Peer Review File

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Reviewer A:

The authors seek to explore the usefulness of CMR-FT as a measure of myocardial dysfunction in patients with FD with or without LVH and / or fibrosis. In this paper, 20 patients diagnosed with Fabry disease have been analyzed and compared with 20 healthy controls. In all of them, different indices derived from magnetic resonance imaging and associated with left ventricular mechanics and the presence or not of myocardial fibrosis have been analyzed and compared.

The study is very interesting because it provides important information at the cardiac level on myocardial structure and myocardial contractility parameters. There are few data on myocardial deformation indices obtained from magnetic resonance imaging in this type of patients.

The study is conducted in a single center with a small sample of cases, which is a weakness.

The inclusion and exclusion criteria are clear. The results are presented clearly and concisely.

The work is well written, it is easy to understand and follow.

However, it has several limitations.

- The main limitation is the small number of patients included. This limitation is known by the authors and is discussed in the limitations section. As it is a rare disease, most studies of this type include very small series.
- Although there are no differences between the group of patients and the control group, the controls should have matched 1: 1 in terms of age and sex. Group 3 of patients presents very important baseline differences with respect to the control group (mean age: 64 vs 40 years old), which means that the results may be biased. Furthermore, this subgroup only includes 3 patients. I consider that each sub-group of patients (1,2,3) should be compared with subgroups of controls of similar age and sex.

Reply: Done as suggested. We separated the normal controls into 3 sex and age matched subgroups, and compared all the indices with 3 Fabry disease subgroups. Please see the new Table 2.

Changes in the text: Please see page 30-31, Table 2.

- There is a high proportion of hypertensive patients (35%). Hypertension can be a cause of myocardial fibrosis and alterations in myocardial deformation parameters. Therefore, it would be necessary to indicate how hypertensive patients have been distributed among the different subgroups. Fabry patients with hypertension, were they taking antihypertensive treatment? What treatment were they taking? Could these treatments influence the results obtained?

In addition, it would be necessary to consider including a similar proportion of subjects with hypertension within the controls. Both forms can present differently in terms of myocardial deformation parameters.

Reply: We agreed with review's comments that hypertension contribute to the abnormality of LV morphology, contractile and tissue characterization. We added hypertension distribution in the new Table 2 (0 patient in group 1, 5 patients in group 2, 2 patients in group 3). All patients with hypertension taking antihypertensive treatment (calcium channel blockers, Beta blockers). All these patients have

their blood pressure under well control (<140/90 mmHg). We reviewed our CMR database, hypertensive patients who underwent CMR exam commonly coexisted with hyperlipidemia, diabetes or atrial fibrillation. Patients with only hypertension and no other cardiovascular risk factors are too few to include as controls at this time. We acknowledged this confounding factor and related bias in the limitation section.

Changes in the text: please see page 30-31, Table 2, and page 17-18, limitation section.

- I recommend including a table with the mutations that the patients present, the enzymatic activity and the lyso-Gb3 levels. It would be interesting to know if the patients had a classic phenotype or late-onset forms of the disease.

Reply: Some patients' gene tests were performed in other hospitals and the reports are not available in our hospital, we only have 7 patients' gene reports, all of them are pathogenic (class I) mutations. In addition, lyso-Gb3 levels did not test in all patients. Therefore, we added a new Table 3 and listed the phenotypes and enzymatic activity in male and female patients respectively.

Changes in the text: please see page 32, new table 3.

- To facilitate reading comprehension, the abbreviations in Tables 1 and 2 should be listed in alphabetical order.

Reply: Done as suggested.

Changes in the text: please see page 29, line 7-8, page 31, line 1-6.

Reviewer B:

This study investigated the ability of CMR-FT as a measure of myocardial dysfunction in patients with Fabry disease (FD) who were divided into three groups. Authors found that GLS and GCS were reduced significantly compared with normal controls and that GLS and GCS showed a significant difference between FD subgroups. Finally, they concluded that the CMR-FT may be useful for monitoring the disease severity for patients with FD. It is an interesting study, the main concerns as follows.

Comments:

1. Methods/CMR image acquisition, please briefly add the imaging parameters for the cine sequences.

Reply: Done as suggested. We added the imaging parameters for the cine sequences.

Changes in the text: please see page 6, line 17-21.

2. Methods/CMR image acquisition, please give some rationale for the MOLLI parameters used—were they optimized for the anticipated native T1 and post-contrast T1 in these patients, or simply the default protocol?

Reply: Done as suggested. We added the descriptions of T1 mapping sequence. All patients had sinus rhythm and heart rate < 90 bpm during CMR exam, we used the default protocol.

Changes in the text: please see page 6 line 22 and page 7 line 1.

3. Methods/CMR analysis, please briefly describe how quality control on the image-derived strain and strain rates was performed.

Reply: Done as suggested. We added the descriptions of strain analysis.
Changes in the text: please see page 8 line 14-17.

4. Methods/CMR analysis: To state that CMR-FT strain is appropriate for tracking disease severity in FD, one would have to demonstrate the reproducibility and inter/intra-observer variability in this patient group, especially given the wall thinning in later stages. Please modify.

Reply: Done as suggested. The intra- and inter-observer variability for the LV strain indices were assessed by the intraclass correlation coefficient (ICC) in all patients. Intra-observer reproducibility was established by the same observer who re-analyzed all patients' images after one month. Inter-observer reproducibility was assessed by a second-independent observer blinded to the first observer's results.
Changes in the text: please see page 9 line 3-7, page 12 line 19-22, page 13 line 1.

5. Conclusions: The findings may be related to the severity of FD cardiac involvement but not to progression, as that could not be determined given the study design. Please clarify.

Reply: Done as suggested. We revised the conclusion.
Changes in the text: please see page 18 line 10-11.

6. Typo need to revise as "cardic" should perhaps be "cardiac"

Reply: Done as suggested.
Changes in the text: please see page 2 line 4.

7. Please edit "gold" to "reference", as gold standard mainly refers to the only completely reliable standard, which would be histology, not imaging. Highly accurate imaging can act as a proxy of histology being a "reference" standard.

Reply: Done as suggested.
Changes in the text: please see page 4 line 10.