Author's response to reviews

Title: Age and gender specific normal values of left ventricular mass, volume and function for gradient echo magnetic resonance imaging: a cross sectional study

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Author's response to reviews:

Dear Editor,

Thank you for reviewing our manuscript. We thank the Reviewers for their comments and have now made changes in the manuscript in accordance with these comments, and feel the manuscript is improved as a result. We have highlighted all changes in the manuscript and include our point-by-point response below.

We hope that the manuscript is appropriate for publication in BMC Medical Imaging.

Sincerely,

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Reviewer 1: Norbert Watzinger (R1)

R1 GENERAL COMMENTS: The authors assessed left ventricular (LV) mass, volumes and function by cardiac magnetic resonance imaging in order to provide normal values for these morphological and functional parameters and to show gender- and age-related differences. Although, the topic has already been
studied by others as the authors state in their discussion, the major strength of this manuscript lies in the LV volumetric data provided over a large age range from 11 to 81 years. Overall the paper is well written and the data are clearly presented.

R1 MAJOR REVISION 1: Recruitment of the scanned cohort should be described in more detail. Were these volunteers admitted for other reasons or were they actively recruited from the local community? How many individuals and examinations had to be excluded, because of low image quality or other reasons?

RESPONSE: The recruitment of subjects has been clarified, p. 4 lines 2-4.

R1 MAJOR REVISION 2: Data derived from elderly individuals (older than 60 years) rely on measurements in only seven subjects. This should be acknowledged in the limitations.

RESPONSE: This limitation has now been acknowledged, p. 12 line 4-12.

R1 MAJOR REVISION 3: Was testing for normal distribution done in the cohort before applying unpaired Students´t test or ANOVA? Although, the results might not change that much, tests like the Mann-Whitney rank sum test or ANOVA on ranks are more appropriate in a non-normally distributed population.

RESPONSE: Testing showed normal distribution and this has been clarified in the Statistics section of the Methods, p. 6 lines 9-10.

R1 MINOR REVISION 1: Results section, paragraph 1. I should read “Data from 94 of the 96 subjects have,…..”

RESPONSE: This has been changed, p. 8 line 1.

R1 MINOR REVISION 2: Results section, paragraph 4 and 5. All volumetric data in the text normalized for body surface area (BSA) should be given in ml/m2 as in tables and figures.

RESPONSE: This has been corrected throughout the Results, p. 8-9.

R1 DISCRETIONARY REVISION 1: Some data regarding LV mass and wall stress have already been published from this cohort, as the authors state in the results section and the discussion. The authors write in their previous paper (Cain PA, et al. Clin Physiol Funct Imaging 2007; 27: 255), that circumferential wall stress did not change with age in contrast to LV mass. In the current
manuscript a gradual decline in ejection fraction with advancing age is found, mainly ascribed to a lesser decline in enddiastolic volumes compared to endsystolic volumes. Therefore, enddiastolic and endsystolic wall stress calculations could be of interest to clarify the gradual increase of natriuretic peptides with increasing age.

 RESPONSE: We acknowledge that such calculations may be of interest, but we did not measure natriuretic peptides in the current study and thus we respectfully choose not to make this suggested discretionary revision.

REVIEWER 2: Juha Koskenvuo (R2)

R2 GENERAL COMMENTS: This manuscript entitled "Age and gender specific normal values of left ventricular mass, volume and function for gradient echo magnetic resonance imaging: a cross sectional study" by Dr Peter A Cain and colleagues is an important report of clinical application of cardiovascular magnetic resonance. Patient population is big enough for creating reference values and also statistics seem to be reasonable. This data is worth of publication but not in its present form.

R2 MAJOR REVISION 1: Study aims- they are talking about physiological variation and reference values as different tasks. It is confusing as they mean the same thing with these terms. However, at first, I thought that they have studied day-to-day or intra-day variation of these parameters which they have not done.

