Atrial Electrophysiological Remodeling and Fibrillation in Heart Failure

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Supplementary Issue: Calcium Dynamics and Cardiac Arrhythmia

ABSTRACT: Heart failure (HF) causes complex, chronic changes in atrial structure and function, which can cause substantial electrophysiological remodeling and predispose the individual to atrial fibrillation (AF). Pharmacological treatments for preventing AF in patients with HF are limited. Improved understanding of the atrial electrical and ionic/molecular mechanisms that promote AF in these patients could lead to the identification of novel therapeutic targets. Animal models of HF have identified numerous changes in atrial ion currents, intracellular calcium handling, action potential waveform and conduction, as well as expression and signaling of associated proteins. These studies have shown that the pattern of electrophysiological remodeling likely depends on the duration of HF, the underlying cardiac pathology, and the species studied. In atrial myocytes and tissues obtained from patients with HF or left ventricular systolic dysfunction, the data on changes in ion currents and action potentials are largely equivocal, probably owing mainly to difficulties in controlling for the confounding influences of multiple variables, such as patient's age, sex, disease history, and drug treatments, as well as the technical challenges in obtaining such data. In this review, we provide a summary and comparison of the main animal and human electrophysiological studies to date, with the aim of highlighting the consistencies in some of the remodeling patterns, as well as identifying areas of contention and gaps in the knowledge, which warrant further investigation.

KEYWORDS: failing ventricle atrial remodeling

Introduction

Atrial fibrillation (AF) is the most commonly observed arrhythmia in the clinic, and it is associated with complications such as stroke, heart failure (HF), and sudden death.[1] Recent studies indicate that more than ~33 million people are affected by AF worldwide,[2] and this number is expected to grow as the general population ages. The incidence of HF is also growing alarmingly worldwide, and AF can be both a cause and a consequence of HF, which in part substantially complicates treatment efforts when both comorbidities coexist.[3] The likelihood of AF is also seen to increase with the severity of HF, ranging from ~10% in HF patients classified under New York Heart Association (NYHA) Class I, to ~50% in those classified with NYHA Class IV symptoms.[3] Even though the ionic and structural remodeling that underlies the now-classically established paradigm of "AF begets AF"[4] is fairly well understood,[5] the same cannot be said regarding how AF is initiated and sustained in the context of HF. It is important to understand the underlying mechanisms because AF in HF patients is associated with increased mortality and morbidity.[1] The pathophysiological mechanisms underlying the development of AF in HF are multifactorial and complex, in addition to involving changes in electrical properties, structural modifications, neurohormonal alterations, and activation of inflammatory as well as oxidative stress pathways.[1,3] In this review article, we mainly focus on our current understanding of the atrial electrophysiological remodeling occurring in HF and how it can lead to sustained arrhythmias. Most of the available insights regarding the ionic and molecular mechanisms of atrial electrophysiological changes have been primarily obtained via experimental studies using animal models of HF, even though substantial gaps remain.[6] We begin by examining the data obtained regarding electrophysiological remodeling occurring in the human atrium during left ventricular (LV) dysfunction or HF.

Altered Atrial Electrophysiological Substrate in Humans with Ventricular Dysfunction

Sanders et al examined the atrial electrophysiological properties in patients with severely reduced LV ejection fraction (LVEF ~25%), and their *in vivo* studies showed that compared to age-matched controls, patients in the HF group demonstrated

