Periodic Repolarization Dynamics: A New Electrocardiographic Phenomenon and Its Implications

Konstantinos D Rizas[1], MD, Tuomo Nieminen[2], MD, Petra Barthel[3], MD, Christine S Zürn[1], MD, Mika Kähönen[4], MD, PhD, Jari Viik[5], PhD, Terho Lehtimäki[6], MD, PhD, Kjell Nikus[7], MD, Christian Eick[1], MD, Tim O Greiner[8], DVM, Hans P Wendel[8], PhD, Peter Seizer[1], MD, Jürgen Schreieck[1], MD, Meinrad Gawaz[1], MD, Georg Schmidt[3], MD and Axel Bauer[1 *], MD

[1] Medizinische Klinik III, Abteilung für Kardiologie und Herz-Kreislauferkrankungen, Eberhard Karls University, Tübingen, Germany

[2] Division of Cardiology, Helsinki University Central Hospital, Helsinki, Finland

[3] 1. Medizinische Klinik, Technische Universität München, Germany

[4] Department of Clinical Physiology, University of Tampere and Tampere University Hospital, Tampere, Finland.

[5] Department of Biomedical Engineering, Tampere University of Technology, Tampere, Finland

[6] Department of Clinical Chemistry, Fimlab Laboratories, School of Medicine at University of Tampere, Tampere, Finland.

[7] Heart Centre, Department of Cardiology, Tampere University Hospital, Tampere, Finland

[8]Department of Thoracic, Cardiac and Vascular Surgery, Eberhard Karls University, Tübingen, Germany

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Address for correspondence:

Prof. Dr. med. Axel Bauer

Medizinische Klinik III, Abteilung für Kardiologie und Herz-Kreislauferkrankungen

