TITLE PAGE

The importance of interactions between atrial fibrillation and heart failure

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Author contribution: Khan MA wrote the article, Satchithananda DK and Mamas MA critically revised the manuscript.

Conflict of Interest:

None.

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ABSTRACT

Heart failure (HF) and atrial fibrillation (AF) are amongst the commonest cardiovascular conditions encountered in clinical practice and frequently coexist. Over the last decade, they have evolved into global cardiovascular epidemics. This, in turn, has huge clinical and economic implications.

There is ample evidence that AF and HF have a mutually deleterious effect on each other. AF is not only a marker of HF severity but also affects HF prognosis independently.

This article presents the close pathophysiological relationship between AF and HF and the adverse prognostic consequences of this bi-directional interaction. The scope of various therapeutic modalities and their potential impacts are discussed briefly.

KEY POINTS

1. HF and AF have been recognised as global cardiovascular epidemics.
2. They frequently co-exist, are inter-dependent and have a mutually adverse prognostic impact.
3. Rate control remains the mainstay of therapy with rhythm control reserved for a specific group of patients.
4. Stroke prevention is one of the most important aspects of AF care in the HF population.

KEY WORDS

Atrial fibrillation, Heart failure, Pathophysiology, Prognosis, Thromboprophylaxis.

INTRODUCTION

Heart failure (HF) and atrial fibrillation (AF) are amongst the commonest cardiovascular conditions encountered in clinical practice and frequently coexist. Up to 40% of patients with HF either have or go on to develop AF and approximately 40% of patients with AF present with (or develop) HF.[1] Heart failure predicts the development of AF and conversely the presence of AF predicts the development of HF. Both are increasingly prevalent phenotypic manifestations of a multitude of different primary or secondary cardiac pathologies (see figure 1).

The prevalence of HF and AF has steadily increased over the years. This is in part through an ageing population and as development of more effective therapy improves outcomes associated with other cardiovascular conditions (such as myocardial infarction). In Europe, HF has an estimated prevalence of 30 million with 1 in 5 lifetime-odds of developing HF.[2] Similarly 2% of Europeans have AF with a projected prevalence of 14 -17 million by the year 2030.[3] The lifetime risk of AF is 1 in 4 (as derived from community-based cohorts in Framingham and Rotterdam studies).

INTERACTIONS BETWEEN HF AND AF

a) Prognosis

The presence of AF is associated with an increased risk of mortality in patients with HF.[4] This adverse prognosis is observed in patients with left ventricular (LV) systolic dysfunction (HF with reduced ejection fraction – HFREF) as well as those with preserved left ventricular function (i.e. HF with preserved LV systolic function – HFPEF). For instance, the SOLVD (Studies Of Left Ventricular Dysfunction) trial demonstrated that even in asymptomatic patients with an LV ejection fraction of <35%, mortality was 34% when AF was present and 24% when it was not. The mortality in new onset AF (12%) was also greater than for persistent AF (7%).[5] Sub-group analysis of the CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity) study revealed that AF has an independent and deleterious effect on long-term all-cause cardiovascular mortality in HF patients. The absolute mortality risk was highest in patients with LVEF <35%, however,

those with HFPEF had the highest relative risk of death (HR 1.37, 95% CI 1.06 to 1.79) in contrast to HFREF (HR 1.22, 95% CI 1.04 to 1.43).[6] Similarly, meta-analysis by Mamas et al. (using data derived from 16 studies and incorporating over 50,000 patients) showed that AF has a negative impact on total HF mortality with an odds ratio of 1.40 (95% CI 1.32-1.48, P<0.0001) in randomised trials and 1.14 (95% CI 1.03-1.26, P<0.05) in observational studies. Again, this was applicable to HFREF as well as HFPEF patients.[4]

We have previously summarised scientific evidence showing the negative prognostic effect of AF in HF patients (See Tables 1 and 2).[7] However, it is not entirely clear whether AF per se is the cause of increased mortality or merely a marker of more advanced HF.

