The complex interaction between atrial fibrillation and heart failure in elderly patients

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Abstract

Heart failure (HF) and atrial fibrillation (AF) often coexist. Subjects with permanent AF show the highest prevalence of HF. Patients with incident AF have HF in a great number of cases and, reciprocally, in patients with incident HF, an AF can be frequently found. The simultaneous presence of the two conditions is associated with mortality rates higher than those observed in individuals with only one or none of them. Interestingly, HF and AF could synergistically promote in elderly patients the development of disability and dementia. Inflammatory mechanisms coupled with changes of renin-angiotensin system, hormonal pathways and neuro-mediators could simultaneously promote left atrium remodeling and sustain both HF and AF. Beta-blockers and digoxin seem to have small therapeutic effect and limited influence on prognosis in these very complex patients. Sinus rhythm restoration could slow down the progression of disability in symptomatic subjects. Recent evidence seem to suggest that upstream therapy coupled with rehabilitation, and that AV node ablation associated with cardiac resynchronization therapy could benefit subjects with HF and AF. In conclusion, elderly patients simultaneously presenting problems of cardiac function and arrhythmia are an important challenge for geriatric medicine, and request important efforts to improve their functional profile and prognosis.

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The epidemiologic insight of the problem

Heart failure (HF) has a high prevalence in patients with atrial fibrillation (AF), and, reciprocally, AF has a high prevalence in patients with HF, as demonstrated by the specific age-related results of some registries and population-based studies (Table 1). The results of the EURObservational Research Programme on Atrial Fibrillation (EORP-AF) Long-Term General Registry, which enrolled subjects showing at least one arrhythmia episode in the last 12 months, demonstrated that HF was the main reason for admission in hospital or consultation in 10.4% of the whole population. The proportion of patients with HF significantly differed according to the type of AF, ranging from a minimum of 4.6%, for paroxysmal AF, to 19.7%, for permanent AF (Figure 1) [1].

Most of the new cases of the arrhythmia develop in the 5 years preceding and following the diagnosis of HF [2]. Indeed, the concepts that AF begets HF and that HF begets AF are now widely accepted. More in detail, in the Framingham Heart Study, among the 1737 subjects with new onset AF (mean age: 75±12 years), a diagnosis of HF was found in 37% of cases, while among the 1166 participants with incident HF (mean age: 79±11 years), the prevalence of AF was 62%. Accordingly, the risk to develop the arrhythmia was more than two times higher in HF patients (HR=2.18; 95%CI=1.26-3.76), similar to the risk of incident HFpEF - HF with preserved ejection fraction (EF) - (HR=2.34; 95%CI=1.48-3.70), and higher than the risk of a new HFrEF - HF with reduced EF - (HR=1.32; 95%CI=0.83-2.10) in AF subjects [3].

From epidemiology to pathophysiology and *vice versa*

HF and AF have an interrelated pathophysiology. In fact, some characteristics of HF, such as the increased filling pressures of left ventricle, the higher amount of atrial fibrosis and remodeling, the activation of neuro-hormonal pathways, and the triggering of pulmonary veins automaticity can promote arrhythmia development. Furthermore, in AF patients, left ventricular hypertrophy could be also a marker of an abnormal ankle-brachial index, thus unrevealing the presence of a significant arterial disease [4]. At the same time, AF with rapid and irregular ventricular rates and the reduced cardiac output can originate or worsen HF [5]. Epidemiological data showed that, in elderly individuals, the persistent forms of the arrhythmia can be associated with clinical and laboratory variables typical of a frail condition [6]. More recently, the pre-ablation study of patients with paroxysmal AF evidenced values of

