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Review

Redox control of cardiac remodeling in atrial fibrillation ☆

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ABSTRACT

Background: Atrial fibrillation (AF) is the most common arrhythmia in clinical practice and is a potential cause of thromboembolic events. AF induces significant changes in the electrophysiological properties of atrial myocytes and causes alterations in the structure, metabolism, and function of the atrial tissue. The molecular basis for the development of structural atrial remodeling of fibrillating human atria is still not fully understood. However, increased production of reactive oxygen or nitrogen species (ROS/RNS) and the activation of specific redox-sensitive signaling pathways observed both in patients with and animal models of AF are supposed to contribute to development, progression and self-perpetuation of AF.
Scope of Review: The present review summarizes the sources and targets of ROS/RNS in the setting of AF and focuses on key redox-sensitive signaling pathways that are implicated in the pathogenesis of AF and function either to aggravate or protect from disease.
Major Conclusions: NADPH oxidases and various mitochondrial monooxygenases are major sources of ROS during AF. Besides direct oxidative modification of e.g. ion channels and ion handling proteins that are crucially involved in action potential generation and duration, AF leads to the reversible activation of redox-sensitive signaling pathways mediated by activation of redox-regulated proteins including Nrf2, NF-κB, and CaMKII. Both processes are recognized to contribute to the formation of a substrate for AF and, thus, to increase AF inducibility and duration.
General Significance: AF is a prevalent disease and due to the current demographic developments its socio-economic relevance will further increase. Improving our understanding of the role that ROS and redox-related (patho)-mechanisms play in the development and progression of AF may allow the development of a targeted therapy for AF that surpasses the efficacy of previous general anti-oxidative strategies. This article is part of a Special Issue entitled Redox regulation of differentiation and de-differentiation.

1. Introduction

Reactive oxygen species (ROS) are generated under physiological conditions in the cardiovascular system. They can alter the redox status of various molecular targets which quite specifically leads to functional alterations of e.g. ion channel activity or activation of a variety of redox-sensitive signal transduction pathways. However, under pathophysiological conditions and, in particular, in chronic disease, persistent excessive amounts of ROS (oxidative stress) may cause secondary unspecific damage by compromising vital cellular functions such as oxidative phosphorylation. Of note, the production of different oxidants affects distinct presets of target proteins through modifications that are specific both with respect to the oxidant and the site of modification, most frequently well-defined cysteinyl side chains. The so-called antioxidant redox systems in the different cellular compartments, e.g. glutathione, NADPH, thioredoxin (Trx), and peroxidases, are, however, not in equilibrium and independently maintained at distinct redox potentials. "Oxidative stress" may thus, more timely, be defined as the chronic disturbance of redox circuits and redox-responsive signal transduction pathways [1–4].

The formation of ROS/RNS species and redox signaling have been implicated in physiological processes in the heart such as excitation-contraction coupling (ECC), but are also playing a critical role in the pathophysiology of heart and cardiovascular diseases such as heart failure, left ventricular hypertrophy, coronary artery disease, and cardiac arrhythmia. There are excellent recent reviews on signal transduction by ROS, including ones on redox regulation in cardiovascular/cardiac disease [1,5–16]. In this review we specifically focus on the role of ROS production and redox signaling in the development and progression of atrial fibrillation (AF). AF is the most common arrhythmia in clinical practice and has been associated with increased "oxidative stress" [17].

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It appears that oxidative events initiate disease-dependent tissue remodeling and promote its progression. For reasons only partly understood, the efficacy of antioxidants to prevent AF and AF-dependent tissue remodeling has been mostly disappointing.

2. Atrial fibrillation and "oxidative stress"

Evidence has been accumulated pointing to a linkage of "oxidative stress" to atrial remodeling during AF [14]. Mihm et al. [18] were the first to demonstrate extensive oxidative damage in atrial myocardium from patients with AF, that was mainly mediated by peroxynitrite and was not observed in similar samples from patients in sinus rhythm (SR). Later it was experimentally shown that rapid atrial pacing led to decreased tissue levels of ascorbic acid, whereas protein nitration was increased along with decreased effective refractory period [17]. All these changes could be prevented by pretreatment with vitamin C. These results provide evidence that tachycardias increase the concentration of ROS and RNS. The nitration and carbonylation of structural proteins impair myocardial energetic and electrophysiologic properties. In the ventricles, tachycardia-induced elevation of ROS/RNS levels may be critical for the induction of apoptosis [19]. Recently, we have shown that rapid pacing of *in vitro* differentiated cardiomyocytes [20] or human atrial tissue slices leads to oxidative modifications of proteins and mitochondrial dysfunction [21].

Several key components of the cardiac excitation-contraction coupling were shown to be highly sensitive to oxidative stress [17,22–25]. Gene expression profiling of atrial tissue samples from patients with SR and AF revealed a decreased expression of anti-oxidative genes, whereas that of five ROS-producing genes was increased [26].

Furthermore, AF has substantial effects on mitochondrial structure and function: Lin et al. [27] detected oxidative damage of mitochondrial DNA and demonstrated diminished ATP synthesis along with increased production of ROS that were due to initial calcium-overload.

Increased production of ROS/RNS and activation of redox-sensitive pathways is associated with microvascular flow abnormalities and occurs immediately after new-onset AF likely representing key initiator mechanisms of AF-related remodeling. This has been shown in patients with lone recurrent AF and for rapid atrial pacing models [22,26,28,29]. Recent studies clearly showed that acute episodes of AF induce redox-sensitive signaling and gene expression in the LV myocardium and compromise microvascular blood flow [21,30,31]).

