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REVIEW

Dispersion of ventricular repolarization: Temporal and spatial

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Abstract

Repolarization heterogeneity (RH) is an intrinsic property of ventricular myocardium and the reason for T-wave formation on electrocardiogram (ECG). Exceeding the physiologically based RH level is associated with appearance of life-threatening ventricular arrhythmias and sudden cardiac death. In this regard, an accurate and comprehensive evaluation of the degree of RH parameters is of importance for assessment of heart state and arrhythmic risk. This review is devoted to comprehensive consideration of RH phenomena in terms of electrophysiological processes underlying RH, cardiac electric field formation during ventricular repolarization, as well as clinical significance of RH and its reflection on ECG parameters. The formation of transmural, apicobasal, left-to-right and anterior-posterior gradients of action potential durations and end of repolarization times resulting from the heterogenous distribution of repolarizing ion currents and action potential morphology throughout the heart ventricles, and the different sensitivity of myocardial cells in different ventricular regions to the action of pharmacological agents, temperature, frequency of stimulation, *etc*., are being discussed. The review is focused on the fact that RH has different aspects – temporal and spatial, global and local; ECG reflection of various RH aspects and their clinical significance are being discussed. Strategies for comprehensive assessment of ventricular RH using different ECG indices reflecting various RH aspects are presented.

Key Words: Temporal; Spatial; Global and local dispersion of repolarization; Action potential duration; Tpeak-Tend interval; Tpeak-Tend dispersion; T-vector; Arrhythmogenesis

Core Tip: A comprehensive assessment of ventricular repolarization process is an important part of electrocardiogram (ECG) diagnostics. First of all, the increased

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repolarization heterogeneity is associated with arrhythmogenesis. Besides, repolarization disturbances reflect the degree of electric remodeling of myocardium related to heart failure degree and mortality. We herein discuss the electrophysiological basis for repolarization heterogeneity and the factors that modulate it. We demonstrate that repolarization heterogeneity has various aspects – temporal and spatial, global and local, and there is a need in different ECG-indices to evaluate all the aspects.

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INTRODUCTION

Repolarization process is cardinally different from depolarization. During depolarization, the elementary (cellular) electric field generators responsible for QRS complex formation are concentrated in narrow (approximately 0.8-1 mm) regions of space that separates the excited myocardium (cells with peak action potential) from unexcited one (cells with resting potential)[1]. In contrast, during repolarization the elementary electric generators are dispersed in almost the entire volume of the ventricles, with small gradients in membrane potential between the neighbouring cells. All ventricular cells, the repolarization of which is not yet completed, contribute to cardiac electric field generation.

T-wave is a result of repolarization heterogeneity (RH) – non-simultaneous end-of-repolarization in different ventricular layers and regions. This heterogeneity arises from: (1) Different activation times; and (2) Different action potential duration (APD) of ventricular cells, due to the heterogeneous distribution of repolarizing currents[2]. The global RH in the heart ventricles is defined by the areas of the earliest and the latest repolarization – the difference in end-of-repolarization times in these areas and in their location (temporal and spatial heterogeneity, correspondingly).

In normal heart, physiological heterogeneities in structure, electrical and mechanical activity are crucial for normal, efficient excitation and pumping[3]. Due to multiple reasons (impaired function of outward K+ currents in cardiac myocytes, which may be caused by genetic defects or result from various acquired pathophysiological conditions, including electrical remodelling in cardiac disease, ion channel modulation by clinically used pharmacological agents, and systemic electrolyte disorders seen in heart failure, such as hypokalaemia), the level of RH could increase[4].

Exceeding the physiologically reasonable level of RH could lead to the development of life-threatening ventricular arrhythmias[4-6]. In this regard, an accurate and comprehensive evaluation of RH on the basis of electrocardiogram (ECG) is of importance. This review focuses on various aspects of RH (temporal and spatial, global and local) – their electophysiological basis, ECG reflection and clinical significance.

ELECTROPHYSIOLOGICAL BASIS FOR RH

The reason for different action potential morphology and different sensitivity of myocardial cells to the action of pharmacological agents, temperature, frequency of stimulation, *etc.* is the heterogenous distribution of repolarizing ion currents throughout the heart ventricles. There are differences in repolarizing currents across ventricular walls[7,8], between the left and the right ventricles, between the apex and the base of the ventricles, and between anterior and posterior ventricular surface[9,10].

