Author's response to reviews

Title: Quantifying late gadolinium enhancement on CMR provides additional prognostic information in early risk-stratification of nonischemic cardiomyopathy: a cohort study

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Author's response to reviews: see over
Dear Editors,

We thank you for your valuable comments concerning our manuscript and allowing us to resubmit the revised version. We have made changes to our manuscript according to reviewers’ comments, and we believe that the manuscript has improved. In the following are also our point-by-point answers to reviewers’ comments.

In addition to these corrections, we have made one correction in the abstract (page 2, line 14) and the results section (page 9, line 8): the prevalence of ventricular arrhythmias was incorrectly summarized as 42%, but the correct value is 40%. This correction does not affect any other results or analyses in this study.

The running reference numbers in the Cover Letter differs from the corresponding numbers in the manuscript.

Thank you for your time and looking forward hearing from you.

Helsinki 6th July 2014,

Yours Sincerely

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Reviewer 1: Benjamin Cheong

1). Overall, the paper is well written.

Thank you.

2). ABSTRACT, CONCLUSIONS line 5/6, Pg 2. “Even though the final diagnosis is indefinite in NICM”. Is there a typo or what do the authors meant by “indefinite”?

“Indefinite” means here the same as “uncertain”, i.e. the specific diagnosis or etiology of nonischemic cardiomyopathy is not yet known.

Correction: “Indefinite” changed to “uncertain” in the whole manuscript.

3). In page 5, METHODS/STUDY DESIGN, coronary artery disease (CAD) was defined as........ At page 6, it is evident some do not have angiography nor SPECT. How many patients were there?

Text corrected as (page 6, lines 8-10):

“Patients examined with neither angiography nor SPECT (n=37, 43%) were relatively young (in median 45 years), had only few CAD risk factors (in median 1 out of 5, interquartile range 0 - 1) and evident nonischemic etiology for symptoms.”

4). Page 6 CMR PROTOCOL, line 18 and 22 – “interslice gap 100%”. Do the author meant gap of 6 mm in the cine and 8 mm in the DE-MRI?

Yes. Corrected in the manuscript as ”…100% (6 mm)…” and ”…100% (8 mm)…”.

5). Pg 7 DE-MRI analysis. Looking through the RESULT section, the authors did not described regarding the “morphology” of the DE – are they mid-myocardial (for dilated cardiomyopathy)? Mid-myocardial or transmural for hypertrophic cardiomyopathy (HCM)? Patchy enhancement in the trabeculation in patient with non-compaction?

In our clinical practice, the distribution of LGE was visually assessed in consensus by an experienced cardiac radiologist and cardiologist. Disease specific patterns on LGE were sought using standard criteria [1]. However, our study purpose was to evaluate the prognostic value of the quantification of LGE and SWMA extent in suspected or newly diagnosed NICM, irrespectively of the final diagnosis. Nevertheless, we do acknowledge that “Also, importantly, after the etiology of NICM is diagnosed, LGE volume should be interpreted in the context of that disease.” (Discussion, page 13, lines 16-17)
Whilst visual estimation is used almost by everybody in clinical practice and with good accuracy when compared to quantitative analysis, the scoring system used in this study (very similar to Kim and Judd NEJM 2000 paper) would be more applicable to patient with CAD. In addition, patients with amyloidosis would be very difficult to score by visual estimation. Whilst one can still use the scoring system, e.g. patient with thin mid-myocardial DE would score 1 for each segment, would formal quantitative analysis provide more robust result?

This study was not mainly a methodology study and formal quantitative analysis (planimetry) or new semi-automatic signal-threshold based methods to estimate LGE extent may provide more accurate results in some cases. However the visual scoring method, which we used, “…has been shown to be rapid and accurate method to estimate LGE both in ischemic and nonischemic cardiomyopathies [2-4].” (Introduction, page 4, lines 14-16)

6). Pg 9 RESULTS LINE 1. Do 7 of the left ventricular hypertrophy patients have hypertrophic cardiomyopathy (HCM) and should HCM be counted as NICM?
LINE 2:What would inflammatory cardiomyopathy consists of e.g. myocarditis?

Those 7 patients with left ventricular hypertrophy (without hypertension) did not fulfill the diagnostic criteria of HCM and were not counted as NICM. Inflammatory cardiomyopathy consists of myocarditis nonspecific, eosinophilic myocarditis, cardiac sarcoidosis, giant cell myocarditis and pericarditis.

7). Pg 9 RESULTS LINE 11-14. This sentence is not quite clear. Are comparisons made between DE+ versus DE- and SWMA + vs SWMA -? This should be stated clearly. Same as in LINE 14 to 16.

