

Format for ANSWERING REVIEWERS



May 18th, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 10465-review.doc).

Title: Arrhythmogenic Right Ventricular Cardiomyopathy, is Cardiac Magnetic Resonance imaging (cMR) an effective test?

Author: Santhi Chellamuthu, Alyson M Smith, Steven M Thomas, Catherine Hill, Peter W G Brown, Abdallah Al-Mohammad

Name of Journal: *World Journal of Cardiology*

ESPS Manuscript NO: 10465

The manuscript has been improved according to the suggestions of reviewers:

1. Format has been updated
2. Revision has been made according to the suggestions of the reviewers

(1) Reviewer 1: It is a paper about CMR in ARVC I have some suggestions: Please change the title: Is cardiac magnetic resonance imaging an effective test for ARVC diagnosis? Introduction: It is not clear at the end of Introduction why this study was done or the objective of this study? Discussion: Please, compare the results of this study with other ARVC studies.

- The title has been changed from "Arrhythmogenic Right Ventricular Cardiomyopathy, is Cardiac Magnetic Resonance Imaging (cMR) an effective test??" to "Is cardiac MRI an effective test for Arrhythmogenic right ventricular cardiomyopathy diagnosis? The title has been shortened (limited to 12 words) according to BPG's Revision Policies.
- The objectives of this study and why this study was done have been added at the end of the introduction
- Discussion: The study has previously been compared to studies looking at the results of CMR in the diagnosis of ARVC – see references 26-28. This has been added to – looking at the negative predictive of CMR in this context.

(2) Reviewer 2: The manuscript is well written and highly organized. The readability is excellent. In this retrospective analysis of 114 patients referred for cMR because of arrhythmias or family history of sudden death, the results of cMR were classified depending on both functional and tissue characterisation and the clinical information were used. The assessment and judgment of the images of cMR was performed jointly by radiologist and cardiologist. This study shows that cMR has an important role in the diagnosis of ARVC as it allows 3-D visualization of the ventricles and cMR is sometimes useful in finding other disorders for patient's symptoms. Please indicate this abbreviation in the text on the last line before Conclusion: "MDT".

- The word MDT was replaced by multidisciplinary team meeting.

(3) Reviewer 3: The manuscript from Chellamuthu et al. examined 114 referrals for cMR with either suspected ARVC or with a first degree relative with ARVC, and compared retrospectively the results of cMR against the clinical diagnosis. They showed 4 patients (4%) had major cMR findings for ARVC, 13 patients (11%) had minor cMR findings, 2 patients had non-specific cMR findings and 95 patients had a negative cMR. The 75% and 15% of referrals who had major and minor cMR findings had a positive clinical diagnosis, respectively. None of the 81 available patients with negative cMR had ARVC. They concluded that cardiac MR is a useful tool for excluding ARVC, because of the high negative predictive value. Major comments; They showed only the cMR findings with functional and structural alterations, presumably according to Task Force Criteria for ARVC. I have interests to the tissue characteristics of RV and LV wall. I think the manuscript becomes better when the existence and extent of late gadolinium enhancement in ventricular walls are shown. The predictive values of cMR for ARVC may differ in different patients groups. The referrals of this study consisted of arrhythmias (30%), family history (20%), and others (50%). The authors should discuss more about the predictive values in different patient populations. Minor comments; Abstract: please clarify the positive and negative predictive values of cMR for clinical diagnosis of ARVC. Introduction: Please describe more about previous discussion for the critical role of cMR in the diagnosis of ARVC. Discussion: please describe a short summary in the beginning of Discussion. Table 3: The position of data in first section should be corrected.

- The existence and extent of late gadolinium enhancement has been added to the results section. Interestingly, only one patient had extensive RV free wall enhancement.
- Positive predictive value for cMR in different groups for major and minor criteria has been added as a separate table format.
- Sensitivity, specificity, positive and negative predictive values of cMR for clinical diagnosis have been added to the abstract.
- Introduction: Previous studies about the role of cMR has been included
- Discussion: this has been added to the beginning of the discussion. This study has shown that in this cohort of patients 15% fulfill imaging criteria for ARVC, with a subsequent 75% of cases fulfilling Task Force criteria for the diagnosis of ARVC if they had a major CMR criterion. Conversely a negative CMR scan for ARVC on imaging criteria translated into no subsequent diagnosis of ARVC.
- The position of the data in the first section in Table 3 has been corrected.

(4) Reviewer 4: This is a retrospective study of patients with suspected ARVC who were screened with cMR. The study group totalled 114 patients over a 4 year period. the indications for performing the cMR were were very valid and suspicious of ARVC. The review of this data should have undergone formal ethical approval. Patient consent may well have been waived but IRB approval was necessary and needs to be obtained or a formal waiver issued which will not be the case. This is an important study in that it has a powerful negative predictive value and this makes the cMR very clinically valuable. However the human research ethics committee or IRB must review this protocol and approve it.

- Approval was obtained from institutional clinical audit and effectiveness department for service evaluation.

(5) Reviewer 5: Accurate diagnosis of ARVC is critical for the patients' outcome. This manuscript describes usefulness of CMR to exclude ARVC in patients who are suspected for this critical disease. The manuscript is concise and well presents the patient population. Although the data in the manuscript appear to be able to exclude ARVC by established CMR criteria for the disease, the results were not supported by appropriate statistical analyses highlighting the relations between CMR, clinical symptoms including patients and their family histories, prognosis (even short-term outcome after the ARVC diagnosis), and other clinical examinations, such as echocardiographic and electrocardiographic findings. The authors' statement in conclusion sounds this reviewer too strong without appropriate statistical analyses. Thus, authors' statement in conclusion is not validated. This reviewer strongly recommends that authors should analyze the obtained data by appropriate statistical analyses, such as hazard ratios, multiple comparisons, and sensitivity and specificity of CMR diagnosis of ARVC. Thus, the lack of statistical analyses significantly reduces this reviewer's interest regarding the conclusion of negative diagnosis of ARVC.

- Statistical analysis of the results has been added to the manuscript, however hazard ratios and multiple comparisons have not been done due to small patient numbers and lack of a control group – see limitations section in manuscript.

3. References and typesetting were corrected

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

Sincerely yours,