In transmural plane, *in vitro* studies revealed three types of cells: Epicardial (with the shortest APD), endocardial and M-cells with the longest APD, belonging to the deep layers of the myocardium (Figure 1)[7,8]. In interventricular septum, M-cells were less pronounced than in the free walls of the ventricles[11]. In epicardial and M-cells, the morphology of phase 1 is characterized by a prominent transient outward current (Ito)-mediated notch responsible for the 'spike and dome' morphology[8]. M cells are distinguished from the other cell types in that they display a smaller slowly activating delayed rectifier current (IKs), but a larger late sodium current (late INa) and sodium-

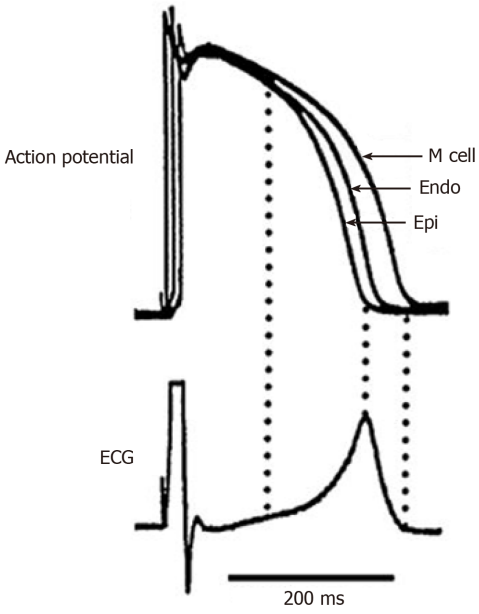

Figure 1 Transmembrane action potential and pseudo electrocardiogram recordings from a canine arterially perfused ventricular wedge preparation reveal the cellular basis for the T wave. Top: Action potentials simultaneously recorded from endocardial, epicardial, and M region sites; Bottom: Electrocardiogram recorded across the wedge; the peak and the end of T-wave correspond to the end-of-repolarization of epicardial and M-cells, correspondingly. Compiled from Figure 2[8]. ECG: Electrocardiogram.

calcium exchange current (INa-Ca). These ionic distinctions underlie the longer APD and steeper APD-rate relationship of the M-cells, which is more pronounced in the presence of antiarrhythmic agents with class III actions[8].

In vivo experiments did not confirm the existence of M-cells and a substantial transmural APD gradient[12-14]. This fact can be explained, firstly, by electrotonic interaction in myocardium *in vivo*, which partially eliminates intrinsic differences in the electrophysiological properties of the cells across ventricular wall[15,16]. Secondly, M-cells can be functionally detected at a low frequency of stimulation, while at physiological frequencies, transmural electrophysiological differences between the cells are significantly reduced[17,18]. It should also be noted that APD recorded *in vivo* is always significantly less than those recorded *in vitro*[14].

At the same time, *in vivo* as well as *in vitro* studies confirm the existence of apicobasal, anteroposterior and left-to-right differences in repolarizing ion currents[12,19-22]. Apico-basal differences were found in the expression of those channel proteins which are involved in mediation of the transient outward K(+) current and the slow delayed rectifier K(+) current: Expression of Kv1.4, KChIP2, KvLQT1 and MinK was significantly higher in apical than in basal myocardium in both canine and human hearts[19]. Prominent differences in the magnitude of the I(to) 1-mediated action potential notch were found in cells isolated from the right and the left canine ventricular epicardium; the influence of this current, although small, is more important in the left ventricle[20-22].

APD GRADIENTS IN THE HEART VENTRICLES

Transmural gradient

Transmural APD gradient is mostly pronounced in isolated myocardial cells and wedge preparations extracted from different ventricular regions – left ventricle[23-25], right ventricle[26], interventricular septum[27,28]; it is resulted from APD differences between epi- and M-cells (*in vitro*), and between epi- and endo cells (*in vivo*). The magnitude of transmural APD gradient recorded *in vitro* reached 100 ms and more[24], and it depended on the wall thickness (the largest transmural APD gradient was recorded in the interventricular septum, the smallest one - in the right ventricle[28,29]) and location (transmural APD gradient was different at the apex and at the base of the ventricles[23]).

