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Is Extensive Atrial Fibrosis in the Setting of Heart Failure Associated with a Reduced Atrial Fibrillation Burden?

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Abstract

Atrial Fibrillation (AF) affects 10 to 50% of patients with chronic heart failure (HF) and is associated with poor long-term prognosis. AF is commonly associated with atrial structural remodeling (ASR), principally characterized by atrial dilatation and fibrosis. However, the occurrence of AF in the full spectrum of ASR encountered in patients with HF is poorly defined. Experimental studies have presented evidence that extensive ASR can be accompanied with a reduced burden of AF, secondary to a prominent depression of atrial excitability. This reduction in AF burden is associated with severe atrial fibrosis rather than with dilatation. Clinical studies of patients with HF point to the possibility that advanced ASR is associated with a less frequent AF occurrence than moderate ASR. Our goal in this review is to introduce the hypothesis that AF is less likely to occur in severe vs. moderate atrial ASR in the setting of HF and that it is severe atrial fibrosis-associated depression of atrial excitability that reduces AF burden.

Keywords

Atrial fibrillation; heart failure; structural remodeling; fibrosis; cardiac arrhythmias; atrial dilatation; electrophysiology

Introduction

AF is encountered in 10 to 50% of patients with chronic HF and is associated with poor long-term prognosis.[1, 2] HF is accompanied by various degrees of atrial structural remodeling (ASR).[3] AF is strongly associated with ASR,[3–10] but the occurrence of AF in the full spectrum of ASR is poorly defined. Recent experimental data indicate that a high degree ASR encountered in HF can be associated with a reduced burden of AF.[11] The current review examines the occurrence of AF over a wide spectrum of atrial size, volume, and fibrosis (hallmarks of ASR),[4] in both experimental and clinical studies. Apart from atrial

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There are no conflicts of interest.

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dilatation and fibrosis, ASR generally consists of multiple factors, including hypertrophy, inflammatory and fatty infiltrations, apoptosis, and changes in compliance.[4, 6] However, there are little to no data relative to the range of these parameters in HF and their impact on the development of AF. In this review, the term ASR is used to depict this broad interpretation of ASR.

Functional severity of HF often poorly correlates with cardiac performance

Worsening of the New York Heart Association (NYHA) functional severity is generally associated with an increased prevalence of AF.[1] However, the functional NYHA classification is based on symptoms that often poorly correlate with cardiac performance and remodeling.[2] The relationships between AF occurrence, ASR, and HF functional class are poorly understood.

Window of vulnerability for development of AF during the progression of experimental HF

A number of groups have used ventricular tachypacing (VTP) to create a systolic non-ischemic dilated cardiomyopathy (DCM) canine models of HF characterized by progressive development of cardiac structural remodeling, which is greater in the atria than in the ventricles (Fig. 1).[11–14] AF occurrence in this canine HF model has been clearly associated with the development of ASR.[11, 13, 14] However, AF inducibility using a single extrastimulus has been shown to be higher at moderate vs. advanced levels of ASR, pointing to a window of vulnerability for AF inducibility during the progression of HF and associated accentuation of ASR (Figs. 1 and 2).[11] A reduction of AF inducibility in advanced ASR is associated with a major prolongation of atrial effective refractory period (ERP) and rate-dependent depression of excitability (Fig. 2). This dramatic prolongation of ERP is due to the development of post-repolarization refractoriness (PRR; i.e., when ERP is longer than action potential duration at 70–90% repolarization), secondary to the depression of atrial excitability (Fig. 2B). The steep increase in ERP and reduced AF vulnerability during the transition from early to late HF are associated with a slight increase in atrial size, but a much greater increase in atrial fibrosis (Fig. 2A). During the development of VTP-induced HF, atrial size increases rapidly in the early phase followed by a much slower enlargement in the late stages (Fig. 2).[11, 15, 16] In contrast, atrial fibrosis increases progressively (Fig. 2).[11, 12] Thus, while AF is strongly associated with atrial fibrosis, this arrhythmia is less likely to occur in severe vs. moderate atrial fibrosis in the canine VTP-induced HF model. The reduced AF burden with advanced fibrosis is likely due to severe depression of atrial excitability (Fig. 2). At advanced stages of HF, about 50% of atrial area is either inexcitable or barely excitable, reflecting significant degradation of atrial viability and/or functionality.[11]

