Beat-to-beat variability of repolarization: a new parameter to determine arrhythmic risk of an individual or identify proarrhythmic drugs

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ABSTRACT

Hypertrophy and heart failure are associated with an enhanced propensity for cardiac arrhythmias and a high mortality rate. Altered repolarization might play a role in the occurrence of these ventricular arrhythmias. Beat-to-beat variability of repolarization duration (BVR) has been proposed as a parameter for detection of an unstable, and less controlled repolarization process that precedes the actual tachyarrhythmia. To investigate the relevance of BVR in identifying individuals at risk for arrhythmic events, this parameter was studied in dogs with remodeled hearts and increased susceptibility to arrhythmias due to chronic complete atrioventricular block. Progression of electrical remodeling (prolongation of repolarization times), vulnerability to arrhythmias and sudden cardiac death were reflected in baseline values of BVR. Furthermore, BVR showed a strong predictive value in the screening for pro-arrhythmic effects of drugs. Thus, BVR can be used to identify 1) individuals at risk for ventricular tachycardias and 2) drugs with proarrhythmic properties. *(Anadolu Kardiyol Derg 2007: 7 Suppl 1; 73-8)*

Key words: ventricular repolarization, Torsade de Pointes, arrhythmias, electrophysiology

Introduction

Heart failure is a multi-factorial disease in which many different adaptations may be responsible for the very high mortality seen in this patient group. It has been estimated that about half of these patients die from an arrhythmia, accounting for >500.000 deaths a year worldwide. The prevalence for sudden death is present in all categories of the New York Heart Association functional classification, indicating that a depressed cardiac contractility is only part of the arrhythmia story (1). Many arrhythmogenic mechanisms have been identified to contribute to this predisposition, including reentrant and focal sources. One of the electrophysiological hallmarks of heart failure is the increase in ventricular repolarization times (QT-time), as detected on the electrocardiogram (ECG), through more local recorded signals with catheters (monophasic action potential duration (MAPD), electrogram (EGM)) and in tissue and in isolated cells (the duration of the action potential) (2-4). It has been assumed that this aspect of electrical remodeling is important to explain the enhanced susceptibility of arrhythmias in many patients. But how can we detect who is at risk? This information is not only relevant to guide treatment (implantable cardioverter defibrillator (ICD) yes or no), but also to inform the physician and the patient about what situations and/or drugs should be avoided so that a further challenge on repolarization and possibly on life may be prevented. Especially, the proarrhythmic risk of drugs that block the rapid component of the delayed rectifier current (IKr) has been a topic of intense discussion in the scientific, pharmacologic and clinical societies (5, 6). It is a future aim not only to define whether such a drug that affects repolarization is safe or unsafe, but also to identify patients at risk for certain types of drugs. To quote Sir Richard Sykes (rector of Imperial College, London and former chairman of GlaxoSmithKline) "Future must lie in identifying sections of the population most likely to suffer from adverse effects from a drug, so they can be excluded" (7).

In this review, we will address this double challenge: 1) how to identify individuals at risk for repolarization dependent arrhythmias, and 2) how to establish the proarrhythmic risk of a repolarization prolonging drug. For that, it is necessary to elaborate on dog studies in which the severity of electrical remodeling is related to ventricular arrhythmias (1a) and to introduce a new parameter to quantify arrhythmic risk (2). Finally, drug induced arrhythmias will be discussed (3), before the concepts will be integrated.

Ventricular remodeling in chronic atrioventricular block dog

Mechanisms of remodeling have been extensively studied by our group in dogs with chronic complete atrioventricular (AV) block. This model allows examination of electrical, mechanical and structural changes in the heart and their effect on susceptibility to arrhythmias as remodeling progresses.

We identify three stages in the development of a non-remodeled heart to a state of compensated hypertrophy: 1) sinus rhythm (SR), 2) acute AV-block (AAVB) and 3) chronic AV-block (CAVB).