Crucially involved in redox-regulation and the mounting of anti-oxidative response mechanisms are three important groups of enzymes, the glutaredoxins (GRX), peroxiredoxins (PRX), and thioredoxins (TRX; including the thioredoxin interacting protein, TXNIP). These enzymes are extensively referred to elsewhere in this issue (e.g. Gellert et al.). With respect to AF, much less is known on their expression, activity, and specific function. Available data indicate decreased expression of PRX3 (along with decreased superoxide dismutase (SOD) levels) in atrial tissue of dogs subjected to 2 weeks ventricular tachypacing [32]. In two series of acute rapid pacing *in vivo* (pig), we observed elevated atrial mRNA expression of PRX3, SOD2, and thioredoxin reductase (TXNRD1) [30,31]. Clearly, further work is required to precisely define the role of TRXs, PRXs, and GRXs in the development and progression of AF.

3. Sources of ROS/RNS

During AF several mechanisms and sources contribute to elevated ROS/RNS levels. One important source of ROS is represented by mitochondria, which are subject not only to severe structural and morphological alterations (e.g. swelling and disturbance of cristae structure) during AF, but also get compromised functionally. Oxidative phosphorylation (OXPHOS) and respiration are reduced in atrial tissue slices or *in vitro* differentiated cardiomyocytes in response to RAP [20,21]. Inhibition of electron transfer within the respiratory chain by impairment of mitochondrial ATP-production either at the level of adenine nucleotide transport or ATP-synthesis has been shown to increase production of superoxide anion radicals by the respiratory chain [33]. Superoxide anion is predominantly formed at complexes I and III of the respiratory chain [34].

Interestingly, mitochondrial morphology and function could be largely preserved by limiting calcium influx via blockage of L-type calcium channels with verapamil. This finding is supported by a recent study from Mason et al. [35] showing that mibefradil, which blocks L-type and T-type Ca^{2+} channels, and verapamil prevent the oxidation of cellular constituents and exhibit cytoprotective effects. Mibefradil was found to be more potent than verapamil at preventing lipid peroxide formation.

The mitochondrial Ca^{2+} transport system translates elevated cytosolic Ca^{2+} concentrations into increased mitochondrial Ca^{2+} concentrations [36], a mechanism which mediates swelling of mitochondria and inhibits OXPHOS [37,38]. Accordingly, inhibition of mitochondrial Ca^{2+} influx was protective in a rat model of ventricular tachycardia [39].

Besides the frequency-dependent increase in cytosolic Ca^{2+}-concentrations during AF, also ischemia and AF-dependent decrease of microcirculation provoke alterations in cellular ionic homeostasis, in particular of calcium and sodium ions. It is well established that ischemia creates a substrate for AF maintenance [40,41]. Increased NCX currents and spontaneous Ca^{2+}-release events contribute to increased spontaneous ectopy [42]. In pulmonary veins (PV), hypoxia-induced EAD and DAD as well as reoxygenation-induced PV burst firing represent important pro-arrhythmogenic mechanisms [43].

A second important source of ROS during AF is a family of seven NADPH-dependent enzymes consisting of the "NADPH oxidases" Nox 1-5 and Duox 1-2 [44]. The NADPH oxidase originally discovered in neutrophils is composed of the membrane-associated subunits $p22^{phox}$ and Nox plus the four cytosolic regulatory subunits $p47^{phox}$, $p67^{phox}$, $p40^{phox}$, and the small GTPase *rac1* or *rac2* [45]. Different isoforms for the key catalytic subunit, Nox, exist in nonphagocytic cells, including cardiac myocytes, fibroblasts, and endothelial cells. Although nonphagocyte NADPH oxidases show some constitutive activity, their activity can be further up-regulated in response to a broad variety of stimuli that are common to major risk factors of AF such as hypertension and diabetes and include angiotensin II (AngII), endothelin-1 (ET-1), growth factors, cytokines, and mechanical stress [46–49]. Nox2 and Nox4 are the isoforms predominantly expressed in cardiac cells. Nox1 is expressed particularly in vascular smooth muscle cells and responsible for extracellular superoxide production in coronary arterial myocytes [50]. Nox4, which in contrast to Nox2 does not require the presence of regulatory oxidase proteins $p47^{phox}$ or the GTPase *rac*, produces mainly hydrogen peroxide and only very small amounts of superoxide intracellularly [51]. Nox4 has been implicated in cardiomyocyte differentiation through redox activation of c-Jun, which in turn up-regulates GATA-4 expression levels [52]. In cardiomyocytes, increased Nox4 expression is associated with mitochondrial dysfunction and apoptosis [53,54]. A very recent study showed that the overexpression of Nox4 in zebrafish embryos induces a arrhythmogenic phenotype [55]. This effect is mediated by increased ROS production and subsequent activation of CaMKII.

Accumulating evidence indicates that Nox1 contributes to the hypertensive response to AngII [50,56]. Increased left ventricular (LV) expression of Nox2, Nox1, and Nox4 has been observed in an animal model of acute AF [30,31]. The AT1 receptor antagonist, irbesartan, and the multichannel inhibitor, dronedarone, efficiently prevented the up-regulation of Nox2 [30,31].