Greater inducibility of AF in early vs. late stages of VTP-induced HF has also been reported in sheep and goats *in vivo*.[15, 17] In VTP-induced HF models, the duration of AF is relatively brief (commonly < 30 min).[11, 14, 15]

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"AF window" has not been observed in non-HF experimental settings, likely due to a much less advanced ASR than in HF. In models of experimental AF not mediated by HF, persistent rapid atrial activation causes a significant ASR.[5, 10, 13] Such ASR, however, is generally much less extensive than that caused by pressure and volume overload (i.e. "HF").[3, 11–13, 16]

Is AF occurrence lower in HF patients with severe vs. moderate ASR?

The extent to which the observed experimental "AF window" correlates with cases of clinical HF is not clear. In the clinic the causes and progression of HF and AF are much more heterogeneous, AF is spontaneous and not electrically-induced, and the duration of AF is commonly much longer than in the VTP-induced HF model. Moreover, both ASR and AF in patients with HF can be influenced by therapeutic interventions capable of reversing ASR and/or modulating development of AF (e.g., ivabradine reverses cardiac remodeling[18] but promotes AF[19]). Few data are available concerning AF burden in patients with HF who possess a broad spectrum of ASR.

Left ventricular ejection fraction, ASR, and AF

HF is generally divided into two basic types based on left ventricular ejection fraction (LVEF), the proportion of blood pumped out of the heart during a single contraction expressed as a percentage, with a normal range between 50 and 75%. The two types are: HF with preserved and reduced LVEF (HFpEF and HFrEF, respectively). The LVEF border line between HFpEF and HFrEF is within 40–50% in different studies.[20–30] Patients having a mid-range LVEF (between 40–49%) have been increasingly recognized as a distinct subtype of HF.[24, 26–28]

Reduced LVEF is associated with both atrial and ventricular structural remodeling.[29, 31] Mean left atrial (LA) size and maximum volume are typically greater in patients with HFrEF vs. HFpEF, irrespective of the presence of AF (Table 1).[29, 31, 32] Some studies, however, report no significant difference in LA maximum volume between HFrEF and HFpEF patients (Table 1).[33, 34] Patients without HF, including those with hypertension, commonly have significantly smaller average LA size/volume than HFpEF patients (Table 1).[29, 31, 32, 35] LA size and fibrosis generally inversely correlate with LVEF, so that LA size and fibrosis increase progressively as LVEF declines.[36–38]

The prevalence of AF in hypertensive non-HF patients is significantly lower than in age-matched patients with HF (Fig. 3).[29, 39, 40] Among those with HF, AF prevalence is reportedly higher in patients with HFpEF vs. HFrEF (Table 2; Fig. 3).[20–30] In patients with LVEF of 40–49% (mid-range LVEF patients), AF prevalence is either similar or slightly lower than in patients with LVEF of ≥50 and significantly higher in those with LVEF of <40%.[24, 26–28] In all but one of these studies (in which AF was chronic[20]), the type of AF was not specified (commonly referred to as "AF history" or "AF at presentation")[21, 24–28, 30] and there appears to be a mixture of paroxysmal, persistent, and permanent AF.

Interestingly, in large studies involving HFrEF or mixed HFrEF and HFpEF patients (n=3,513–99,810), those with AF had a significantly higher mean LVEF than those with SR (Table 3).[23, 41–44]

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Thus, while average LA size/volume is progressively larger in patient populations with either no HF, HFpEF, and HFrEF, the prevalence of AF is not, displaying a bell-shaped relationship pointing to a lower AF burden in HF patients with severe vs. moderate ASR (Fig. 3, Tables 1 and 2).

