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The canine model with chronic, complete atrio-ventricular block

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Abbreviations:
AV, Atrio-ventricular;
AAVB, Acute complete atrio-ventricular block;
BVR, Beat-to-beat variability of repolarization;
CAVB, Chronic complete atrio-ventricular block;
CAVBr, CAVB resistant to drug-induced TdP;
CAVBs, CAVB susceptible to drug-induced TdP;
DAD, Delayed after depolarization;
ΔMAPD, Interventricular dispersion of repolarization, LV MAPD-RV MAPD;
EAD, Early after depolarization;
ECG, Electrocardiogram;
ERP, Effective refractoriness period;
HW/BW, Heart weight/body weight index;
LQTs, Long-QT syndrome;
LV, Left ventricle;
MAP, Monophasic action potential;
MAPD, Monophasic action potential duration;
MEB, Multiple ectopic beat;
PVT, Polymorphic ventricular tachyarrhythmia;
RV, Right ventricle;
SCD, Sudden cardiac death;
SEB, Single ectopic beat;
SR, Sinus rhythm;
STV, Short-term variability;
TdP, Torsades de Pointes;
VF, Ventricular fibrillation

ABSTRACT

Proarrhythmic susceptibility to drug-induced Torsades de Pointes is restricted to individuals with a predisposed phenotype characterized by a reduced repolarization reserve. Additional factors are often involved in a further impairment of repolarization, possibly culminating with dangerous ventricular polymorphic tachyarrhythmias. Drugs that block repolarizing currents represent such an additional hit.
The dog model with chronic, complete atrio-ventricular block has been used frequently for proarrhythmic drug screening. The ventricular remodeling seen after ablation of the AV node enhances the susceptibility for repolarization-dependent arrhythmias. In this review, we 1) describe the cellular and molecular basis of ventricular remodeling, 2) validate the CAVB dog as a drug screening model and 3) introduce a new surrogate predictive proarrhythmic parameter: beat-to-beat variability of repolarization.

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1. Introduction

Several publications point to the high incidence of ventricular arrhythmias and sudden cardiac death (SCD) in heart disorders associated with myocardial hypertrophy (Levy et al., 1990; Ghali et al., 1991; Zipes & Wellens, 1998; van Opstal et al., 2001c; Hedman et al., 2004). Polymorphic ventricular tachycardias (PVTs) are without question dangerous as they occur unexpectedly and can degenerate into ventricular fibrillation (VF) (Chugh et al., 2000; Ackerman, 2004; Wever & Robles de Medina, 2004). PVTs can occur due to various heart disorders, such as congenital long-QT syndromes (LQTs): up till now there are more than 300 different mutations known in various ion channels responsible for LQTs. In each congenital syndrome, the repolarization abnormality is caused most frequently by a dysfunction in a single ion current e.g. I_{Ks} in LQT1 and I_{Kr} in LQT2 or a persistent late I_{Na} in LQT3. Less explored are the acquired LQTs as detected in phenotypes with pathologic overload of the heart resulting in ventricular hypertrophy (Levy et al., 1987; Haider et al., 1998) and/or heart failure (Tomaselli & Zipes, 2004). Relatively new are the cathecolaminergic polymorphic ventricular tachycardias (CPVT) in structurally and electrophysiologically normal hearts but with dysfunctional calcium cycling due to mutations in genes, encoding for functional proteins of the sarcoplasmic reticulum (Keating & Sanguinetti, 2001; Priori et al., 2003; Sauer et al., 2007; Tester & Ackerman, 2007). These facts underline the intricate importance of both electrical function and excitation–contraction coupling in ventricular arrhythmogenesis.