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In SR, the atria and ventricles contract synchronously and the ventricular heart rate is determined by the sinus node (Fig. 1, left panel). The AAVB, the stage immediately after the ablation of the AV-node, is characterized by a slow idioventricular rhythm (IVR) (Fig. 1, middle panel). Reduction of cardiac output is limited by neurohumoral activation (8, 9). The slow heart rate, altered activation and loss of atrioventricular synchrony all can trigger several remodeling mechanisms with which the heart tries to compensate in the long run. After several weeks this remodeling process reaches a stable situation (CAVB), in which compensated hemodynamics is now associated with biventricular hypertrophy, an increased cellular contractility and prolonged repolarization times (electrical remodeling) (10). At the cellular level, current densities of components of the delayed rectifier (IKr and IKs) are decreased, which is confirmed on the molecular level by a down-regulation of the ion channel subunit expression levels. This results in a reduction in repolarization strength, visible as QT prolongation and an increase in the duration of the left ventricular monophasic action potential (LV MAP) (Fig. 1, right panel), which makes the animal susceptible to drug induced arrhythmias. A normal cell possesses redundancy in repolarizing currents, its repolarization reserve, which can be recruited to withstand internal and external factors that challenge the cell's control over the action potential duration (11). Factors that decrease the repolarization strength (i.e. electrical remodeling, bradycardia or pharmacological IKr block) can reduce this reserve to a point where the repolarization process can no longer be controlled and becomes unstable. This results in ectopic beats and eventually triggered arrhythmias. In the CAVB model, administration of an Ikr blocker as the final hit can uncover this increased susceptibility to arrhythmias. Recorded electrophysiological parameters and arrhythmic response to a pharmacological challenge characterize the different stages of electrical remodeling in the AVB dog.

Beat-to-beat variability of repolarization

Abnormal repolarization has been related to increased risk of cardiac arrhythmias and sudden cardiac death. Several parameters are used to quantify deviations in specific aspects of cardiac repolarization: either measuring T-wave morphology (notched T-waves (12), microvolt T-wave alternans (13)) or measuring repolarization duration (QT interval (14), T_{peak}-T_{end} (15) or QT variability index (16)).

Recently, our group proposed beat-to-beat variability of repolarization duration (BVR) as an additional parameter to quantify arrhythmic risk (17). The BVR is a measure of temporal dispersion, which captures the variation in repolarization between subsequent beats and is evaluated at resting heart rates.

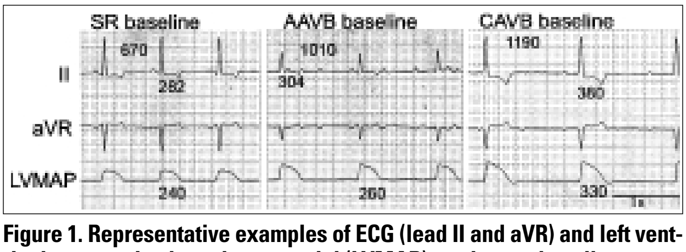

Figure 1. Representative examples of ECG (lead II and aVR) and left ventricular monophasic action potential (LVMAP) tracings at baseline recorded at the three stages of the dog model: sinus rhythm (SR), acute AV-block (AAVB) and chronic AV-block (CAVB). Printed values (top to bottom) are RR, QT and LVMAP duration. ECG is calibrated to 1mV/cm. MAP signal to 20mV/cm. Printed at 25mm/s.

ECG- electrocardiogram

We quantify BVR using the duration of the left ventricular MAPD, but QT interval or transmembrane action potential duration of isolated cells can also be used. Monophasic action potentials (MAP) are recorded using catheters placed on the endocardium of the left ventricular wall. The morphology of the signals recorded from these catheters resemble local trans-membrane action potentials (18). A Poincaré plot is created by plotting MAPD of each beat versus MAPD of the preceding beat. Beat-to-beat variability of repolarization can now be quantified as short term variability (STV) of MAPD, which is calculated as the distance of the points in the plot to the line of identity, averaged over 30 consecutive beats: $STV=\sum_{1\text{-}30}|MAPD_n-MAPD_{n-1}|/(30^*\sqrt{2})$ (17). Figure 2a shows an example of a left ventricular MAP tracing (left panel) with a detailed view of the corresponding Poincaré plot (right panel).

