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Atrial Fibrillation in Heart Failure—Diagnostic, Therapeutic, and Prognostic Relevance

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Abstract

Purpose of Review Atrial fibrillation (AF) and heart failure (HF) commonly coexist and are associated with an increased risk of hospitalization, morbidity, and mortality. Both conditions develop into epidemics due to the ageing of the population and lead to poorer prognosis for the individual patients. Therapeutic strategies include treatment with oral anticoagulation, and rate and rhythm control concepts to prevent stroke and improve the cardiovascular outcome.

Recent Findings Especially in HF patients, data suggest that catheter ablation of AF is superior to medical treatment. In patients with both AF and HF undergoing catheter ablation, significant increases in left ventricular ejection fraction and quality of life and decreases in related symptoms and major adverse cardiac events are reported. In addition, catheter ablation has been shown to reduce mortality and HF hospitalization in the medium term.

Summary For patients with AF and HF, an effective individualized therapeutic strategy to minimize potential complications and improve clinical outcomes is needed. Catheter ablation of AF seems to provide advantages in HF patients with AF. However, results of further long-term studies are awaited.

Keywords Atrial fibrillation · Heart failure · Rate control · Rhythm control · Catheter ablation

Introduction

Atrial fibrillation (AF) is the most common sustained rhythm disorder worldwide. Furthermore, the presence of heart failure (HF) increases in the general population, especially in the elderly [1]. Both AF and HF show an epidemic development increasing in incidence and prevalence [2] and imposing a major challenge on healthcare systems [3]. Moreover, the two conditions commonly coexist [4], leading to a higher risk of stroke, hospitalization, morbidity, and mortality [5–7]. Risk factors and pathophysiology of diseases are closely interrelated. Therefore, it has been suggested that the onset of AF is often a consequence of HF [8]. On the other hand, AF is associated with an increased risk of HF [9]. For this reason, it is particularly important and challenging to find an individual and effective therapeutic strategy to minimize potential complications and improve clinical outcomes in patients with AF and HF. In this review, we focus on the diagnostic, therapeutic, and prognostic relevance of AF in this specific patient group.

This article is part of the Topical Collection on *Comorbidities of Heart Failure*

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Epidemiology and Pathophysiology

There is a global rising prevalence of AF, which is associated with the increasing age and increasing presence of risk factors in the population. Experts estimate that there will be around 14 to 17 million AF patients in the European Union by 2030 [10–12]. In addition, about 1 to 2% of the general population in developed countries suffer from HF. Here, an increase up to 17% can be observed in the elderly as well as a higher occurrence in men than in women [13–15]. The epidemic pattern of both diseases is almost identical.

Caused by similar risk factors such as hypertension, diabetes mellitus, obesity and coronary artery disease, and similar aetiology, AF and HF often tend to coexist [16] although the precise interrelation is not fully understood yet. Atrial remodelling due to complex interaction of structural, neurohumoral, and inflammatory changes playing an essential role in the development of AF in patients with HF has been described (Fig. 1). This results in an enlargement of the left atrial size, atrial fibrosis, and conduction abnormalities [17, 18].

Conversely, AF leads to loss of the atrial systole, ventricular chronotropic dysregulation, and an irregular and rapid ventricular rhythm. These mechanisms promote the occurrence of HF-related symptoms or the occurrence of HF per se. It can be summarized that the focus of the development of HF is also based on a cellular and neurohumoral imbalance as well as on extracellular remodelling [19–21]. Moreover, the remodelling process is supported by the activation of the renin-angiotensin-aldosterone system [22].

Diagnostic Procedures

In most cases, patients develop one disease, either AF or HF, before the other. However, in at least one third of all patients, both conditions occur simultaneously [23]. According to current guidelines [24], HF-related symptoms and signs should be asked for and observed by the attending physician at every hospital stay. Further diagnostic procedures include an electrocardiogram, echocardiography, and the determination of the plasma concentration of natriuretic peptides. Applying these methods, one can evaluate the individual therapy response and monitor the stability of the diseases in the long term in a simple way. Other diagnostic tests like chest x-ray, cardiac magnetic resonance, or coronary angiography are also useful to confirm the diagnosis or to identify possible other causes, for example pulmonary, renal, or hepatic diseases.