Eberhard-Karls-Universität Tübingen

Otfried-Müller-Str. 10

72076 Tübingen

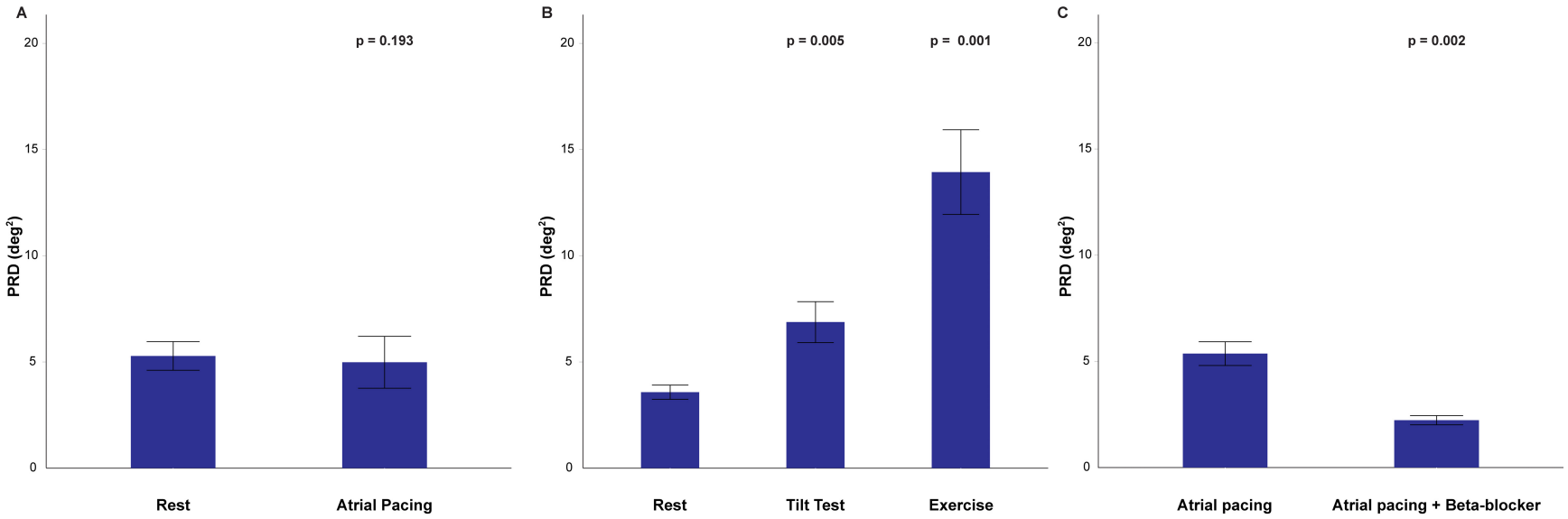
Germany

Tel: +49 7071 29 82922

Fax: +49 7071 29 4550

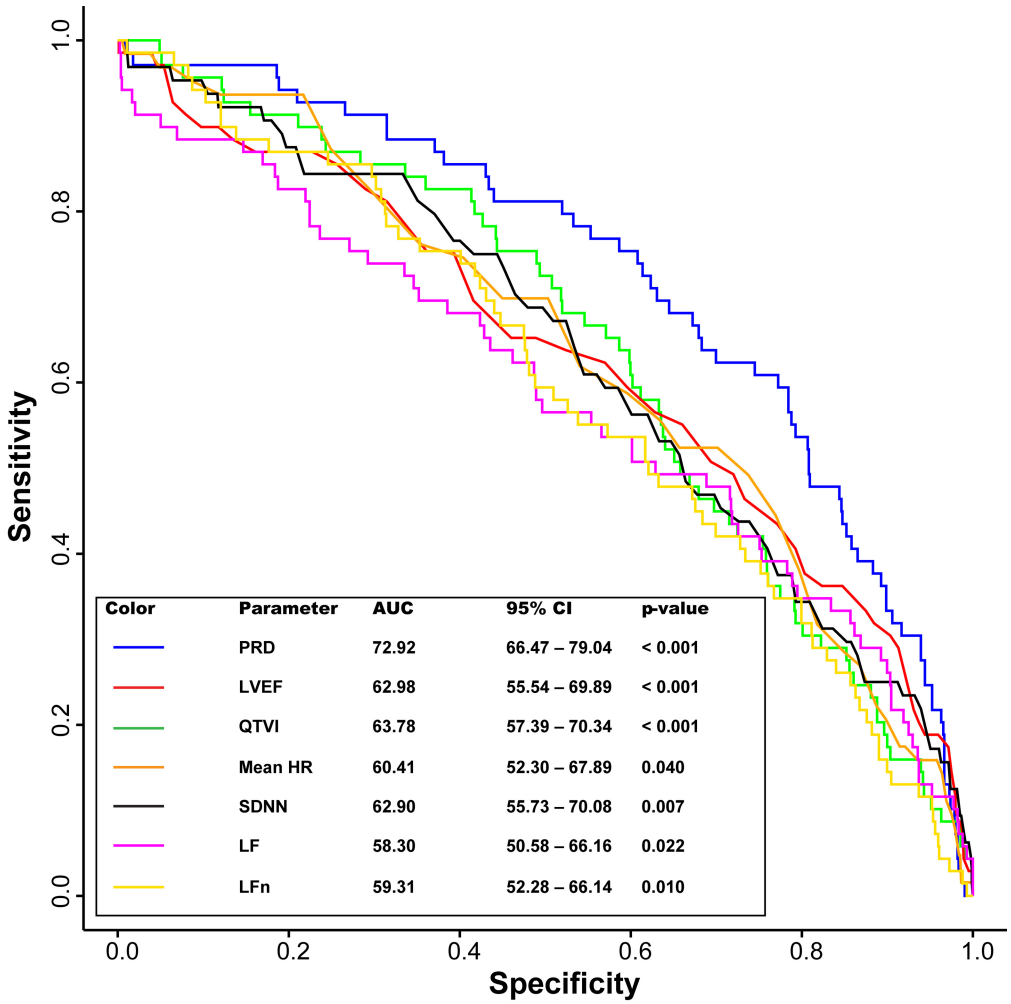
Email: axel.bauer@med.uni-tuebingen.de

Supplemental Figures



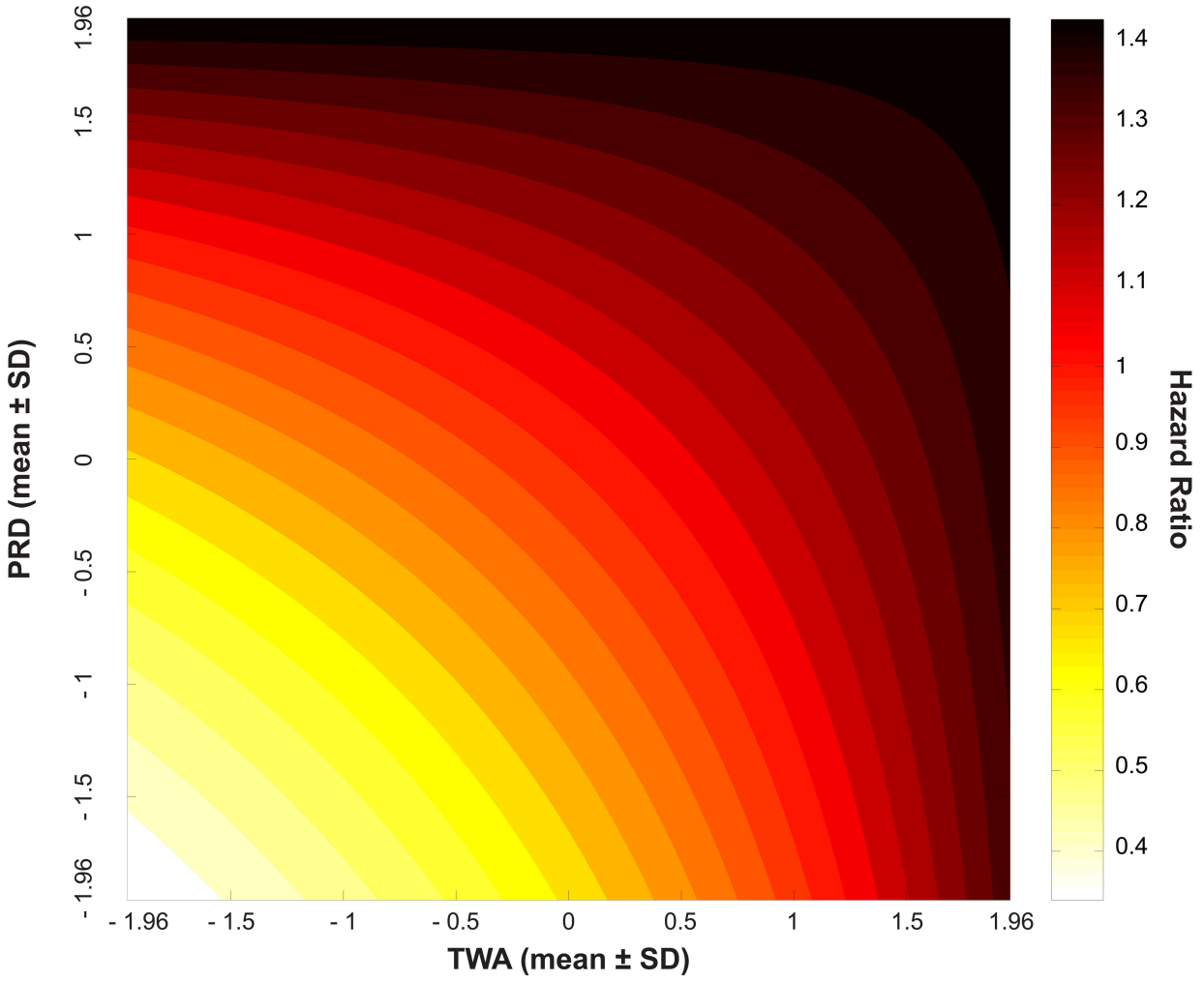
Supplemental Figure 1

(A) Effects of fixed atrial pacing on PRD in 10 patients undergoing a clinically indicated electrophysiological study. Pacing with constant heart rate had no significant effect on the PRD (5.28 ± 0.67 vs. 4.99 ± 1.22, p = 0.193). **(B)** Effects of 45° head-up tilt and low-intensity exercise on PRD in 11 healthy volunteers. Both tilt test and exercise significantly increased PRD from 3.57 ± 0.33 deg^2 to 6.88 ± 0.96 deg^2 (p = 0.005) and 13.94 ± 2.00 deg^2 (p = 0.001) respectively. **(C)** Effects of pharmacological adrenergic blockade on PRD in 10 patients undergoing a clinically indicated electrophysiological study. Fixed atrial pacing was used to ensure constant heart rate. Intravenous administration of 0.1mg/kg metoprolol caused significant suppression of PRD in all subjects (5.36 ± 0.56 vs. 2.23 ± 0.22, p = 0.002). All barplots illustrate mean values with error bars representing the standard error of the mean.



