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P-wave dispersion: an update

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ABSTRACT

P-wave dispersion (PWD, Pd or Pdis) is a noninvasive electrocardiographic (ECG) marker for atrial remodeling and predictor for atrial fibrillation (AF). PWD is defined as the difference between the widest and the narrowest P-wave duration recorded from the 12 ECG leads. Increased P-wave duration and PWD reflect prolongation of intraatrial and interatrial conduction time with lack of a well-coordinated conduction system within the atrial muscles, with inhomogeneous, asynchronic, pro-inflammatory and anti-inflammatory effect mediated by interleukin-6 (IL-6) in patients with the CG + GG genotype IL-6 -634C/G polymorphism [1] and discontinuous propagation of sinus impulses mainly between the left and right atria, interstitial/extracellular fibroblast activation and collagen deposition with fibrosis (via TGF-β) in atrial tissue, insufficient blood supply, significant not isotropic myoelectric activity, and thin wall thickness and consequent expansion tendency all well-known electrophysiological characteristics in patients with atrial arrhythmias and especially paroxysmal atrial fibrillation (PAF) [2].

1. Excess amount of reactive oxygen species (ROS) and P-wave duration and P-wave dispersion relationship

In experimental and even clinical scenarios of AF extracellular fibrosis and inflammation as well as downregulation of several ion channels and gap junctions, nexus or macula communicans have been documented in atrial tissue. Both AF and cardiac heart failure (CHF) are associated with excess amount of reactive oxygen species (ROS). These can cause trigger activity type arrhythmias (early after depolarizations (EADs) and delayed after depolarizations (DADs)), reentry and potential therapeutic targets [3]. Due to triggered activity, arrhythmias are often due to problems in the ion channels in the heart muscle cells. They can also occur as a side effect of certain anti-arrhythmic drugs such as digitalis. Excess amount of ROS alters multiple cardiac ion currents: Activation of CaMKII, c-Src, and PKC may mediate several important effects of ROS on ion currents resulting in arrhythmia. ROS produces Na^+ current reduction (via PKC and c-Src, also via abnormal splicing mRNA) and reduction conduction velocity, abnormal splicing, activation of CaMKII, c-Src, and PKC are among emerging new antiarrhythmic therapeutic targets. ROS may also alter intracellular Ca^{2+} handling in a way that generates arrhythmia.

ROS may stimulate the inward L-type Ca^{2+} current (direct or via CaMKII activation facilitating after depolarization, which can facilitate EADs) with abnormal depolarization during phase 2 or phase 3. ROS is also responsible by inhibition of K+ channels I_{to}, I_{Kr}, I_{Ks} and K_{ATP} with consequent abnormal repolarization.

ROS causes adversely affected splicing of mRNA of cardiac Na^+ channels resulting in abnormal truncated cardiac Na^+ channel proteins and a reduction in normal Na^+ channels.

In the extracellular matrix ROS promotes cardiac fibrotic process (via TGF-β) with reduction in conduction velocity and impaired myocyte-myocyte coupling due to collagen deposition.

ROS impairs gap junction affecting assembling of Cx43, resulting in reduced myocyte coupling and velocity facilitation of reentry.

Activation of Ca^{2+}/CaM-dependent kinase II, c-Src tyrosine kinase, protein kinase C, and abnormal splicing of cardiac Na^+ channels are among the recently discovered molecular mechanisms of ROS-induced arrhythmia.

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ROS produces NCX activation, increasing inward current afterdepolarization and increasing late Na^+ current (phase 2 of action potential) facilitating afterdepolarization. A new selective cardiac late Na^+ current inhibitor confers concurrent protection against autonomically induced atrial premature beats (APBs), and dual protection against vulnerability to ischemia-induced AF, and reduces atrial and ventricular repolarization abnormalities before and during adrenergic stimulation without negative inotropic effects [4].

In summary, ROS affects CaMKII: Ca^{2+}/calmodulin-dependent protein kinases II; CX43: connexin 43; NCX: Na^+/Ca^{2+} exchanger; PLB: phospholamban; RYR: ryanodine receptor; SERCA: sarco-/endoplasmic reticulum Ca^{2+}-ATPase; TGF-β: Transforming Growth Factor-β; ZO-1: Zonula Occludens-1. Fig. 1 shows the main action points of ROS.