AF and HF etiology

Patients with ischemic heart disease and DCM HF etiologies usually have a greater cardiac structural remodeling and a lower AF prevalence than patients with hypertensive HF prime etiology (Table 4).[23, 25, 45]

A larger LA size/volume can be associated with a lower AF burden in patients with but not without HF

The clinical data presented above (Fig. 3; Tables 1, 2, and 4) suggest that severe ASR can be associated with a reduced AF burden. There are studies that directly compare AF occurrence as a function of ASR. In numerous studies a larger LA size/volume/fibrosis has been associated with a higher risk for development of AF.[7, 8, 46, 47] However, these studies included few or no patients with HF.

Patients with HF commonly have a significantly greater mean atrial size/volume/fibrosis than patients without HF (Table 1 and Fig. 3). Few studies have reported AF burden as a function of atrial size/volume in patients with HF. The risk of new onset AF or AF recurrence could have either positive[48, 49] or no[50, 51] association with baseline LA size/volume. The prevalence of AF history was greater in 4^{th} vs. 1^{st}-3^{rd} quartiles of LA volume index in mildly symptomatic systolic HF patients (16 vs. 10%, respectively, <0.001).[36] Gavazzi et al. found that systolic HF patients with mild DCM had a smaller LA dimension and greater prevalence of persistent AF than patients with a “typical” form of DCM (22% vs. 3%, respectively; <0.001).[52] Melenovsky et al. reported that HFpEF patients had smaller maximum LA volume and higher AF prevalence than HFrEF patients (42 vs. 26%, respectively, <0.0001).[29]

Thus, while the occurrence of AF over the full spectrum of ASR is poorly understood, a larger LA size/volume can be associated with a lower AF prevalence in select HF populations.[29, 52] There is no such association reported in non-HF populations,[7, 8, 46, 47] perhaps due to a poor representation of patients with advanced ASR.

Atrial fibrosis and enlargement in the clinical HF—While there is generally a direct relationship between atrial fibrosis and size,[9] there are no clinical data that we are aware of that compare the degree of atrial enlargement to the extent of atrial fibrosis over a wide range, as in experimental models of HF (Fig. 2A).[11, 12, 16] Also, we are not aware of data correlating AF occurrence over a broad range of atrial fibrosis encountered in HF.

ASR and AF

The relation between AF and ASR can be very complex. AF may cause and be caused by ASR.[3–5] Patients with AF may have little ASR, and patients with no history of AF may have severe ASR.[3, 4] Nevertheless, patients with AF commonly have a larger LA size/volume/

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fibrosis than patients with sinus rhythm[4, 9, 29, 52] which is likely to be attributable to the development of AF-mediated ASR.[4, 5]

Atrial dilatation and fibrosis are the principal hallmarks of ASR and both are associated with AF occurrence.[4, 6] AF is commonly associated with a significant atrial dilation, but this arrhythmia, including persistent AF, may occur without atrial fibrosis.[4, 5, 53] The extent to which atrial fibrosis and dilatation contribute to development of AF is poorly understood and can be importantly modulated by atrial electrical remodeling principally characterized by abbreviation of the atrial ERP.[4–6]

How can severe fibrosis “suppress” AF?

Severe atrial fibrosis seems to be a marker of advanced electrical depression of the atrium. Prominent atrial fibrosis and dilatation are commonly associated with prolongation of atrial ERP and AF cycle length as well as a decrease in AF dominant frequency,[11, 54–61] perhaps due to depression of atrial excitability (Fig. 2).[11] Note that AF-induced atrial fibrosis is much less advanced than that caused by pressure and volume overload.[3–5, 13, 16, 53] In experimental HF models, atrial ERP prolongs progressively as the extent of atrial dilatation and fibrosis increases.[11, 15, 56] Prolongation of ERP is generally greater following an increase in fibrosis than increase in atrial size (Fig. 2A). Severe atrial fibrosis in the setting of HF has been shown to be associated with marked rate-dependent atrial electrical depression characterized by a prolonged ERP secondary to the development of PRR (Fig. 2).[11]

Abbreviation of the ERP is a well-known risk factor for the development of AF and prolongation of ERP is a therapeutic strategy used to terminate AF and prevent its development irrespective of the mechanism responsible for AF.[5, 62] The significantly prolonged atrial ERP in the setting of severe atrial fibrosis likewise acts to prevent and terminate AF (Fig. 2).[11] It is noteworthy that AF occurrence is still greater in severe when compared to little or no atrial fibrosis (Fig. 2).