The transmural APD gradient is even attributed a key role in T-wave formation and it is assumed as "the symbol of repolarization dispersion"[30,31]. Although, this is true

only for a ventricular wedge preparation (Figure 1), but in the whole heart dispersion of repolarization (DOR) and T-wave are resulted from several gradients[32-34]. *In vivo* experiments did not reveal a substantial transmural APD gradient in the heart ventricles[12-14].

Apicobasal gradient

Apicobasal gradient was detected in almost all animal and humans studies. However, its direction was found to be different in various species and sometimes controversial. APD recorded at the apex were longer than those recorded at the base of the ventricles in human[35-37], rabbit[38,39], dog[12,13], and pig[40]. In other studies, the apical APD were shorter than the basal ones in rabbit[41], pig[42], guinea pig[43], rats[44,45], and chicken[46]. The controversial direction of apicobasal APD gradient in the same species can be explained by the high sensitivity of repolarization to temperature conditions, which could vary in different studies. In some cases, apicobasal gradient was dominating and responsible for cardiac electric field formation[47,48].

Left-to-right gradient

Along with the transmural and apicobasal gradients, the left-to-right gradient was revealed in human and several animal species. APD in the right ventricle were longer than in the left ventricle in human[49], rabbit[50], pig[40] and guinea pig[51]. The opposite interventricular gradient was recorded in dog[52,53] and rat[44,45].

Anterior-posterior gradient

APD measured on the anterior surface of the heart ventricles were shorter than posterior APD in human[37], dog[54,55], and rabbit[56].

EFFECT OF ACTIVATION SEQUENCE ON REPOLARIZATION

Activation sequence affects RH in two ways. First, it contributes to repolarization sequence, because end of repolarization time of myocardial cell is a sum of activation time and APD, and repolarization gradients are combinations of activation and APD gradients. Second, activation sequence can directly effect on APD magnitude, especially at heart stimulation. APD were longer in the center of stimulation, and decreased towards the periphery[57]. The transfer of stimulus from endo- to epicardium prolonged epicardial APD and shortened endocardial APD, and, correspondingly, changed the transmural repolarization gradient[16,58,59]. The reversed activation sequence mostly affected APD of M cells[58]. Thus, earlier activation was associated with longer APD. Nevertheless, the relationship between early activation and longer APD is ambiguous: In rabbit hearts, repolarization sequence in general corresponded to those of depolarization, *i.e.*, the shorter APD were associated with the earlier activation times[60].

REPOLARIZATION GRADIENTS IN THE HEART VENTRICLES

Repolarization gradients in the heart ventricles responsible for T-wave genesis are formed as a result of superimposed gradients of activation times and APD. Nevertheless, the magnitudes of APD gradients usually exceed the magnitudes of activation gradients, therefore APD gradients determine the sequence of repolarization to a greater extent, and changes in repolarization occur almost always because of APD changes.

The analysis of contribution of different parts of the canine heart ventricles to dispersion in repolarization times showed that transmural gradient contributed only 13% to the total DOR, while apicobasal, interventricular, and anterior-posterior gradients contributed the remaining 87%[54]. Simulation studies support that transmural, apicobasal, interventricular and anteroposterior repolarization gradients are all essential to T-wave genesis[32-34].

FACTORS MODULATING RH

Repolarization is rather sensitive than depolarization to the changes in external and internal conditions such as fluctuations in temperature, concentration of various ions,

heart rate, electrical remodeling associated with various pathologies. Inhomogeneous changes in action potentials' morphology modify and amplify the temporal and/or spatial heterogeneity of repolarization. Exceeding the physiologically based level of RH can lead to the development of life-threatening ventricular arrhythmias[5,6]. In this regard, the analysis of both temporal and spatial RH parameters is of importance.

In experimental diabetes mellitus, there were substantial changes in spatial but not in temporal repolarization gradients. In mice, there were increased apicobasal and left-to-right gradients[61]; in rabbit, apicobasal gradient was decreased but a large anteroposteral gradient arised[62-64].