1.1. Modified from [3]

1) Excess of reactive oxygen species (ROS); 2) CaMKII activation or Ca^{2+}/calmodulin-dependent protein kinases II; 3) c-Src activation (SRC proto-oncogene, non-receptor tyrosine kinase); 4) PKC (Protein kinase C) enzymes play important roles in several signal transduction cascades. Abnormal splicing, activation of CaMKII, c-Src, and PKC are among emerging new antiarrhythmic; 5) mRNA of Na^+ current; 6) Impair gap junction CX43 conduction resulting in reduced myocyte coupling; 7) NCX: Na^+/Ca^{2+} exchanger. The NCX removes a single Ca^{2+} ion in exchange for the import of three Na^+ ions. It is considered one of the most important cellular mechanisms for removing Ca^{2+}; 8) Phospholamban (PLB): It is a 52-amino acid integral membrane protein that regulates the Ca^{2+} pump in cardiac muscle and skeletal muscle cells; 9) Ryanodine receptor (RyR) participates in different signaling pathways involving Ca^{2+} release from intracellular organelles. It is the major cellular mediator of Ca^{2+} induced Ca^{2+} release (CICR) in animal cells. RyR2 is primarily expressed in myocardium; 10) Sarco-/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) resides in the sarcoplasmic reticulum (SR) within myocytes. It is a Ca^{2+} ATPase that transfers Ca^{2+} from the cytosol of the cell to the lumen of the SR at the expense of ATP hydrolysis during muscle relaxation; 11) Transforming Growth Factor-β (TGF-β) leads to the activation of different downstream substrates and regulatory proteins, inducing transcription of different target genes that function in differentiation, chemotaxis, proliferation, and activation of many immune cells; 12) Zonula Occludens-1 (ZO-1) or tight junction protein. It is located on a cytoplasmic membrane surface of intercellular tight junctions. The encoded protein may be involved in signal transduction at cell—cell junctions; 13) Extracellular fibroblasts activation and collagen deposition; 14) Increase in L-type Ca^{2+} current; 15) Increase in late Na^+ current. Selective inhibition of cardiac late I_{Na} with eleclazine confers dual protection against vulnerability to ischemia-induced AF and reduces atrial and ventricular repolarization abnormalities before and during adrenergic stimulation without negative inotropic effects. 16) Na^+ current reduction; 17) ATP-sensitive K^+ channel (KATP channel) inhibition; 18) I_{to}, I_{Ks} and I_{Kr} inhibition; 19) Transcription; 20) Splicing; 21) microRNA; 22) Translation.

2. Normal limit values of P-wave dispersion (PWD)

The normal value of PWD is 29 ± 9 ms. Aytemir et al. [5] refer a maximum PWD value of 36 ms. PWD ≥40 ms indicates the presence of heterogeneous electrical activity in different regions of the atrium that might cause atrial tachyarrhythmias (ATAs). Thus, PWD is a strong predictor of ATAs and especially AF.

2.1. Possible scenarios where P-wave dispersion could be present

A) Physiological

- ➢ **Young athletes of high performance:** PWD is increased in young athletes of high performance and is positively correlated with training duration and baseline heart rate. The increase in PWD is secondary to a significant decrease in Pmin [6].

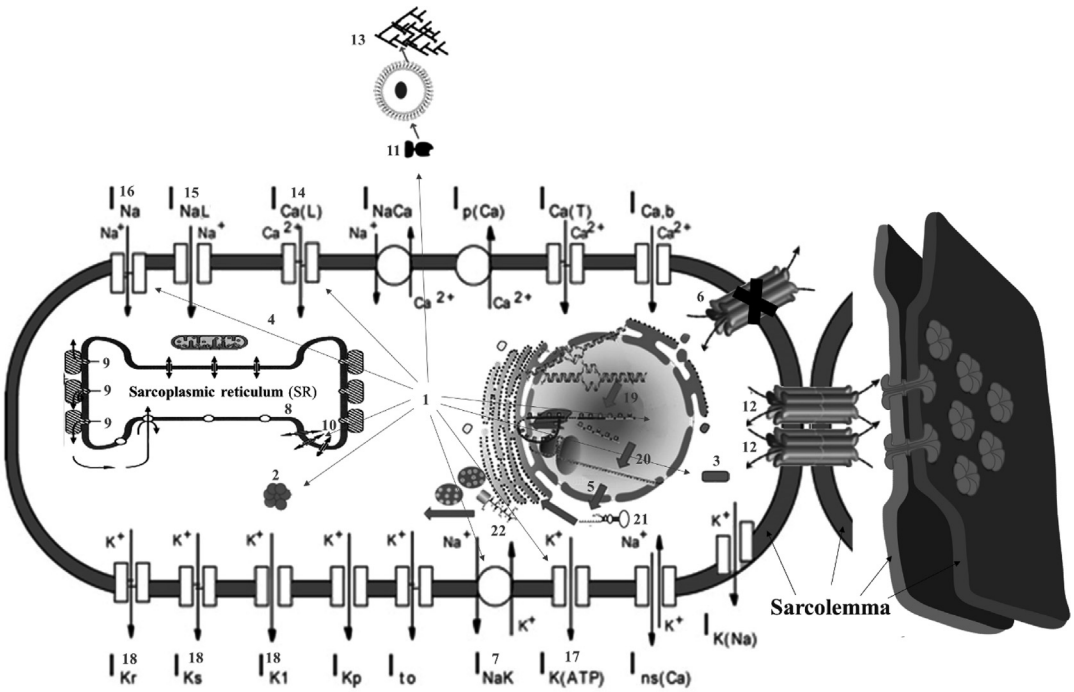

Fig. 1. Main action points of ROS.

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