Clinical Outcome

Patients with concurrent HF and AF have a significantly worse prognosis in comparison with individuals with only one of the two conditions due to a higher morbidity and mortality rate [23]. This is especially relevant for patients with mild-to-moderate HF. Previous investigators have shown that patients with a preserved left ventricular ejection fraction have a poorer prognosis compared with individuals with systolic dysfunction [25, 26]. Furthermore, both conditions decrease the quality of life [5] and increase the risk for the occurrence of stroke [27]. Similarly, patients admitted to hospital due to HF with concurrent AF are at a higher 3-year risk of all-cause mortality, all-cause readmission, and readmission for HF and stroke [28].

Furthermore, tachycardia-mediated cardiomyopathy is a common result of long-lasting AF episodes or other tachycardiac arrhythmias, may lead to a reduced left ventricular ejection fraction, and is a potential reversible condition. Therefore, the development of tachycardia-mediated cardiomyopathy should be prevented in patients with HF with the aim to improve their prognosis [29, 30].

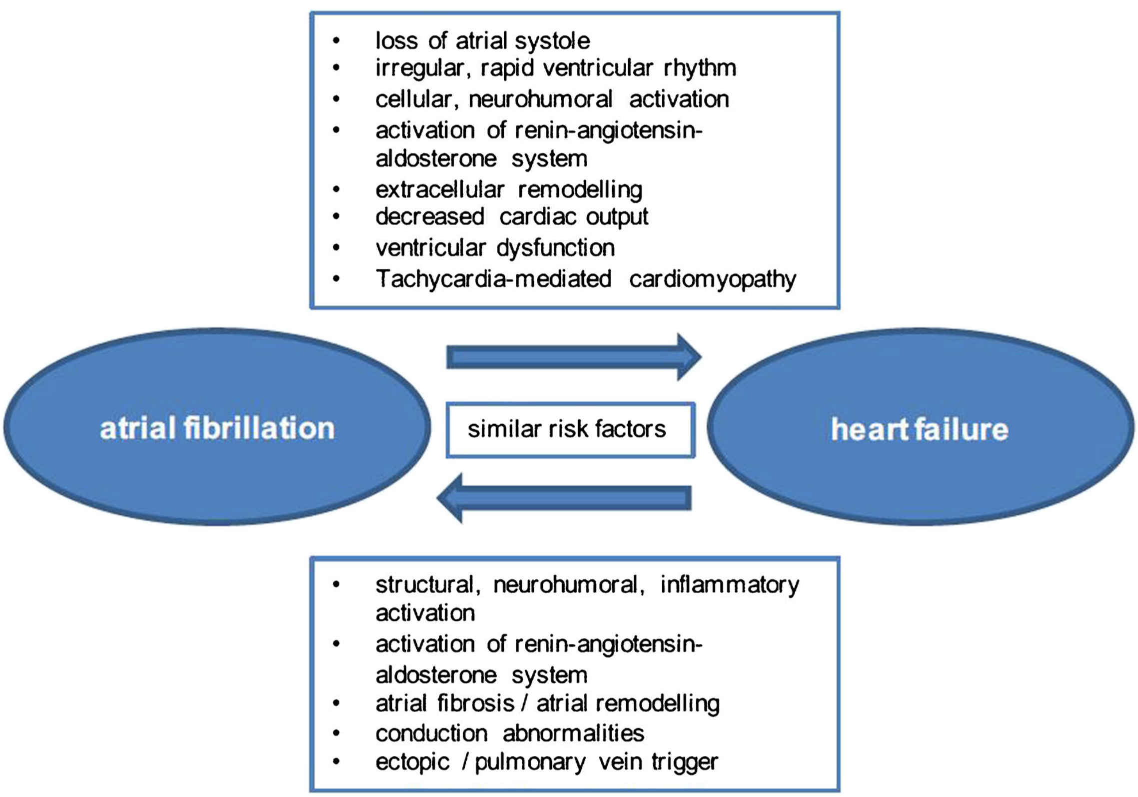

Fig. 1 Pathophysiology of atrial fibrillation and heart failure

Moreover, many HF patients are supplied with an internal cardiac defibrillator to prevent sudden cardiac death. Given the high frequency of AF in HF patients [31], inadequate therapies of the defibrillator caused by the arrhythmia are a feared and not rare complication. Subsequently, such episodes can often result in post-traumatic stress disorders or true depressions. These accompanying factors can additionally affect cardiovascular outcomes in a negative way.

Anticoagulation and Stroke Prevention

AF patients with a reduced left ventricular ejection fraction are at highest risk for thromboembolic events, which most often occur due to a left atrial appendage thrombus. The presence of HF results in a four times higher risk for thromboembolic events per year, while the sole presence of AF is associated with a fivefold higher risk in comparison with other patients [27]. Therefore, it is an important task for the attending physicians to prevent stroke events in this susceptible group of patients.