To comprehend and study PVTs, animal models are imperative and of great value. For almost a century, the chronic, complete atrio-ventricular block (CAVB) dog has been used as an experimental model (Erlanger & Blackman, 1910). However, just in the last decades, research attention has shifted to its use for proarrhythmic screening of drugs. Its enhanced susceptibility for (drug-induced) Torsades de Pointes (TdP) makes it an ideal model. TdP is a feared PVT characterized by a twisting shape of QRS complexes and T waves around the isoelectric line of the ECG. TdP is often described in a setting of prolonged QT interval as an adverse reaction of various pharmaceutical compounds with class-III effects, although the first TdP published was recorded in the absence of drugs in a patient with complete AV-block and bradycardia (Dessertenne, 1966). In recent years, several drugs have been withdrawn from the market due to drug-induced QT prolongation and reported TdP (Haverkamp et al., 2000; Roden, 2004). Nevertheless, drug-induced TdP is a rare arrhythmia with an incidence of less than 1 case in 10,000 to 100,000 exposures (Haverkamp et al., 2000; Fenichel et al., 2004). Hence, if we would simply appeal to “our inside Sherlock Holmes”, the first suspect in the evaluation of the proarrhythmic risk for a given therapeutic dose of a drug, would be the individual predisposition. Additionally, it became evident that other factors disturbing the repolarization process increase the heart vulnerability for ventricular arrhythmias.

The concept of repolarization reserve comprises and explains the individual differences in the proarrhythmic outcome. Repolarization reserve was initially defined as a complex of multiple mechanisms to achieve normal repolarization (Roden, 1998). In healthy hearts, repolarization reserve is not impaired by the pharmacological block of one type of outward potassium current, as the other repolarizing currents may compensate and control the repolarization (Biliczki et al., 2002). In other words, there is a redundancy in currents responsible for the repolarization process, prohibiting adverse effects of a single channel block. But when challenged with multiple hits, repolarization reserve can be reduced to such an extent that it becomes inadequate with the probability to culminate in potentially lethal PVTs, such as TdP (Volders et al., 1999; Van Opstal et al., 2001a; Akar et al., 2002; Biliczki et al., 2002; Roden, 2006; Milberg et al., 2007). In fact, the repolarization reserve is the ability of the heart to withstand one or more arrhythmogenic challenges (Thomsen et al., 2004). The latter also includes various heart diseases in which complex remodeling processes decrease the repolarization reserve, reflected in a vulnerability to repolarization-dependent ventricular arrhythmias. Therefore the choice for animal models to detect proarrhythmic properties of drugs should consider this predisposition, mimicking the vulnerable patient. In addition, the tested drug should be administered in doses relevant to its therapeutic plasma concentration to determine its proarrhythmic risk. When one considers not the drug but the predisposed individual as the culprit, alternative techniques could be developed to detect the susceptible patients for ventricular arrhythmias. This identification could exclude them from receiving drugs with proarrhythmic properties.

Regarding the cardiac safety assessment of drugs, two current guidelines were adopted in 2005 by the regulatory bodies of the European Union and United States. These guidelines assign both a preclinical strategy (ICH-S7B, 2005) as a clinical approach (ICH-E14, 2005, www.ich.org). The pre-clinical guidelines describe an integrated risk evaluation of a compound to delay ventricular repolarization using four levels of approach: ion channel assay, action-potential parameters, electrocardiogram (ECG) parameters and proarrhythmic effects. Still in this approach the importance of the phenotype of the animal model has been ignored.

Thus, we will discuss in this review the importance of the phenotype, in particular the CAVB dog model. Furthermore, we will introduce an electrophysiological parameter that characterizes both the vulnerable phenotype and predicts drug-induced TdP: beat-to-beat variability of repolarization (BVR). Finally, we will assess the validity of the model in proarrhythmic drug screening.

2. Proarrhythmic susceptibility: reduced repolarization reserve in the CAVB dog

2.1. Remodeling in the CAVB dog

There are several techniques to ablate the atrio-ventricular (AV) node: 1) injection with formaldehyde (37%) into the AV node region, 2) direct current shock, 3) clamping or crushing the region of the AV node, 4) ligation or section of the His bundle, 5) heating the area by radio-frequency (RF ablation) or 6) freezing the AV node (cryo-ablation). In the last years, the preference turned to minimal invasive transvenous approaches using catheter-delivered RF energy to induce a third degree AV-block (Timmermans et al., 2002).

By ablation of the AV node, the ventricular rate drops from roughly 115 to 40–50 beats/min. In the early hours there is competition between foci for dominancy. The acute bradycardia produces volume overload, leading to an increase in left ventricle end-diastolic pressure