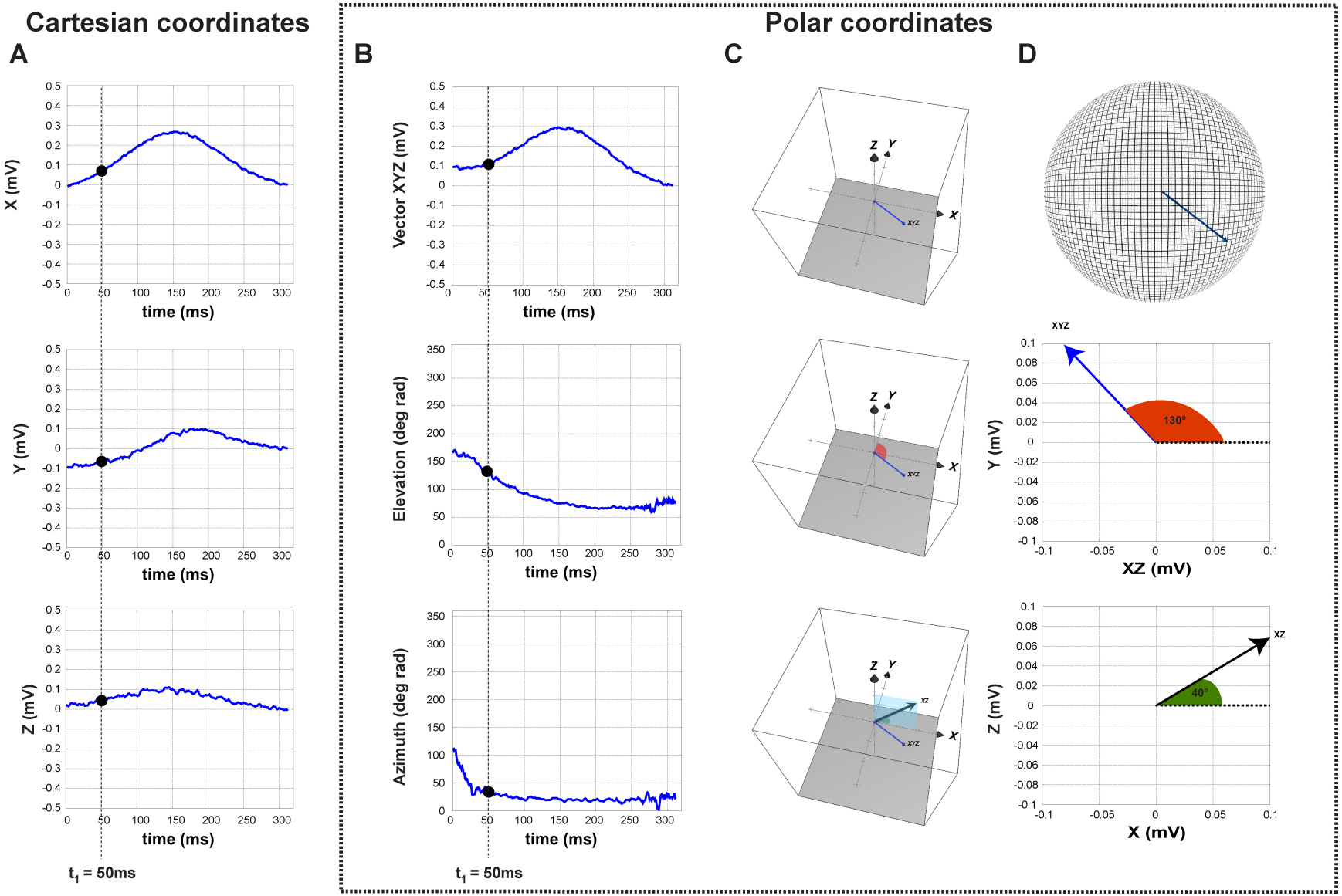
Supplemental Figure 2

Receiver-operator characteristic curves for predicting 5-year mortality yielded by various risk variables in a cohort of 908 patients surviving an acute myocardial infarction. PRD = periodic repolarization dynamics, LF = low frequency power of heart rate variability (p = 0.005 for the difference from PRD), LFn = LF in normalized units (p = 0.003 for the difference from PRD), LVEF = left ventricular ejection fraction (p = 0.014 for the difference from PRD), mean HR = mean heart rate (p = 0.004 for the difference from PRD), QTVI = QT variability index (p = 0.007 for the difference from PRD), SDNN = standard deviation of all NN intervals (p = 0.038 for the difference from PRD).



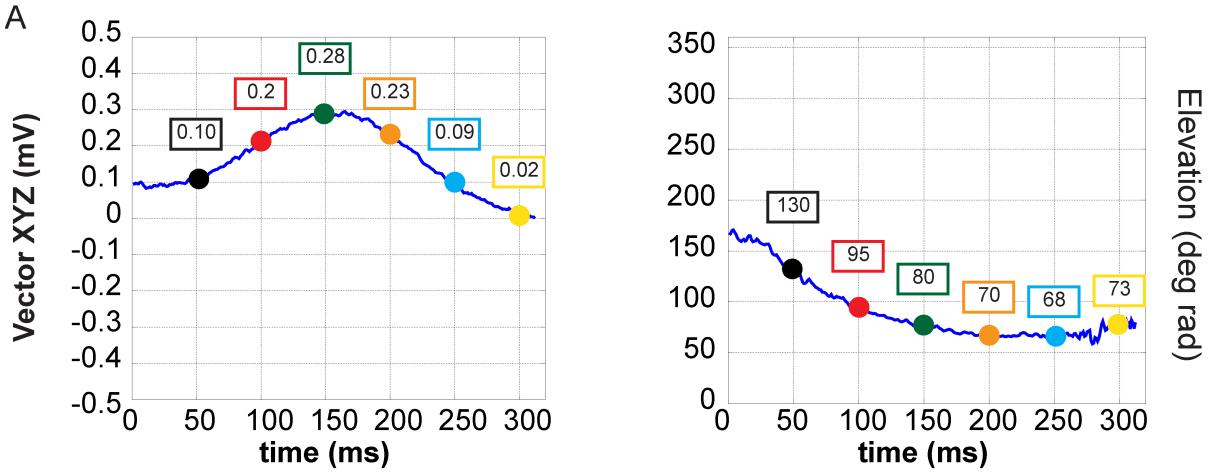
Supplemental Figure 3

Response surface plot illustrating the relative hazard ratios (HR) assessed for different levels of PRD and TWA for all-cause mortality. The HR for mean PRD and mean TWA was defined as the reference and depicted in the center of the graph (relative HR = 1). The HR for different combinations of PRD and TWA was calculated and compared to the reference HR (color bar). We considered changes in PRD and TWA at ± 1.96 standard deviations around the mean value. PRD affected the HR at all levels of TWA, which proves its incremental prognostic information.

