Format for ANSWERING REVIEWERS

March 21, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: WJC-8229-revised Ms).

Title: Distribution of Late Gadolinium Enhancement in Various Types of Cardiomyopathies -Significance in Differential Diagnosis, Clinical Features and Prognosis-

Author: Hiroshi Satoh, Makoto Sano, Kenichiro Suwa, Takeji Saitoh, Mamoru Nobuhara, Masao Saotome, Tsuyoshi Urushida, Hideki Katoh and Hideharu Hayashi.

Name of Journal: *World Journal of Cardiology*

ESPS Manuscript NO: 8229

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated
Please see the revised manuscript.
2 Revision has been made according to the suggestions of the reviewer
Please see the attached "Response to reviewers".
3 References and typesetting were corrected
We add three references and correct English as suggestion of reviewers.

Thank you again for publishing our manuscript in the *World Journal of Cardiology*.

Sincerely yours,

Hiroshi Satoh, MD
Hamamatsu University School of Medicine
1-20-1, Handayama, Hgashi-ku, Hamamatsu,
431-3192, japan.
TEL +81-53-435-2267, FAX +81-53-434-2910, e mail satoh36@hama-med.ac.jp

Response to reviewer 1 (00039411):

We thank the reviewer for thorough reading, positive overall comments and careful constructive criticism. We have tried to be responsive to the reviewer's comments, and revised the manuscript following the suggestions. We appreciate the review and hope that the reviewer will find our revised manuscript acceptable.

MF1,3,4,8,9.

Thank you for your correction of our English. The words you pointed are corrected properly.

MF1: Page 3, line 11;

Previous version: responsibility to treatments

Revised version: response to treatments

MF3: page10, line 12;

Previous version: expression

Revised version: expressions

MF4: page 10, line 14;

Previous version: standard for

Revised version: standard tool for

MF 8: page 45, line 9;

Previous version: atira

Revised version: atria

MF9: page 47, line 9;

Previous version: chmbers

Revised version: chambers

MF2: I think this is a little confusing. Are you talking about NICM? If that, why in this paragraph do you mention myocardial ischemia and infarction? Or you're referring to DCM in general. I suggest to rewrite this paragraph more clearly…

We thank for the reviewer's comment. We would like to mention that the etiology of DCM might generally include undiagnosed ischemia or infarction (please see ref. 16 and 22), but it is somewhat confusing as the reviewer suggested. Since we have described this issue in the former section (Section 3), we delete ischemia and infarction from the comment.

Page 7, line 18;

Previous version:

DCM is not a single tree of disease spectrum but may include several undetermined etiologies, such as chronic myocarditis, tachycardia-induced cardiomyopathy, undiagnosed sarcoidosis, myocardial ischemia, myocardial infarction with remodeling, and end-stage HCM[16,24].

Revised version:

DCM is not a single tree of disease spectrum but may include several undetermined etiologies, such as chronic myocarditis, tachycardia-induced cardiomyopathy, undiagnosed sarcoidosis, and end-stage HCM[16,24].

MF5: Inferoseptal septum and sometimes anterolateral wall are other portions of the LV that are

difficult to see and quantify with echo---

We agree to the reviewer`s comment. I change the comment as below.

Page 10, line 14;

Previous version:

Although trans-thoracic echocardiography has been the standard for the diagnosis of HCM, CMR is capable of identifying regions of LV hypertrophy not readily recognized by echocardiography[6-8]. Especially, echocardiography has limitations for visualizing the LV apex, and several studies have shown the usefulness of CMR for the detection of apical hypertrophy and apical aneurysm[11,35,36].

Revised version:

Although trans-thoracic echocardiography has been the standard tool for the diagnosis of HCM, it has limitations for precise visualization of whole ventricles and quantification of hypertrophy. CMR is capable of identifying regions of LV hypertrophy not readily recognized by echocardiography[6-8], especially for apical hypertrophy and apical aneurysm[11,35,36].

MF6: It's very important to mention the differential diagnosis in LV "hypertrophic pattern" that may mimic HCM, but can be differentiated with CMR, like Fabry's disease, amyloidosis. Although it's is mentioned in the next paragraphs, I suggest to enhance the relevance of the technique in the differential diagnosis workup…

We thank for the reviewer's suggestion, and change the comment to enhance the relevance of cine- and LGE-CMR techniques.

Page 13, line 9;

Previous version:

Although a certain part of DCM patients also shows such diffuse types of LGE distribution, detailed analyses of both cine-CMR and LGE-CMR can help differentiation of end-stage HCM from DCM.

Revised version:

Detailed analyses of both cine-CMR and LGE-CMR can help differentiation of end-stage HCM from DCM and other secondary cardiomyopathies that exhibit LV dysfunction with hypertrophy (e.g. cardiac amyloidosis and Anderson-Fabry disease).