Corrected as follows: (starting from page 9, line 21)

“At baseline, the presence of LGE (vs. absence of LGE) and SWMA (vs. absence of SWMA) were significantly associated with NYHA-class, CHF and LVEF. Both LGE positive (vs. LGE negative) and SWMA positive (vs. SWMA negative) patients had significantly higher NYHA-class (II vs. I, p = 0.001 for both), more frequent CHF (56% vs. 16%, p = 0.002; 64% vs. 7%, p < 0.001) and decreased median LVEF on CMR (45% vs. 60%, p < 0.001; 42% vs. 65%, p < 0.001). At baseline, there were no significant differences associated with the presence of LGE (vs. absence of LGE), or SWMA (vs. absence of SWMA), in myocardial injury biomarkers, arrhythmias or conducting abnormalities.”

8). A lot of papers suggested that DE-MRI is associated with VT / arrhythmias. In TABLE 2, it appears (from the p-values) that those with DE has similar incidence of VT when compared to those without DE. Any thoughts? Maybe patient numbers are small to detect a difference.

Indeed, at baseline the presence of LGE, or SWMA, were not significantly associated with VF or sustained VT, although during follow-up LGE and SWMA were significant prognostic risk factors. We think that the reason is in small patient numbers. Interestingly, however, none of the 3 patients with VF (2) or sustained VT (1) at baseline and without LGE and SWMA had further events during follow-up. These previously healthy patients with severe arrhythmias were a woman with VF and
eventual diagnosis of long-QT syndrome, a woman with finally unexplained VF and a man with right ventricular outflow tract VT.

9). Pg 9. Do SWMA correlates with the presence and locations of DE?

Yes. Added to text (page 9, lines 16-19):

“In all 1462 segments (17 segments/patient x 86 patients) the extent of LGE and SWMA were significantly associated (p<0.001). Of all segments, 403 (28%) had LGE and 472 (32%) SWMA. Abnormal motion was found in 20% of segments without enhancement and in 75% of segments enhancing more than 50%.”

10). Please kindly spell out abbreviations like HCM (Page 11 line 20).

HCM, as other similar abbreviations, spelled out when first mentioned in the text.

11). The DISCUSSION is quite well written. Perhaps, the authors should also say a few words on T1 mapping and may be useful in NICM. T1 mapping is still not widely done, as the sequence may not be commercially available; there appears to be variability between which sequence to use e.g. MOLLI, short MOLLI…….; a haematocrit has to be taken as well for ECV estimation; and sometimes the indication of the CMR is vague – e.g. to access heart failure. A few words would be nice to complete the discussion.

Added to the text (starting from page 14, line 20):

“Also, it must be reminded that LGE visualizes only myocardial enhancement in relation to “normal” myocardium and has limited ability to detect diffuse myocardial changes. Recently introduced extracellular volume quantification method based on gadolinium-enhanced CMR and myocardial T1-mapping seems to be useful in detecting diffuse myocardial fibrosis or homogeneously distributed infiltration, seen in many forms of NICM, thus potentially providing further prognostic information [5].”

12). Table 3 and 4. Please use the same fonts.

In all tables, we use now the same font style and the same font size.

13). The Diagrams are quite well done.
Reviewer 2: Mahwash Kassi

1. 3/12 (MER) Sentence needs revision
   Recommend removing suspected at the beginning of the sentence.
   The word “Suspected” removed here.

2. 3/18-19 (MER) Not clear as to what the authors are eluding to here. Does this mean if we know by risk stratification that the diagnosis is poor, we would not do further diagnostic workup?
   We mean here that if the diagnosis or etiology is still unclear in newly diagnosed NICM, the presence of risk markers, e.g. ventricular arrhythmias, low ejection fraction or myocardial changes visualized by CMR, would justify us to use potentially harmful invasive procedures to reach the final diagnosis and also the use of more intensive patient surveillance or preventive treatment during cardiac examinations.
   Recommend gearing focus from diagnosis to prognosis in the introduction as that is the prime objective of the study.

3. 4/2-3 (MER) Sentence needs revision
   Remove histopathologically. A more comprehensive definition of LGE might be helpful for the readers.
   The word “histopathologically” removed.
   Corrected the sentence as follows: “LGE, i.e. delayed enhancement on CMR images after intravenous injection of gadolinium-contrast, visualizes increases in the regional extracellular space related to myocardial necrosis, fibrosis, oedema or infiltration.” (page 4, lines 2-4)

4. 4/8-9 (MER) I do not completely agree with the notion that “there is limited information on prognosis of LGE.” Agreed, this is a newer concept but there is adequate published regarding the role in prognosis in non-ischemic cardiomyopathy. Also, not sure how non-selected patients would make a difference to how the study is conducted. Please elaborate.
   In other words, agreed that the authors are contributing to already published data by sharing their own center’s experience, but the data regarding LGE is not limited.
Indeed, there is growing published data on the value of LGE in specific NICMs, such as dilated cardiomyopathy, hypertrophic cardiomyopathy, infiltrative heart disease, myocarditis or cardiac sarcoidosis. However, there is still limited and controversial information on whether the presence of LGE and quantification of LGE extent give additive prognostic information, compared to other traditional cardiac risk factors, in nonselected consecutive patients with newly diagnosed NICM, reflecting the usual real-life clinical scenario.