The CHA2DS2-VASc score provides a simple tool to classify individuals with regard to their stroke risk (low-, intermediate-, and high-risk group) and the need for oral anticoagulation (OAC). According to current guidelines [32], treatment with OAC is recommended in non-valvular AF patients with a CHA2DS2-VASc score ≥ 2 in risk-benefit consideration, if there are no absolute contraindications. The vitamin K antagonist warfarin is a prime example of effective OAC treatment over the last decades. A few years ago, novel oral anticoagulants including apixaban, rivaroxaban, dabigatran, and edoxaban were introduced. Compared with warfarin, these drugs have similar effects regarding the prevention of stroke and are associated with lower rates of gastrointestinal bleeding and intracranial haemorrhage [33, 34].

The bleeding risk of patients, in whom OAC treatment is recommended, additionally, can be assessed by the HAS-BLED score. The possibility of percutaneous left atrial appendage closure or surgical exclusion should be considered in OAC patients with high risk for bleeding complications or severe thromboembolic events.

Conservative Approach and Rate Control

The treatment of cardiovascular risk factors and comorbidities is essential in the treatment both of HF and in AF. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have been reported to reduce the risk of AF and prevent atrial remodelling in patients with HF [35]. Additionally, diuretics and mineralocorticoid receptor antagonists represent important treatment options in the management of HF-related symptoms. Further reports showed that angiotensin-converting enzyme inhibitors significantly decrease mortality, sudden cardiac death, and HF-related hospitalization. A similar effect was observed for candesartan as well [36].

Beta-blocker medication can contribute to a reduction of mortality in HF patients [37]. Rate control should be considered in HF patients, in whom it is hard to achieve and to maintain sinus rhythm. Effective rate control can be reached by the use of beta-blockers, glycosides, or calcium channel blockers. Due to their negative inotropic effect, treatment with non-dihydropyridine calcium channel blockers is not recommended in HF patients with reduced left ventricular function [38]. Concerning an ideal striving heart rate, there was no significant benefit in patients with a heart rate < 80 beats per minute in comparison with the individuals < 110 beats per minute [39]. Nevertheless, current guidelines prefer to aim a heart rate < 110 beat per minute at rest in AF patients with combined reduction of left ventricular function [32].

Regarding the mortality in AF patients, many studies like the AFFIRM, DIAMOND-CHF, or AF-CHF trials reported no significant difference in mortality between patients undergoing rate or pharmacological rhythm control therapy [40–42].

Rhythm Control

In AF patients, cardiac output decreases significantly due to an impaired atrial systole. Restoring sinus rhythm through rhythm control therapy results in hemodynamic improvement and increased stroke volume. Subgroup analyses in the AFFIRM and RACE trial showed that AF patients with reduced left ventricular function benefit from maintaining sinus rhythm [40, 43]. Restoration of sinus rhythm can be achieved by electrical cardioversion or by treatment with antiarrhythmic drugs. Electrical cardioversion is recommended in both haemodynamically unstable and symptomatic AF individuals. Especially in patients with HF, recurrence rates of AF after electrical cardioversion are high [44]. To overcome this problem, antiarrhythmic drug treatment for example with amiodarone or dofetilide can be helpful to maintain sinus rhythm in the long term (dofetilide is not approved in Europe). The use of antiarrhythmic drugs is commonly limited by extracardiac side effects including thyroid, hepatic, and pulmonary toxicity [45]. Lower rates of extracardiac side effects are described by the use of dronedarone because of the absence of iodine fractions. However, the use of dronedarone is not recommended in HF patients with left ventricular dysfunction. This statement is based on studies, which were prematurely terminated due to higher mortality rates in this particular population [46–48].

Catheter Ablation of AF in Patients With HF

Catheter ablation has become a cornerstone in rhythm control therapy [49, 50] showing superiority to antiarrhythmic drug therapy in terms of maintaining sinus rhythm [51]. Thus, AF-related symptoms can be reduced and quality of life can be increased. Based on currently available evidence, performance of catheter ablation may play a decisive role in AF treatment of patients with HF in order to improve cardiovascular outcome (Table 1). Nevertheless, HF patients often need multiple procedures because of higher recurrence rate [52, 53]. In addition, higher complication rates are described compared with patients without HF [62]. Therefore, the decision to perform catheter ablation should always be subjected to an individualized risk-benefit assessment.

