Author’s response to reviews

Title: Heart Rate in Patients with Reduced Ejection Fraction: Relationship Between Single Time Point Measurement and Mean Heart Rate on Prolonged Implantable Cardioverter Defibrillator Monitoring

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Author’s response to reviews:

Editor Comments:

Comment E1. Please also address these stylistic points: Title page: please provide the email addresses of all authors

Response and Manuscript Change E1. This has been updated.

Comment E2. Please rename 'Introduction' to 'Background', and include a Conclusion header after Discussion section

Response and Manuscript Change E2. These have been renamed and header added.

Comment E3. The ethics and consent information should be moved into the Declarations section. Please advise whether consent was written or verbal.

Response and Manuscript Change E3. The ethics and consent information was moved to the Declarations section and written informed consent was specified.
Comment E4. Author contributions: did authors KN, PCA, CF and CL provide any further contribution to the study? At present, their contribution does not warrant authorship but rather being acknowledged.

Response and Manuscript Change E4. The contributions are as follows:

KN – Study design, manuscript preparation
PCA – Statistical analysis
CF – Manuscript preparation and revision
CL – Statistical analysis, manuscript preparation

Reviewer #1. Chih-Yu Yang, M.D., Ph.D.

Comment R1-1. In this manuscript, Dr Habal et al. examined the relationship between resting heart rate (HR) and mean HR in patients with ICD and reduced LVEF. This study is interesting, but there are however some concerns about this article.

Response R1-1. We thank the reviewer for their acknowledgement.

Comment R1-2. The patient cohort of the present study is unique, who were on ICD and their LVEF were less then 40%. I would like to suggest that the article title should be revised accordingly.

Response and Manuscript Change R1-2. We agree with the reviewer and have revised the title as follows (Title page):

Heart Rate in Patients with Reduced Ejection Fraction: Relationship Between Single Time Point Measurement and Mean Heart Rate on Prolonged Implantable Cardioverter Defibrillator Monitoring

Comment R1-2. The resting HR seems to be recorded only once. If so, it doesn't mean that resting HR is not a good therapeutic target, whereas it's the "single on measurement" of resting HR not an ideal one. Therefore, I would like to suggest that the conclusions and related texts should be revised.

Response R1-2. We acknowledge that this was a single measurement and thus it is possible that multiple measurements, on the same day or averaged over multiple visits may provide additional benefit. However, we do note that the overall mean of the heart rates using either method (resting ECG and ICD heart rate) was very similar and there was good correlation between the methods
Moreover, from a practical perspective in a busy clinical setting, it is likely that only a single time point measurement will be obtained.

Manuscript Change R1-2. We have revised the paper accordingly as follows:

The Abstract conclusions (p.2 line 18) now reads:

While resting HR correlated with mean HR in patients with reduced LVEF, and in important subgroups, the limits of agreement were unacceptably wide raising concern over the use of single time point resting HR as a therapeutic target.

The Highlights (p.3 line 19) now reads:

This raises concern for the use of resting single time point HR as a therapeutic target.

The Discussion (p.11 line 1) now reads:

From a clinical perspective, this suggests that single time point resting HR is an imperfect surrogate for mean HR when titrating pharmacotherapies.

The Discussion (p.13 line 20) now reads:

Thirdly, resting HR was taken at a single time point near the end of the clinic visit after the patient had been seated or recumbent and thus, in some instances the patient may have moved or become anxious, thus transiently raising their resting HR.

The conclusion (p.14 line 8) now reads:

In conclusion, while there is good correlation between single time point resting HR and mean HR as determined from the ICD histogram, the limits of agreement are unacceptably wide and resting HR is frequently above the mean.

Comment R1-3. In the first paragraph of page 8, authors mentioned that there were 20 patients being paced whereas another 34 patients weren't. This study should better include the result of such subgroup analysis (paced vs non-paced) of association between resting and mean HR, since the "paced" HR doesn't represent the actual condition of spontaneous heart beating.