At electrical heart stimulation, the location of stimulus effected on APD and, correspondingly, on repolarization gradients: APD were longer in the center of stimulation, and decreased towards the periphery[57,59,65].

In Tako-Tsubo cardiomyopathy, the ischemic-like Wellens' ECG pattern coincides and quantitatively correlates with apicobasal gradient of myocardial edema as evidenced by using cardiovascular magnetic resonance imaging[66]; dynamic negative T-waves and QTc prolongation are likely to reflect the edema-induced transient inhomogeneity and an increased RH between apical and basal left ventricular regions. An increase in apicobasal repolarization gradient on endo- and epicardium was also found in patients with cardiomyopathy and ventricular arrhythmia vulnerability[67]. In Brugada syndrome, APD shortening in the right ventricle strengthens the left-to-right repolarization gradient and spatial RH[68].

In hypertrophic cardiomyopathy, ECG analysis allowed to reveal the mechanism of cardiomyopathy: Ionic remodelling and action potential prolongation in hypertrophied apical and septal areas (T-wave inversion with normal QRS complex), or abnormal Purkinje-myocardial coupling causing abnormal QRS morphology in leads V4-V6[69].

In hypothermia, which is used for protection of myocardium from hypoxic injury, APD of all myocardial cells, including conducting system and pacemakers, prolong nonuniformly as a result of an increase in repolarizing currents[70,71]; the nonuniform APD prolongation leads to the increase in both temporal and spatial RH[5,72,73]. Epicardial APD prolong to the larger extent than endocardial ones, resulting in the inversion of transmural repolarization gradient at hypothermia[30]. Apicobasal, left-to-right and anteroposteral repolarization gradients were inversed at hypothermia, too[73]. Earlier, T-wave inversion at hypothermia was associated with the inversion of transmural[30] or apicobasal[73] repolarization gradients. The recent *in silico* studies demonstrated that transmural repolarization gradient do not play a crucial role in the cardiac electric field inversion under hypothermia, and the inversion of epicardial repolarization gradients (apicobasal, anterior-posterior and interventricular) causes T-wave inversion regardless of transmural gradient direction[74].

In hypoxia/ischemia, APD shortening is associated with electrolyte imbalance in conditions of oxygen supply termination/limitation[75], and increase in extracellular potassium concentration[76]. Hyperkalemia leads to sodium channels' inactivation and slower conduction velocity[77], as well as to shorter repolarization, since it enhances potassium currents[77,78]. In addition, APD shortening at hypoxia may be associated with the release of catecholamines, which enhance the calcium-dependent chlorine current ICl (Ca) and activate the cAMP-dependent chlorine current ICl (cAMP)[79]. *In vitro* studies showed that subepicardial layers were more sensible to ischemia than subebdocardial ones[80,81], although *in vivo* there were no transmural differences in response to ischemia[82]. At ischemia, a significant increase in left-to-right repolarization gradient was observed[83]. In general, ischemia enhanced both temporal and spatial RH[84].

DOR: TEMPORAL AND SPATIAL, ITS ECG-REFLECTION AND CLINICAL SIGNIFICANCE

Temporal aspect

The quantitative temporal measure of RH is DOR – the time difference between the earliest and the latest end of repolarization in the heart ventricles. A number of experimental studies demonstrated that an increased DOR promotes arrhythmogenic substrate formation[4-6]. Table 1 summarizing ECG-indices with their ability to evaluate the degree and the nature of ventricular RH and the degree of arrhythmic risk.

The most "traditional", but perhaps the least accurate index of DOR is QT interval dispersion. Because of the low reproducibility of clinical data, almost two decades ago it was concluded that QT dispersion gives a poor assessment of DOR[85,86]. From

Table 1 Physiological meaning and cut-off values of electrocardiogram -indices of ventricular repolarization