Critically depressed atrial excitability in the setting of advanced ASR can be due to a number of factors, including 1) reduction of steady-state availability of the sodium channel, 2) decrease in the rate of recovery from inactivation of the sodium channel, and 3) reduction in electrotonic interactions (mediated by fibrosis and gap junctional changes). Importantly, advanced fibrotic remodeling may be associated with a major depolarization of resting membrane potential (which reduces the steady-state availability of the sodium channel and slows the recovery from inactivation of the sodium channel).[11, 63]

Compact, patchy, defuse, and interstitial fibrosis are all observed in HF and these diverse types of fibrosis may affect AF generation in different ways.[11, 13, 14, 58, 64] However, the occurrence and distribution of various types of fibrosis in the course of HF-associated ASR development and their association with AF generation are poorly defined.

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Structural remodeling: the atrium vs. ventricle in HF

Healthy atria have more fibroblasts and fibrosis than healthy ventricles and this distinction is amplified in the setting of HF.[4, 11, 12] Sustained pressure and volume overload, a major cause of cardiac remodeling in HF,[3] lead to greater and more rapid structural remodeling in the atria than in the ventricles (Fig. 1B) [11, 12, 17] due in large part to the fact that atria are thinner and smaller than the ventricles. AF itself produces both atrial and ventricular structural remodeling, with more extensive structural remodeling occurring in the atria.[4] In the setting of sustained pressure and volume overload, the atrium appears more likely than the ventricle to achieve severe structural remodeling that is accompanied with a limited ability of the atrium to maintain rapid activation (Fig. 2).

The hypothesis

The occurrence of AF in the full spectrum of ASR is poorly defined. Our principal goal in this review is to introduce the hypothesis that AF burden is reduced under conditions of severe vs. moderate atrial fibrosis in the setting of HF (Fig. 4). Advanced atrial fibrosis is associated with rate-dependent depression of atrial excitability that acts to reduce AF burden. This hypothesis is based largely on experimental findings derived from VTP-induced experimental models of HF (Fig. 1-2). To the best of our knowledge, there are no clinical data permitting assessment of AF burden in the full spectrum of atrial fibrosis encountered in HF, so the hypothesis remains speculative. However, the available clinical data indicate either directly[29, 52] or indirectly (Fig. 3; Table 1 and 2) that a larger atrial size can be associated with a lower AF burden in patients with HF. Atrial size positively correlates with atrial fibrosis.[9, 38] The available data highlight the need for clinical studies aimed at providing a direct test of the hypothesis that severe fibrosis is associated with a lower burden of AF than moderate fibrosis in patients with HF.

Considerations for the design of clinical studies to test the hypothesis

In contrast to the straightforward relationship between HF severity and the development of atrial fibrosis encountered in experimental models of VTP-induced HF (Fig. 1 and 2), the relationship between HF and atrial fibrosis encountered in the clinic is much more heterogeneous, being affected by HF etiology, approaches to therapy, co-morbidities and development of AF, among many other factors. Accordingly, a test of the proposed hypothesis in the clinical settings is not easily achieved.

The proposed hypothesis presumes that severe atrial fibrosis-associated electrical depression acts to suppress AF in all HF etiologies, types of AF, and stages of HF. We are not aware of any clinical studies reporting the prevalence of AF in severe vs. mild/moderate atrial fibrosis in specific HF etiologies or stages. There is indirect evidence for the manifestation of an “AF window” in DCM, i.e., systolic HF patients with mild DCM have been reported to have a smaller LA size and greater prevalence of persistent AF than patients with more severe DCM (22% vs. 3%, respectively).[52] Clinical data relative to the prevalence of long- vs. short-duration AF in severe vs. mild/moderate atrial fibrosis are also lacking. The attainment of severe atrial fibrosis may be different in the various HF etiologies and should be studied.

