cut offs should be highlighted with dashed lines for better interpretation of the graph. The same comments are made for Figure 3 (after correction of the legend).

10) The values shown in each figure correspond to those measured in each stage of the test. Each value is separated according to CFR <2 or ≥2. The white circles correspond to CFR < 2 regardless of the stage, and we look for the correlation with HR. We have modified the legend and shall add dashed lines for better interpretation of the graph. In addition, and for a better understanding, we have added in the legend that it corresponds to CFR in each stage.

11) In the Summary, the aim of the study is not clearly stated, the exact location of the measure of flow velocity is not depicted (proximal, distal?), and the definition of CFR is not given.

11) We think that the objective is well described; however, we have given further explanation following the reviewer’s suggestion. We have cleared up the exact localization of the measurement of flow velocity and added the definition of CRF.

WE ARE THANKFUL TO THE REVIEWER FOR HIS VALUABLE COMMENTS AND WE HAVE CONSIDERED ALL HIS SUGGESTIONS.