Drug-induced Torsade de Pointes

Torsade de pointes (TdP) is a ventricular polymorphic tachyarrhythmia characterized by a twisting shape of QRS complexes and T waves around the isoelectric line of the ECG (19) (Fig. 2b). This arrhythmia can stop spontaneously or degenerate into ventricular fibrillation and sudden death. Although originally diagnosed in circumstances of AV-block and severe bradycardia, TdP can also be initiated by an adverse reaction to various pharmaceutical compounds with class-III effects. In the recent years, several cardiovascular or non-cardiovascular drugs have been withdrawn from the market due to QT prolongation and TdP (5, 6, 20). Drug induced TdP is a rare arrhythmia with, for some drugs, an incidence of less than 1 case in 10.000 or 100.000 exposures, creating difficulties for the detection of proarrhythmic properties of drugs (5, 6, 21). Therefore, proarrhythmic animal models were developed, including the CAVB dog (5), and several drugs that block I_{Kr} (cardiovascular or non-cardiovascular) have been tested for cardiac safety assessment. Such models also offer the opportunity to study the mechanisms of proarrhythmia and TdP.

To study the potential of a drug to induce TdP, we prefer a serial experimental design in which several drugs can be administered i.v. in different experiments using the anesthetized CAVB animal as it own control. We often used dofetilide as a gold

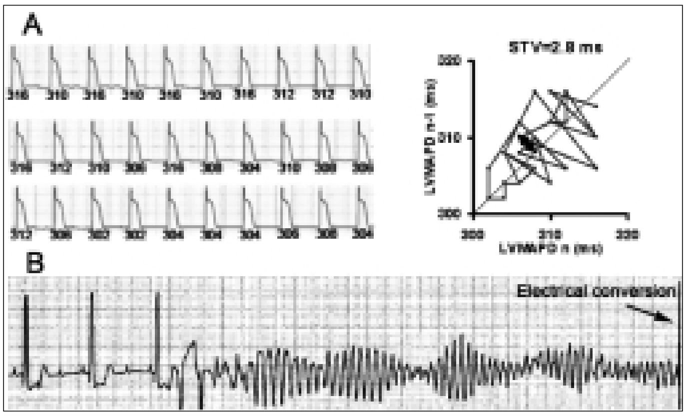

Figure 2. A. In the left panel a tracing of thirty consecutive monophasic action potentials is shown with their respective MAP durations. Shown in the right panel is a Poincaré plot of MAP durations. Short term variability (STV) is calculated as the average distance of the points of the plot to the line of identity (arrow).
B. ECG tracing (lead II) of a drug induced TdP episode, which needed cardioversion.

ECG- electrocardiogram, MAP- monophasic action potential, TdP- torsade de pointes standard for induction of TdP arrhythmias. Dofetilide is an IKr blocker used for the treatment of atrial fibrillation and ventricular tachycardia. But one of its known side-effects is TdP, with an incidence of 3.3% in a selected patient population with congestive heart failure (22). However, in our anaesthetized CAVB dog model a similar dose of dofetilide induced TdP in 74% of the dogs (23), confirming the high sensitivity of the model. Based on this arrhythmic response, we can split the CAVB dogs in two phenotypes: dofetilide susceptible and dofetilide resistant animals (26%).

Beat-to-beat variability of repolarization to determine the severity of electrical remodeling and arrhythmic risk

BVR as measure of severity of electrical remodeling

We investigated the use of BVR as a measure of severity of electrical remodeling in the AVB dog. As mentioned, several remodeling processes are initiated after the induction of AV block. Among them electrical remodeling has been well described at several levels: in the intact heart (QT, MAPD), at the cellular (APD, ion currents) and at the molecular level (expression of ion channel subunits). Over the years, several investigations using these dogs have been performed (8-10, 17, 23-31). The response of the CAVB dog has been well preserved, but was not always quantified on aforementioned cellular or molecular level. To compare severity of electrical remodeling with BVR in these investigations, the heart rate corrected QT interval (QT_c) will be used in this review (Table 1a).

The sudden bradycardia after the transition from SR to AAVB, before electrical remodeling is initiated, leaves QTc unchanged while uncorrected QT and LV MAPD are prolonged (normal frequency dependency). However, at chronic AVB, with electrical remodeling, QTc is severely prolonged (SR: 294±17 ms, AAVB: 286±30 ms, CAVB: 382±51 ms; Table 1a).