b) Symptoms of HF

AF is more likely to occur in patients with more severe HF symptoms (e.g., NYHA I - 10%, NYHA 4 – 50%). Prolonged exposure to AF with a fast ventricular response also contributes to LV systolic dysfunction – a tachycardiomyopathy.

c) Stroke risk

AF confers a greater degree of stroke risk in HF patients as the presence of HF carries a weighting of 1 point in the CHADSVASC risk stratification tool for AF and stroke. The risk of stroke is equivalent both in HFREF and HFPEF alike at a rate of up to 4.4% per 100 patient years.[8]

TREATMENT OF AF IN PATIENTS WITH HF

Treatment algorithms for both are extensively discussed in guidelines elsewhere [9] and are beyond the scope of this article. However, the main principles of the treatment of AF in patients with HF can be summarised as follows:

a)   Rate or rhythm control

The commonest form of **rate control** is with AV nodal blocking agents such as beta blockers, rate controlling calcium channel antagonists (provided LV systolic function is preserved) and digoxin. [9] Management of both occurring together is extrapolated from trials in AF that contain between 20 –

30% of patients with HF and HF trials that contain between 10-30% of patients with AF.

The optimum target rate to achieve in AF is, however, difficult to determine with any degree of precision. Current guidelines define adequate rate control in atrial fibrillation as maintenance of the ventricular rate response between 60 and 80 beats/min at rest and between 90 and 115 beats/min during moderate exercise.

Special considerations for AF ventricular rate control in HF include:

- The optimum heart rate suggested in the AF-CHF trial (in which rate versus rhythm strategies were compared in HFREF patients) was 80 bpm at rest and <110 bpm with exertion. This trial also demonstrated no significant benefit in rhythm compared to rate control.[11]

- Beta blockers are the most commonly indicated. [9] It is unclear whether the beneficial prognostic effects of beta blockers in sinus rhythm in patients with HFREF are generalizable to similar patients with AF[10], but currently beta blockers remain the preferred rate control agent in HFREF.

- Digoxin is suggested in patients unable to tolerate beta blockers – this may include patients with acute decompensated HF in whom the negative inotropic effect of beta blockers may exacerbate congestion.

- The role of cardiac glycosides in HF and AF has lately become controversial due to reports suggesting increased mortality in HF and AF patients on digoxin therapy.[11] This evidence is based on observational studies and post hoc analysis and should therefore be viewed with these limitations in mind. So far, DIG trial is the only randomised controlled trial (RCT) in patients with HF and sinus rhythm but it did not present a direct comparison between digoxin and other rate control agents. On the other hand, there is no RCT studying patients in AF with digoxin. Moreover, there is the confounding bias that physicians are likely to prescribe digoxin in patients who are more unwell and may have a higher overall mortality anyway. Nevertheless, it would be prudent to say that till we have more robust data available,

digoxin should be used with caution in HF patients keeping serum levels less than 1.2 ng/mL.[12]

On the other hand, *rhythm control* strategies (using anti-arrhythmic medications) have shown no benefit over rate control in terms of mortality, stroke prevention or hospitalisation. However, they can be reserved for patients who are intolerant to rate control medications or remain symptomatic despite adequate rate control. A number of trials have looked at rate versus rhythm control. AF-CHF (Atrial Fibrillation in Congestive Heart Failure) trial prospectively randomized 1376 HFREF patients to amiodarone or rate control medication. The cohort was followed up for 3 years looking at all-cause mortality, stroke and HF admission. The difference in mortality in the two arms was not significant (27% and 25% respectively). In addition, there was increased morbidity from torsades and bradycardia in the rhythm control arm.[13] Similarly, Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM)[14] and Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE)[15] trials have demonstrated similar findings. The latter, however, were not exclusive to HF patients and arguably, were under-represented by a younger patient cohort who may be more symptomatic as well as in an earlier phase of the disease and thus, are likely to gain more from rhythm control as compared to a rate control strategy. It follows, therefore, that rhythm control should be reserved for patients who are particularly symptomatic with AF despite adequate rate control.

