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The pro- or antiarrhythmic actions of polyunsaturated fatty acids and of cholesterol☆

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ABSTRACT

In this review, the pro- and anti-arrhythmic effects of a diet rich in fish oil fatty acids and of hypercholesterolemia will be discussed in relation to two major mechanisms of arrhythmogenesis (triggered activity and re-entry). Whereas a diet rich in fish oil is pro-arrhythmic in relation to re-entry based arrhythmias (as occur in acute myocardial ischemia) and anti-arrhythmic in relation to triggered activity based arrhythmias (as occur in heart failure), the reverse is true for hypercholesterolemia. Changing the lipid composition of cardiomyocytes likely has powerful pro- or anti-arrhythmic consequences, depending on the mechanism of arrhythmias, and has corresponding therapeutic potential.

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1. Introduction

Sudden cardiac death constitutes a large medical and societal challenge, especially in the Western world (Zipes & Wellens, 1998). Its causes are multiple and include ventricular fibrillation (VF) in patients with acute myocardial ischemia, ventricular tachycardia (VT) in patient with myocardial infarction (MI) (Janse & Wit, 1989), VT developing into VF in patients with heart failure (Kjekshus, 1990), and VT/VF in patients with channelopathies like the long QT syndromes (Mizusawa, Horie, & Wilde, 2014). Rare disease like Brugada Syndrome and J-wave syndromes are also associated with VF (Brugada & Brugada, 1992; Hoogendijk et al., 2010; Miyazaki, Shah, & Haissaguerre, 2010). The mechanisms of these arrhythmias are largely different and therefore the arrhythmias have different vulnerable factors to target for treatment or prevention (Working group on arrhythmias of the European society of cardiology, 1991). It is therefore not surprising that pharmacological prevention of life-threatening arrhythmias is unsuccessful and in some cases harmful. The CAST study has marked a turn in the development of novel anti-arrhythmic drugs because it explained the antagonistic effects of some antiarrhythmic drug (CAST, 1989). Indeed, a compound may be anti-arrhythmic in the setting of heart failure, but may prove to be pro-arrhythmic in the setting of acute myocardial ischemia and vice versa. When developing novel anti-arrhythmic drugs and novel

Abbreviations: DAD, delayed after depolarization; EAD, early after depolarization; ECG, electrocardiogram; LDL/HDL, low/high density lipoprotein; LQT(S), long QT (syndrome); SCD, sudden cardiac death; TA, triggered activity; VT, ventricular tachycardia; VF, ventricular fibrillation; QTc, corrected QT interval.

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pharmacological targets we should take the mechanisms of arrhythmias and their vulnerable factors into account.

In the following I will briefly discuss some (but not all) mechanisms underlying life-threatening arrhythmias and how they are related to common arrhythmia syndromes. Furthermore, I will discuss how the electrophysiological effects of the membrane content of fatty acids or cholesterol can act as a target for anti-arrhythmic therapy. The data will show that these novel interventions do not differ from pharmacological anti-arrhythmic therapy in the sense that their efficacy is equally dependent on the type of arrhythmias studied, and that they may be pro-arrhythmic in some conditions and anti-arrhythmic in other. In some highly selected patient groups, however, in which the mechanism of the threatening arrhythmia is known or can be anticipated, dietary interventions may be used as anti-arrhythmic therapy. With the advent of non-invasive activation and repolarization mapping techniques (Zhang et al., 2015) the early definition of arrhythmia mechanisms and the localization of the arrhythmia origin is becoming feasible, thus guiding mechanism specific, patient tailored therapy that includes dietary anti-arrhythmic therapy. A comprehensive review by Billman on the effects of omega-3 polyunsaturated fatty acids, with specific focus on epidemiological studies, on the effects on heart rate and on atrial and ventricular fibrillation has appeared earlier (Billman, 2013).

2. Mechanisms of arrhythmias

Many reviews have been published on arrhythmia mechanisms (Coronel et al., 2013; Janse & Wit, 1989; Janse et al., 2001) and I will only touch on some of the major mechanisms, re-entry and triggered activity. Arrhythmias are traditionally classified as those caused by abnormal impulse generation and those with abnormal impulse propagation. This classification system is of limited value because arrhythmias are often initiated ('triggered') by abnormal impulse generation and then maintained by abnormal impulse propagation. The abnormalities may have been present before the advent of the arrhythmia and then constitute the 'substrate'. Pharmacologic (or non-pharmacologic) interventions aimed at either or both the trigger and the substrate can abolish or prevent the arrhythmia.

2.1. Re-entry (ischemia induced VT/VF)

The majority of the ventricular arrhythmias are caused by re-entrant mechanisms ('abnormal impulse propagation') (Janse, 1986). Re-entry is defined as an activation sequence caused by a single wavefront that re-excites the site of origin. The work of Mines has laid the basis of our understanding of re-entrant arrhythmias, and already anticipated that re-entry could be of clinical importance (Mines, 1913, 1914). The proof that re-entry plays a role in clinical arrhythmias came only later when the arrhythmias associated with the Wolff-Parkinson-White (WPW) syndrome was attributed to re-entry (or circus movement tachycardia) (Boukens & Janse, 2013). Janse et al. have demonstrated that ischemia-associated arrhythmias also were caused by re-entry (Janse et al., 1980).