Baseline values of BVR respond to electrical remodeling in the different stages of the CAVB dog model in a similar way as QT_c (Table 1b). Figure 3a shows representative examples of Poincaré plots for SR, AAVB and CAVB. Be aware of the difference in scale compared to Figure 2a. At the transition from SR to AAVB, the value of BVR increases from 0.7±0.1 ms to 1.2±0.6 ms. Possible explanations might be the increased RR interval variability (23) or rate dependence of BVR. At chronic AVB, when electrical remodeling is complete, BVR stabilizes at an elevated level (2.6±0.9 ms). Figure 3b illustrates the relation between QT_c and BVR. It confirms that severity of electrical remodeling (increase in QT_c) is reflected in an increase of BVR.

Table 1. Baseline values of QTc and beat-to-beat variability of repolarization (BVR) at different stages of the chronic AV-block dog model: sinus rhythm (SR), acute AV-block (AAVB) and chronic AVB (CAVB)

a. Baseline QTc in the 3 groups of dogs

Reference	SR	AAVB	CAVB
[17]			413±42
[31]	310±10		423±32
[25]		282±29	378±52
[24]			460±67
[26]			361±54
[23]	288±18	293±38	376±46
[30]		284±25	366±59
Pooled data	294±17 (n=16)	286±30 (n=31)	382±51*† (n=133)

*p<0.05 vs SR, † p<0.05 vs AAVB.

b. Baseline BVR in the 3 groups of dogs

Reference	SR	AAVB	CAVB
[17]			3.3±1.2
[31]	0.8±0.1		2.4±0.2
[25]		1.3±0.3	2.7±0.9
[24]			2.0±0.8
[26]			2.3±0.7
[23]	0.7±0.1	0.7±0.1	2.3±0.6
[30]		1.5±0.9	2.7±1.2
Pooled data	0.7±0.1	1.2±0.6*	2.6±0.9*†

*p<0.05 vs SR, † p<0.05 vs AAVB.
All values in ms expressed as Mean±SD.

Prognostic value of BVR at baseline

The severity of electrical remodeling also has consequences for the susceptibility to arrhythmias in the AVB dog. Where in SR or AAVB dofetilide in combination with anesthesia never induces TdP, there is a high TdP incidence in CAVB (74%). Moreover some dogs (10%) die suddenly in the absence of proarrhythmic drugs or anesthesia (25, 29).

Therefore, within the group of CAVB dogs we can discriminate three phenotypes: 1) animals that die from spontaneous arrhythmias (SCD), 2) animals that only show arrhythmias after a pharmacological challenge and 3) animals that are resistant to both spontaneous and drug-induced arrhythmias. Most likely, these differences in arrhythmic response can be explained by a different degree of electrical remodeling and baseline BVR values, expecting the highest values in dogs that die suddenly and the lowest values in drug resistant animals. This has been

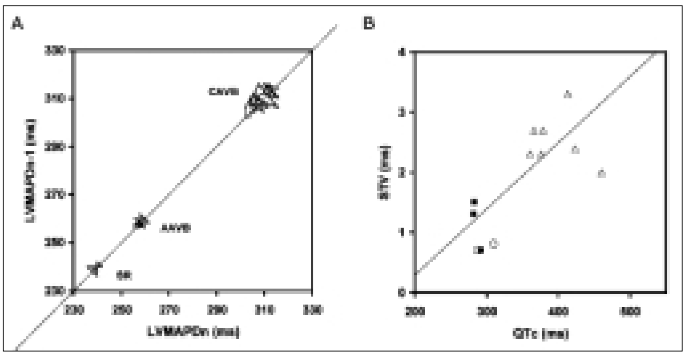

Figure 3. A. Representative Poincaré plots of baseline left ventricular monophasic action potential durations (30 beats) at the three stages of the dog model.
B. Relation between baseline values of QTc and beat-to-beat variability of repolarization at sinus rhythm (SR), acute AVB (AAVB) and chronic AVB (CAVB) with regression line (p<0.01, R2=0.56). Data from Tables 1a and 1b.