Inhibition of Nox by apocynin has been recently shown to attenuate RAP-dependent electrical remodeling, AF inducibility and duration in rabbits [57].

Interestingly, with increasing duration of AF ROS production is shifted from NADPH oxidase to other cellular sources of ROS, that include mitochondrial oxidases (xanthine oxidase, [58]), monoamine oxidase [59], and uncoupled eNOS [60]. This mechanism well explains the observation that statins, which reduce ROS production by NADPH

oxidases via inhibition of Rac1, are effective in acute models of AF and in patients with post-operative AF, but fail to reduce ROS production in models of long-lasting AF or patients with permanent AF.

eNOS is a homodimeric enzyme that oxidises L-arginine to NO and L-citrullin. For this reaction, eNOS requires different cofactors, of which tetrahydrobiopterin (BH_4) and Ca^{2+}-activated calmodulins are essential for optimal activity (for excellent review, see [61]). In addition, phosphorylation at various sites critically influences eNOS activity, with phosphorylation of Ser1177 by PKCα or AMP-dependent kinase (AMPK) being important regulatory mechanisms. BH_4 facilitates enzyme dimerization and stabilizes the active form that produces predominantly NO [62]. In the absence of BH_4 or upon oxidation of a significant fraction of it to BH_2, eNOS uncouples to monomers which generate large amounts of superoxide anions and, subsequently, of ONOO · instead [61].

It has been shown in an *in vivo* animal model that the atrial endocardium produces large amounts of NO, which is impaired during AF by reduced expression of eNOS [63]. Reduced plasma levels during AF of NO are restored after successful cardioversion into sinus rhythm [64,65]. In contrast to the observed down-regulation of eNOS in pig models of AF [63,66], 8 days of atrial tachypacing in dogs caused an up-regulation of atrial eNOS levels [67,68]. In a sheep model of persistent AF, eNOS was down-regulated at the mRNA level, whereas protein levels remained unchanged [69]. Although in that study NOS activity has not been measured, increased expression of Rac1 together with increased tissue nitrotyrosine levels make oxidative uncoupling of eNOS likely. This view is supported by reduced plasma levels of nitrite/nitrate [69].

Conflicting results were also found with regard to the impact of eNOS polymorphism (T-786C, G894T, and intron 4b/a) on the occurrence of AF. Bedi et al. analyzed 340 patients with congestive heart failure with and without AF [70]. In that study AF was present in 51/340 patients (15%) and was significantly associated with the eNOS 894T/T genotypes (odds ratio 3.2), whereas there were no significant associations between AF and eNOS 786 or eNOS intron 4 genotypes. A weak predisposing influence of the eNOS T-786C allele to non-valvular AF (NVAF) has been shown, which appeared to be increased by the contemporary presence of a S38G allele of minK, a β-subunit of I(ks) potassium channels [71]. In contrast, Gensini et al. compared endothelial NO synthase (eNOS) T-786C, G894T, and 4a/4b polymorphisms in 148 patients with persistent AF, compared with 210 control subjects [72]. In that study analysis of eNOS polymorphisms showed no significant differences in genotype distribution and allele frequency between patients and controls. In another study, the T-786C allele, although being associated with hyperhomocysteinemia, was not associated with an increased risk for NVAF [73]. A recent meta-analysis reveled a positive association between the eNOS T-786C allele and AF risk among Caucasians but not among mixed populations [74].

AF is associated with increased levels of ADMA, an endogenous inhibitor of eNOS [66,75]. Importantly, restoration of normal sinus rhythm by electrical cardioversion is accompanied by normalization of ADMA levels within 24 h. AF and RAP per se up-regulate ADMA, which is associated with an increase of ischemic myocardial markers (TnT and TnI). Elevated ADMA levels influence NO generation and may thereby cause the microcirculatory flow abnormalities observed in AF [66]. Altered NO generation is also known to influence mechanical performance of the ventricles and, therefore, increased ADMA levels might be related to abnormalities in Ca^{2+} handling and contractility [76,77]. AF or rapid pacing has been shown to reduce eNOS expression, an effect which could be attenuated by the angiotensin type 1 receptor blocker, olmesartan [78]. Similarly, losartan prevented the reduction of eNOS expression after myocardial infarction, which prevented subsequent AF induction [79]. However, alterations in eNOS expression and activity might depend on concomitant diseases, rather than on the presence of AF *per se*. This view is supported by an immunohistological study showing no independent association of AF and endocardial/myocardial eNOS expression in atrial samples [80].

An excellent recent study identified the monoamine oxidase (MAO) as a substantial source of ROS in the human myocardium, specifically in right atrial appendage (RAA) [59]. MAO is a mitochondrial enzyme catalyzing the oxidative deamination and, thus, inactivation of catecholamines. This reaction generates H_2O_2. MAO has been assigned a causal role in cardiac dysfunction in response to pressure overload due to oxidative stress [81,82]. The findings of Anderson et al. [59] confirm and significantly extend previous data that associated atrial NADPH oxidase-derived ROS production with post-operative AF. The findings of their study imply a clinically relevant role of MAO in determining the myocardial redox balance and demonstrate that MAO is associated with an increased risk for post-operative-AF [59].

