Author's response to reviews

Title: Quantitative analysis of left atrial function in asymptomatic patients with b-thalassemia major using real-time three-dimensional echocardiography

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To: Cardiovascular Ultrasound

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Quantitative analysis of left atrial function in asymptomatic patients with b-thalassemia major using real-time three-dimensional echocardiography - Revision.

Dear Editor,

Thank you for your kind and prompt response. After taking into thoughtful consideration the reviewers’ remarks we proceeded to our manuscript revision. Herein we provide a point-by-point response to the raised concerns by the two reviewers.

Reviewer: Matteo Cameli

Reviewer's report:

The topic is interesting; the study appears quite well conducted for design and contents.

References and pictures are lacking. Some other points should be addressed:
- Being novel measurements of LA function is necessary to provide a feasibility analysis and Bland Altman agreement plot regarding intra- and inter-observer reproducibility of such measurements.

The study population consisted of young persons with normal BMI and thus adequate acoustic windows, while cardiac chamber dimensions were within the normal range. Therefore it was feasible to assess LA volume with RT3D in all cases. Moreover intra and inter observer agreement was assessed (k measure of agreement), as stated in the methods, statistic analysis and results sections.

- Please provide an additive good-quality figure depicting the way to measure these new parameters.

Additive figures have been provided and the previous one has been replaced.

- Considering the still relatively low temporal and spatial resolution of 3D imaging, it would be really useful for the manuscript to present data also regarding 2D analysis through quantitative software (strain rate, speckle tracking echocardiography) and to accordingly perform a comparison with 3D STE ones: Cardiovasc Ultrasound. 2009 Feb 8; 7:6. Feasibility and reference values of left atrial longitudinal strain imaging by two-dimensional speckle tracking. Cameli M, Caputo M, Mondillo S, Ballo P, Palmerini E, Lisi M, Marino E, Galderisi M.

In the discussion section we have provided data regarding the implementation of strain imaging (2D strain and 3D speckle tracking) in the clinical assessment of LA function (new references have been added: 20,21,24 including the study by Cameli et al). As stated in the manuscript the purpose of this study was not to compare speckle tracking with 3D volumetric assessment. Of course it is acknowledged in the discussion section that the absence of data from strain imaging that could
provide useful insights into the pathophysiologic basis of the disease is a limitation of our study. Moreover QLAB software (current version is 8.1) is not designed for atrial 2D-3D speckle tracking analysis.

- Provide Tables with a better quality. Correct the term “diastoly” in Table 2. Remove Greek words from the Tables.

We have removed the term “diastoly” from table 2 and all Greek words from the tables.

- The manuscript needs an intensive revision of English.

The manuscript has been thoroughly reviewed in order to eliminate grammar and syntax errors.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: No competing interests declared.

Reviewer: Rosa Sicari

Reviewer’s report:

In the present manuscript, Aggeli et al. try to address the role of left atrium measured by 3-D echocardiography in beta-thalassemic patients. Authors conclude that left atrial emptying is reduced in patients vs. Controls. The study is interesting but there are a few issues that authors should address:
**Please clarify how the patient population was selected.**

Patients were retrospectively enlisted in the study based on clinical characteristics and recent echo and CMR findings and as stated in the manuscript (see “study population” in the methods section - exclusion criteria).

**What is the time from diagnosis to echo evaluation?**

According to patient history the age of diagnosis was about $7 \pm 3$ months. Since then the patients are closely followed-up by the Thalassaemia Unit, of 1st Dept. of Paediatrics (University of Athens), at “Aghia Sophia” Children's Hospital.

**Please clarify why they underwent 3D echo.**

Patients underwent 3D echo, since there is evidence that 3D provides a better and more accurate estimation of chamber volumes, comparable with those of CMR and CT. Moreover, it is well established that LA volumes evaluation offers significant clinical information on patient outcomes. Thus 3D echo seems a reasonable approach for the assessment of our study population. In order to make this more comprehensive for the readers we have further clarified this statement in the manuscript in the ‘discussion” section.

**Please specify how the control group selected.**

Controls have been matched for age, sex and BMI. Moreover persons who had hypertension, diabetes mellitus or known structural or valvular cardiac lesions were excluded. In other words control group consisted only of healthy individuals with normal systolic and diastolic heart function in order to eliminate confounding factors. To clarify this for the readers we have stated this information in the “study population” section.
In the abstract section of the manuscript numbers on EF should be given.

EF numbers have been added in the abstract session (see results).

Please report in graph format some of the data reported in tables (note that table 5 is in Greek)

Table 5 data has been reported as a Graph and all Greek words have been removed.

The major problem with beta-thalassemic patients is LV dysfunction in late stages of disease.

Please expand in the discussion section of the manuscript the pathophysiologic mechanism at the basis of left atrial dysfunction. Moreover, state clearly the clinical implications of the present results.

We have expanded the pathophysiological aspects of LA dysfunction in the Discussion section. In the conclusion section we further clarify the clinical impact of our study.

Due to the nature of the journal it would be important to have sample cases uploaded.

Video and sample photos have been uploaded.

Level of interest: An article whose findings are important to those with closely related research interests.

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests: I declare that I have no competing interests.
We do hope that we have provided adequate data in the light of the raised concerns, in order to raise the clinical impact of our study. We would be grateful if you consider the revised manuscript for publication in *Cardiovascular Ultrasound*.

Kind Regards,

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