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A proper test of the hypothesis requires that AF burden be evaluated over the full spectrum of atrial fibrosis encountered in patients with HF (Fig. 4). Concomitant measurement of atrial size/volume may be useful, but the putative "AF window" may not be detected on the basis of atrial size/volume changes (Fig. 2A). The correlation between the full ranges of atrial size/volume and atrial fibrosis in the patients with HF is unknown and should be established.

Clinical quantification of atrial fibrosis is best achieved using magnetic resonance imaging (MRI).[47, 65] Cardiac MRI provides a noninvasive tool for quantification of myocardial fibrosis by probing the retention of gadolinium-contrast agent in myocardial tissue. Late-gadolinium enhancement (LGE) cardiac MRI is employed in many studies for measurement of myocardial scarring in wide variety of pathologies. T1 mapping can be used to provide a direct measurement of the extracellular volume fraction of the myocardium. In contrast to LGE, T1 mapping can be used to measure diffuse myocardial fibrosis. These two techniques can be used the study the relationship between the patchy, focal or diffuse nature of fibrosis and the propensity to development of AF.

While data on AF at time of presentation may suffice for the determination of an "AF window", data regarding AF burden would be preferable. However, quantification of AF burden is not easily achieved in the clinic. Intermittent rhythm monitoring has been shown to be unreliable in estimating true AF burden.[66] Continuous monitoring devices such implantable loop recorders or pacemakers are therefore recommended for this purpose.

Evidence in support of the hypothesis that severe atrial fibrosis is attended by electrical depression can be obtained by concomitant measurement of ERP. The depression of excitability with progressive fibrosis is expected to prolong ERP, due to development of PRR, which occurs when the ERP value exceeds that of the action potential duration (APD) (Fig. 2). APD can be estimated *in vivo* by measurement of the monophasic action potential duration or the activation-recovery-interval using unipolar recordings from the same site. It is noteworthy that atrial ERP is commonly prolonged in patients with structural heart disease.[55, 60] For these reasons, it would be helpful to determine whether atrial ERP progressively prolongs with aggravation of atrial fibrosis in patients with HF, as in experimental HF studies (Fig. 2).[11, 15]

The search for "AF window" can be done in a "snap-shot" fashion in studies involving different groups of HF patients having various extents of atrial fibrosis or in longitudinal studies involving the same group of patients in whom atrial fibrosis develops progressively to a severe level over a period of time.

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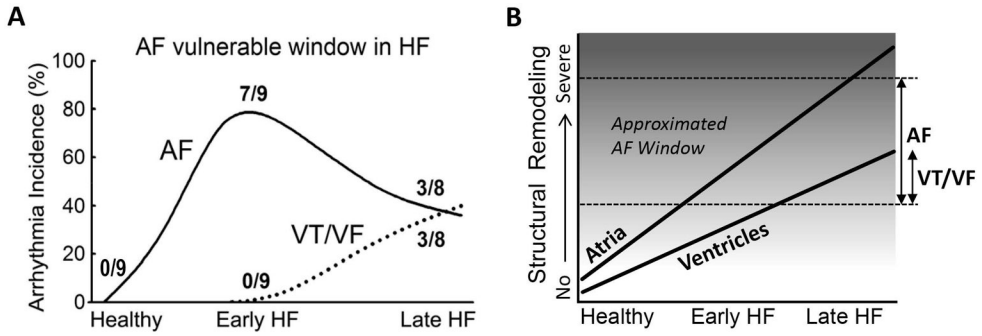

Figure 1. A temporal window of vulnerability for development of AF with advancing HF in a canine experimental model.

A: Incidence of AF and ventricular tachycardia and fibrillation (VT/VF) as a function of duration of ventricular tachypacing (2–3 weeks of pacing = "Early HF," and 5–6 weeks of pacing = "Late HF"). The highest AF vulnerability occurs relatively early in the course of development of HF, whereas VT/VF develops later. **B:** Schematic representations of the temporal distinction in atrial and ventricular arrhythmia susceptibility, which is associated with more rapid and greater structural remodeling in the atria.[11, 12] The dotted lines approximate the range of atrial structural remodeling in which AF is most likely to occur (i.e., "AF window"). Note that the atrium has a greater amount fibrosis under baseline conditions than the ventricle.[4, 11] The scale in the Y axis is qualitative. Modified from Burashnikov et al,[11] with permission.