Repolarization heterogeneity aspect	T-wave index	Cut-off values (arrhythmogenesis)
Maximal end of repolarization/maximal APD values	QT	450 ms (males), 460 ms (females)[119]
Maximal end of repolarization/maximal APD values in conditions of QRS widening	JTend	
The proportion between the minimal and the maximal APD	Tpeak-Tend/QT	0.22[122]; 0.23[123]; 0.31[114]
	T-wave symmetry	≤ 1.7[98]
The global repolarization dispersion	Tpeak-Tend	≥ 103.3 ± 17.4 ms[86,87]; ≥ 142 ms[114]
	T-wave amplitude and T-wave area, calculated on the basis of T-vector or Root Mean Square ECG	
	Ventricular gradient, or QRS-T integral	
Local differences in repolarization dispersion	Tpeak-Tend dispersion	35 ms[113]; 42 ms[114]
	Lead-to-lead differences in Tpeak and Tend instants between adjacent leads	
Local differences in the end of repolarization times	QT dispersion	39 ms[114]; 93 ms[124]
Early repolarization (plateau phase)	JTpeak	
The difference in the spatial sequence of depolarization and repolarization	Spatial QRS-T angle	135°[89,94-99]
The general direction of repolarization sequence	T-vector projection onto the heart ventricles	
	T-loop complexity	
The relative magnitudes of apicobasal, anterior-posterior and left-to-right repolarization gradients	Ratio between X, Y, Z components of T-vector	
The location or the areas of the shortest and the longest APD	T-vector projection onto the heart ventricles	
Electrical instability of ventricular myocardium at cellular level	Macrovolt and microvolt T-wave alternans	
	Beat-to-beat T-vector variability	

APD: Action potential duration; ECG: Electrocardiogram.

theoretical viewpoint, QT dispersion reflects local differences in the latest (T-wave end), but not the earliest repolarization; thus, it reflects DOR only partially.

The more accurate index of DOR is Tpeak-Tend interval - a useful arrhythmic risk stratification tool in a wide variety of pathologies[87-89]. It was proven both experimentally and in silico that Tpeak-Tend directly reflects DOR magnitude[56,90-92]. Although, a serious problem in using Tpeak-Tend for diagnostics is the discrepancy between the cut-off values resulting from different T-end determining method (baseline or tangent) as well as different number of ECG leads involved in calculations. In some studies, Tpeak-Tend was not a predictor of arrhythmia[93,94]; however, this does not decease its clinical significance, but suggests that mechanisms of triggering arrhythmias are not necessarily associated with increased DOR, and the search for new arrhythmogenic indices should be continued. The alternative relative assessments of DOR magnitude are T-wave amplitude, width, area and symmetry[95-99] (Table 1).

Spatial aspect

Traditionally, the term DOR is associated with temporal RH. However, since the regions of early and late repolarization differ both in time and location, DOR is a vectorial parameter, directed from point A (the region of the earliest end of repolarization) to point B (the region of the latest end of repolarization) (Figure 2). The spatial characteristic of RH is T-vector of vectorcardiogram – a three-dimensional total electric vector of ventricular repolarization, which can be calculated on the basis of standard ECG set[100].

T-vector amplitude is not directly equal to DOR: The first is calculated in mV, and the second in ms. However, from physical viewpoint, T-vector amplitude must be

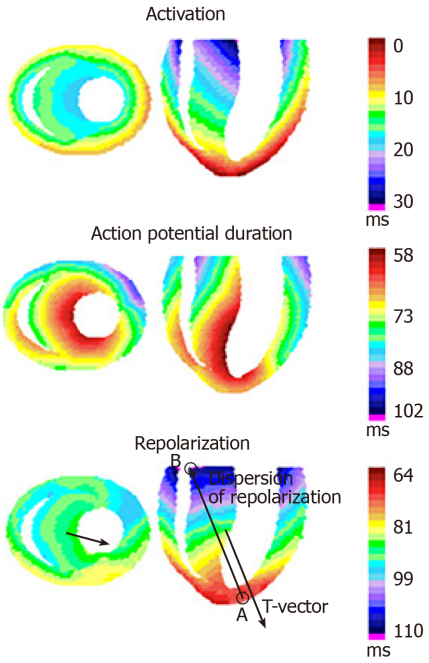

Figure 2 Realistic activation sequence, action potential duration distribution and end-of-repolarization sequence in the rabbit heart ventricles' model, simulated from intramural and epicardial measurements[56]. The middle transversal and longitudinal cross-sections of the model and the corresponding T-vector projections are shown. Transmural, apicobasal, anterior-posterior and left-to-right gradients in activation times, action potential duration and end-of-repolarization times, reconstructed from experimental data, are presented. A and B – the regions of the earliest and the latest end-of-repolarization, correspondingly. T-vector direction is parallel but opposite to the general direction of repolarization sequence.

proportional to DOR magnitude, and the relationship between T-vector components (Tx, Ty and Tz) must reflect the proportion between ventricular repolarization gradients in corresponding directions.