4. Redox-regulated signaling pathways

Although the excessive production of ROS/RNS may well lead to cellular damage, physiological levels rather induce reversible and site-specific protein modifications that define “redox signaling” processes which are subject to stringent spatial and temporal regulation [8]. Covalent modification of cysteine thiols or oxidation of iron–sulfur-clusters in proteins, S-glutathionylation, and S-nitrosylation/S-nitrosation (SNO) has all been identified as major mechanisms mediating ROS-specific effects (for review see [8]). It is well established that these mechanisms contribute to AF development and progression by altering e.g. ion channel activity (see chapter 5). More recently, the oxidation of methionine which results in the formation of methionine sulfoxide, and the regeneration of methionine by the thioredoxin-dependent methionine sulfoxide reductase (Msr) has been identified as an additional mechanism linking ROS with AF [14,83]. In their conclusive study, Purohit et al. show that oxidized Ca^{2+} and calmodulin-dependent protein kinase II (CaMKII) plays a crucial role in mediating the AngII/RAP-dependent induction of AF [83]. AngII, elevated plasma and tissue levels of which are common to most risk factors for AF, and RAP were shown to turn CaMKII constitutively active by the oxidation of its methionine amino acid residues 281/282 [83,84]. This increase in the amounts of oxidized CaMKII occurred without any changes of total amounts of CaMKII. The substantial contribution of AngII in this activation has been emphasized by demonstrating that inhibitors of angiotensin-converting enzyme (ACEi) or angiotensin II type I receptor blockers (ATRBs) prevent CaMKII oxidation/activation [83]. Mechanistically, activated CaMKII increases Ca^{2+}-leak from the sarcoplasmic reticulum via enhanced phosphorylation of RyR2 [85]. Elevated diastolic Ca^{2+} concentrations are responsible for the resulting increase in AF inducibility and duration. In this way, CaMKII functions as a cellular sensor for ROS that links the important pathogenetic factors AngII, Nox, and Ca^{2+} with AF.

Nuclear factor-κB (NF-κB) is a key transcription regulator coupling redox state to the transcriptional regulation in various pathophysiological settings, including AF [86]. Elevated intracellular calcium levels, AngII and ROS, PDGF, CTGF and TGF-β1, all associated with AF-dependent structural remodeling, are major activators of the immediate early response transcription factor NF-κB [1,21,31,87–92]. Interestingly, increased Rac-1 levels may also contribute to NF-κB activation during RAP or AF [93–95].

Typical target genes of NF-κB are pro-inflammatory cytokines such as interleukin-8 and TNFα, but also the endothelial adhesion molecules ICAM-1 and VCAM-1, the endothelial oxidized low density lipoprotein (lectin-like) receptor, LOX-1, and the cardiac sodium channel SCN5A [21,86–88]. NF-κB contributes also to the induction of heme oxygenase 1 (HO-1) expression [96]. HO-1 is a redox-sensitive inducible protein that contributes to cytoprotection against “oxidative stress” under a wide range of unrelated conditions [97]. The HO-1 promoter contains responsive elements for NF-κB, AP-1 and 2, and Nrf2, the latter being of critical importance for HO-1 expression [98].

Besides its critical contribution to structural (fibrosis), electrical, and endocardial/endothelial remodeling in the atria during RAP and AF, rapid atrial pacing also led to an activation of the NF-κB pathway in

the left ventricle [31]. Consistent with this ventricular activation of NF-κB, the expression of established down-stream targets of NF-κB were up-regulated which included VEGFA [99,100], Fn14, CCL2 [101], HIF1A [91,102] as well as DnaJ family members, DNAJA4 and DNAJB9, that have been described as co-chaperones for the ATPase activity of Hsp70 and function to protect stressed cells from apoptosis [103]. Both DNAJA4 and DNAJB9 are antioxidant response element (AREs)-regulated genes activated through nuclear factor-erythroid 2-related factor 2 (Nrf2) in response to oxidative stress. After phosphorylation by e.g PKC, Nrf2 translocates to the nucleus where it binds to AREs and trans-activates target genes of e.g. enzymes such as peroxiredoxin I that regulate the intracellular amounts of ROS [104].

Recent data indicate that the cellular redox state is subject to regulation by miRNAs through modulating Nrf2-dependent antioxidant gene expression or attenuating activities of ROS handling enzymes [105]. These mechanisms in turn can affect miRNA expression/activity [106–108]. Mounting evidence demonstrates the importance of miRNAs for the regulation of cardiac physiology (for excellent recent review, see [109]). In particular, miRNAs regulate cardiac excitability and arrhythmogenesis, which was first shown for the abundantly expressed miRNAs in the heart, miR-1, -133, and 328 [110–112]. Meanwhile, the number of miRNAs with an established role in cardiac remodeling or altered expression during AF has substantially increased [109,113–115]. Of these AF-associated miRNAs, a few have been already identified as regulators of ROS generation (miR-25, miR-146a) [105].