AVB- atrioventricular block

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validated in a recent investigation (23). Baseline BVR values were the highest in the SCD animals (5.4±1.4 ms (25)), followed by CAVB dogs that show TdP arrhythmias only after dofetilide (2.5±0.4 ms (23)), while the lowest values of BVR are indeed seen in the dofetilide resistant group (1.7±0.4 ms (23), Fig. 4, CAVB white bars). Thus, BVR captures the differences in repolarization reserve and susceptibility to spontaneous or drug induced arrhythmias.

Limited data are available using BVR in humans. Hinterseer et al. (32) compared BVR derived from QT interval for patients with a history of drug induced arrhythmias (dLQTS, n=13) to a healthy control group (n=13). Despite similar values of rate corrected QT interval, patients in the dLQTS group had a higher BVR compared to control (6.2±4.2 ms vs 4.2±2.1 ms, $p<0.05$). Even in a setting without any pharmacological challenge and normal repolarization duration, BVR identified the reduced repolarization reserve and higher propensity for drug induced arrhythmias in the dLQTS group.

Beat-to-beat variability of repolarization to determine proarrhythmic potential of drugs

BVR and drug-induced torsade de pointes

To further explore the relation between proarrhythmia and BVR, we assessed the effect of several proarrhythmic drugs on BVR. Repolarization parameters (QT_c and BVR) were evaluated before the first drug induced ectopic beat and compared to baseline values. In the CAVB dog model, TdP can be induced by numerous I_{Kr}-blockers. After dofetilide, it can be seen that the drug prolonged the QT_c interval and increased BVR (Table 2) leading to TdP in the majority of the animals. When this study population is divided according to their proarrhythmic outcome into dofetilide-susceptible and dofetilide-resistant animals, we found that BVR increased only in the group where TdP occurred (Fig. 4), while QT_c prolonged in both groups (23). Furthermore, when these proarrhythmic doses of drugs are given in SR or AAVB dogs no arrhythmia was induced and no increase in BVR was observed, whereas QT duration was significantly increased in both situations (23). This indicates that QT prolongation and TdP are not always causally linked. To evaluate alternative parameters, like BVR, in determining arrhythmic properties of medication, we set out a number of experiments: the dose dependent induction of TdP with d-sotalol, another class-III antiarrhythmic, was one study methodology. A high dose (4mg/kg) resulted in 75% TdP occurrence, whereas with a low dose (2mg/kg) only 25% of the animals showed TdP (Table 2). The only parameter reflecting this dose dependency was BVR: with the high dose BVR increased, while with the low dose it did not change significantly, although the 25% inducibility still accounted for a tendency towards increasing values (3.5±1.5 ms to 5.5±1.6 ms (17), Table 2).

A more black and white picture was seen with sertindole, an antipsychotic drug. At a clinically relevant dose (0.2 mg/kg) there was no significant increase in BVR and no TdP, while at a high dose (1 mg/kg) BVR increased and TdP was induced in 76% of the individuals (26). A similar observation was seen for NS-7, a drug in development for anti-stroke therapy, but now by changing the infusion time. The fast infusion did increase BVR and induced TdP in 50% of the cases, while the slow infusion of NS-7 did not induce TdP nor did it increase BVR (from 2.1±0.2 ms to 2.5±1.0 ms (31), Table 2). Thus, drug-induced TdP is associated with an increase in BVR.

Beat-to-beat variability of repolarization and safe drugs

To further validate the assumption that BVR reflects arrhythmic risk we assessed the effect of several non-proarrhythmic drugs on BVR; expecting that safe drugs would not increase the value of BVR. The antiarrhythmic drug amiodarone is known to prolong repolarization duration, but is free of TdP in our experimental setting (28). Although amiodarone prolonged the QT interval, it did not increase BVR (from 2.4±0.2 ms to 2.4±0.4 ms (17), Table 2).