an increased atrial effective refractory period (ERP) in the low lateral right atrium and distal coronary sinus, but no change in the heterogeneity of ERP.[7] Further, in the same study, electroanatomical mapping data showed regional slowing of impulse propagation, as well as a greater instance of fractionated electrograms (indicative of fibrosis).[7] Inducibility of AF in patients with HF was increased, as was the duration of sustained AF.[7] Fedorov et al showed, by optical voltage mapping in human coronary-perfused atrial–ventricular free wall preparations, that atrial action potential duration (APD) and functional refractory period were longer in failing hearts than in nonfailing hearts.[8] Increased atrial fibrosis has also been associated with reduced LVEF in patients.[9] Xu et al provided evidence for atrial extracellular matrix remodeling in explanted hearts of patients with dilated cardiomyopathy and end-stage HF.[10] The protein level of the tissue inhibitor of metalloproteinase (TIMP-2) was downregulated, whereas that of matrix metalloproteinase (MMP-2) was upregulated in patients with permanent and/or persistent AF, compared to the levels in the donor left atrium.[10] Cellular studies have also been conducted to examine the ionic basis of atrial electrophysiological remodeling due to HF in humans, and these have provided varied results. Koumi et al found that the APD at 90% repolarization (APD_{90}) was longer, the resting membrane potential (V_{rest}) was more depolarized, and the plateau phase amplitude was smaller in myocytes isolated from the right atrial appendage from HF patients (median age: 50 years), compared to controls (median age: 38 years).[11] These investigators found reduced single-channel densities for both the inward rectifier K^+ current I_{K1} and the acetycholine (Ach)-activated K^+ current I_{KACh}, in addition to a reduced sensitivity to activation by ACh in the latter, in HF tissues, compared to control hearts.[11] However, the mean open life times and single-channel slope conductance of these two currents were similar in HF and control samples.[11] It must be noted, however, that in the study conducted by Koumi et al in 1994, out of 30 HF patients, six were in chronic AF, four in paroxysmal AF, and the remaining were in sinus rhythm.[11] In contrast, when Schreieck et al investigated the electrical properties of atrial cells obtained from patients with normal LVEF (>60% as criterion; mean age: 31 years; lateral left atrial wall as source of cells) and reduced LVEF (<45% as criterion, mean age: 65 years; right atrial appendage as source), they did not find any significant difference in either APD_{90} or V_{rest} between groups, but the plateau level of atrial action potentials in HF was lower, compared to controls.[12] These investigators excluded not only all patients with AF but also those with a left or right atrial enlargement >45 mm. When they investigated the underlying ionic mechanisms, they found increased density of the Ca^{2+}-independent transient outward K^+ current, I_{to1}, in human atrial myocytes of patients with reduced LV function, no change in its voltage dependence or decay, but faster recovery from inactivation.[12] There was reportedly no difference in the density of the background or sustained K^+ currents; the latter is primarily composed of the atrial-specific ultra-

rapid delayed rectifier current, I_{Kur}.[13] However, it was not clear whether the use of beta-blockers was a criterion for the exclusion of patients in this study[12]; this is important, because such a treatment is associated with decreased density of I_{to1} in the human atrium.[14] The most recent investigation was conducted by Workman et al[15], whose findings were again different from those of previous reports. In atrial cells isolated from patients in sinus rhythm (right atrial appendage) with a reduced LVEF (<45%), APD_{90} was shorter than in patients with higher EF, although, intriguingly, there was a small increase in the maximum upstroke velocity of the action potential (V_{max}), but no change in Vrest.[15] There was also a significant positive correlation between LVEF and the atrial cellular ERP; lower LVEFs were associated with shorter ERPs. Patch clamp studies showed that there were no differences in the densities of I_{K1}, I_{Kur}, or the L-type Ca^{2+} current, I_{CaL}.[15] However, the density of I_{to1} was reduced by ~34% and there was a positive shift in its activation voltage in patients with LV systolic dysfunction (LVSD), compared to those with no LVSD.[15] This reduction in I_{to1} was also observed when patients were subanalyzed by treatment with beta-blockers.[15] It is noteworthy that I_{to1} reduction in human atrial cells should be expected to increase, rather than decrease, APD_{90},[16] and the ion current mechanisms that account for the APD shortening in patients with LVSD remain elusive. Atrial dilatation is seen commonly in the course of cardiac failure.[3] In trabeculae and myocytes taken from dilated atria, APD_{90} was shorter and the plateau was markedly depressed compared to trabeculae and myocytes from nondilated atria.[17] However, it must be noted that the ventricular dysfunction was not quantified in these patients. Action potential changes were explained with more severely depressed I_{CaL} compared to the reduction in total outward current.[17] However, absence of change in I_{CaL} has also been reported in atrial cells obtained from explanted hearts with dilated atrial appendages,[18] while Dinanian et al have shown that decreased I_{CaL} was associated with reduced LV function and mitral valve disease.[19] Thus, overall, there is a lot of discrepancy, particularly among the various cellular studies characterizing atrial ionic and action potential remodeling in human HF, which could be related to cell damage during isolation, varied characteristics of patients and/or their exclusion criteria, or experimental conditions (temperature, recording solutions, and so on). Finally, recent studies indicate an emerging difference in the atrial dysfunction in HF patients, classified as with either preserved or reduced EF; the former group was seen to be associated with increased left atrial stiffness and burden of AF, in contrast to the increased dilatation and eccentric remodeling seen in the latter.[20] However, the precise electrostructural determinants of this pathophysiological remodeling and their role in precipitating AF remain unclear.