For the initiation of re-entry an intricate interaction between the wavefront (the activation wave) and the wave tail (the repolarization wave) is required (Samie & Jalife, 2001). Conduction velocity may be slowed (as in myocardial ischemia) and may facilitate that the activation wave coincides with the end of repolarization in another region of the heart. A shortening of repolarization (as occurs in myocardial ischemia) thus may facilitate this (Janse, Capucci, Coronel, & Fabius, 1985). It will lead to a premature activation. Secondly, in the presence of heterogeneity of repolarization (Janse et al., 1985), a closely coupled premature activation originating from the area with the early repolarization may encounter block ('unidirectional block') that will force the premature activation wave to circumvent the area of block. If the site of origin has recovered from inactivation of the sodium channel at the appropriate time (f.e. facilitated by a steep restitution slope), the premature activation front may re-enter into the area of origin (Child et al., 2015; Coronel, Wilms-Schopman, & Janse, 2011; Coronel, Wilms-Schopman, Opthof, & Janse, 2009).

The relation between the conduction velocity and the refractory period has been laid down in the concept of wavelength that is the mathematical product of the two (Smeets, Allessie, Lammers, Bonke, & Hollen, 1986). The wavelength is the theoretical path length. If a circle with a circumference of the wavelength fits in the myocardium, re-entry is possible. The shorter the wavelength, the more easy it is to induce re-entry. It follows that slow conduction velocity and/or a short refractory period facilitate the onset of re-entrant arrhythmias. The concept is only theoretical, because the conduction velocity decreases when the activation wave encroaches on the tail of the wave, and restitution characteristics dynamically alter the action potential duration (or the refractory period). Finally, in some forms of re-entry (anatomical re-entry, whereby the activation path is determined by a pre-existing anatomic circular path of myocardium (e.g in WPW-syndrome and tachycardia during myocardial infarction), an excitable gap is part of the wavelength.

High resolution mapping of activation and repolarization has led to a more accurate mathematical description of re-entry in the form of rotors or re-entrant drivers (Chen, Mandapati, Berenfeld, Skanes, & Jalife, 2000). In particular, wave front-wave tail interactions follow a pattern that is determined by wave front curvature around the vortex (singularity point) of the rotor (Pandit & Jalife, 2013). During sustained arrhythmias these singularity points move three dimensionally in the myocardium, although they tend to anchor at sites of structural or functional heterogeneities (Pandit & Jalife, 2013).

A classical anti-arrhythmic strategy for the prevention or termination of a re-entrant arrhythmia is to prolong action potential duration with class 3 anti-arrhythmic drugs (Camm et al., 1993). This will both hamper initiation and maintenance of the arrhythmia.

2.2. Triggered activity (heart failure induced VT/VF)

Whereas re-entrant arrhythmias require heterogeneities occurring in a multicellular setting, triggered activity is a primarily cellular mechanism. Two types of triggered activity (TA) are distinguished: those caused by early after depolarizations (occurring during the repolarization phase of the action potential, Fig. 1A) and those caused by delayed after depolarization (occurring following completion of the repolarization phase of the action potential, Fig. 1B). The after depolarizations may reach the threshold level for (re)activation and thus lead to a (triggered) action potential.

Early after depolarizations (EADs) typically occur when the action potential plateau is prolonged. The latter can be detected on the ECG by a prolongation of the QT-interval. The resulting long QT-syndrome can be either acquired or have a genetic origin. Several groups of drugs that inhibit one of the repolarizing ion channels (some as a side effect) are associated with a QT-prolongation and with ventricular arrhythmias based on triggered activity.(see websites mentioned in (Postema et al., 2013)) The genetic LQT syndromes are multiple and are each associated with mutation in one of the ion channels (or their subunits) responsible for repolarization. A characteristic tachycardia related to triggered activity by early after depolarizations is a specific subtype of polymorphic ventricular tachycardia that shows beat by beat changes in the QRS morphology, giving the impression of the QRS-complexes 'turning around the baseline'. These 'Torsade de Pointes' arrhythmias may terminate spontaneously, or develop into ventricular fibrillation. In heart failure, the action potential duration (and the QT interval) is typically prolonged, and arrhythmias are thought to be caused by triggered 'focal' activity (Janse et al., 2001; Pogwizd, 1994, 1995; Pogwizd, Schlotthauer, Li, Yuan, & Bers, 2001; Vermeulen et al., 1994; Wiegerinck et al., 2008).

In healthy myocardium the myocytes are coupled through gap junctions that allow the exchange of matter and current between adjacent