Periodic Repolarization Dynamics (PRD) identifies patients who profit from ICD implantation, A meta-analysis of the predictive value of PRD

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Background: Periodic repolarization dynamics (PRD) is an electrocardiographic marker that quantifies sympathetic-activity associated instabilities of cardiac repolarization. PRD is a strong predictor of mortality in patients with ischemic (ICM) and non-ischemic cardiomyopathy (NICM) and has been proposed to identify patients who benefit from prophylactic ICD implantation.

Purpose: To conduct a systematic review and meta-analysis concerning the prognostic value of PRD for predicting all-cause mortality in relation to prophylactic ICD-implantation.

Methods: This meta-analysis follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. A total of 25 articles were screened and 7 randomized and non-randomized controlled trials identified. Finally, a total of 5 could be included in the analysis (Fig.1). Patients were stratified into patients with or without prophylactic ICD-implantation (Fig.2). The prognostic value of PRD for predicting all-cause mortality was extracted from published data as hazard ratio (HR) per 1 deg2 increase in PRD. We used inverse-variance-weighted average meta-analysis to calculate fixed and random effect models to estimate the overall predictive value of PRD in both groups. The interaction between PRD and prophylactic ICD-implantation for predicting mortality was calculated using meta-regression analysis. All analyses were performed using CRAN R v. 4.1.2 and the meta-package v 5.2.0.

Results: We included 4,338 patients in this meta-analysis, of whom 3,167 (73%) suffered from ICM and 1,171 (27%) from NICM. 1,906 (44%) patients were treated with an ICD. During an estimated mean follow-up time of 3.2 years, 604 (14%) patients died. Fig. 2 (left) shows patients without ICD treatment (N=2,432, 56%). In these patients, a 1 deg2 increase in PRD was significantly associated with an overall 8% increase in mortality (fixed effect HR 1.08; 95% CI 1.06-1.10; p < 0.001, random effect HR 1.08; 95% CI 1.06-1.11; p < 0.001). Fig. 2 (right) displays the prognostic value of PRD in patients treated by ICD (N=1,906). In these patients, a 1 deg2 increase in PRD was significantly associated with an overall 3% increase in mortality (fixed-effect HR 1.03; 95% CI 1.01-1.05; p < 0.001, random-effect HR 1.03; 95% CI 1.00-1.06; p < 0.001). An increase in PRD was not significantly associated with an increase in mortality in patients from the EU-CERT-ICD and DANISH trial. There was a significant interaction between PRD and prophylactic ICD-implantation for predicting all-cause mortality (p = 0.008).

Conclusion: In patients with ICM and NICM, PRD is a strong predictor of all-cause mortality in patients with and without prophylactic ICD. The significant interaction between PRD and prophylactic ICD-implantation most probably implies a reduction in the risk identified by PRD through ICD implantation. Consequently, PRD could prove a useful tool for identifying patients that might benefit from ICD treatment.

Figure 1
### Figure 2

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Deaths</th>
<th>ICD</th>
<th>Forrest Plot</th>
<th>Hazard Ratio (95% CI) per 1 mg/m² increase in MDI</th>
<th>Weight (numeric)</th>
<th>Weight (median)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART</td>
<td>908</td>
<td>69</td>
<td>0</td>
<td></td>
<td>1.12 (1.06 - 1.17)</td>
<td>15.4%</td>
<td>18.5%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PRO_MI</td>
<td>455</td>
<td>47</td>
<td>46</td>
<td></td>
<td>1.10 (1.05 - 1.15)</td>
<td>14.1%</td>
<td>17.6%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MADIT</td>
<td>856</td>
<td>199</td>
<td>567</td>
<td></td>
<td>1.05 (1.02 - 1.08)</td>
<td>12.7%</td>
<td>23.3%</td>
<td>0.003</td>
</tr>
<tr>
<td>EU-CERT/ICD</td>
<td>1,372</td>
<td>202</td>
<td>909</td>
<td></td>
<td>1.08 (1.03 - 1.15)</td>
<td>10.8%</td>
<td>14.0%</td>
<td>0.001</td>
</tr>
<tr>
<td>DANISH</td>
<td>748</td>
<td>167</td>
<td>385</td>
<td></td>
<td>1.06 (1.03 - 1.10)</td>
<td>39.2%</td>
<td>24.0%</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

**Common effect model**

- Hazard ratio: 1.08 (1.03 - 1.15)
- P-value: < 0.001

**Random effects model**

- Hazard ratio: 1.09 (1.06 - 1.13)
- P-value: < 0.001

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**Heterogeneity: I² = 0%, t² = 0.0005, p = 0.00**

**Heterogeneity: I² = 0%, t² = 0.0005, p = 0.04**

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**Control** → p-interaction = 0.008 → ICD-implantation