Hypoxia-inducible factors (Hifs) are heterodimeric factors that control a hypoxia-induced gene expression panel aimed at counteracting adverse cellular and systemic effects of limitations in oxygen supply. Of the three mammalian isoforms, Hif1α probably is the most intensive studied one. Hif1α levels are regulated by oxygen tension at transcriptional, translational, and post-translational level, with O_2-dependent protein stability being the best characterized regulatory mechanism [116]. Under normoxic conditions, the sufficiently available O_2 is used by prolyl-hydroxylase domain-containing enzymes (PHD) for the corresponding modification of Hif1α, which then becomes a target for ubiquitinylation by von Hippel-Lindau complex and proteasomal degradation [116]. Hypoxia prevents this degradation and facilitates the binding of Hif1α/β heterodimers to hypoxia-response elements in the promoters of target genes that include metabolic and angiogenic factors. In response to RAP or during AF, an increase in Hif-1α expression has been observed, which is accompanied by elevated expression of the Hif-target genes, VEGFA and PPARGC1α [30]. Both factors are known to be induced in response to hypoxia or deprivation of nutrients [117,118]. Under the same conditions, and independent of this canonical HIF-pathway, elevated PPARGC1α levels exert strong angiogenic activity and induce VEGF expression by co-activating ERR-α [117]. Thus, both HIF-1α and PPARGC1α appear to be critically involved in the angiogenic response to AF-dependent flow alterations and may provide protection against ischemic damage.

Another established target gene of HIF is lysyl oxidase (LOX), the expression of which, accordingly, has been shown to be induced in response to hypoxia/ischemia. Recent work established a role of LOX in cardiovascular function and disease, including AF [119–122]. LOX is a copper-dependent amine oxidase expressed and secreted by vascular smooth muscle cells and other fibrogenic cells, which initiates the cross-linking of collagen and elastin [123]. During the oxidative deamination of (hydroxyl)-lysine residues highly reactive semi-aldehydes and H_2O_2 are generated. Catalytic forms of LOX have been also detected in nuclei and cytosol, but their function remains to be elucidated fully [124,125]. Increased expression of LOX together with increased collagen cross-linking has been observed in left atria of patients with AF [119]. AngII and Rac1 were shown to mediate the up-regulation of LOX expression [119]. If and to what extent H_2O_2 generated by LOX contributes to atrial redox signaling and the ROS-dependent generation of AF substrate is not clear, yet. However, LOX and LOX-derived H_2O_2 are potent chemoattractants for monocytes and VSMC [126,127], which could well contribute to AF-related remodeling.

5. Cellular and molecular targets of ROS/RNS

ROS/RNS directly affect a variety of cellular and molecular structures and this, of course, has significant impact on the activity of signaling pathways as described above. Avoiding unnecessary redundancy, the following chapter will focus on the redox-modification of ion channels and selected mitochondrial targets.

5.1. Regulation of ion channels and transporters

Redox-sensitive alterations of Na^+, K^+, and Ca^{2+} handling proteins in the heart have been shown to affect excitation-contraction coupling, and thus, significantly contribute to cardiac dysfunction and cardiac arrhythmias, including AF.

In cardiomyocyte action potential (AP) generation, voltage-gated Na^+ channels provoke membrane depolarization, which leads to a Ca^{2+}-influx via L-type calcium channels. This increase in cytosolic Ca^{2+} is further amplified by a so-called Ca^{2+}-induced Ca^{2+}-release. In this process, ryanodyne receptor/Ca^{2+} release channels (RyR) release Ca^{2+} from the sarcoplasmic reticulum into the cytosol. Ca^{2+}-binding to troponin C leads to the activation of myosin ATPase and facilitates contraction. Relaxation is enabled by (I) re-uptake of Ca^{2+} into the sarcoplasmic reticulum by means of the sarcoplasmic/endoplasmic reticulum calcium ATPase 2 (SERCA2), and (II) Ca^{2+}-efflux mediated by the sarcolemmal Na^+/Ca^{2+}-exchanger (NCX).

Many of these ion handling proteins are subject to regulation by phosphorylation and, thus, the activation of redox-activated protein kinases such as CaMKII, PKC, and PKA represents a crucial mechanism of cardiac ion homeostasis and function. In addition, these targets can be directly redox-modified as described in the following.

5.1.1. Calcium handling

Down-regulation of L-type calcium-channels and altered intracellular calcium handling represent a key mechanism of the electrical remodeling in AF and alterations in intracellular Ca^{2+} levels have been implicated in the pathogenesis and progression from paroxysmal to persistent AF [128–132].

Molecular mechanisms underlying the AF-dependent electrical remodeling to a large part are due to changes at the level of expression or phosphorylation of ion channels, and this is particularly true for calcium channels (expertly reviewed in [132–134]. In addition, the activity of calcium channels can be modified by NO donors (e.g. via S-nitrosylation) and molecules that affect the redox state of cysteine residues [132–136].

The activity of the L-type calcium channel, which in the heart consists of a pore-forming α1c subunit (CACNAC) encoded by the Cav1.2 gene, and β, α2/δ, and γ subunits is substantially affected by cardiac disease, including AF. I_{CaL} currents are 70% lower in patients with AF compared to SR [137–140]. Accordingly, reduced levels of Cav1.2 mRNA have been observed in AF patients and in animal models of RAP [138,141–144]. Furthermore, RAP in vitro at 5 Hz of HL-1 atrial myocytes reduced plasmalemmal levels of the α1c subunit by −72% compared to controls [145]. Data regarding the protein expression, however, are conflicting, with some studies reporting a decrease in L-type Ca^{2+} channel subunit expression similar to what has been observed at the mRNA level [138,142,144], whereas other studies could not detect such differences in response to AF or RAP [146,147].

It has been recently shown that the α1c-subunit is constitutively S-nitrosylated in the mouse heart. Ischemia led to an increase in this SNO-modification, which was associated with inhibition of the channel [148]. Hypernitrosylation of α1c has been also observed in patients with AF and this was inversely correlated to cellular glutathione levels [149].