The AATAC trial could demonstrate that freedom of AF can be more often achieved by catheter ablation compared with amiodarone therapy [51]. Moreover, the CAMTAF investigator described a significantly improved left ventricular function 6 months after ablation in comparison with rate control [57]. In the ARC-HF trial, an improved peak oxygen consumption, B-type natriuretic peptide serum concentration, and Minnesota Living with HF (MLWHF) questionnaire were achieved [56].

In AF patients with concurrent impaired systolic function without any structural heart disease, a significant raise in left ventricular function can be achieved by catheter ablation of AF. Investigators could demonstrate that absence of late gadolinium enhancement predicts recovery of left ventricular dysfunction [58]. Especially in patients with suspected tachycardia-mediated cardiomyopathy, the results of the CAMERA-MRI trail should be taken into consideration to promote a contemporary rhythm control therapy through catheter ablation.

Currently, there are three studies that examine a potential benefit by interventional treatment of AF in HF patients: CABANA, CASTLE-AF, and RAFT-AF. The CASTLE-AF investigators reported a significantly lower rate of the composite hospitalization for worsening HF and all-cause mortality during a 3-year follow-up period in comparison with the medical treatment [59]. Compared with medical treatment strategies, catheter ablation failed to significantly reduce a composite endpoint of all-cause mortality, stroke, serious bleeding, and cardiac arrest [61]. To interpret the results of the CABANA trial optimally, we have to consider the difference between the "intention-to-treat" and "per-protocol" analyses. The expected results of the RAFT-AF trial and the AMICA trial will shed further light in this field and help define the role of catheter ablation for AF in HF patients.

"Pace and Ablate" Strategy—Atrioventricular Node Ablation and Cardiac Resynchronization Therapy

It is often difficult and challenging to achieve and to maintain sinus rhythm in HF patients with concurrent AF. The PABA-CHF trial showed that catheter ablation is superior to atrioventricular (AV) node ablation with following cardiac resynchronization therapy (CRT) device implantation for the composite of improved ejection fraction, 6-min walk distance, and MLWHF in comparison with AV node ablation with combined CRT [54]. Nevertheless, the "pace and ablate" strategy is especially suitable for AF patients with reduced left ventricular function and a wide QRS complex, who already failed to other treatment options by restraining rapid and irregular intrinsic ventricular rates. Subsequently, a maximal possible rate control therapy should be used to achieve a share of almost 100% biventricular pacing and to avoid inappropriate shocks of an internal cardiac defibrillator.

Irrespective of the PABA-CHF results, through this method, an AV synchrony can be achieved and the mortality can be significantly reduced [63]. Additionally, left ventricular function, NYHA class, and AF-related symptoms can be improved. However, other data suggest that there is no benefit on the long-term outcome. The APAF-CRT trial shows that "pace and ablate" is superior to rate control in HF patients with concurrent permanent AF and narrow QRS complex regarding reduction of HF and hospitalization. Moreover, an improved quality of life in elderly patients has been reported [60].

Surgical Therapy

Prior to the development of catheter ablation, surgical therapy was an important option in AF treatment, particularly in patients undergoing concomitant cardiac surgery for other reasons, e.g. valve replacement. The technique is mostly based on Cox-Maze surgery or modifications and is based on a "cut and sew" concept, which combined left atrial appendage exclusion. Some patients, who have already failed to medical treatment options, received multiple catheter interventions, or are not suitable for ablation, may prefer a stand-alone AF surgery [64]. In these cases, the intervention can be performed through a minimally invasive thoracoscopic technique. Through an epicardiac access, an intraoperative mapping with subsequent radiofrequency ablation can be performed. Previous studies have reported a higher level of AF freedom without compromising mortality as a result of this therapy but with higher complication rates compared with conventional catheter ablation of AF [65, 66]. Thus, the need for pacemaker implantation is more frequent than after a surgical AF therapy [32].

Conclusion

HF patients with concomitant AF have a poorer prognosis compared with patients with only one of both diseases as a result of increased hospitalization rates, morbidity, and mortality. Based on shared risk factors and pathology, one condition can lead to the other and vice versa. It is challenging but

Table 1 Presentation of the most significant studies of HF patients with concurrent AF (*AAD* antiarrhythmic drug, *AF* atrial fibrillation, *AV* atrioventricular, *CRT* cardiac resynchronization therapy, *HF* heart failure, *ICD* implantable cardioverter defibrillator, *LAEF* left atrial ejection fraction, *LVEF* left ventricular ejection fraction, *MRI* magnetic resonance imaging, *MLWHF* Minnesota Living with HF, *NA* not available, *NYHA* New York Heart Association, *QoL* quality of life, *TIA* transient ischemic attack)