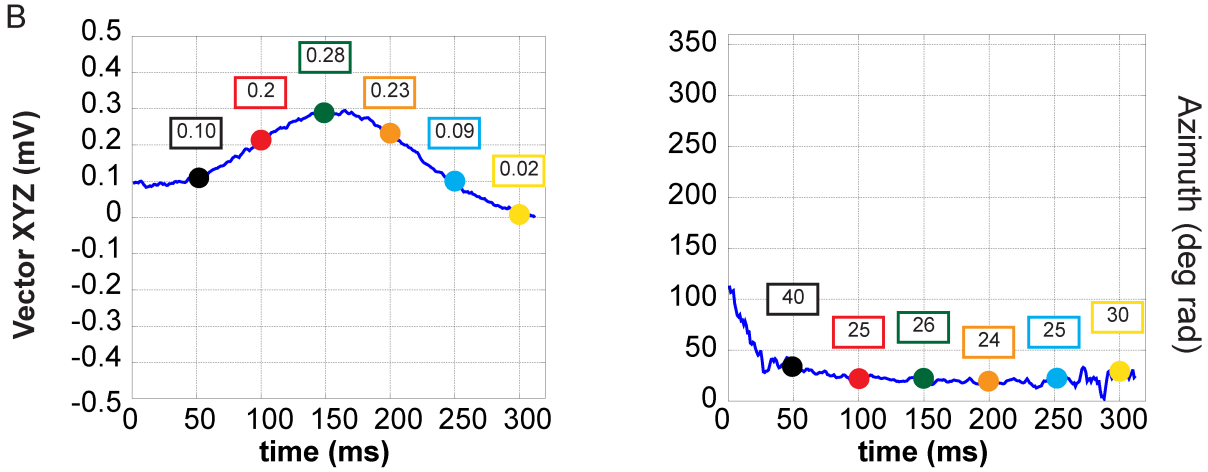

Cartesian coordinates
Polar coordinates
A
B
C
D
X (mV)
Y (mV)
Z (mV)
time (ms)
t1 = 50ms
Vector XYZ (mV)
Elevation (deg rad)
Azimuth (deg rad)
XYZ
XZ (mV)
X (mV)
130°
40°
XZ

Supplemental Figure 4

(A) A Cartesian system of coordinates (X,Y,Z) was transformed into **(B)** a time series of polar coordinates defined by two angles (elevation and azimuth) and the "resultant-force" amplitude XYZ. **(C)** For a given time point t_1, elevation and azimuth were assessed as follows: the vector XYZ (defined by X, Y, and Z in the Cartesian coordinate system) was plotted in space (upper panel) and decomposed into two orthogonal vectors, one on the Y-axis (middle panel) and one on the transverse (XZ) plane (lower panel). **(D)** The angle between the vector and the Y-axis was termed the elevation (middle panel), with an angle of 0° defined as the vector pointing in the caudal direction. The angle between the vector on the transverse plane and the X-axis was called the azimuth (lower panel), with 0° corresponding to the left and 90°corresponding to the forward direction.



$$WAE = \frac{(130 * 0.1) + (95 * 0.2) + (80 * 0.28) + (70 * 0.23) + (68 * 0.09) + (73 * 0.02)}{(0.1 + 0.2 + 0.28 + 0.23 + 0.09 + 0.02)} = 84.87°$$

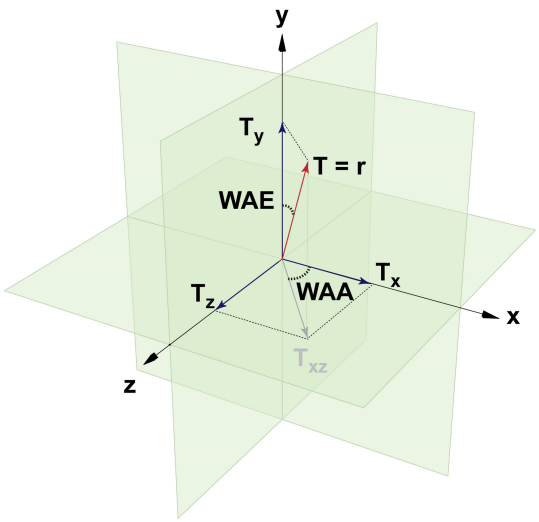


$$WAA = \frac{(40 * 0.1) + (25 * 0.2) + (26 * 0.28) + (24 * 0.23) + (25 * 0.09) + (30 * 0.02)}{(0.1 + 0.2 + 0.28 + 0.23 + 0.09 + 0.02)} = 26.79°$$

Supplemental Figure 5

Example calculation of the weight-averaged azimuth (WAA) and the weight-averaged elevation (WEE).