Table 2. Drug-induced TdP and repolarization parameters (QTc, BVR) in chronic AV-block dogs

Drug	QTc, ms		BVR, ms		TdP,	Reference
	control	drug	control	drug	%	
Dofetilide	376±46	467±66 *	2.3±0.6	4.2±1.5 *	74	23
d-Sotalol 4 mg/kg	415±47	484±52 *	3.0±0.7	8.6±3.8 *	75	
d-Sotalol 2 mg/kg	410±37	475±60 *	3.5±1.5	5.5±1.6	25	17
Sertindole 1 mg/kg	361±54	452±63 *	2.3±1.0	5.1±2.0 *	76	
Sertindole 0.2 mg/kg	367±54	439±78 *	2.3±1.0	3.2±1.0	0	26
NS-7 3 mg/kg in 5 min	420±40	480±50	2.6±0.3	6.0±1.4 *	50	
NS-7 3 mg/kg in 60 min	425±20	460±30	2.1±0.2	2.5±1.0	0	31
Amiodarone	340±40	470±75 *	2.4±0.2	2.4±0.4	0	17, 28
Moxifloxacin	466±78	556±63 *	2.0±0.9	3.0±1.3	0	
Azithromycin	450±42	416±48	2.2±0.6	2.3±0.5	0	24

*-$p<0.05$ vs. control; values are expressed as Mean±SD
AV- atrioventricular, BVR- beat-to-beat repolarization variability, TdP- Torsade de Pointes

The antibiotic moxifloxacin, used as a gold standard for QT prolongation assessments in human volunteers (thorough phase 1 QT studies (33)), was administered serially in CAVB dogs. All dogs were found to be susceptible to dofetilide-induced TdP. This test revealed that an extensive prolongation of repolarization duration, similar to dofetilide, is not associated with induction of TdP (24). Again, the absence of TdP with this drug was linked with an unchanged value of BVR. In the same susceptible group azithromycin, one of the most prescribed antibiotics today, was also tested. Again the absence of TdP at plasma concentrations relevant to the clinical practice, was associated with an unaltered BVR, supporting the idea that a stable BVR is characteristic for a safe drug (17, 24, 28) (Table 2).

Integration

Abnormalities in cardiac repolarization have been linked to progression of heart failure and increased risk for sudden cardiac death. Beat-to-beat ventricular repolarization has been proposed to quantify temporal variation as one aspect of altered repolarization. Figure 4 summarizes our findings; baseline values (open bars) reflect the severity of electrical remodeling, which determines the risk for spontaneous or drug induced arrhythmias. Individuals prone to drug induced arrhythmias present with higher BVR values than their drug resistant counter parts. This makes BVR a candidate parameter for identification of patients at risk.

Furthermore, BVR can detect the proarrhythmic potential of drugs (closed bars). Unsafe medication results in an increase of BVR, while safe drugs leave BVR unaffected (Table 2).

Further research is needed, including human studies, to evaluate the applications of BVR in risk stratification.

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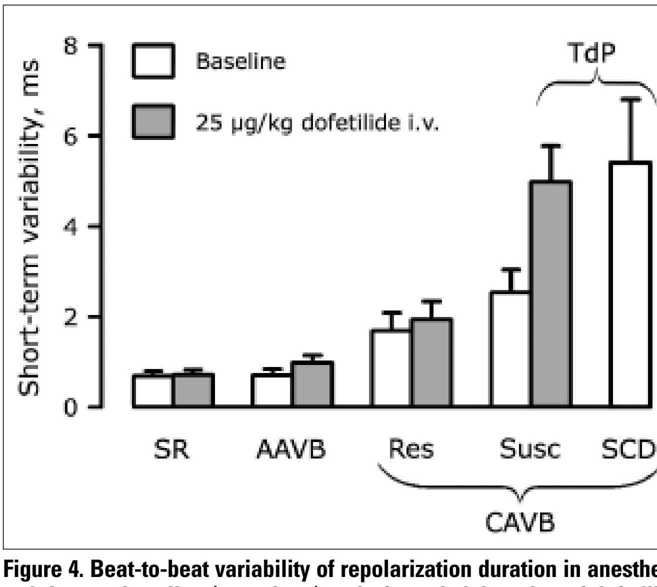

Figure 4. Beat-to-beat variability of repolarization duration in anesthetized dogs at baseline (open bars) and after administration of dofetilide (grey bars) for sinus rhythm (SR), acute AV-block (AAVB) and three subgroups of chronic AV-block: dofetilide resistant (Res), dofetilide susceptible (Susc) and dogs that died suddenly (SCD). Data from (23) and (25).

AV - atrioventricular

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