Response R1-3. We agree with the reviewer that pacing could affect the results. For this reason, we excluded patients who were paced >40% of the time (in the atrium, if an atrial lead was present, or in the ventricle if not). Moreover, for the chamber (atrium or ventricle) used for heart
rate determination, the mean percentage of time being paced was low (6.6%). However, to further address this issue we performed an additional analysis of i) patients who were not paced (<1%, as this is the lower limit on the ICD) and ii) patients who were paced >1% and iii) patients with a CRT device (amongst whom atrial heart rate was used in this analysis).

Manuscript Change R1-3. We have included this as a Supplementary Table 1.

We have also included this information in the Results text on p.9 line 19 as follows:

Given that pacing could affect the ICD HR, we performed a sensitivity analysis of the patients paced < 1% in the cardiac chamber from which the mean HR was determined, those paced > 1%, and those with a CRT device in situ (Supplementary Table 1). In all three groups the mean difference remained low (0.3, -0.2, and -0.7 respectively), the correlation was moderate to strong (0.80, 0.60, and 0.61 respectively), and the limits of agreement were wide (-13.6, 14.1; -9.8, 9.4; -14.2, 12.7 respectively).

Reviewer #2. Meifeng Xu:

Comment R2-1. This study analyzed the relationship between resting heart rate (HR) and mean HR on implantable cardiac defibrillator (ICD) in patients with left ventricular ejection fraction (LVEF) <40%. The results indicate that there is good correlation between resting HR and mean HR as determined from the ICD histogram. However, the limits of agreement are unacceptably wide and resting HR is frequently above the mean. These findings may raise concern for the strategy of using a single time-point method of HR assessment to titrate negative chronotropic therapies.

Response R2-1. We thank the reviewer for this accurate summary.

Comment R2-2. Minor issues need to be addressed. It is not very clear why authors performed this study, i.e. is there any significance of this study to guide the therapy in the patients with cardiovascular disease?

Response R2-2. At present, single time point heart rate (HR) in the clinical setting is most frequently used to determine the appropriateness of uptitrating/adding heart rate lowering therapies. What our study contributes is evidence to suggest that i) single time point HR is not representative of mean HR over time and ii) single time point HR frequently overestimates mean HR on prolonged monitoring. Given the negative prognostic implications of elevated HR as outlined by our group (Habal et al, 20147) and others along with the addition of Ivabradine to heart failure guideline directed medical therapy, the clinical practice of prescribing these therapies is likely to increase. We therefore suggest that, based on our findings, an alternative method of HR assessment should be considered (eg. prolonged monitoring or highest frequency HR interval on ICD interrogation) prior to initiating and/or uptitrating these therapies.
Manuscript Change R2-2. We have addressed this in the Discussion as follows (p.13, line 2):

In the context of these concerns, our findings suggest that an alternative method of HR assessment to supplement single time point measurements, should be considered by clinicians. Since many of these patients will have an ICD, either the mean HR or highest frequency HR interval could be used in order to reduce the risk of iatrogenic bradycardia. Long-term studies are then required to assess whether this method will also have prognostic implications.

Comment R2-2. The authors mentioned that average resting and ICD mean HRs were 67.9±10.1 and 67.8 ±9.6 bpm, respectively. There was good correlation in the overall cohort (r=0.79). Did authors calculate the p value of this correlation factor?

Response R2-2. We have updated our analysis to include a p-value (p < .001) for the overall cohort and the subgroups (p < .001 for the HR < 70 bpm subgroup, p < .001 for the beta-blocker subgroup).

Manuscript Change R2-2. This has been added to the text in the Results (p. 8 line 9) which reads as follows:

There was good linear correlation (r = 0.79; p < .001) between these two measurements (Figure 1a).

The Results (p. 8 line 17) has been modified to read as follows:

Moderate correlation (r = 0.62; p < .001) was found in this subgroup of patients.

The Results (p. 9, line 4) has been modified to read as follows:

There was excellent correlation (r = 0.91, p < .001) between the resting and mean HR amongst patients taking intermediate-to-high dose beta-blockers (Figure 3a).

Comment R2-3. Please give the full words when the abbreviations are used first time, e.g., "ICD", "LVEF" on page 2.

Response and Manuscript Change R2-3. This has been updated in the text on page 2.