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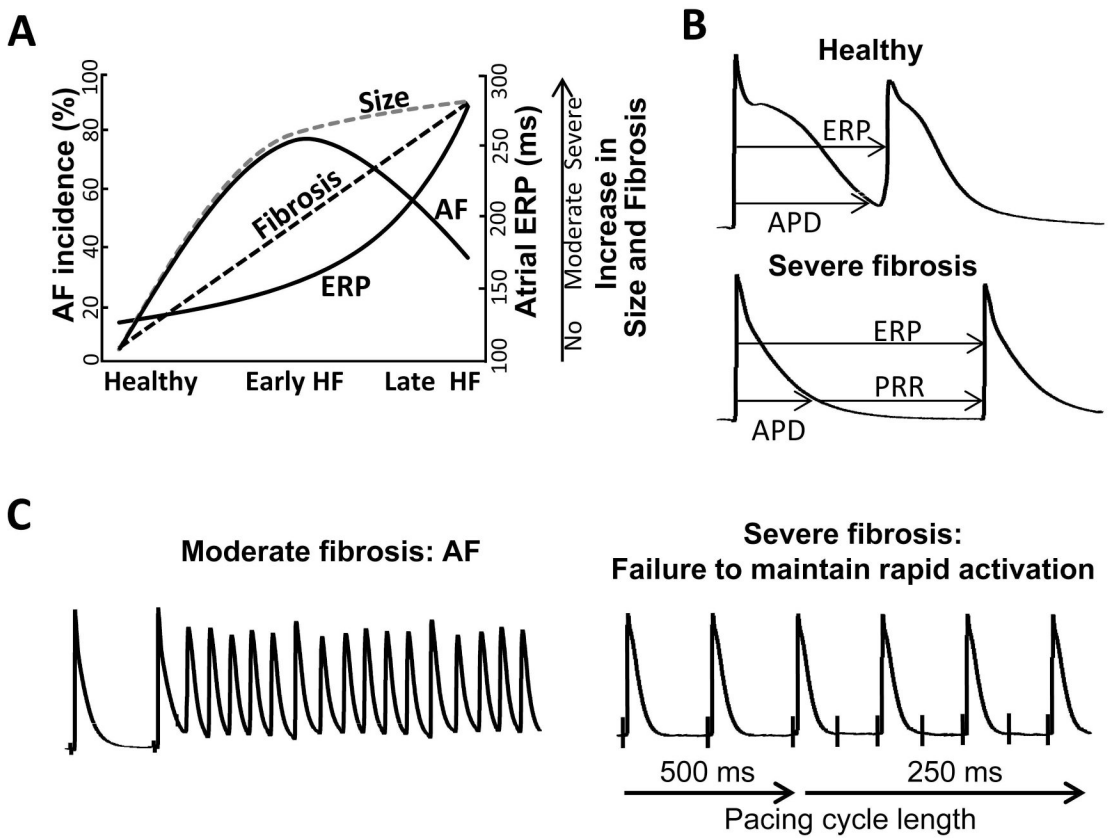

Figure 2. A proposed mechanism for suppression of AF in the setting of advanced fibrosis in the experimental HF: severe depression of atrial excitability.

A-C: Advanced atrial fibrosis appears to be a marker of prominent electrical depression of the atrium. Atrial enlargement develops much faster during early vs. late stages of HF whereas atrial fibrosis increases progressively during both early and late HF.[11, 12, 15, 16] A high AF inducibility in early HF is associated with advanced atrial dilatation but moderate fibrosis. A reduction of AF vulnerability in late HF is accompanied by both severe atrial enlargement and fibrosis. Severe atrial fibrosis is associated with a prominent depression of atrial excitability, manifesting as a dramatic prolongation of the atrial effective refractory period (ERP) due to post-repolarization refractoriness (PRR). Advanced rate-dependent depression of atrial excitability acts to reduce AF occurrence. Panels B and C depict transmembrane action potentials illustrating the end of ERP in a healthy atrium and the development of PRR in an atrium with severe fibrosis isolated from a late HF heart. The left part of panel C shows an episode of AF induced by a single extrastimulus. The right part of panel **C** illustrates an example showing that acceleration of stimulation rate from a pacing cycle length of 500 to 250 ms is associated with a 2:1 activation failure, due to the prolonged PRR. Panels B and C are from Burashnikov et al,[11] with permission.