MF7: This cutoff point depends on sensibility and specificity. Some authors suggests 2.3 or 2.5 as a cutoff point- There are other criteria, like non-compacted left ventricular mass correlated with total LV mass, and non-compacted left ventricular mass indexed by body surface area…

The reviewer is correct. So we change the comment as below.

Table 1;

Previous version:

Non-compacted / compacted > 2.2

Revised version:

High non-compacted / compacted myocardial ratio

Response to reviewer 2 (00258717):

Satoh and colleagues present a very thorough and clinically relevant manuscript reviewing the value of CMR in differentiating between cardiomyopathic processes. The authors focus particular attention on patterns of LGE, in addition to alternative abnormalities potentially detected by CMR. The topic is important and timely, but several issues warrant attention.

We thank the reviewer for thorough reading, positive overall comments and careful constructive criticism. We have tried to be responsive to the reviewer's comments, and revised the manuscript following the suggestions. We appreciate the review and hope that the reviewer will find our revised manuscript acceptable.

1. *The authors highlight the possibility of ICM despite having patent coronary arteries. While this is possible, it is rare. The more common conundrum is the presence of CAD in the setting of an underlying NICM. Perhaps both possibilities should be acknowledged.*

   We thank for the reviewer's suggestion. Actually, it is more common problem that patients with DCM have become to have CAD in their natural courses. We add the comment below in the revised manuscript.

   Page 6, line 13 (addition);

   Conversely, it is also a common situation that patients with DCM have coronary arterial disease during their natural courses.

2. *The authors state that "the early diagnosis of ICM can accelerate treatment with β-adrenoceptor blockers and renin-angiotensin-aldosterone inhibitors." Given that these therapeutic interventions are recommended for both ICM and NICM, the distinction seems unwarranted.*

   The reviewer's suggestion is correct. We change the comments as below.

   Page 7, line 3;

   Previous version:

   Patients with ICM have worse outcome but may benefit from revascularization and/or aneurysmectomy and from secondary prevention with aspirin and statins. Thus, the early diagnosis of ICM can accelerate treatment with β-adrenoceptor blockers and renin-angiotensin-aldosterone inhibitors.

   Revised version:

   The differential diagnosis of ICM and NICM is also crucial for management of patients with cardiac dysfunction. Treatment with β-adrenoceptor blockers and renin-angiotensin-aldosterone inhibitors are recommended for both ICM and NICM. Patients with ICM have worse outcome but may benefit from revascularization and/or aneurysmectomy and from secondary prevention with aspirin and statins.

3. *The authors report finding several patterns of LGE in patients with DCM. The figure legend clarifies that these images are taken from a previous publication, but the language in the text suggests that the authors identified these patterns while caring for patients or in a study. Please clarify the text.*

Figure 2 is derived from our article (Machii, Satoh et al. Magn Reson Imag, 2014). So we cited in the text as "We found various patterns of LGE as described in Figure 2. ---". However, the comment is confusing as the reviewer suggested, and we change the comment in the revised manuscript as shown below.

Page 8, line 8;

Previous version:

We found various patterns of LGE as described in Figure 2.

Revised version:

Our recent study showed various patterns of LGE as described in Figure 2[13].

4. *On page 12, the following statement is not clear: "Additionally, stress perfusion CMR could be used in HCM to further stratify the risk for SCD, since a study on single-photon emission computed tomography (SPECT) could identify the significance of inducible ischemia for cardiac death."*

We clarify the comment below in the revised manuscript.

Page 12, line 14;

Previous version:

Additionally, stress perfusion CMR could be used in HCM to further stratify the risk for SCD, since a study on single-photon emission computed tomography (SPECT) could identify the significance of inducible ischemia for cardiac death[52].

Revised version:

Additionally, stress perfusion CMR could be used to further stratify the risk for SCD, since inducible myocardial ischemia is another risk in HCM, which was proven by a study on single-photon emission computed tomography (SPECT) [52].

5. *It would be helpful to indicate the numerical specificities of nodular, circumferential and subepicardial and subendocardial LGE distribution for sarcoid and not simply to state that these findings are highly specific.*

According to the reviewer's suggestion, we add the specificity of characteristic types of LGE distribution in the revised manuscript.

Page 15, line 3;

Previous version:

Additionally, we and other investigators found that nodular, circumferential and subepicardial and subendocardial types of LGE distribution were highly specific for patients with sarcoidosis (Figure 4)[57,58].

Revised version:

Additionally, we and other investigators found that nodular, circumferential, and subepicardial and subendocardial types of LGE distribution exhibited high specificity for differential diagnosis from DCM (97-100%, Figure 4)[57,58].