Since medications used for rhythm control (e.g. class 1a, class 1c agents, dronedarone) all have an increased mortality in HFREF, any rhythm-control technique that obviates the need for antiarrhythmic agents offers a clear advantage. Pulmonary vein isolation by using various catheter ablation techniques has emerged as an encouraging option in this regard. Its role in HF has shown early promise, but remains to be defined [16] particularly in terms of long-term prognosis. To date, a number of small trials have shown very promising results[17, 18] (as risks of the procedure are not increased and mortality appears to be improved) while larger randomised trials are underway[19, 20]. Depending upon the results, AF ablation may potentially

become an important first-line option in patients with HF. Finally, surgical ablation techniques (such as Cox Maze procedure) are available to patients undergoing cardiac surgery. They have been shown to be safe and effective including in patients with HF.

Pacing strategies can also be employed in patients with both AF with a fast and slow ventricular response (bradycardia pacing with subsequent rate control medications) and in patients with refractory AF with fast ventricular response (pacemaker implantation with subsequent AV node ablation). This "pace-and-ablate" strategy, however, does not eliminate AF per se. Studies conducted so far are small, non-randomised and mostly from single centres. Results are promising but further larger trials are warranted.

Lastly, development of newer anti-arrhythmic drugs such as selective atrial-specific ion-channel blockers (e.g., Vernakalant) may offer an advantage over previously available ones but their role in HF population needs further studies.

b)   Thromboprophylaxis

Patients with AF and HF have their risk of stroke and systemic embolism doubled as compared to either condition alone.[21] Hence, thromboprophylaxis with oral anticoagulants is of paramount importance and has been shown to be safe and effective.[22] Warfarin is thrice as effective as aspirin and novel oral anticoagulants (NOACs) are at least as good as warfarin. NOACs include inhibitors of either thrombin (Dabigatran) or activated factor X (Apixaban, Edoxaban and Rivaroxaban). Results from major trials (RELY, ARISTOTLE, ENGAGE AF-TIMI48, ROCKET respectively) have been encouraging.[23] Dabigatran was the first NOAC introduced into clinical practice. Comparison with warfarin in the RELY trial shows that its dose of 110mg twice daily is superior for bleeding but non-inferior for thromboembolic protection while 150mg twice daily is non-inferior for bleeding but superior for thromboembolic protection. Apixaban, on the other hand, has been shown to be superior to warfarin in efficacy and associated with less gastrointestinal, intracranial and other major bleeding. Other factor X inhibitors are non-inferior to warfarin and associated with less intracranial and other major bleeding but higher gastrointestinal haemorrhage. Rivaroxaban and Edoxaban have the

added advantage of being once daily as well. Importantly, several NOAC reversal agents are currently in development and Idarucizumab (which is a fully humanized monoclonal antibody fragment) has recently received global approval as a specific reversal agent for Dabigatran.[24]

Finally, a small number of patients are unable to receive oral anticoagulation due to drug intolerance or bleeding contra-indications. Left atrial appendage occlusion devices (such as Watchman device) hold promise in such cases but need further experience and long-term data.[25]

CONCLUSIONS

The prevalence of both AF and HF are increasing and they frequently co-exist. Concurrence of AF and HF is associated with a higher risk of morbidity and mortality than either condition alone. There is no clear-cut evidence so far that rhythm control is superior (in terms of long-term mortality) to rate control. Radiofrequency catheter intervention techniques are promising and it is hoped that larger trials (looking at outcome data) would help incorporate these into the standard management algorithm. Finally, novel oral anticoagulants are a welcome addition to the therapeutic armamentarium available to the clinician. Future insights into mechanisms of disease and development of new therapeutic modalities continues to hold promise in this challenging field.