 RESPONSE: The aims of both the Abstract (p. 2 lines 5-7) and the Background (p. 3, last paragraph) have been clarified with regards to the issue of reference values and physiological variation.

R2 MAJOR REVISION 2: The earlier observed difference between volumetric parameters of SSFP and gradient echo derived CMR should be discussed.

 RESPONSE: This discussion has been clarified, p. 12 lines13-17.

R2 MAJOR REVISION 3: Effect of temporal resolution, valsalva or muller maneuver during breath-hold sequence and gating (prospective vs retrospective) on LV parameters should be discussed shortly.

 RESPONSE: We feel that discussion of these issues could be incorporated into the manuscript, however, they do not add to the understanding of the message of the manuscript or limitations of the study. A temporal resolution of 50 ms, as used in the current study, is accepted as adequate (Pennell DJ, J Cardiovasc Magn Reson, 2002). Breath hold at end expiration, as used in the current study,
is standard in CMR (Pennell DJ, J Cardiovasc Magn Reson, 2002), and is not the same as either Valsalva’s or Muller’s maneuver which were not used in the current study. The difference between prospective triggering and retrospective gating upon end diastolic and end systolic images is at most minimal. Thus, with all respect, a discussion of these issues has not been added.

R2 MAJOR REVISION 4: Study population. Reader likes to know how many people were tried to recruit and how many participated to the study. Do this cohort really represent normal population? It may be difficult to answer. Races of the study subjects should be mentioned.

RESPONSE: Recruitment and race have been clarified, p. 4 lines 2-4.

R2 MINOR REVISION 1: Use lower instead lesser word in results section of abstract.

RESPONSE: This has been changed, p. 2 line 15.

R2 MINOR REVISION 2: Background-second paragraph-first sentence: It does not make sense.

RESPONSE: This sentence has been clarified, p. 3 lines 6-8.

R2 MINOR REVISION 3: Study population: It should be make clear what reference limits were used for children to prove them healthy. Adult values are really abnormal in young teenagers.

RESPONSE: Both adolescents and adults all conformed to the same inclusion and exclusion criteria stated in the first paragraph of the Methods, p. 4. Notably, blood pressure was lower in the adolescents as shown in Table 1.

R2 MINOR REVISION 4: Results: the unit for all BSA adjusted values should be XX/m2 not xx/g2.

RESPONSE: This has been corrected throughout the Results, p. 8-9.

R2 MINOR REVISION 5: Discussion: Describe shortly previous studies and the amount of the study subjects on them.

RESPONSE: This is stated in the first sentence of the Results, p. 8 lines 1-2.

R2 MINOR REVISION 6: Abstract-First sentence- reformulate. Don't use
un-opened abbreviations

RESPONSE: This has been clarified, p. 2, first sentence.

R2 MINOR REVISION 7: Results- ii): End-diastolic and end-systolic volume, no end diastolic and systolic volume.

RESPONSE: This has been changed, p. 8 line 14.

R2 DISCRETIONARY REVISION 1: Use CMR consistently. No MRI.

RESPONSE: This has been changed throughout the manuscript.

R2 DISCRETIONARY REVISION 2: Use valvular regurgitation. No leakage.

RESPONSE: This has been changed, p. 4 line 8 and p. 12 line 1.

R2 DISCRETIONARY REVISION 3: Linguistic revision may improve the manuscript.

RESPONSE: The manuscript has now undergone linguistic revision.

REVIEWER 3: Oronzo Catalano (R3)

R3 GENERAL COMMENTS: The study was designed to give age and sex specific normal ranges of left ventricle (LV) volumes, mass and function for cardiac magnetic resonance (CMR) exams at 1.5 Tesla (T), using gradient echo (GE) sequences. The aim of the study is clear, methods are overall appropriate, results well exposed and conclusions adequately supported by data. However, discussion of the study results and comparison with previous published studies are lacunose.