6. Several grammatical errors are made throughout the manuscript.

According to the reviewers' suggestion, we correct spelling and grammatical errors in the revised manuscript.

Response to reviewer 3 (00227531):

This is a excellent review of the current role of MR in cardyomyopathies, performed by a team with wide experience on the topic. I suggest to publish it as it is

We thank the reviewer for thorough reading and positive overall comments. We appreciate the review and hope that the reviewer will find our revised manuscript acceptable.

Response to reviewer 4 (00575396):

We thank the reviewer for thorough reading, positive overall comments and careful constructive criticism. We have tried to be responsive to the reviewer's comments, and revised the manuscript following the suggestions. We appreciate the review and hope that the reviewer will find our revised manuscript acceptable.

-It is a paper about LGE in many cardiomyopathies. - I have some suggestions: - First, I missed a detailed description about noncompation cardiomyopathy and endomyocardial fibrosis (EMF). I`d suggest it.

We thank for the reviewer's suggestion. This review is focused mainly on the distribution of late gadolinium enhancement in cardiomyopathies. We just mentioned high non-compacted / compacted myocardial ratio in patients with LV non-compaction because there is no characteristic features in terms of LGE distribution in noncompaction cardiomyopathy (please see the final paragraph of "8. Other cardiomyopathies and table 1".

On the other hand, EMF was initially recognized in some parts of Africa, but has become to be recognized in other areas of the tropical zone. Furthermore, LGE-CMR can contribute largely to the early diagnosis of EMF (Salem et al. 2011). Therefore, we add a paragraph of EMF in "8. Other cardiomyopathies", 3 references, and columns in Table 1 in the revised manuscript.

Page 22, line 12 (addition);

v) **Endomyocardial fibrosis (EMF)**

EMF is the most frequent restrictive cardiomyopathy especially affecting poor children and young adults in the tropical zone. The characteristic features are fibrotic tissue deposition in the endocardium of the inflow tract and apex of one or both ventricles. The pathogenesis of EMF is poorly understood, but early hypereosinophilia may play a role[99].

Cine-CMR can clearly demonstrate distorted ventricles with normal or reduced volume and enlarged atria. LGE-CMR can also show areas of LGE in the endocardium where the histopathological examination revealed extensive fibrous thickening, proliferation of small vessels and scarce inflammatory infiltrate. The LGE pattern may have a "V sign" at the ventricular apex, characterized by a 3-layer appearance of myocardium, thickened fibrotic endocardium, and overlying thrombus[100]. The relationships between increased LGE burden and worse NYHA functional classes, and increased probability of surgery and mortality rate are reported [100].

Since the reports of EMF have been increasing in areas where the disease had not been previously recognized, the role of CMR may increase for the early diagnosis of EMF[101].

Page 44, line 4 (addition):

99 Mocumbi AO, Yacoub S, Yacoub MH. Neglected tropical cardiomyopathies, II: endomyocardial fibrosis: myocardial disease. *Heart* 2008; **94:** 384–390 [PMID: 18276824]

100 Salemi VM, Rochitte CE, Shiozaki AA, Andrade JM, Parga JR, de Ávila LF, Benvenuti LA, Cestari IN, Picard MH, Kim RJ, Mady C. Late gadolinium enhancement magnetic resonance imaging in the diagnosis and prognosis of endomyocardial fibrosis patients. *Circ Cardiovasc Imaging* 2011; **4:** 304-311 [PMID: 21415124]

101 Mocumbi AO, Falase AO. Recent advances in the epidemiology, diagnosis and treatment of endomyocardial fibrosis in Africa. *Heart* 2013; **99:** 481-487 [PMID: 23680893]

Table 1 (addition):

Endomyocardial fibrosis	Inflow tract to apex	Subendocardial	Diffuse	Distorted ventricles with normal or reduced volume and enlarged atria

- English language should be improved: Please chance trans-thoracic to transthoracic; follow up to follow-up; trans-esophageal to transesophageal.

We change the spelling according to the reviewer's suggestion.

- Not all cardiomyopathies present midwall or subepicardial enhancement, EMF present subendocardial, so I`d suggest include: most cardiomyopathy and not all.

We thank for the reviewer's suggestion. We change the comment below in the revised manuscript.

Page 2, line 9 and page 3, line 5;

Previous version:

LGE in NICM generally does not correspond to any particular coronary artery distribution and is located in the mid-wall to subepicardial layer.

Revised version:

LGE in NICM generally does not correspond to any particular coronary artery distribution and is mostly located in the mid-wall to subepicardial layer.

- Abstract and core tip: at last line: please change responsibility to decision - Core tip: please change ; to :

I thank for the reviewer's comment. Because another reviewer also suggested a change in the term, we change "responsibility" to "response" in the revised manuscript.