T-vector direction reflects the general sequence of repolarization, but in the opposite way: T-vector is oriented from the regions of late repolarization towards the regions of early repolarization (Figure 2). Substantial changes in T-vector direction, even if DOR magnitude is within normal range (*e.g.*, experimental Diabetes Mellitus[61-64]), indicate a large-scale electrical heart remodeling.

T-vector provides important information in addition to "scalar" DOR value[101]: The amplitudes of cardiac potentials' peaks and the time of their occurrence on ECG depend on lead location, while vectorcardiogram provides objective, "weighted" values; Ventricular gradient (three-dimensional QRS-T integral) reflects the distribution of the action potentials' morphology in the heart ventricles[102]; ST-vector reflects the presence and peculiarities of ischemia; A distorted, twisted T-loop (the trajectory of T-vector projections on anatomical planes during ventricular repolarization) indicates pathological repolarization, while normal T-loop has a correct smoothed shape[103-105].

Besides T-vector direction itself, the angle between T-vector and QRS-vector (QRS-T angle) is highly informative regarding spatial RH[106,107]. In healthy people, repolarization is practically opposite to depolarization, and QRS-T angle is relatively small (≤ 105°)[101,108]. An increased QRS-T angle (≥ 135°) indicates the changes in repolarization sequence, and, correspondingly, the changes in repolarization gradients resulted from electrophysiological disturbances in ventricular myocardium – the altered distribution if ion channels and action potentials' durations[105,109]. An increased QRS-T angle was shown to be the most reliable predictor of the risk of life-threatening arrhythmias and death from heart disease compared with other ECG parameters[105,109-111].

LOCAL DOR *VS* GLOBAL DOR

DOR magnitude along with T-vector reflects the total (global) temporal and spatial repolarization pattern in the heart ventricles, but do not reflect the local electrophysiological heterogeneities. At the same time, increase in local RH may be

more relevant for arrhythmia development than increase in global DOR: The regions with the greatest local repolarization time differences often serve as sources for ectopic beats and Torsade de pointes[111-113].

The same condition (*e.g.*, myocardial ischemia) can lead to the increase in both local and global DOR, and in such a case the global and local repolarization changes are hardly distinguishable, and specific novel markers for local DOR magnitude are need. Dispersion of Tpeak-Tend interval (the difference between the earliest Tpeak and the latest Tend among 12 standard leads) was proposed as a possible specific marker for the local DOR[114,115]. Besides, mathematical simulations showed that local increase in DOR can be expressed in increased lead-toâ€'lead differences in Tpeak and Tend instants between adjacent anatomically ordered standard leads [aVL, I, aVR(-), II, aVF, III, and V1-V6], even if global DOR, Tpeak-Tend interval and Tpeak-Tend dispersion are within a normal range[116].

OTHER REPOLARIZATION PARAMETERS

In some cases, indices characterizing duration and morphology of action potentials (QT, JTpeak and JTend intervals)[117-120], as well as electrical instability of ventricular myocardium at cellular level (macrovolt and microvolt T-wave alternans, beat-to-beat T-vector variability)[121,122] may be of clinical importance (Table 1).

CONCLUSION

Both temporal (the time difference between the earliest and the latest end of repolarization in the whole ventricles, and the local differences in end of repolarization times) and spatial (the general direction of ventricular repolarization sequence and the relative magnitudes of repolarization gradients) heterogeneity of ventricular repolarization are of clinical importance. The complex use of different ECG indices (Tpeak-Tend interval and its dispersion, T-vector and T-loop parameters, QRS-T angle, *etc.*) provides information about temporal and spatial, global and local characteristics of ventricular repolarization for better heart state assessment.

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