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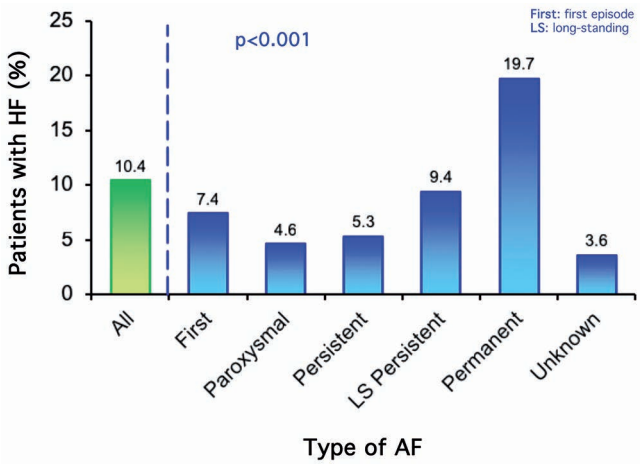

Figure 1. Heart failure (HF) as the main reason for admission in hospital / consultation by type of atrial fibrillation (AF) in the 11096 patients enrolled in the EURObservational Research Programme on Atrial Fibrillation (EORP-AF) Long-Term General Registry. Adapted from: Table 2, Boriani *et al.* Europace 2018;20:747-57, doi:10.1093/europace/eux301, with permission of the Oxford University Press on behalf of the European Society of Cardiology. This material is not included under the open access license of this publication.

myocardial energetics and left ventricular EF lower than those observed in controls with stable sinus rhythm. These findings let us hypothesize that even lone AF could be a marker of an occult cardiomyopathy characterized by a subtle LV dysfunction [7]. Indeed, the impact of AF on mortality is significant and additive to that of HF, particularly at an advanced age. The Cardiovascular Health Study Investigators demonstrated in 5673 subjects (mean age: 73 years) followed up for 13 years that mortality grew form 43%, in those without AF and HF, to 66% (AF present) and 74% (HF present), to reach 85% in individuals with both conditions. Basing on these findings, the simultaneous presence of AF and HF was associated with a three times higher mortality risk [8]. The Framingham Heart Study results confirm these findings. During the follow-up, which was stopped after a length of 8 years, both HFrEF (HR=2.73; 95%CI=2.12-3.48) and HFpEF (HR=1.83; 95%CI=1.41-2.37) were associated with a significantly increased mortality risk after a new episode of AF [3].

HF and AF are important in the elderly not only for their adverse effects on survival. Incident dementia and disability are associated with the arrhythmia [9]. In fact, the loss of atrial contraction and of atrio-ventricular synchrony, which characterize AF, lead to the reduction of LV systolic function and cardiac output. These modifications, through heart failure and stroke development, can further originate alterations of physical performance, functional status and neuro-cognitive profile [9]. Some evidence supports these associations. First, in the Framingham Heart Study, MRI scans showed that cardiac index reduction was related to a parallel decrease of total brain volume [10]. Interestingly, later, the AGES-Reykjavik Study found an intriguing inverse association between the arrhythmia burden (*i.e.*, sinus rhythm *vs.* paroxysmal

Table 1. Specific age-oriented epidemiological associations between heart failure and atrial fibrillation in some registries and population-based studies.

Study	Type of study	Age-related result	Reference
Acute Decompensated Heart Failure National Registry (ADHERE)	In-hospital patients	Prevalence of AF in >70 years - LVEF >40%: 36% - LVEF <40%: 41%	Maisel WH *et al.* Am J Cardiol 2003; 91 (6 Suppl 1):2-8
Olmsted County Study	Population Study (1990-98)	4-year incidence of AF in >65 years old subjects with abnormal LV relaxation: 18%	Tsang TS *et al.* Am J Cardiol 2004; 93:54-58
National, Heart, Lung, and Blood Institute - Sponsored Cardiovascular Research Network (CVRN)	Discharged from hospital patients and outpatients(2005-8)	≥75 years subjects - Pre-existing AF: 65.7% - Incident AF: 56.8%	McManus DD *et al.* JAMA 2013; 2: e005694
EURObservational Research Programme (EORP) -AF General Pilot Registry	Registry of in-hospital and ambulatory patients with AF (2012-13)	Prevalence of HF in AF patients ≥75 years: 55%	Fumagalli S *et al.* JACC: Clinical Electrophysiology 2015; 1:326-334
	Patients admitted for HF in UK (2000-13)	Prevalence of AF in - 70-79 years: 36.8% - 80-89 years: 42.4% - 90-99 years: 40.5%	Ziaei F *et al.* Int J Cardiol 2016: 214:410-1
PREFER in AF	Registry of AF patients (2012-13)	Prevalence of HF in >80 years AF subjects: 30.3%	Hanon O *et al.* Int J Cardiol 2017; 232:98-104
Swedish Heart Failure Registry	Registry of HF patients (2000-12)	Highest observed AF prevalence in men >90 years with HFpEF: 77%	Sartipy U *et al.* JACC: Heart Failure 2017; 5:565-574
Framingham Heart Study	Population Study (1968-2014)	Lifetime risk of AF in 75 years old subjects with elevated risk due to history of HF or MI (median follow-up: 8 years): 35.1%	Staerk L *et al.* BMJ 2018; 361:k1453

