Effect of Heart Rate on Ventricular Repolarization in Healthy Individuals Applying Vectorcardiographic T Vector and T Vector Loop Analysis

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Background: Ventricular repolarization (VR) is strongly influenced by heart rate (HR) and autonomic nervous activity, both of which also are important for arrhythmogenesis. Their relative influence on VR is difficult to separate, but might be crucial for understanding while some but not other individuals are at risk for life-threatening arrhythmias at a certain HR. This study was therefore designed to assess the “pure” effect of HR increase by atrial pacing on the ventricular gradient (VG) and other vectorcardiographically (VCG) derived VR parameters during an otherwise unchanged condition.

Methods: In 19 patients with structurally normal hearts, a protocol with stepwise increased atrial pacing was performed after successful arrhythmia ablation. Conduction intervals were measured on averaged three-dimensional (3D) QRST complexes. In addition, various VCG parameters were measured from the QRS and T vectors as well as from the T loop. All measurements were performed after at least 3 minutes of rate adaptation of VR.

Results: VR changes at HR from 80 to 120 bpm were assessed. The QRS and QT intervals, VG, QRSarea, Tarea, and Tamplitude were markedly rate dependent. In contrast, the Tp-e/QT ratio was rate independent as well as the T-loop morphology parameters Tavplan and Teigenvalue describing the bulginess and circularity of the loop.

Conclusions: In healthy individuals, the response to increased HR within the specified range suggests a decreased heterogeneity of depolarization instants, action potential morphology, and consequently of the global VR.

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Heterogeneity of ventricular repolarization (VR) is due to intercellular differences in depolarization instants and action potential (AP) morphology.¹ VR modulation is very complex and heart rate (HR), autonomic nervous system activity, gender, and age are some of the major influencing factors.² Increase in VR heterogeneity might set the stage for sustained arrhythmias.³ Therefore, evaluation of its modulating factors is required for improved understanding of arrhythmia mechanisms. Since QT dispersion on the surface electro-

cardiogram (ECG) was abandoned, several other ECG indices, that is, Tamplitude, Tarea, the interval between the T-wave peak and end (Tp-e), its ratio to the entire QT interval (Tp-e/QT), QRS-T angle, and QRS-T area angle have been proposed to reflect VR heterogeneity in experimental, clinical, and computer simulation studies, where higher values in general represent increased heterogeneity.^{4–10} The ventricular gradient (VG) (also QRSTarea or QRST integral) is the vector sum of the QRSarea and Tarea. Furthermore, theoretical

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evidence has been presented that the VG is an index of heterogeneity of AP morphology.^{1,11}

Our group has applied vectorcardiography (VCG) based on the orthogonal X, Y, Z lead system for the noninvasive study of global (here: entire heart) VR, as suggested by Badilini et al.¹² Different conditions in which significant VR changes take place have been studied, for example, the development of "cardiac memory," "cardiac fatigue," and coronary occlusion-induced ischemia in humans and pig.^{13–17} In addition to ECG-based measures providing estimates of VR duration, VCG provides information about other aspects of VR reflected by T vector and T vector loop (from here: T loop) morphology parameters, is less operator dependent and more anatomically representative than scalar ECG.^{13–17}

The effect of HR on the AP and VR duration has been extensively studied and documented by many investigators since the seminal work on the QT interval by Bazett in 1920.^{18,19} The "pure" HR effect on the VG and other vectorcardiographically (VCG) derived VR parameters is, however, incompletely known.

The cause of the change in HR (e.g., positional and activity changes with alterations in vagal and/or sympathetic tone, disease states, etc.) might have direct, rate-independent effects on VR.^{20–22} As part of a project to define both HR and autonomic nervous system influences on VCG-derived VR measures and in order to evaluate the effect of HR increase as a single factor, the design with atrial endocardial pacing at different HRs was chosen in this study, keeping other factors as constant as possible.

METHODS

This study was conducted with the approval of the Human Research Ethics Committee of Umeå University, and in accordance with the Helsinki Declaration (2000) for Ethical Principles for Medical Research Involving Human Subjects.