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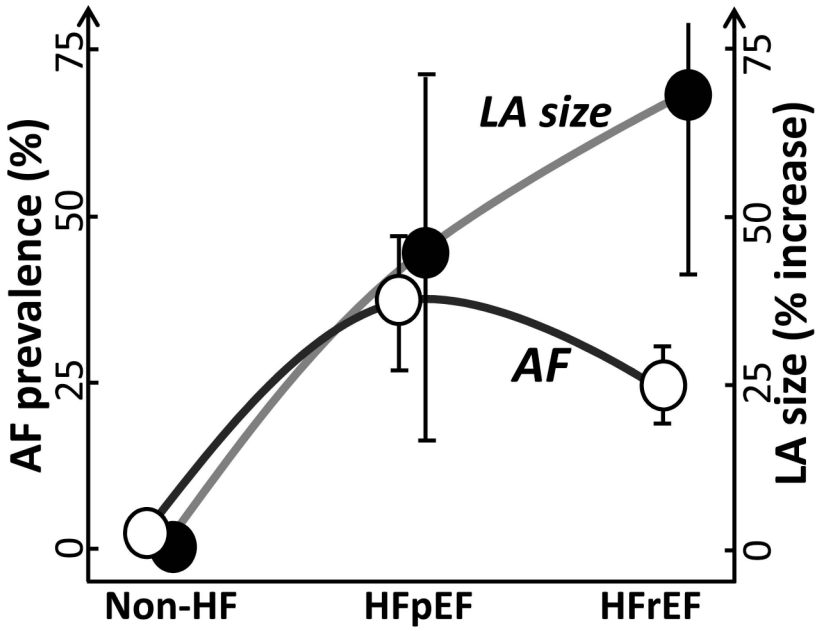

Figure 3. Relationship between AF prevalence and LVEF-associated left atrial (LA) size/volume in the clinic.

LA size/volume serves as a surrogate for atrial structural remodeling in clinical setting. In the absence of HF (hypertensive patients), LA size/volume is commonly normal or near normal and is associated with a low prevalence of AF. The mean LA size/volume is much greater in the setting of HF, but is relatively smaller in HFpEF when compared with HFrEF patients. AF prevalence increases dramatically in patients with HF, more so in patients with preserved LVEF vs. reduced LVEF (HFpEF vs. HFrEF, respectively). Please see Table 1 and 2 for the numerical data.

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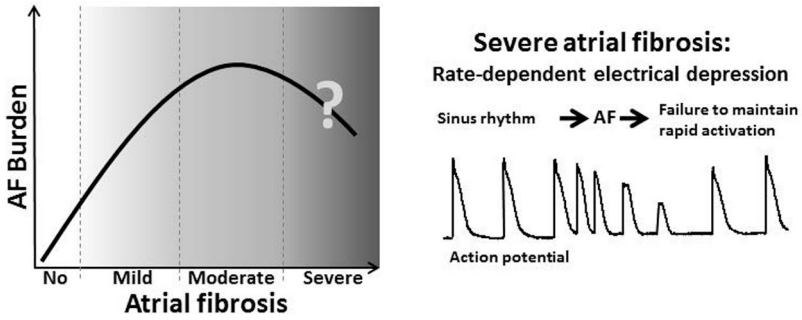

Figure 4. The hypothesis: Aggravation of atrial fibrosis is associated with increased AF burden, but severe atrial fibrosis "reduces" AF.