In addition, and as mentioned above, the activity of L-type Ca^{2+} channels is regulated by reversible phosphorylation. Early work already demonstrated that the β-adrenergic receptor-dependent activation of these channels is due to phosphorylation by the cAMP-dependent PKA [150,151]. This finding has been confirmed by subsequent work over decades and was shown to be true for the G_s-coupled β1- and β2-receptors [152]. There are other G_s-coupled receptors in the heart that may contribute to AF-dependent increase in I_{CaL}, but these effects are less well studied. Several G_i-coupled receptors are known to interfere with the β-adrenergic activation of I_{CaL}, while hardly affecting basal I_{CaL}. The muscarinergic M_2 receptor is one such well-studied example [153], others include receptors for adenosine, opioids, and atrial natriuretic factor (ANP) [152]. In addition, strong depolarization has been proposed to cause a voltage-dependent conformational change of the channel that facilitates its PKA-mediated phosphorylation [154]. PKA is localized to the L-type Ca^{2+} channel by A-kinase anchoring protein 79/150 (AKAP79/150) [155,156]. AKAP also recruits the Ca^{2+}-dependent phosphatase, calcineurin, to the membrane. Activation of the latter represents an important regulatory mechanism of nuclear factor of activated T-cells (NFAT)-mediated hypertrophic response during AF [157–160]. Serine residues 1574 and 1700 as well as threonine 1704 have been identified as cAMP/PKA-dependent phosphorylation sites in L-type Ca^{2+}-channels [161,162]. However, a recent study showed that β-adrenergic regulation of the L-type Ca^{2+}-channels does not require phosphorylation at serine 1700 [163].

Protein phosphatase 2A (PP2A) and the cGMP/PKG pathway have also been identified as enzymes responsible for phosphorylation of this channel [164,165].

Inhibition of cellular Ca^{2+} entry by verapamil, an inhibitor of I_{CaL}, prevented the loss of intracellular thiols and attenuated mitochondrial changes during tachycardia [20,21]. Nonphysiologic Ca^{2+} entry and, in particular, increased mitochondrial Ca^{2+} levels play a pivotal role in the impairment of mitochondria upon rapid pacing. Although no increase in mitochondrial Ca^{2+} has been found during atrial fibrillation by electron probe microanalysis [166], inhibition of mitochondrial Ca^{2+} influx by ruthenium red had a protective effect in a rat heart model of ventricular tachycardia [39]. The finding that verapamil protects from oxidative stress is supported by a study from Mason et al. [35]; they showed that mibefradil, which blocks L-type and T-type Ca^{2+} channels, and verapamil prevent the oxidation of cellular constituents and have cytoprotective effects.

RAP- and AF-dependent alterations in Ca^{2+}-handling are also due to impaired Ca^{2+} release from the sarcoplasmic reticulum, which in part results from impaired coupling between Ca^{2+} channels and sarcoplasmic ryanodine receptors (RYRs), particularly RYR2. RYR2 mediates the Ca^{2+} release from the sarcoplasmic reticulum in response to I_{CaL}-mediated Ca^{2+} influx in cardiomyocytes.

An enhanced open probability of RYRs has been demonstrated after RAP in dogs as well as in patients with sustained AF [167]. Although this increases the frequency of Ca^{2+} sparks in atrial myocytes [168], it does not translate easily in increased ectopic activity. Hyperphosphorylation of RYRs due to increased CaMKII activity has been shown to increase Ca^{2+} leak from the sarcoplasmic reticulum and, thus, diastolic Ca^{2+} concentrations [85]. Accordingly, mutation S2814A in RYR2, which prevents phosphorylation by CaMKII, has been shown to reduce Ca^{2+} leak and susceptibility to induced AF [169]. Mice deficient for the RYR2-stabilizing protein FKBP12.6 are more susceptible to spontaneous and induced AF [169].

Redox modification of RYR leads to alterations of conformation and channel activity [135]. For RYR1, a channel-activating nitrosylation of amino acid residue C3635 has been demonstrated [170,171]. This activation of RYR1 is achieved at physiological nanomolar concentrations of NO only when thiols are in a reduced state (at low pO_2) [172]. In cardiac muscle, RYR2 activity was demonstrated to also depend on pO_2, but RyR2 was not activated or S-nitrosylated directly by NO, but required S-nitrosoglutathione of the cysteine 3602 instead [173]. RYR nitrosylation depends on NOS1 activity and in the heart RYR2 is co-localized with NOS1. Thus, NOS1 deficiency but not the lack of NOS3 affects SNO-modification of RYR2 [135,174]. Recent studies demonstrated that elevated levels of cytosolic reduced glutathione (GSH) increase Ca^{2+} leak from the sarcoplasmic reticulum and Ca^{2+} sparks due to redox-dependent intermolecular crosslinking of RYR subunits [175].

RAP and AF also lead to increased phosphorylation of sarcoplasmic/endoplasmic reticulum calcium ATPase 2 (SERCA2) and phospholamban (Plb). SERCA activity, which is essential for the regulation of cardiomyocytes' intracellular Ca^{2+} concentration, is regulated by its inhibitor, Plb. Altered phosphorylation of Plb has been observed in AF [31]. Recent data suggest an increased activity of SERCA2 in long-standing persistent AF [176]. This is in full accordance with an increase in the inhibitory phosphorylation of Plb in pAF [176]. Reduced levels of SERCA mRNA have been described for patients with AF [177]. However, amounts of SERCA and Plb protein were not different between SR and AF patients [178]. Decreased SERCA activity in the heart has been associated with increased nitrosylation of SERCA [179]. The decline of SERCA activity with increasing age has also been suggested to be due to S-nitrosylation [180].