Trial	Year	No.	Inclusion criteria	Intervention	Follow-up	Primary endpoint	Results
DIAMOND-CHF (Torp-Pedersen et al.) [41]	1999	1518	• New or worsening congestive HF • NYHA class III or IV in preceding month or paroxysmal nocturnal dyspnoea	Dofetilide (762) vs. placebo (756)	36 months	Death from any cause	No effect on mortality
Chen et al. [52]	2004	377	• Symptomatic, AAD-resistant AF • LVEF < 40%	Catheter ablation in patients with normal (283) vs. impaired LVEF (94)	14 months	AF recurrence, LVEF, QoL, complication rates	Higher AF recurrence rates in impaired LVEF group
Gentlesk et al. [53]	2007	366	• Symptomatic, AAD-resistant AF • LVEF < 50%	Catheter ablation in patients with normal (299) vs. impaired LVEF (67)	6 months	AF recurrence, LVEF, LAEF	No difference in catheter ablation success, improved LVEF in impaired LVEF group
AF-CHF (Roy et al.) [42]	2008	1376	• NYHA class II to IV • LVEF ≤ 35%	Rhythm control (682) vs. rate control (694)	60 months	Death from cardiovascular causes	No difference
PABA-CHF (Khan et al.) [54]	2008	81	• Symptomatic, AAD-resistant AF • NYHA class II or III • LVEF < 40%	Catheter ablation (41) vs. AV node ablation + CRT (40)	6 months	Composite (ejection fraction, 6-min walk distance, MLWHF score)	Catheter ablation was superior
MacDonald et al. [55]	2011	41	• Persistent AF • NYHA class II to IV • LVEF < 35%	Catheter ablation (22) vs. rate control (19)	6 months	Change in MRI-LVEF	No difference
ARC-HF (Jones et al.) [56]	2013	52	• Persistent AF • NYHA class II to IV • LVEF < 35%	Catheter ablation (26) vs. rate control (26)	12 months	Peak $V0_2$	Catheter ablation was superior
CAMTAF (Hunter et al.) [57]	2014	50	• Persistent AF • NYHA class II to IV • LVEF < 50%	Catheter ablation (26) vs. rate control (24)	12 months	LVEF at 6 months	Catheter ablation was superior
AATAC (Di Biase et al.) [51]	2016	203	• Persistent AF • NYHA class II or III • LVEF ≤ 40% • Dual-chamber ICD or CRT	Catheter ablation (102) vs. amiodarone (101)	36 months	Freedom from AF	Catheter ablation was superior
CAMERA-MRI (Prabhu et al.) [58]	2017	68	• Persistent AF • LVEF ≤ 45%	Catheter ablation (33) vs. rate control (33)	6 months	LVEF	Catheter ablation was superior
CASTLE-AF (Marrouche et al.) [59]	2018	363	• Symptomatic, AAD-resistant AF • NYHA class II or III • LVEF < 35% • Dual-chamber ICD or CRT with home monitoring	Catheter ablation within 48 h (179) vs. medical rate or rhythm control (184)	≥ 3 years	Composite (death, HF hospitalization)	Catheter ablation was superior
APAF-CRT (Brignole et al.) [60]	2018	102	• Permanent AF • N arrow QRS (≤ 110 ms) • At least one HF hospitalization in the previous year	AV node ablation + CRT (50) vs. rate control (52)	24 months	Composite (death caused by HF, HF hospitalization, HF worsening)	AV node ablation + CRT was superior
CABANA (Packer et al.) [61]	2019	2204	• ≥ 2 paroxysmal or 1 persistent AF episodes in the last 6 months • Age ≥ 65 years • Age < 65 years + ≥ 1 risk factor for stroke	Catheter ablation (1008) vs. medical rate or rhythm control (1096)	5 years	Composite (all-cause mortality, stroke, serious bleeding, cardiac arrest)	Catheter ablation did not reduce composite primary endpoint
RAFT-AF	In progress	1000	• High AF burden • NYHA class II to IV • LVEF < 45% or ≥ 45%	Catheter ablation vs. medical rate control ± AV node ablation + CRT	5 years	Composite (all-cause mortality, HF hospitalization)	N/A

important to find effective therapeutic strategy for the individual patients that minimizes potential complications and improves clinical outcomes. In parallel, the need of risk factor reduction, treatment with both oral anticoagulation, and HF medication should always be kept in mind. Catheter ablation for AF seems to be a suitable approach in HF patients with AF with superior outcome compared with rate or pharmacological rhythm control.

Compliance with Ethical Standards

Conflict of Interest Clara Stegmann declares no conflicts of interest.
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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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