Patients 20–80 years of age, scheduled for ablation therapy for atrioventricular nodal reentrant tachycardia (AVNRT), concealed Wolff-Parkinson-White (WPW; i.e., without preexcitation) or ectopic atrial tachycardia (EAT) were considered for participation in the study. The inclusion criteria were a medical history not suggestive of coronary artery disease, a normal ECG and absence of hypertrophy on echocardiographic examination, and, in patients

older than 55 years of age, a normal coronary angiogram. All chronic medications were discontinued 4 days before catheterization and no medication was given before or during the procedure.

After successful ablation, a 5-F four-electrode catheter was placed in a high lateral position in the right atrium. Pacing was performed using a standard pacing and recording system (EP-Tracer Version 3.0, CardioTek, Maastricht, The Netherlands).

Pacing Protocol

Pacing was started at a rate 5–10 bpm higher than the patient's resting HR avoiding interference with the spontaneous rhythm and lasted 6 minutes. The pacing rate was then increased stepwise with 10 bpm for periods of 4 minutes until the Wenchebach point (block) occurred or the HR reached 150 bpm. For this particular study, only HRs up to 120 bpm were used to avoid interference between the atrial pacing artifact and the preceding end of the T wave, while higher rates were used in a previous study focused on the ST segment.²³

VCG

VCG recording and analysis were performed as described in detail elsewhere, and the same terminology and definitions of parameters were used;^{13–16} for illustrations see ref. 15 or 16. In brief, a MIDA 1000 system (Ortivus AB, Danderyd, Sweden) was used. This system uses eight electrodes positioned according to the Frank orthogonal lead system (X, Y, and Z). In order to allow sufficient time to reach rate adaptation and VR steady state, only the last minute of all 4-minute recordings was used for analysis. An averaged 3D QRST complex was constructed from all cardiac cycles recorded during a 15 seconds sampling period, and the mean of four such averages from the last 1-minute period was used in our analysis.

All parameters were analyzed offline using customized software. The averaged 3D QRST complexes were used for assessing the conventional QRS, QT, and Tp-e intervals from which the Tp-e/QT ratio was calculated; QT was HR corrected both according to Bazett and Fridericia as $QTcB = QT / RR^{1/2}$ and $QTcF = QT/RR^{1/3}$ (RR in seconds). In addition, VG or QRST area, QRSarea and Tarea ($\mu V s$), which are the spatial areas formed by the moving heart vector during the QT, QJ, and JT

intervals, respectively, were computed from the QRS complex in the three orthogonal directions: $QRST_{area} = (QRST_x^2 + QRST_y^2 + QRST_z^2)^{1/2}$, $QRS_{area} = (QRS_x^2 + QRS_y^2 + QRS_z^2)^{1/2}$, and $T_{area} = (T_x^2 + T_y^2 + T_z^2)^{1/2}$ (μV s). The QRS-Tarea angle was defined as the angle between the QRSarea-vector and the Tarea-vector (0° – 180°). The amplitude of the maximum QRS and T vectors (mV) in space was defined as well as their relation, that is, the QRS-T angle (0° – 180°). Generally, the wider these angles, the more abnormal they are, although there is a wide range for normality as well as a gray zone between "normal" and "abnormal."⁴ The spatial orientation of the maximum T vector was defined by its azimuth and elevation. Tazimuth is the angle in the transverse plane (0° left, $+90^\circ$ front, -90° back, and 180° right). Telelevation is the angle in the cranio-caudal direction by us defined from 0° (caudal direction) to 180° (cranial direction). The human T loop is normally elongated (elliptical) and located in one (preferential) plane in space with the maximum vector pointing forward, downward, and to the left. The preferential plane was computed for each individual and the T loop was characterized by two parameters: Teigenvalue (roundness; unitless) and Tavplan (bulginess; μV). Teigenvalue was computed as the squared quotient between the two largest perpendicular axes (eigenvalues) of the T loop in this plane $(d1/d2)^2$ (where $d1 \geq d2$). The T loop has a high Teigenvalue in a healthy individual, but can never have a more abnormal value than 1, for the special case of a circle. The third axis perpendicular to d1 and d2 is normally close to zero and was therefore disregarded in the computation of Teigenvalue, but it is reflected by Tavplan. Tavplan was computed as the mean distance between the periphery of the T loop and both sides of the preferential plane. This parameter reflects the loop's lack of planarity, where higher values represent a more bulgy and abnormal T loop.^{15,16} At any instant, the T vector value reflects the VR heterogeneity, and an increase in Tavplan is due either to a larger T vector or larger variation in its direction on both sides of the preferential plane during VR.