Atrial Remodeling in Animal Models of HF

The atrial electrical remodeling occurring due to ventricular dysfunction has been studied extensively in animal models

(mainly tachypacing-induced or myocardial infarction (MI)-induced HF).[5] In atria of dogs with short-term (three–six weeks) ventricular tachypacing-induced HF, the inducibility and duration of sustained AF[21] or atrial tachycardia (AT)[22] were substantially enhanced. Focal activations were commonly seen in both canine and ovine HF models, originating near the crista terminalis,[23] pulmonary vein regions,[23–25] or vein of Marshall.[25] In atrial recordings from whole hearts, the ERP was either increased (three weeks of ventricular tachypacing)[22] or unchanged (five weeks of ventricular tachypacing); in the latter case, although there was no change in refractoriness heterogeneity, or conduction velocities, the heterogeneity of conduction was substantially increased, and discrete regions of slow conduction were observed.[21] The heterogeneity in atrial conduction index was observed even in a short-duration (two weeks) tachypacing-induced HF model.[26] A commonly observed characteristic in the HF models was enhanced fibrous tissue content in the atria,[26,27] with reports of both extensive interstitial[21,25] and diffuse fibrosis.[24] The number and size of atrial fibrotic patches were also larger in HF samples compared to the same in controls.[24] In addition to fibrosis, the HF-induced atrial conduction abnormalities may also be partially due to changes in the expression of connexins (Cxs); although their density was not altered (mRNA and protein levels of Cx40 and Cx43), Cx43 was dephosphorylated, the ratio of Cx40/Cx43 was increased, and Cx43 was redistributed toward transverse cell boundaries in HF versus control hearts.[26] In a rabbit model with eight weeks of MI, the threshold for inducing AF was decreased, and this was shown to be associated with increased propensity of APD alternans, but no changes in either mean APD or conduction velocity were observed.[28] In addition to the whole heart, the atrial cellular electrophysiological remodeling in HF has been studied extensively, and this has shed light on the underlying ionic mechanisms. In the short-term model of ventricular tachypacing in dogs, the atrial cells were hypertrophied, and the APD was not changed at slower pacing frequencies but increased in duration at rapid pacing frequencies.[29] The densities of I_{CaL}, I_{to1}, and the slow delayed rectifier K$^+$ current I_{Ks} were reduced in HF samples compared to those in controls, but there was no change in their voltage dependencies or kinetics.[29] The densities of the K$^+$ currents I_{K1}, I_{Kur}, I_{Kr}, and the T-type Ca^{2+} current I_{CaT} were not altered, but that of the electrogenic Na$^+$–Ca^{2+} exchanger, I_{NCX}, was increased.[29] In contrast, in the long-term tachypaced canine model of ventricular HF (four months of tachypacing), the APD$_{50}$ and APD$_{90}$ were significantly shortened in atrial isolated cells; this corresponded with a substantially shortened atrial ERP, as measured *in vivo*.[27] Such atrial APD shortening resulting from long-term congestive HF was confirmed in a subsequent study.[30] The ionic changes reported included increased I_{to1} and decreased I_{K1}, I_{Kur}, and I_{Ks}.[27] Upon studying I_{CaL} under action potential clamp conditions, the HF atrial action potential reduced the integral of I_{CaL} in control healthy cells, with a larger reduction in myocytes from HF