The importance of interactions between atrial fibrillation and heart failure

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The importance of interactions between atrial fibrillation and heart failure

TABLES

Table 1. Prognostic impact of AF in HF: Summary of randomised trials

Author	Setting	Number	LVEF	Mean follow up (years)	%AF	Number (%) deaths		P-VALUE
						SR	AF	
Carson et al.	V-HEFT I&II	1427	LVEF <45%	2.5	19	480/1221 (39)	75/206 (36)	NS
Dries et al.	SOLVD	6517	LVEF< 35%	2.8	6	1395/8098 (23)	149/419 (34)	<0.0001
Mathew et al.	DIG	7788	All LVEF included	3.1	11	2231/6922 (32)	375/866 (43)	<0.0001
Crijns et al.	PRIME II	409	LVEF<35%	3.4	21	153/325 (47)	50/84 (60)	<0.05
Swedberg et al.	COMET	3029	LVEF<35%	4.8	20	874/2429 (36)	258/600 (43)	<0.0005
Olsson et al.	CHARM	7601	All LVEF included	3.1	15	1466/6451 (23)	365/1148 (32)	<0.001
Pederson et al.	DIAMOND	3587	LVEF< 35%	N/A	24	1951/2661 (73)	634/818 (77)	<0.001

SR: sinus rhythm; AF: atrial fibrillation; LVEF: left ventricular ejection fraction.

The importance of interactions between atrial fibrillation and heart failure

Table 2. Prognostic impact of AF in HF: Summary of observational studies

Author	Setting	Number	LVEF	Mean follow up	%AF	Number (%) deaths		P-VALUE
						SR	AF	
Middlekauff et al.	Heart Transplantation	390	LVEF < 35%	265 days	19	123/315 (29)	36/75 (48)	<0.005
Stevenson et al.	Heart Transplantation	750	LVEF < 40%	2.0 years	22	336/584 (45)	104/160 (61)	<0.01
Mahoney et al.	Heart Transplantation	234	LVEF < 45%	1.1 years	27	26/171 (15)	14/63 (22)	NS
Ahmed et al.	Medicare Alabama	944	All LVEF included	4.0 years	27	439/711 (62)	166/233 (71)	<0.01
Wojtkowska et al.	Bilaystok, Poland	120	LVEF < 30%	3.0 years	50	26/60 (43)	33/60 (55)	NS
Corell et al.	Danish HF clinic Network	1019	LVEF < 45%	1.9 years	26	180/750 (24)	89/269 (33)	<0.05
Pai and Varadarajan	Loma Linda VA	8931	All LVEF included	2.5 years	18	2164/7728 (28)	529/1203 (44)	<0.0001
Rivero-Ayerza et al.	EuroHeart Failure Survey	10701	All LVEF included	N/A	43	419/6027 (7)	372/4674 (8)	<0.05
Rusinaru et al.	Somme< France	368	LVEF> 50%	N/A	36	125/236 (53)	84/132 (64)	<0.05
Hamaguchi et al.	Japanese Registry data	2659	All LVEF included	2.4 years	35	N/A	N/A	NS
Shotan et al.	National HF Survey, Israel	4102	All LVEF included	4 years	33	1480/2734 (54.3)	882/1359 (64.9)	0.0001

SR: sinus rhythm; AF: atrial fibrillation; LVEF: left ventricular ejection fraction.

The importance of interactions between atrial fibrillation and heart failure

| Ischaemic heart disease | Valvular disease | Arrhythmia | Cardiomyopathy | Pericardial disease | Secondary cardiac pathology e.g. thyroid disease, systemic or pulmonary arterial |

Cardiac dysfunction at atrial, ventricular, atrio-ventricular or ventriculo-vascular level