Statistics

Mean (standard deviation [SD]) was used for descriptive purposes. Friedman's test was used for analysis of the overall effects and correlation analysis was used to test relations between HR increase

and the parameter changes. Because of multiple statistical testing, parameters were defined as rate-dependent or rate-independent only when the results of Friedman's test and the correlation analysis were consistent, that is, both significant or non-significant; $P < 0.05$.

RESULTS

Altogether 19 individuals (8 men, 11 women) were included. Their mean age (SD) was 45⁽⁹⁾ years and their final diagnoses were AVNRT in nine, concealed WPW in eight, and EAT in two; all of them had normal echocardiography examinations. Depending on the resting HR, pacing was started at 80 or 90 bpm. Our analysis was limited to a maximum HR of 120 bpm because of the appearance of pacing artifacts on the preceding T wave at shorter cycle lengths (higher rates), which distorted the T loops.

Table 1 shows the average value (SD) of each parameter for all available data at different HRs. This table shows also that neither the lowest nor the maximum HRs were the same in all persons. In order to evaluate the effect of an HR change over a range of at least 30 bpm, subjects were therefore divided into two partly overlapping groups with HR ranges of 80–110 ($n = 8$) or 90–120 ($n = 9$) bpm (Tables 2 and 3). In the correlation analysis, however, the differences in the parameter values from the lowest to the highest paced rates (range 10, 20, 30, or 40 bpm) were used for all individuals, that is, 19 paired values. Only when results were consistent over both HR ranges and in the correlation analysis, a judgment was made in relation to HR dependence or independence.

The HR responses were similar in both subgroups for almost all parameters. As expected, the QT interval was rate dependent and decreased significantly with increasing HR. In contrast, the Tp-e/QT ratio had a constant value of on average 0.20–0.21 irrespective of HR.

The most significant HR-dependent changes were observed in VG, Tarea, and Tamplitude, which decreased more than 30% in response to a 30 bpm increase in HR, similar in both groups.

The T vector seemed to move slightly upward (increased Telelevation) and possibly forward (increased Tazimuth) with increased HR, but these changes, along with a numerical widening of the QRS-T angle and QRS-T area angle, were not unequivocally rate dependent.

Table 1. The mean (SD) for each parameter for all available data at different atrial paced heart rates in the study group (n = 19). Note that the number in the column head applies to the specific heart rate

Heart Rate (bpm)	80 n = 9	90 n = 16	100 n = 18	110 n = 16	120 n = 10
QRS (ms)	90 (8)	89 (8)	90 (8)	88 (9)	89 (7)
QT (ms)	360 (19)	346 (17)	330 (13)	314 (10)	300 (13)
QTcB (ms)	416 (22)	425 (21)	427 (17)	425 (13)	424 (19)
QTcF (ms)	396 (21)	397 (19)	392 (16)	384 (12)	378 (17)
Tp-e (ms)	71 (10)	69 (10)	67 (10)	64 (10)	61 (10)
Tp-e/QT	0.20 (0.02)	0.20 (0.02)	0.20 (0.02)	0.20 (0.03)	0.20 (0.03)
QRSarea (μ Vs)	34 (9)	28 (11)	27 (10)	27 (8)	26 (8)
Tarea (μ Vs)	47 (16)	37 (15)	32 (14)	26 (14)	24 (14)
VG (QRSTarea) (μ Vs)	65 (13)	51 (15)	45 (13)	39 (12)	35 (11)
QRS amplitude (mV)	1.39 (0.42)	1.20 (0.41)	1.18 (0.36)	1.22 (0.32)	1.21 (0.28)
Tamplitude (mV)	0.38 (0.11)	0.31 (0.11)	0.28 (0.11)	0.25 (0.11)	0.24 (0.11)
Tazimuth ($^{\circ}$)	32 (17)	29 (25)	33 (25)	33 (25)	29 (26)
Televation ($^{\circ}$)	59 (13)	60 (11)	62 (11)	67 (13)	69 (12)
QRS-T angle ($^{\circ}$)	57 (18)	55 (21)	62 (29)	68 (31)	75 (36)
QRS-T area angle ($^{\circ}$)	72 (18)	75 (24)	78 (23)	84 (26)	88 (28)
Tavplan (μ V)	0.57 (0.20)	0.56 (0.20)	0.58 (0.20)	0.57 (0.18)	0.62 (0.22)
Teigenvalue	75 (74)	44 (49)	40 (60)	32 (40)	21 (15)

VG = ventricular gradient.