In conclusions, we summarize our results as: "In suspected NICM, presenting with ventricular arrhythmias or heart failure, LGE extent gives additional prognostic information compared to traditional risk factors, while the absence of SWMA may give prognostic information beyond normal LVEF. Even though the final diagnosis is uncertain in NICM, extensive amount of LGE should be considered as a sign of poor prognosis."

5. 5/19 – 6/6 (MER) The information regarding the work up may be better represented in a table.

We fully agree on this but unfortunately we have already 5 tables. So, we tried to limit the total number of figures and tables.

It is not entirely clear how it was ensured that the patients did not have ischemic cardiomyopathy if only 4 patients underwent SPECT and 47 underwent angiography.

Text corrected as (page 6, lines 8-10):

“Patients examined with neither angiography nor SPECT (n=37, 43%) were relatively young (in median 45 years), had only few CAD risk factors (in median 1 out of 5, interquartile range 0 - 1) and evident nonischemic etiology for symptoms.”

6. 5/15 (MER) For patients who were deemed to have ischemic cardiomyopathy, please elaborate how this determination was made.

We added following sentences (page 6, lines 10-12):

“Patients were excluded due to ischemic cardiomyopathy if they had documented significant CAD, definition see above, presence of reversible perfusion defect in stress and rest SPECT or presence of CAD in explanted hearts.”

7. 6/4-6 (MER) Please write the “n” for patients who did not have either angiography or SPECT.

Please, see above the correction (Answer to comment nr. 5).

8. 7/10 (MER) Please clarify: Is this score for SWMA the same scoring system used by Scholl et al, in the following study:
Validation of a novel modified wall motion score for estimation of left ventricular ejection fraction in ischemic and non-ischemic cardiomyopathy
In other words, is this a previously validated scoring system?
The SWMA scoring we used has been originally validated in echocardiography studies [6] and later used in CMR studies. The scoring used by Scholl et al. (2012) [7] is slightly modified, including three categories for hypokinesia.

We clarified in the Methods as follows (page 7, 17-21):

“Similarly, SWMA was visually estimated based on the 17-segment model using the scoring method validated for echocardiography and later used in CMR studies [6]. The degree of wall motion abnormality in each segment was scored as 0 (normokinesia), 1 (hypokinesia), 2 (akinesia) or 3 (dyskinesia). The global SWMA score of the left ventricle was then calculated as the sum of all segmental scores.”

9. 7/18 (MER) Elaborate on composite end points

Correction (page 8, line 3):

“composite endpoints” changed to “MACEs”, which is explained as follows:

“After CMR, patients were followed-up for major adverse cardiac events (MACE), including cardiovascular death, aborted sudden death or cardiac transplantation until April 30th 2012, based on information from medical records and mortality data from the national registry of Statistics Finland. For MACEs, event times were measured from the time of CMR to the first event. Aborted sudden death was defined as documented resuscitation from cardiac arrest or appropriate implantable cardioverter-defibrillator therapy, i.e. antitachycardia pacing or shock, for VT or ventricular fibrillation (VF). To meet the endpoint criteria, an event had to be distinct from baseline arrhythmias.” (starting from page 7, line 23)

10. 9/3 (MER) Was there a uniform protocol for deciding upon which disease was considered to cause the cardiomyopathy?

Added to text (page 6, lines 5-6):

“The final diagnosis was reached using all available clinical information following the AHA 2006 guidelines of classification of cardiomyopathies [8].”

11. 11/6 (DR) Please change sub heading “main findings” or remove the subheading

Subheading “Main findings” removed.

12. Analysis (DR) Would recommend doing a subgroup analysis for different etiologies of NICMP and prognosis with LGE and SMWA

The subgroup analysis was left out, since the aim was to study the prognostic value of LGE and SWMA extent in suspected or newly diagnosed NICM. To compensate the heterogeneous study cohort, we gave complete characterization of study patients, including final diagnoses. Also, the number of patients and endpoints would have been too low for sophisticated subgroup analysis.
References


6. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shewenise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ, Chamber Quantification Writing Group, American Society of Echocardiography's Guidelines and Standards Committee, European Association of Echocardiography: Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005, 18(12):1440-1463.
