Author’s response to reviews

Title: Cardiac Left Ventricular Myocardial Tissue Density, evaluated by Computed Tomography and Autopsy

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Author’s response to reviews:

Dear Dirk Krüger, PhD

Senior Editor, BMC Medical Imaging

Thank you for reviewing and considering our manuscript for publication in BMC Medical Imaging. We have read the reviewer’s comments and we have addressed them point-by-point and the manuscript has been revised accordingly. We believe the manuscript has improved. In the following, you will find a point-by-point rebuttal. The rebuttal and CT images testing different settings as suggested by the reviewer has also been attached as a file. We hope you will now find the manuscript eligible for publication.

Best regards,

Alexandra Gheorghe, MD

Response to reviewer

Thank you for the valuable comments and revisions.
1. It would definitely have enhanced the study if Archimedes principle had been used additionally but since this was not performed, let's leave this topic.

Rebuttal: We appreciate this.

2. Regarding LV contouring, all studies in the literature, to my knowledge, have been performed with contrast in the chamber therefore any measurements performed in this study are not validated. Likewise window settings have been optimized for contrast-based studies.

Rebuttal: We comment this now in study limitations. Lines 239-243.

We have also added relevant literature references to the rebuttal regarding LV contouring in living patients on non-contrast scans.

The scans were non-contrast scans, which in a clinical setting makes the differentiation between the LV blood pool and the LV myocardium difficult. However, non-contrast scans are possible in deceased individuals (cf. fig. 1). We chose to perform the present study without contrast to avoid extravasation of contrast media in the examined deceased individuals and thereby omit a possible weight effect on the myocardium.


3. Since boundaries are sensitive to thresholds and windowing, there is a reasonable chance that the difference in density found may be related to this factor.

Rebuttal: We comment this now in study limitations. Lines 258-264.

Boundaries are sensitive to threshold and windowing. We used a HU threshold for myocardial tissue of 50±10, and 1 mm slice thickness for CT evaluations. The CT settings used for this study are optimized for contrast-based studies, and a different cardiac window settings could result in different myocardial volume. Also, different thresholds may apply for epicardial and endocardial borders and partial volume effects may be important. Due to the relatively close HU values of the blood pool and the myocardium, the myocardium may have been overestimated in some cases and underestimated in other cases.
4. I have played around with windowing and found that reducing the window center to a value of about 40, which better represents the myocardial HU, results in an increase in myocardial volume. Increasing width results in a similar effect.

5. I would like to request the authors at least to test the sensitivity of myocardial volumes to changes in these parameters. For example a subset of about 20 cases could be remeasured using a window center of 40-50HU and also testing a different window width.

Rebuttal: This reply covers comments 4 and 5. We have also added some figures to this rebuttal.

We have now tested different levels (around 40-50 HU) and different widths (around 100-50 HU) in order to test the optimal differentiation between blood and myocardium. Considering the image quality, we chose a width of 50 HU and window-center (level) of 45 HU for the reevaluation of 15 randomly chosen cases. The new CT settings showed an overall decrease in LVShV. The image quality improved indeed in some cases, but the image quality diminished in other cases, which might have led to an underestimation of the LVShV. This underestimation was statistically non-significant p>0.5. Although it is possible to differentiate between the myocardium and blood among the deceased individuals, the setting in this study are optimized for contrast studies and we now realize we should have tested different levels/widths before choosing the standard clinical setting.

The settings are explained in methods, lines 122-123.

The statistical test in statistical analyses, line 149.

The results of this analyse is added to result, Lines 180-182 and discussed in;

Discussion, lines 211-216.

Methods: Fifteen randomly chosen LV myocardial tissues were re-analysed using a different cardiac setting with level = 45 HU and width = 50 HU.

Statistical analyses: Bland-Altman analysis was used to assess the re-analysis of LVShV and the degree of inter-observer variability.

Results: The mean difference in LVShV assessment by CT with the new settings in 15 randomly chosen LV myocardial tissue was -19.4 ml (95% CI: -25.5; 65.3), p>0.5.

Discussion: However, these CT settings were optimized for contrast-based studies. Changing the CT settings in 15 randomly chosen cases showed an overall, but negligible and non-significant (p>0.5), decrease in LVShV (mean difference -19.4 ml). We did find that the image quality improved in some cases using these different settings (n=7/15), as a more clear-cut distinction between the blood-pool and the myocardium was achieved. However, in other cases a lot of noise was introduced, so we find that the majority of the scans were in fact better analysed with the original settings.
6. The authors should also discuss the relevance of changes in myocardial blood volume to both mass and volume calculations. The beating myocardium consists of ~25% blood volume. What happens to this volume in the cadaver heart?

Rebuttal: This is now discussed in study limitations, lines 247-253. Relevant literature references are added to the rebuttal and the manuscript.

In vivo, the myocardium consist of intra-myocardial blood-volume. Postmortem, this volume may change, e.g., postmortem extravasation or, conversely, fluid accumulation from leaking and decomposing endocardial structures. Such changes are small and usually only become pronounced with extended postmortem intervals [35]. The deceased individuals in this study were kept at reduced temperature and autopsied rather quickly after declaration of death. Morphological observations as well as quantitative results suggest that elements of the blood are resistant to autolytic effects [36]. Overall, this leads us to assume that no significant organ volumetric changes took place.


Zilg B et al., “Postmortem blood sampling- Comparison of drug concentrations at different sample sites”, Forensic science Int, 278 (2017) 296-303

7. I would tone down the strength of the conclusions and recommendations, to state that current results suggest that myocardial density may currently be underestimated, but that readers need to take into account various assumptions and possible inaccuracies in myocardial volumes measurement.

For example the following sentence should be removed: "However, we determined that this value is not correct, and if a more accurate LVM is desired, then our density value should be used."

Rebuttal: This is taken into consideration, altered and removed, lines 278-285.

Applying the hitherto used myocardial tissue density value (1.055 g/ml) significantly underestimated the LVM. Our proposed new value is the result of post-mortem CT for volume determination, followed by post-mortem dissection for obtaining LV weight. We argue that this allows for a more precise determination of these two basic parameters, but obviously, we are aware that post-mortem anatomy may not be directly translational to clinical studies. Several LVM reference value tables have been produced using myocardial tissue density value of 1.055 g/ml, thus continuing to use this value when converting from LVShV to LVM will not have immediate clinical implications. However, we do think that our study calls for critical evaluation of especially high LVMs and how this value is obtained.