The T-loop bulginess reflected by Tavplan did not change. Although the T loop seemed to become more circular as HR increased, the change in circularity was not statistically significant; please note large SD.

In summary (Fig. 1), in this group of generally healthy individuals changes in atrial paced HR from 80 to 120 bpm showed that the QRS and QT intervals together with VG, QRSarea, Tarea, and Tamplitude were markedly rate dependent, and

Table 2. The effects of stepwise heart rate increase from 80 to 110 bpm (n = 8) on different VCG parameters presented as mean (SD). The correlation analysis was based on the changes from the lowest to the highest atrial paced rate in any individual (n = 19)

Heart Rate (bpm)	80 (n = 8)	90 (n = 8)	100 (n = 8)	110 (n = 8)	Friedman (n = 8) P-value	Correlation Analysis (n = 19)	
						r	P-value
QRS (ms)	91 (4)	89 (3)	89 (4)	86 (8)	0.016	-0.51	0.025
QT (ms)	357 (8)	341 (5)	326 (0)	314 (2)	0.000	-0.74	0.000
QTcB (ms)	412 (9)	417 (6)	422 (0)	426 (2)	0.04	0.35	0.15
QTcF (ms)	393 (9)	390 (5)	387 (0)	384 (2)	0.01	-0.13	0.60
Tp-e (ms)	71 (13)	67 (12)	65 (5)	63 (5)	0.03	-0.38	0.11
Tp-e/QT	0.20 (0.03)	0.20 (0.03)	0.20 (0.02)	0.20 (0.02)	0.35	0.023	0.92
QRSarea (μ Vs)	33 (9)	33 (8)	31 (8)	30 (8)	0.001	-0.53	0.02
Tarea (μ Vs)	50 (12)	46 (10)	38 (6)	32 (5)	0.000	-0.78	0.000
VG (QRSTarea) (μ Vs)	66 (14)	61 (13)	53 (13)	45 (14)	0.000	-0.79	0.000
QRS amplitude (mV)	1.33 (0.41)	1.31 (0.43)	1.29 (0.47)	1.26 (0.46)	0.06	-0.59	0.008
Tamplitude (mV)	0.40 (0.02)	0.37 (0.02)	0.32 (0.01)	0.28 (0)	0.001	-0.64	0.003
Tazimuth ($^{\circ}$)	32 (30)	34 (32)	38 (31)	39 (33)	0.001	0.28	0.25
Televation ($^{\circ}$)	62 (8)	63 (11)	64 (13)	66 (12)	0.07	0.07	0.79
QRS-T angle ($^{\circ}$)	59 (25)	61 (26)	65 (24)	71 (23)	0.04	0.43	0.068
QRS-T area angle ($^{\circ}$)	74 (20)	75 (21)	79 (15)	85 (11)	0.001	0.35	0.15
Tavplan (μ V)	0.58 (0.21)	0.59 (0.25)	0.62 (0.27)	0.60 (0.28)	0.42	0.31	0.19
Teigenvalue	77 (63)	57 (87)	58 (155)	45 (74)	0.33	-0.06	0.79

VG = ventricular gradient.

Table 3. The effects of stepwise heart rate increase from 90 to 120 bpm (n = 8) on different VCG parameters presented as mean (SD) (correlation analysis as in Table 2)