Multi-system activation e.g. neuroendocrine Inflammatory

HEART FAILURE SYNDROME

Adverse remodelling

Atrial dilatation

ATRIAL FIBRILLATION

Abnormal haemodynamics including valvular dysfunction

- **Abnormal ventricular rate**
- **Impaired ventricular diastolic filling especially at faster rates**
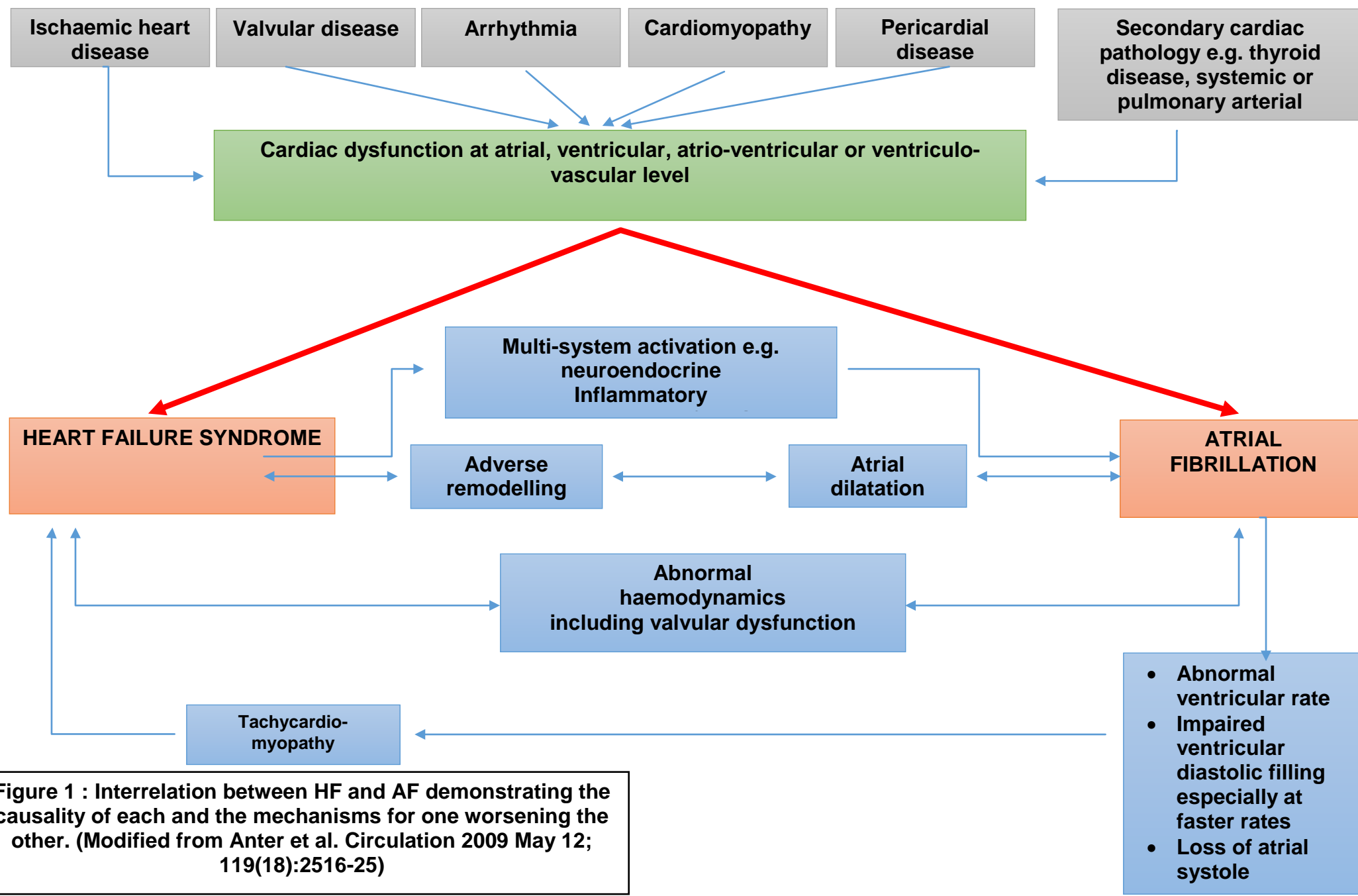- **Loss of atrial systole**

Tachycardio-myopathy

Figure 1 : Interrelation between HF and AF demonstrating the causality of each and the mechanisms for one worsening the other. (Modified from Anter et al. Circulation 2009 May 12; 119(18):2516-25)