dogs.[27] These data point toward a complex electrical phenotype and underlying ionic mechanism changes in the atrium in the presence of HF, depending upon the severity of the condition (short-term versus long-term ventricular pacing),[31] and, in part, mirror the complex and varied phenotypes seen in patients with ventricular dysfunction. Besides sarcolemmal ion channels, significant dysregulation in atrial intracellular Ca^{2+} ([Ca^{2+}]$_i$) homeostasis and its regulatory components/proteins has been reported in ventricular HF models.[28,32–34] After two weeks of ventricular pacing in canines, Yeh et al found that the levels of diastolic Ca^{2+}, [Ca^{2+}]$_i$ transient amplitude, and sarcoplasmic reticulum (SR) load were increased, and that the enhanced SR load was also associated with spontaneous Ca^{2+} release events.[32] The greater SR load was partly attributable to a prolonged APD, as well as an increased calmodulin-dependent protein kinase II phosphorylation of phospholamban, which potentially reduced the inhibition of SR uptake; however, the phosphorylation of SR release channels (ryanodine type-2, RyR2) was not affected, but the total RyR2 and calsequestrin levels were reduced.[32] In contrast to these findings, in the ovine model of tachypacing-induced HF (mean period of tachypacing: ~33 days), the [Ca^{2+}]$_i$ transient amplitude and the density of I_{CaL} were both reduced, the atrial SR content was increased, and the [Ca^{2+}]$_i$ amplitude was similar in controls and HF during β-adrenergic stimulation.[34] In the rabbit MI model (eight weeks of infarction), under β-adrenergic stimulation, the [Ca^{2+}]$_i$ transient amplitude, and the density of I_{CaL} were both decreased in MI compared to controls, and the frequency of spontaneous depolarizations was higher in MI.[28] A decrease in the atrial [Ca^{2+}]$_i$ transient amplitude and SR Ca^{2+} content was also reported following four weeks of MI in rats.[35] In both sheep HF[33] and rabbit MI models,[28] there was a marked decrease in the density and network of the transverse T-tubules, and these structural and functional changes may partially underlie the focal nature of activation of the atrial arrhythmias seen in HF.[6,23] Recent studies have also begun to investigate the properties and proliferation of fibroblasts in mediating enhanced atrial fibrosis in HF.[5] In the dog HF model, various signaling pathways that underlie apoptosis followed by atrial interstitial fibrosis have been identified, which include increased phosphorylation of p38 mitogen-activated protein kinases, JNK, and ERK, which were preceded by increases in tissue levels of angiotensin II.[36] Different ion channels have been identified to exist in atrial fibroblasts, and two K$^+$ channels, namely, the tetraethylammonium-sensitive K$^+$ current and Ba^{2+}-sensitive inward rectifier K$^+$ current, have been shown to affect fibroblast proliferation in the dog HF model.[37,38] The voltage-dependent K$^+$ currents (conducted through Kv1.5 and Kv4.3 channels) were found to be downregulated in HF, and suppressing these currents enhanced fibroblast proliferation, suggesting that they may play an important role in mediating fibrosis.[37] In addition, the density of the I_{K1} current (as well as its mRNA/protein levels) was found to be enhanced in atrial fibroblasts isolated from

HF dogs, compared to that in healthy controls.[38] Overexpression of atrial fibroblast I_{K1} current by lentivirus led to hyperpolarization of V_{rest}, increased store-operated Ca^{2+} entry, and fibroblast proliferation, and it was suggested that microRNA-26a might play a regulatory role.[38] A similar role for regulation of atrial fibrosis was suggested for microRNA-29, which has been shown to be downregulated in the dog HF model and to regulate the expression of extracellular matrix proteins such as collagen and fibrillin.[39] Recent computational studies have also investigated the putative bases of fibroblast effects on atrial electrophysiology, mainly occurring as a result of coupling between myocytes and atrial fibroblasts.[40,41] Simulations indicate that such coupling can modulate V_{rest} and repolarization, predisposing the atrium to arrhythmogenesis.[40,41] However, direct experimental evidence of such coupling in the atrium (or the heart) is still not available. In addition to coupling, fibroblasts/myofibroblasts can influence atrial ion channels and excitability through secretion of factors such as transforming growth factor (TGF)-β1 and platelet-derived growth factor and also by direct physical contact that can lead to dedifferentiation.[42] Another component that may play a role in affecting the electrophysiology and inducing AT/AF, apart from ionic and structural remodeling, in HF is the remodeling of the autonomic nervous system.[43] Ogawa et al examined nerve activity in the dog model of HF and observed that both the left stellate ganglion nerve activity (SGNA) and vagal nerve activity (VNA) were increased in HF compared to those in controls, and that episodes of paroxysmal AT in a majority of cases were induced by simultaneous increases in both SGNA and VNA, followed by vagal withdrawal.[44] However, the precise ionic/molecular mechanisms remain to be determined. In other studies of atrial autonomic remodeling, chronic ventricular tachypacing in pigs was shown to decrease atrial beta-1-adrenoceptor expression,[45] and chronic MI in dogs caused heterogeneous sympathetic nerve sprouting in the atrium, accompanied by increased susceptibility to atrial alternans and AF.[46] Lastly, the ionic mechanisms underlying how inflammation or oxidative stress modulates the atrial electrophysiological remodeling occurring in the context of HF remain incompletely understood (but also see later in the next section).