Heart Rate (bpm)	90 (n = 9)	100 (n = 9)	110 (n = 9)	120 (n = 9)	Friedman (n = 9) P-value	Correlation Analysis (n = 19)	
						r	P-value
QRS (ms)	91 (5)	91 (6)	90 (9)	88 (8)	0.005	−0.51	0.025
QT (ms)	338 (9)	325 (10)	312 (6)	302 (5)	0.000	−0.74	0.000
QTcB (ms)	414 (11)	420 (12)	423 (8)	427 (7)	0.14	0.35	0.15
QTcF (ms)	387 (10)	385 (11)	382 (7)	380 (6)	0.006	−0.13	0.60
Tp-e (ms)	66 (11)	64 (9)	64 (10)	60 (9)	0.029	−0.38	0.11
Tp-e/QT	0.20 (0.03)	0.20 (0.02)	0.21 (0.03)	0.20 (0.03)	0.17	0.023	0.92
QRSarea (μVs)	29 (9)	28 (8)	26 (8)	25 (8)	0.003	−0.53	0.02
Tarea (μVs)	39 (11)	34 (13)	29 (14)	24 (17)	0.000	−0.78	0.000
VG (QRSTarea) (μVs)	53 (15)	47 (13)	40 (13)	35 (12)	0.000	−0.79	0.000
QRS amplitude (mV)	1.24 (0)	1.21 (0.07)	1.19 (0.04)	1.16 (0.06)	0.050	−0.59	0.008
Tamplitude (mV)	0.34 (0.06)	0.29 (0.09)	0.27 (0.10)	0.24 (0.13)	0.001	−0.64	0.003
Tazimuth (°)	24 (4)	28 (1)	29 (2)	28 (4)	0.11	0.28	0.25
Televation (°)	63 (14)	64 (18)	67 (21)	70 (24)	0.017	0.07	0.79
QRS-T angle (°)	51 (32)	62 (29)	67 (30)	76 (33)	0.020	0.43	0.068
QRS-T area angle (°)	72 (41)	76 (36)	83 (32)	88 (31)	0.001	0.35	0.15
Tavplan (μV)	0.61 (0.24)	0.62 (0.30)	0.61 (0.30)	0.65 (0.11)	0.77	0.31	0.19
Teigenvalue	31 (46)	25 (22)	23 (29)	21 (10)	0.43	−0.06	0.79

VG = ventricular gradient.

possibly the QRS amplitude as well. In contrast, the Tp-e/QT ratio was rate independent as well as the T-loop morphology parameter Tavplan and possibly Teigenvalue describing the planarity (bulginess) and roundness (elliptical vs circular) of the loop, respectively. For other evaluated parameters, some rate-dependence might exist.

DISCUSSION

Some components of VR are well known to be HR or interval dependent, such as measures of its duration. In this study, we evaluated the effects of increasing HR by atrial pacing on different noninvasive electrophysiological VCG-derived VR parameters—including indices previously proposed to reflect VR heterogeneity. Our results are based on directly recorded orthogonal X, Y, and Z leads, in contrast to most contemporary research on similar issues in which these leads are derived from a standard 12-lead ECG. The main findings were that changes in atrial paced HR from 80 to 120 bpm not only shortened VR duration but also decreased VCG-derived VR parameters such as VG, QRSarea, Tarea, and Tamplitude. In contrast, T-loop morphology parameters and Tp-e/QT were not affected within this range of HRs.

The decrease in VG can be related to decreasing heterogeneity of AP morphology.¹¹ As HR increases, in the absence of conduction abnormalities, the heterogeneity in both ventricular depolarization instants (QRSarea) and AP morphology (VG) decreases and results in a less heterogeneous global VR. Figure 2 is a simplified illustration of how we interpret the effects of HR increase on the VG's components, QRSarea and Tarea as well as on Tamplitude in this study. However, since VG is the vector sum of QRSarea and Tarea, its value depends also on the angle between these two components and can be calculated as $C = (A^2 + B^2 + 2AB \cos \alpha)^{1/2}$, where C is VG, A is QRSarea, B is Tarea, and α is QRS-T area angle. When the QRS and T vectors point in opposite directions (α is 90–180° and $0 \geq \cos \alpha \geq -1$), the decrease in VG may be interpreted as a sign of increasing VR heterogeneity.¹ In our study, however, the QRS-T area angle is less than 90° and the decrease in Tarea suggests that in otherwise healthy individuals, increasing HR reduces the overall or global VR heterogeneity. This finding contrasts to the results of a study by Zabel et al. in which VR heterogeneity assessed by multiple monophasic AP recordings in isolated rabbit hearts was rate independent.²⁴ Those hearts were, however, paced from a right ventricular site which alters the normal

Figure 1. Box plots illustrating the effects of changes in heart rate between 80 and 110 bpm; (A) the QT interval, (B) the Tpeak-end/QT ratio, and (C) the Tavplan.