NCX currents (I_{NCX}) in response to Ca^{2+} leak from the sarcoplasmic reticulum can cause delayed afterdepolarizations (DADs) that promote AF [181]. In heart failure patients, an increase in the expression of NCX could be demonstrated at both mRNA and protein level [182]. Expression changes were associated with an increased risk for AF in these patients [182]. Functional coupling between NCX and inositol 1,4,5-triphosphate receptor (IP3R) has been shown to contribute to arrhythmic excitability of pulmonary veins and, thus, represents a further mechanism underlying increased AF-susceptibility [183]. AngII, plasma and tissue levels of which are elevated in AF, increased NCX expression and calcium transients in HL-1 cardiomyocytes, associated with the occurrence of frequent premature depolarizations and AF-like electrograms [184]. Both the siRNA-mediated knock-down and the pharmacological blockade of NCX attenuated these arrhythmogenic effects of AngII [184].

First evidence that the NCX is under redox control was provided in 1986 by Reeves et al. [185]. They showed that NCX activity could be greatly enhanced by different combinations of oxidizing and reducing agents. Later it was shown that the ischemia/reperfusion induced inhibition of NCX activity is ROS-dependent and, therefore, could be prevented by free radical scavenger enzymes (superoxide dismutase plus catalase) [186]. Recent work revealed a crucial role of the cytosolic $NADH/NAD^+$ redox couple for the regulation of NCX activity in cardiac myocytes [187]. I_{NCX} was inhibited by both direct loading of NADH or by indirect elevation of NADH by extracellular lactate perfusion. NADH-dependent NCX inhibition could be abolished by the H_2O_2-metabolizing enzyme, catalase [187]. The authors could exclude complex I of the respiratory chain and NOX2 as a major source of ROS.

Evidence indicates that the activity of the NCX isoforms 1 and 2 is increased by NO via cGMP-dependent and independent mechanisms, whereas that of NCX3 is inhibited by NO in a cGMP-independent way [188]. For NCX1, the determinant of NO action has been identified as cysteine 730. This is suggestive of a direct S-nitrosylation of NCX1 [188]. However, biotin-switch assays for SNO on total cardiac lysates identified RyR2, SERCA2a, and L-type Ca^{2+} channels as substrates for SNO, but failed to detect NCX [189].

Inositol 1,4,5-triphosphate (IP_3) increases contractility via increase of atrial and ventricular Ca^{2+}-transients. This mechanism also contributes to the induction of arrhythmia and altered Ca^{2+}-signaling under pathophysiological conditions (expertly reviewed in [190,191]). IP_3 is generated by hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2) in response to receptor-mediated activation of phospholipase C (PLC) isoforms. Different receptor types are capable of PLC activation: G-protein-coupled receptors (via PLCβ) and receptor tyrosine kinases (via PLCγ) [190]. Furthermore, PIP_2 and Ca^{2+} (PLCδ) as well as Ras (PLCε) can activate PLC. Upon formation, IP_3 translocates

to its cytoplasmic targets which are the IP3R isoforms in the ER or SR [190]. The resulting IP_3-dependent Ca^{2+} release from intracellular stores increases the amplitude of systolic Ca^{2+} transients and, thus, increases contractility. The atria, in particular, are very sensitive to arrhythmia in response to various hormones that provoke Ca^{2+} sparks and after-depolarization that way. This has been demonstrated for e.g. endothelin [192,193], bradykinin [194,195], or arginine vasopressin [196]. Interestingly, IP_3Rs have been localized in or close to the nuclei of cardiomyocytes [197–199]. Perinuclear IP_3-evoked Ca^{2+} signals, therefore, can contribute to hypertrophic gene expression [200]. This is in accordance with the established hypertrophic effects of peptide hormones on myocytes [190,201–203]. In patients with AF, enhanced activity and expression of IP_3Rs has been described [177,204,205]. Thus, it is not surprising that in the rabbit heart *in vitro* the administration of the IP3R inhibitor, 2-aminoethoxydiphenyl borate, prevented the induction of different types of AF [206].

Accumulating evidence indicates that IP_3Rs are regulated by the redox state (reviewed in [207]). Various oxidants have been shown to stimulate IP_3R-mediated Ca^{2+} release when administered exogenously [208–213]. Increased sensitivity of IP_3Rs, especially at low concentrations of IP_3, very likely is the underlying mechanism [212,214]. Recent data demonstrate that ROS, in particular superoxide anions, sensitize the IP3R at low and stable IP3 concentrations through a thiol group [214].

5.1.2. Potassium handling

Multiple K^+ channels and currents are regulated by redox-reactions [135,215–219]. S-nitrosylation (SNO) has been reported to increase I_{Ks} by Cys445 modification of the KCNQ1 subunit [220–222]. This results in a substantial shortening of action potential duration (APD), which in turn increases AF susceptibility and duration.