Severe atrial fibrosis is accompanied with advanced rate-dependent depression of atrial excitability that acts to reduce AF burden. The "AF window" is assumed to be observed in HF but not or less likely in non-HF population, due to a greater occurrence of severe atrial fibrosis in the former. Please see text for details.

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Table 1.

LA volume/size in non-HF, HFpEF, and HFrEF Patients.

Parameter	Non-HF	HFpEF	HFrEF	n, patients		References
LA volume (ml)	32	46* (+44%)	48* (+50%)	193/90/84	AF/SR	Gottdiener et al. [33]
Max LA volume (cm^3/m^2)	43	52* (+21%)	68*# (+58%)	48/32/26	SR	Triposkiadis et al [31]
Max LA volume index (ml/m^2)	21	36* (+71%)	38* (+81%)	27/25/20	NA	Kurt et al. [34]
LA size (mm)	44	47* (+7%)	50*# (+14%)	3,482/633/455	AF	Nieuwlaat et al.[32]
Max LA volume (ml)	45	85* (+89%)	104*# (+131%)	40/101/97	AF/SR	Melenovsky et al. [29]
	37±10	**53±19 (+45±32%)**	**62±26 (+68±26%)**			

Mean values from each individual study are shown. Values in brackets in the HFpEF and HFrEF columns are % increase vs. Non-HF.

* p<0.05 vs. control.

# P<0.05 vs. HFpEF.

SR – patients with sinus rhythm only. AF – patients with AF only. AF/SR – mixture of patients with SR and history of AF.

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Table 2.

Prevalence of AF in hypertensive patients without HF and in HF patients with preserved and reduced LVEF.

No HF (%)	HFpEF (%)	HFrEF (%)	P value	n, patients	References
	33	28	<0.0001	21,149/21,118	Fonarow et al, 2007.[24]
	43	34	<0.0001	38,056/48,950	Kapoor et al, 2016.[28]
	55	32	<0.001	539/4,474	Toma et al, 2014.[27]
	27	18	<0.001	10,347/31,625	MAGGIC 2012.[30]
	32	24	<0.001	880/1,570	Bhatia et al, 2006.[21]
	41	29	<0.001	2,167/2,429	Owan et al, 2006.[22]
	35	24	<0.001	6,210/3,914	Gurwitz et al, 2013.[26]
	34	20	<0.001	178/270	Lee et al, 2009.[25]
	25	23	<0.01	3,148/3,658	Lenzen et al, 2004.[20]
	42	26	<0.0001	101/97	Melenovsky et al, 2015.[29]
	29	19	<0.001	809/2,702	De Ferrari et al, 2007.[23]
1.1				39,056	Haywood et al, 2009.[40]
1.6				941	Gerdts et al, 2002.[39]
1.4±0.4	**36±9**	**25±5**			

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Table 3.

LVEF in HF-REF or mixture of HF-REF and HF-PER patients with sinus rhythm and AF in large studies.

Sinus rhythm (%)	AF (%)	P value	n, patients	References
34 ± 10	36 ± 11	<0.001	809/2,702	De Ferrari et al, 2007.[23]
32 ± 11	34 ± 12	<0.001	2,657/1,391	Tveit et al, 2011.[41]
39 ± 17	42 ± 17	<0.001	68,455/31,355	Mountantonakis et al, 2012.[43]
27.6 ± 8.1	29.0 ± 7.7	<0.001	1,195/2,071	Mentz et al, 2012.[42]
27 (20,35) *	31(24,43) *	<0.001	4,330/2,677	Abualnaja et al, 2015.[44]

In %. Mean±SD.

* -median with 25th and 75th percentile.

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Table 4.

AF prevalence as a function of the primary etiology responsible for HF

IHD (%)	DCM (%)	HPT (%)	VHD (%)	n, patients	References
14	20	31	49	1,529/886/445/315	De Ferrari et al, 2007.[23]
27	34	39	42	1,306/242/428/291	Pecini et al, 2011.[45]
17	-	36	39	278/ - /140/42	Lee et al, 2009.[25]

IHD – ischemic heart disease; DCM – dilated cardiomyopathy; HPT – hypertension; VHD – valvular heart disease.