repolarization pattern and therefore might overshadow any effect of HR changes. Furthermore, the HR adaptation of the Tamplitude seems to be dependent on proper function of I_{kr} , and is im-

paired in long QT syndrome (LQTS) type 2 and in healthy individuals receiving sotalol.²⁵

In our study, the Tp-e/QT ratio had a constant value with a mean (SD) of 0.20–0.21 (0.03) irrespective of HR, consistent with results based on measures from ECG-lead V_6 .¹⁰ This ratio is significantly greater in patients at risk for arrhythmic events such as those with long and short QT syndrome, Brugada syndrome, and also in patients with acute myocardial infarction.¹⁰ It suggests that a disproportional prolongation of the Tp-e relative to the QT interval points out a propensity for ventricular arrhythmias, which deserves further study.

A widened QRS-T angle was proposed as an independent predictor of cardiovascular mortality.⁴ This angle seemed to widen in response to increasing HR, although the changes we observed were within a range that supposedly is normal.

Methodological Aspects

In humans undergoing angioplasty short-lasting coronary occlusion resulted in an increasing Tavplan (more distorted T loop) and decreasing Teigenvalue (more circular T loop), which were most pronounced in the presence of ECG signs of hypertrophy.^{13,14} In addition, our group recently showed that episodes of ventricular fibrillation were preceded by a significantly exaggerated distortion of the T loop (i.e., increased Tavplan) during myocardial infarction induced by balloon occlusion of the left anterior descending artery in a porcine model.¹⁷ The present study reveals that Tavplan was not affected by HR changes within the physiological range of 80–120 bpm in humans. Furthermore, Tavplan remained unaffected by cardiac fatigue, which significantly altered Tamplitude, Tarea, and Tp-e.¹⁶ Increase in Tavplan is due either to a larger T vector or larger variation in its direction on both sides of the preferential plane during VR, and its prognostic value regarding subsequent arrhythmic events requires further investigation.

HR correction within this range showed increasing QTcB and decreasing QTcF, Tables 2 and 3.

Implications

Overdrive pacing is a well-known means of suppressing arrhythmia propensity, for example, in the immediate phase after atrioventricular junctional (His' bundle) ablation and ventricular pacing.²⁶ Pacing has also been used in subsets of LQTS patients.²⁷ If atrial pacing at higher rates can

Figure 2. A simplified illustration of the effects of change from a lower (A) to a higher (B) heart rate on the ventricular gradient's components, QRS area and Tarea, and the relation to Tamplitude. Box-plot inserts show VG (1), Tarea (2), and Tamplitude (3).

result in a similar decrease in global VR heterogeneity in patients with propensity for ventricular arrhythmias (e.g., LQTS patients) as in healthy individuals in this study, it might improve arrhythmia prevention in such patients, which can be tested in those who already carry a pacemaker or an implantable cardioverter defibrillator (ICD).

Our results are also relevant when studying the VG and other VR changes in response to different interventions which might also affect HR, for example, perturbations of the autonomic nervous system, which usually result in HRs in the range studied here.^{20,28,29}

Limitations

The resting HR, and consequently the lowest paced rate of 80–90 bpm, was somewhat higher than would be expected in healthy individuals, which partly was due to the discontinuation of beta-blockers in some patients 4 days before the study and partly because the study was performed after several hours of fasting and an ablation procedure, which might affect autonomic tone. Transesophageal stimulation is, however, not a better alternative from this aspect (due to pain, etc.), and it is for ethical reasons difficult to perform a study

like this before an ablation procedure (of unknown duration) has been successfully completed. Patients with permanent atrial pacing leads would be an alternative, but they are in general much older, less healthy, and frequently on various medications.

Our results are valid only for relatively small and smooth increments within the HR range of 80–120 bpm, which, however, are relevant for reasons discussed in the previous section.

CONCLUSIONS

Changes in atrial paced HR from 80 to 120 bpm not only shortened VR duration but also decreased VCG-derived parameters such as VG, QRS area, Tarea, and Tamplitude. It is therefore conceivable that in response to this increase in HR, in otherwise healthy individuals, there is a decrease in heterogeneity of ventricular depolarization instants, AP morphology, and consequently global VR. In contrast, Tp-e/QT and T-loop morphology parameters were not affected within this range of HRs.

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