Kv1.5 generates the ultrarapid component of the I_{Kur} and determines membrane potential and action potential plateau in the atria. Kv1.5 contains 6 intracellular cysteines which is in line with its widely described redox-sensitivity [135]. This current is inhibited by SNO [223]. Recent work demonstrated that SNO functions as a fate switch diverting Kv1.5 from recycling to a degradation pathway in myocytes [218]. Kv4.3, generating the transient outward K^+ current (I_{to}), is subject to SNO. However, and despite the fact that NO and NO-inhibitors alter Kv4.3 currents, SNO has no effect on the activity of this channel [224].

5.1.3. Sodium handling

Cardiac Ca^{2+} handling is closely linked to Na^+ handling. Along with the NCX described above, the N^+/K^+ pump and cardiac Na^+ channels are critical regulators of cardiac sodium ion handling and AP architecture. The cardiac Na^+ channel is composed of the pore-forming α-subunit, Nav1.5, and a β-unit serving regulatory functions. Methionine residues in Nav1.5 have been implicated in the sensitivity against oxidation of Nav1.5 [225]. ROS have been shown to directly regulate sodium currents. Effects involved include an increase of late I_{Na} which may lead to prolonged AP and favors the occurrence of early afterdepolarizations (EAD) [226,227]. The persistence of the late I_{Na} has been shown to depend on S-nitrosylation of Nav1.5, which in turn is coupled to NOS1 activity [228]. Available data suggest that in addition to S-nitrosylation cardiac Nav1.5 activity could also be regulated by direct cysteine oxidation, preferably under conditions of elevated ROS production [229]. As reviewed expertly recently [230], Nav1.5 is substrate of phosphorylation by protein kinases including PKA, PKC, and CaMKII. Therefore, redox-regulation and direct oxidative modification of these kinases contribute to dysregulation of cardiac Na^+ handling.

The cardiac Na^+–K^+ pump maintains transmembrane ion gradients for Na^+ and K^+ and is, thus, critically involved in the generation of action potential in these cells. The Na^+–K^+ pump has been shown to be regulated by glutathionylation of cysteine 46 in the β-subunit [231]. FXYD-domain containing ion transport regulator 1 (FXYD1, phospholemman), a member of a family of membrane proteins that associate with the Na^+–K^+ pump complex, has been recently shown to be subject of glutathionylation. This glutathionylation of FXYD1 is important for the reversal of the Cys46-modification of the β-subunit of the Na^+–K^+ pump [232]. A consistent model of AngII and β1-adrenergic stimulated, protein kinase-dependent oxidative regulation of the cardiac Na^+–K^+ pump has been proposed, which indeed has important implications for cardiac physiology and disease, including AF [233].

5.2. Mitochondria and metabolism (OXPHOS)

Studies on atrial tissue have shown that an AF- or RAP-induced calcium-overload of cardiomyocytes induces ultrastructural alterations including morphologically altered mitochondria [20,21,28,234]. AF is associated with a higher demand of energy of cardiomyocytes resulting in transiently decreased concentrations of high energy phosphates and mitochondrial NADH [28,234]. AF, however, is associated with ischemia and impairment of microvascular flow, which have even been observed in the ventricles [1,30,31]. It is fully established that even mild ischemia is associated with compromised mitochondrial function and requires metabolic adaption to maintain adequate ATP generation and cardiac output [235]. There are controversial reports concerning the effect of tachyarrhythmia like AF on the activity of mitochondrial enzymes. Using a canine model, decrease in the activities of the mitochondrial complexes III and V have been reported during rapid pacing [236], whereas no changes were found in the activities of the complexes IV and V in goats subjected to AF [28]. Rapid pacing *in vitro* of intact cardiomyocytes, besides causing significant structural mitochondrial changes, led to a severe impairment of mitochondrial ATP production and endogenous respiration in combination with decreased ATP/AMP ratio [20,21].

AF-dependent flow restrictions and the associated relative or absolute restriction of oxygen and nutrients supply lead to activation of multiple signalling pathways that are aimed at the improvement of oxygen supply, angiogenesis, cell survival, and adaption of metabolism [1]. The activation of redox-sensitive transcription factors, namely HIF-1α and PPARGC1, is crucially involved in these protective changes in metabolism, which include a shift from aerobic metabolism and fatty acid utilization to glucose utilization via pyruvate oxidation, or even to glycolytic metabolism [237,238]. HIF-1, together with c-myc, has been identified as mediator of the induction of HK2. This mechanism contributes to shift glucose away from mitochondrial utilization and has also antioxidative effects [239,240]. In accordance with the observed increase in PPARGC1 and HIF-1α expression, RAP provoked profound changes in the ventricular expression of important metabolic genes including hexokinase 2 (HK2), glycogen synthase kinase 3β (GSK-3β), muscle isoform of glycogen phosphorylase (PYGM), and acyl-coenzyme A dehydrogenase (ACADL) [30].

6. Conclusions

ROS/RNS and redox signaling have been implicated in physiological processes in the heart such as excitation-contraction coupling. Clinical data and evidence from experimental studies demonstrate a crucial role of ROS/RNS also in the pathophysiology of the heart and cardiovascular diseases, including cardiac arrhythmia. Redox-signaling contributes to tissue remodeling and self-perpetuation of AF, but is also capable of initiating protective mechanisms. Therefore, and despite of so far rather disappointing results, antioxidant/redox-modifying therapy may still represent a reasonable strategy for prevention and therapy of AF, provided that redox-regulated processes can be fully resolved both spatially and temporally, and target/compartment specificity of interfering compounds could be further improved.

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