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Short-Lasting Episodes of Torsade de Pointes in the Chronic Atrioventricular Block Dog Model Have a Focal Mechanism, While Longer-Lasting Episodes Are Maintained by Re-Entry

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ABSTRACT

OBJECTIVES This study investigated the arrhythmogenic mechanisms responsible for torsade de pointes (TdP) in the chronic atrioventricular block dog model, known for its high susceptibility for TdP.

BACKGROUND The mechanism of TdP arrhythmias has been under debate for many years. Focal activity as well as re-entry have both been mentioned in the initiation and the perpetuation of TdP.

METHODS In 5 TdP-sensitive chronic atrioventricular block dogs, 56 needle electrodes were evenly distributed transmurally to record 240 unipolar local electrograms simultaneously. Nonterminating (NT) episodes were defibrillated after 10 s. Software was developed to automatically detect activation times and to create 3-dimensional visualizations of the arrhythmia. For each episode of ectopic activity (ranging from 2 beats to NT episodes), a novel methodology was created to construct directed graphs of the wave propagation and detect re-entry loops by using an iterative depth-first-search algorithm.

RESULTS Depending on the TdP definition (number of consecutive ectopic beats), we analyzed 29 to 54 TdP: 29 were longer than 5 beats. In the total group, 9 were NT and 45 were self-terminating. Initiation and termination were always based on focal activity. Re-entry becomes more important in the longer-lasting episodes (>14 beats), whereas in all NT TdP, re-entry was the last active mechanism. During re-entry, excitation fronts were constantly present in the heart, while during focal TdP, there was always a silent interval between 2 consecutive waves (142 ms) during which excitation fronts were absent. Interbeat intervals were significantly smaller for re-entry episodes—220 versus 310 ms in focal. Electrograms recorded in particular areas during NT TdP episodes had significantly smaller amplitude (0.38) than during focal episodes (0.59).

CONCLUSIONS TdP can be driven by focal activity as well as by re-entry depending on the duration of the episode. NT episodes are always maintained by re-entry, which can be identified in local unipolar electrograms by shorter interbeat intervals and smaller deflection amplitude. (J Am Coll Cardiol EP 2017;3:1565–76)

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ABBREVIATIONS AND ACRONYMS

2D = 2-dimensional

3D = 3-dimensional

APD = duration of the ventricular action potential

CAVB = chronic atrioventricular block

EAD = early afterdepolarization(s)

ECG = electrocardiogram

IQR = interquartile range

LQT = long QT

LV = left ventricle

NT = nonterminating

PVT = polymorphic ventricular tachycardia

RV = right ventricle

TdP = torsade de pointes

VF = ventricular fibrillation

Torsade de pointes (TdP) is a specific type of abnormal heart rhythm that can lead to sudden cardiac death and is responsible for 20% of the sudden unexplained deaths (1). Two definitions are being used for TdP, first, as a polymorphic ventricular tachycardia (PVT) that exhibits distinct characteristics on the electrocardiogram (ECG) such as varying amplitude or typical twisting, "twisting of the Pointes" (2). Second, in clinics, any arrhythmia in the setting of long QT (LQT) syndrome ranging from (multiple) premature ectopic beats to monomorphic ventricular tachycardia to PVT that is either self-terminating or can degenerate in ventricular fibrillation (VF) is often considered a TdP. In this paper, we used the latter definition and investigated the corresponding ECG characteristics of each episode. Prolongation of the QT interval is associated with an increased risk of developing TdP. The prolongation can be inherited, leading to different LQT syndromes (LQT1 to LQT15) (3).

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These arise from mutation of 1 of the genes, which via altered channel dynamics, cause prolongation of the duration of the ventricular action potential (APD) and thus lengthening the QT interval. In addition, prolongation can be a dangerous side effect of drugs (acquired LQT syndrome). TdP as a prescription drug side effect has been a major liability and reason for withdrawal of medications from the marketplace (4); examples include terfenadine, sertindole, astemizole, grepafloxacin, cisapride (5). In many cases, this effect can be directly linked to QT prolongation mediated predominantly by inhibition of the hERG channel. Whether re-entry or abnormal impulse formation (focal mechanism) or both are involved in TdP is still unclear, but of paramount importance to understand the mechanism of this arrhythmia and possible therapies.

In recent years, it has been argued that the start of TdP is due to a focal beat, which is most probably related to early afterdepolarizations (EAD), which occur due to reduced repolarization reserve (6–13). However, the mechanism underlying TdP perpetuation is still under debate. In animal experiments, some investigators claim that a focal mechanism is the basis of the perpetuation of a TdP (7,11–16), and others claim that nonstationary re-entry is responsible (9,10,17). In other studies, both mechanisms are observed (6,8,14). Also in theoretical studies, both mechanisms were proposed. These studies show that for re-entrant activity, the typical twisting ECG pattern may be due to the drift of a re-entrant circuit (18–21) or meandering of a re-entry spiral wave (22). In cases of focal mechanism, twisting of the ECG may be caused by multiple shifting foci generated by EAD (23,24), or a competition between focal beats generated by fixed heterogeneities with reduced repolarization reserve (25).

Therefore, important questions are how the mechanism of TdP could affect its dynamics and whether there are any specific markers that could determine the mechanism of TdP. In this study, these questions were approached by the application of novel directed-graph algorithms to these unique experimental data obtained in a highly susceptible arrhythmogenic model: the anesthetized chronic atrioventricular block (CAVB) dog model, which is known for its contractile, structural, and electrical adaptations (26). Eventually, the ventricular remodeling (27) reduces repolarization reserve and subsequently predisposes about 70% of canine hearts to develop TdP as a result of a dofetilide challenge.

METHODS

DETAILED ELECTRICAL MAPPING EXPERIMENTS. All animal experiments were performed in accordance with the guidelines formulated by the European Community for the use of experimental animals (EU Directive 2010/63/EU) and with approval from the Committee for Experiments on Animals of Utrecht University (the Netherlands). After pre-medication including atropine, methadone, and acepromazine, anesthesia was induced in 5 CAVB dogs by pentobarbital and maintained by isoflurane 1.5% in a N_2O:O_2 mixture (2:1). After exposing the heart, 56 needles were inserted in the left ventricle (LV) and right ventricle (RV) and in the septal wall as previously described (28): 30 needles in the LV; 18 in the RV; and 8 in the septum, see also Online Figures 1 and 2. All needles were composed of 4 electrode terminals, each recording unipolar electrograms (ActiveTwo system, Biosemi, Amsterdam, the Netherlands). Dofetilide (25 μg/kg/5 min) was then administered in an effort to induce TdP. If arrhythmia episodes lasted over 10 s, the heart was defibrillated.

ARRHYTHMIA EPISODES. In the previous studies performed in CAVB dogs, a TdP episode was defined as an arrhythmia of at least 5 ectopic beats (not including the first paced beat). Because this definition is based on a rather arbitrary number of ectopic beats on one hand, and that this study investigates the association between the mechanism(s) involved with