Therapy for AF in HF

Currently, the main therapy for AF can be broadly classified as rate or rhythm control,[1] and we will focus on the latter aspect in this review. Rhythm control strategies for maintaining sinus rhythm consist of either catheter ablation or the use of antiarrhythmic drugs.[47] The main antiarrhythmic drugs used in HF patients include amiodarone and dofetilide.[1,47] Although the multiple ion channel blocker amiodarone (eg, I_{Na}, I_{Kr}, I_{Kur}, I_{to1}, I_{CaL}, I_{Ks}, I_{KAch}, and β-receptors) is the most effective available antiarrhythmic, it may be associated with significant cardiac adverse consequences (bradycardia, QT interval prolongation) and noncardiac toxicities including pul-

monary, thyroid, and liver toxicities.[1] Dofetilide, a selective blocker of I_{Kr}, may increase the risk of QT interval prolongation and torsade de pointes, and inpatient electrocardiographic monitoring is necessary for its use.[1] Recent clinical trials show that catheter ablation has more success in achieving freedom from AF, compared to amiodarone, in patients with congestive HF.[48] However, antiarrhythmic drugs constitute the mainstay of treatment in AF,[49] and therefore more efforts are needed to develop newer drugs, especially as recent efforts to use improved variants of amiodarone (dronaderone) proved contraindicatory because of increased mortality, particularly in HF patients.[50] Efforts to develop newer therapies have also been explored in experimental animal models of HF. The renin–angiotensin–aldosterone system is known to be activated in HF,[51] and Shroff et al explored whether selective aldosterone blockade could prevent atrial arrhythmias in HF.[52] Their study in a dog model of HF found that eplerenone treatment significantly suppressed atrial arrhythmia inducibility, prolonged atrial ERP, but did not affect atrial dilatation.[52] Because oxidative stress and inflammation may also be involved in HF-related atrial remodeling, Shiroshita-Takeshita et al investigated the effects of simvastatin on the AF substrate in a dog HF model.[53] Their results showed that simvastatin attenuated atrial conduction abnormalities, decreased fibrosis, and suppressed fibroblast proliferation, which led to a reduced duration of induced AF episodes.[53] The antifibrotic drug pirfenidone significantly attenuated arrhythmogenic atrial remodeling and AF induction in HF dogs, in part by reducing TGF-β1 expression (which is profibrotic).[54] In addition to these upstream therapy approaches, gap junctions have also been targeted, with mixed results. The gap junction modifier rotigaptide (ZP123) did not affect inducibility of AF in a dog HF model.[55,56] In contrast, a novel agent F-16915 significantly reduced the duration of AF inducibility in dog HF models, which was partly attributed to dephosphorylation of Cxs.[56] Finally, recent studies indicate that ranolazine suppressed the peak atrial I_{Na} in HF dogs and promoted postrepolarization refractoriness; it was thus able to either suppress induction of AF (70% of cases) or reduce AF frequency and duration.[57] These data suggest ranolazine as a new possible alternative antiarrhythmic drug to prevent the recurrence of AF in HF patients. However, all these drugs/their derivatives need to undergo comprehensive clinical trials and tests, before their efficacy is reliably proven. Autonomic nerve remodeling also potentially plays a role in initiating AF in HF, and emerging therapies include ablation of ganglionated plexi, or even renal sympathetic denervation.[43]

Future Studies

There is a need to improve mechanistic insights into the pathophysiology of atrial remodeling occurring in HF. Identifying novel time-dependent signaling pathways that underlie electrostructural remodeling by means of proteomics

and metabolomics analyses[58] will help identify novel therapeutic targets, including reactive oxygen species that are now thought to play an important role in the progression of AF toward its permanent form.[59] The pathophysiology underlying HF or concomitant comorbidities, such as hypertension, obesity, diabetes, sleep apnea, chronic kidney disease, or a combination thereof, will also be important in determining patient- or disease-specific therapy.[60] In addition to traditional ionic and upstream targets, recent studies indicate an important regulatory role for microRNAs and noncoding long RNAs in the pathogenesis of HF[61,62]; it remains to be determined whether these new targets can also help ameliorate the arrhythmogenic atrial electrophysiological substrate associated with HF and prevent initiation and/or recurrence of AF.

Acknowledgment

Author Contributions

Wrote the first draft of the manuscript: SVP. Contributed to the writing of the manuscript: SVP, AJW. Agree with manuscript results and conclusions: SVP, AJW. Jointly developed the structure and arguments for the paper: SVP, AJW. Made critical revisions and approved final version: SVP, AJW. Both authors reviewed and approved of the final manuscript.

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