A Projections of a repolarization vector

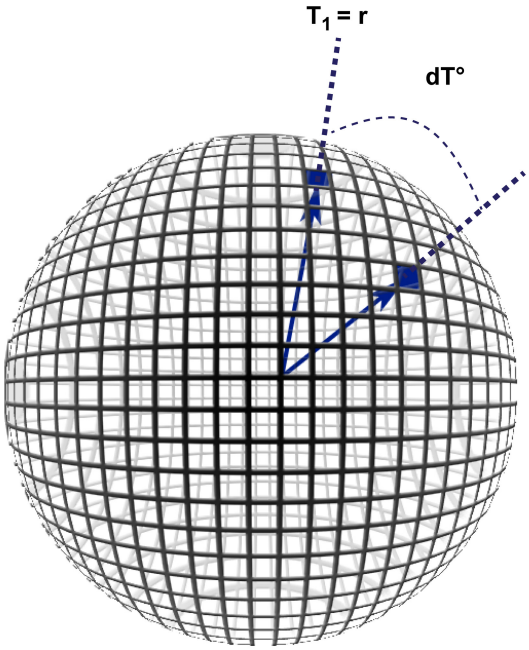


$T_x = r * \sin(WAE) * \cos(WAA)$

$T_y = r * \cos(WAE)$

$T_z = r * \sin(WAE) * \sin(WAA)$

B Angle between two repolarization vectors



$|T_1| * |T_2| * \cos(dT°) = T_{1x} * T_{2x} + T_{1y} * T_{2y} + T_{1z} * T_{2z}$

$r^2 * \cos(dT°) = T_{1x} * T_{2x} + T_{1y} * T_{2y} + T_{1z} * T_{2z}$

$T_{1x} * T_{2x} = r^2 * \sin(WAE_1) * \cos(WAA_1) * \sin(WAE_2) * \cos(WAA_2)$

$T_{1y} * T_{2y} = r^2 * \cos(WAE_1) * \cos(WAE_2)$

$T_{1z} * T_{2z} = r^2 * \sin(WAE_1) * \sin(WAA_1) * \sin(WAE_2) * \sin(WAA_2)$

$dT° = \text{acos} (\sin(WAE_1) * \cos(WAA_1) * \sin(WAE_2) * \cos(WAA_2) + \cos(WAE_1) * \cos(WAE_2) + \sin(WAE_1) * \sin(WAA_1) * \sin(WAE_2) * \sin(WAA_2))$

C Example

T_1: $WAE_1 = 30$ and $WAA_1 = 45$

T_2: $WAE_2 = 35$ and $WAA_2 = 50$

$dT° = \text{acos} (\sin(30) * \cos(45) * \sin(35) * \cos(50) + \cos(30) * \cos(35) + \sin(30) * \sin(45) * \sin(35) * \sin(50))$

$dT° = \text{acos} (0.1304 + 0.7094 + 0.1553) = 5.672°$

Supplemental Figure 6

Calculation of the angle *dT*° between two successive repolarization vectors T_1 and T_2.

(A) Projection of a vector T on the three orthogonal axes X, Y and Z. **(B)** Two repolarization vectors T_1 and T_2 with length *r* are projected on a virtual sphere. The dot product of the two vectors is used to calculate the angle *dT*° between T_1 and T_2. **(C)** Example calculation for angle *dT*° between vectors T_1 and T_2.

Supplemental Tables

Supplemental Table 1

Comparison between low-frequency oscillations of heart rate and repolarization in the physiological cohorts. Variables are presented as mean value ± standard error of the mean.

Atrial-pacing cohort						
	PRD	**p-value**	**ln (LF)**	**p-value**	**LFn**	**p-value**
Resting*	5.28 ± 0.67		6.13 ± 0.43		0.72 ± 0.05	
Fixed atrial pacing	4.99 ± 1.22	0.193	0.45 ± 0.38	0.002	0.18 ± 0.03	0.002
Adrenergic-activation cohort						
	PRD	**p-value**	**ln (LF)**	**p-value**	**LFn**	**p-value**
Resting*	3.57± 0.33		7.09 ± 0.33		0.48 ± 0.05	
Tilt-table testing	6.88 ± 0.96	0.005	7.29 ± 0.18	0.465	0.72 ± 0.05	0.002
Exercise testing	13.94 ± 2.00	0.001	4.06 ± 0.34	0.001	0.42 ± 0.08	0.413
Adrenergic-blockade cohort						
	PRD	**p-value**	**ln (LF)**	**p-value**	**LFn**	**p-value**
Atrial pacing*	5.36 ± 0.56		-1.03 ± 0.84		0.23 ± 0.10	
Atrial pacing & Beta-blocker	2.23 ± 0.22	0.002	-0.98 ± 0.70	0.461	0.17 ± 0.04	0.945