R3 MAJOR REVISION 1: The main concern with the study by Cain et al. is methodological but linked to the study rationale too. The authors used GE cine sequences to evaluate left ventricle volumes, mass and function. Nowadays, GE cine sequences are seldom employed for this purpose with 1.5 T scanner. Indeed, balanced steady-state free precession (SSFP) sequences have rapidly become the gold standard for cine cardiac imaging at 1.5 T, as a result of their high SNR performance and excellent blood-myocardium contrast. As properly cited by the authors, in a recent study by Maceira et al. age and gender specific normal ranges of LV parameters with SSFP sequences have been already reported. Moreover, the advocated use of 1.5 T GE normal ranges as references
for CMR exams at 3.0 T is not a clear rationale for the study (it should have been best conducted with a 3.0 T scanner).

RESPONSE: The rationale for using 1.5T reference values for 3T has been removed. The rationale for the study remains in accordance with the aims of the study stated in the final paragraph of the Introduction.

R3 MINOR REVISION 1: Abbreviations in the abstract are not always adequately explained.

RESPONSE: This has been clarified, p. 2.

R3 MINOR REVISION 2: The sentence in the abstract “SV and EF decline rapidly in adolescence and then slowly throughout life” is not adequately supported by data.

RESPONSE: Adjustments to this sentence have now been made so that the conclusions are adequately supported by the data, p. 2, second-to-last sentence.

R3 MINOR REVISION 3: It is not clear if an equal number of subjects was included in each decade of age (it would seem no). This might be important as a previous study by Bellenger et al. [JCMR, 2000], suggested a minimum sample size of 10–15 patients to detect between groups significant differences in the left ventricle parameters.

RESPONSE: This is now discussed in the Limitations, p. 12 lines 4-12.

R3 MINOR REVISION 4: In the 'Tracing of endocardial and epicardial contours' section of methods: what does it mean “...measurements (...) in each image frame were calculated in the short-axis views to minimize partial volume effects.”?

RESPONSE: This has now been clarified, p. 5 lines 10-12.

R3 MINOR REVISION 5: Reproducibility analysis correctly included bias (mean difference of repeated measure) but should also report coefficient of variance (CoV = standard deviation of repeated measures as percent of their mean) or Bland-Altman coefficient of reproducibility, which are better known variability indexes than interclass correlation coefficient. Moreover, reproducibility data are incomplete lacking mass, ejection fraction and stroke volume results and an intraobserver analysis.

RESPONSE: The coefficients of variation and repeatability are now defined in
the Methods (p. 6 lines 12-16) and given for the interobserver variability for all data, p. 9, last paragraph. Data on intraobserver variability are not given. Interobserver variability is by construction greater than the intraobserver variability, and thus interobserver variability, which we present, is the measure of greatest clinical interest compared to the intraobserver variability.

R3 MINOR REVISION 6: R2 is not the same of Pearson's correlation coefficient

RESPONSE: This has been clarified, p. 6 line 17.

R3 MINOR REVISION 7: At the end of 'Left ventricular stroke volume and ejection fraction' section of Results: what does it mean “... a curvilinear decline .....from ~0.7 to ~0.6 with age.” ?

RESPONSE: This has been clarified, p. 9 lines 12-13.

R3 MINOR REVISION 8: In comparison to the study by Maceira et al., how do the authors explain the opposite trend through life of end-systolic volume and ejection fraction in female sex?

RESPONSE: This is now discussed, p. 11 lines 8-14.

R3 MINOR REVISION 9: The relation between LV parameters and growth hormone/IGF levels is largely presumptive and not supported by data.

RESPONSE: We are very clear that we do not present data on this matter, but feel that such a hypothesis-generating discussion is still of interest to the readership. Thus, we have softened the tone of this discussion, p. 11 lines 15-22.

R3 MINOR REVISION 10: The paper needs a linguistic revision.

RESPONSE: The manuscript has now undergone linguistic revision.