Author's response to reviews

Title: Practical Approach to Stress-Echocardiography in Patients With Idiopathic Dilated Cardiomyopathy

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Reviewers

Reviewer 1

Thank you for your thoughtful analysis of our paper. We tried to answer to all of your comments, as it is described below.

Comment 1. "... The title does not reflect the real subject of the review. Maybe "Stress echocardiography in dilated cardiomyopathy: instructions for use" might be more appropriate. ..."
Answer: We agree that the change of the title may be appropriate and that the title suggested by the reviewer may attract more attention of the potential readers so we changed the title accordingly.

Comment 2. "... An adjunctive paragraph on the routine clinical approach of the authors to this set of patients would be highly informative due to their long-lasting experience in the field. ..."
Answer: We believe that this issue is addressed in the second paragraph of the section What role for stress-echocardiography?. Views expressed in this paragraph pretty much reflect routine clinical approach to stress-echocardiography in DCM patients in our laboratory. We think that, at least at this time, would be inappropriate to suggest what protocol to use or what index to measure since there are no studies to support supremacy of one protocol or index over the other. However, if the reviewer thinks that this paragraph should be changed to explicitly reflect personal perspective we are willing to do so.

Comment 3. "... It would be interesting if authors could stress that in the face of an overall similar prognostic accuracy of dobutamine and dipyridamole, the latter is more feasible, safer and not influenced by beta-blocking agents. ..."
Answer: We agree that this is an important point. Readers can conclude that dipyridamole has better safety profile than dobutamine since we explicitly stated, in the Dipyridamole paragraph of the section Prognostic significance, that dipyridamole is less arrhythmogenic and better tolerated than dobutamine. To further stress better feasibility of dipyridamole stress-echocardiography we changed the following sentence in the Dipyridamole paragraph:

"... Reported overall feasibility of dipyridamole stress-echocardiography in this study was 99.2%, which is significantly higher than previously reported feasibility of dobutamine stress-echocardiography ..."

Additionally, we decided to add a sentence in the Dipyridamole paragraph that indicates that potential advantage of dipyridamole stress-echocardiography is that it is not influenced by beta-blocking agents.

"... Potential advantage of dipyridamole over dobutamine stress-echocardiography is that the former is not affected by the use beta-blocking agents which are frequently used in DCM patients ... ."

Comment 4. "... The figures are not well defined ... "
Answer: We believe the figures and figure legends are readable and understandable. If you still think that something should be clarified please specify.
Comment 5. "... On pg.5 first line 0.84 mcg should read 0.84 mg ...", Answer: We apologize for the mistake and we changed it accordingly.

Comment 6. "... There are some typing mistakes throughout the manuscript ...", Answer: Again we apologize for the omissions. We corrected all typing mistakes that we were aware of.

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Reviewer 2

Authors would like to thank you for your in-depth analysis of our paper. We tried to address all concerns that you expressed.

General comments

Comment 1. "... In general I would state that these complicated patients, in which the diagnosis is difficult are best evaluated with multiple imaging techniques. So not only echo, but also scan and angio. So I would suggest to put these techniques also in the manuscript and provide a kind of flow chart when and which technique can lead the reader to the final diagnosis of DCM. ...", Answer: This review was aimed to put stress-echocardiography in the context of prognostic stratification in patients with idiopathic dilated cardiomyopathy. It is beyond any doubt that stress-echocardiography is a valuable tool for differentiation of etiology of left ventricular systolic dysfunction, but we also believe that by discussing this issue we would blur the initial idea behind the manuscript, that is prognosis and not diagnosis of these patients. This topic deserves separate paper that will make an in-depth analysis of this problem. However, if the reviewer insists that we should discuss the issue of diagnosis we are willing to do so, but have to warn that this would lengthen the manuscript by more than a page.

Comment 2. "... Also I would suggest to add some simple measurements such as wall thickness measured at rest and during stress ...", Answer: This might be very useful suggestion. However, we are not aware of the studies that tested potential prognostic significance of stress induced changes in left ventricular wall thickness in pts with DCM.

Comment 3: "... Next to these subjective measurements such as wall motion evaluation I would discuss the potential of Doppler velocities and strain ...", Answer: Once again excellent remark, but we are not aware on any published prospective data that have evaluated quantitative stress-echocardiography in prognostic stratification of these patients. The only available data comes from a small study that suggested only significant correlation between low-dose dobutamine induced changes in segmental myocardial velocities and global LVEF, without addressing potential prognostic implications (Fulop T. Hegedus I, Edes I. Examination of left ventricular contractile reserve by Doppler myocardial imaging in patients with dilated cardiomyopathy. Congest Heart Fail 2001;7:191-5.). We acknowledged potential prognostic significance of tissue Doppler and strain rate imaging in the section Future directions.

Specific comments

Comment 1. "... page 3/ para 3: the sentence is confusing: normal perfusion of the legs as a cause of fatigue. Perhaps insufficient increment? ...", Answer: This sentence does not imply that fatigue was due to normal perfusion of the legs but rather that patients who stopped exercise because they subjectively felt fatigue had normal blood flow through their lower limbs. Subjective feeling of fatigue was probably not due to incapacity of the left ventricle to pump blood, but due to skeletal muscle deconditioning or lack of patient`s enthusiasm to push themselves to their exercise limits.

Comment 2. "... page 4/ para 2: perhaps dobutamine dose should be replaced by plasma concentration, which correlates better with contractile reserve. Also beta-blockers will shift the dose-response curve to the right. ...."
Answer: We agree that measurement of plasma concentrations of dobutamine is theoretically more sound than simple dosing of intravenous infusion, but this approach would be far more difficult to take in busy clinical practice rendering stress-echocardiography in DCM patients too complex and its availability is questionable. Therefore, we believe that stress-echocardiographic protocols in this setting should be as simple as possible and resemble as much as possible to protocols used for CAD. At this point, it is still not clear whether patients should be tested on or off beta-blockers. However, the majority of investigators prefer to test patients while they are off these agents for 48 hours, so beta-blockers have no or negligible effect on dobutamine dose-response curve.

Comment 3. "... Page 8 / para3: Side effect of dobutamine in patients with poor LV function are arrhythmias and hypotension. Please provide the reader with an overview of the frequency of side effects, and perhaps possible relation with low potassium, diuretics and arrhythmias..." Answer: Exact overview of dobutamine side-effects is not frequently reported in the literature. Pratali et al. have reported on overall incidence of complex ventricular arrhythmias of 8%, including nonsustained VT in less than 2% of patients. In authors experience these data appear realistic in real-life clinical setting, and are detailed in the manuscript. To clarify the issue of hypotension during dobutamine stress-echocardiography we added the following sentence in the paragraph High-dose dobutamine of the Prognostic significance section.

"... Hypotension, defined as decrease in systolic blood pressure by more than 30 mmHg, is very rare in the absence of complex ventricular arrhythmias and, in authors experience, occurs in less than 1% of patients with angiographically documented idiopathic DCM...."

There are absolutely no data on association of low potassium and frequent use of diuretics with increased incidence of complex arrhythmias during stress-echocardiography in DCM. Common sense suggests that there may be an increase in incidence of arrhythmias in potassium depleted patients, but this remains speculative at this point. To direct the readers to take this speculation into account we added the following sentence in the same paragraph.

"... Although there are no data on the association of complex ventricular arrhythmias and serum potassium concentrations, it may be postulated that complex arrhythmias are more frequent in potassium depleted patients. Therefore, it appears prudent to check serum potassium level prior to high-dose dobutamine stress-echocardiography ...."