* reference condition; p-value denotes difference from reference

Supplemental Table 2

Multivariable models including periodic repolarization dynamics (PRD) for the prediction of 5-year total mortality in a cohort of 908 patients surviving acute myocardial infarction.

Model 1: Clinical marker and PRD		
Risk variable	**Hazard ratio (95% CI)**	**p-value**
GRACE score ≥120	4.28 (2.47 – 7.40)	< 0.001
PRD ≥ 5.75 deg^2	3.49 (2.14 – 5.70)	< 0.001
Relative IDI	85%	< 0.001
Model 2: Clinical marker, structural marker, and PRD		
Risk variable	**Hazard ratio (95% CI)**	**p-value**
GRACE score ≥120	4.02 (2.34 – 7.06)	< 0.001
LVEF ≤ 35%	2.27 (1.31 – 3.95)	0.003
PRD ≥ 5.75 deg^2	3.14 (1.91 – 5.18)	< 0.001
Relative IDI	45%	< 0.001

Model 3: Clinical marker, HRV, and PRD

Risk variable	Hazard ratio (95% CI)	p-value
GRACE score ≥120	4.21 (2.43 – 7.30)	< 0.001
Mean HR > 75 bpm	1.22 (0.62 – 2.40)	0.557
SDNN ≤ 70 ms	1.69 (0.95 – 3.02)	0.075
PRD ≥ 5.75 deg^2	3.37 (2.06 – 5.52)	< 0.001
Relative IDI	67%	< 0.001

Model 4: Clinical marker, structural marker, HRV, and PRD

Risk variable	Hazard ratio (95% CI)	p-value
GRACE score ≥120	3.94 (2.26 – 6.86)	< 0.001
LVEF ≤ 35%	2.31 (1.33 – 4.01)	0.003
Mean HR > 75 bpm	1.20 (0.62 – 2.33)	0.591
SDNN ≤ 70 ms	1.74 (0.98 – 3.09)	0.057
PRD ≥ 5.75 deg^2	3.03 (1.84 – 5.01)	< 0.001
Relative IDI	38%	< 0.001

Model 5: Clinical marker, structural marker, HRV, PRD, and respiratory rate		
Risk variable	**Hazard ratio (95% CI)**	**p-value**
GRACE score ≥120	3.52 (2.01 – 6.16)	< 0.001
LVEF ≤ 35%	2.29 (1.33 – 3.95)	0.003
Mean HR > 75 bpm	1.13 (0.58 – 2.20)	0.710
SDNN ≤ 70 ms	1.77 (1.00 – 3.14)	0.048
Respiratory rate (continuous)	1.17 (1.07 – 1.29)	< 0.001
PRD ≥ 5.75 deg^2	3.01 (1.83 – 4.94)	< 0.001
Relative IDI	30%	< 0.001

HR = heart rate, HRV = heart rate variability, GRACE = Global Registry of Acute Coronary Events, LVEF = left ventricular ejection fraction, Relative IDI = relative integrated discrimination improvement in various models after the addition periodic repolarization dynamics in the multivariable logistic regression model, SDNN = standard deviation of all normal-to-normal intervals.

GRACE score, LVEF, mean HR and SDNN were dichotomized at predefined cutoff values of ≥ 120, ≤ 35%, > 75 bpm, and ≤ 70 ms respectively. The upper quartile of PRD (5.75 deg^2) was used for dichotomization. Respiratory rate was included as scalar factor in the multivariable model. The GRACE score combines several clinical risk factors, including patient age, history of previous myocardial infarction and congestive heart failure, ST-segment deviation, elevated cardiac enzymes, renal impairment, systolic blood pressure and HR upon admission, and percutaneous coronary interventions during the hospital stay.