AF, atrial fibrillation; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; LV, left ventricular; LVEF, LV ejection fraction; MI, myocardial infarction.

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AF *vs.* persistent or permanent AF) and total brain volume, always estimated with MRI [11]. Lastly, in the AF Competence NETwork, it was shown that also learning and memory skills progressively reduced following the arrhythmic burden [12].

The problematic therapy of AF in HF patients

Therapy of HF and AF in elderly individuals presents some relevant controversial issues. HF, especially if associated with AF, acts as a prothrombotic cause. In particular, endothelial dysfunction, blood flow stasis, platelet activation, and the influence on the coagulation cascade contribute to a higher than normal thrombogenic status [13]. Historical data showed that mean daily dose of warfarin in AF patients should be reduced when HF is present. Indeed, the results of the registrative studies of all the direct anticoagulants seem to be consistent with unaltered drug efficacy and safety in subjects with and without HF [13].

Present Guidelines for the management of AF recommend the use of beta-blockers and digoxin (Class I, Level of Evidence B) for rate control in patients with HF, especially if with reduced EF [14]. However, the results of a meta-analysis found that beta-blocker therapy was effective to reduce mortality and hospital admissions in HF subjects with severe systolic dysfunction only if sinus rhythm was present. The benefit of treatment was lost in patients with AF [15]. Furthermore, even digoxin seems to show no benefits on survival in AF elderly patients independently of the presence of HF [16]. At this regard, a recent sub-analysis of the ARISTOTLE found that the effect of digoxin on mortality, independently of the presence of HF, was apparently neutral in AF patients if treatment was started before the beginning of the study. However, mortality was significantly higher in those individuals who need to begin digoxin therapy during the conduction of the study (HR=1.78; 95%CI=1.37-2.31) [17]. Furthermore, all-cause death was directly related to digoxin concentration, with a greater level of drug in those who died (0.62 *vs* 0.55 ng/mL, p<0.0001), and a mortality risk 19% higher for each 0.5 ng/mL increase of drug concentration (HR=1.19; 95%CI=1.07-1.32) [17].

Sinus rhythm restoration could represent a useful tool to improve cardiac function in elderly patients with persistent AF. Indeed, in a recent experience, an effective electrical cardioversion produced an improvement of longitudinal strain - a marker of left ventricular performance assessed with speckle tracking analysis of the echocardiogram - in 43 of the 48 (90%) subjects (age: 73 years) evaluated few hours after the procedure. All segments of the cardiac silhouette showed a better performance [18]. These positive changes could explain the significant increase of physical performance, as evaluated with the Short Physical Performance Battery (SPPB), in those who maintained the sinus rhythm at the follow-up evaluation (mean length: 141 days). Interestingly, no difference was present in those patients in whom AF relapsed (Δ SR *vs* AF = +1.1±0.4, p=0.018) [19].

Psychological profile seems to exert a relevant role on prognosis of patients with HF and AF. In the AF-CHF trial (mean age: 66 years; left ventricular EF ≤35%), cardiovascular death was significantly higher in patients with elevated depressive symptoms as assessed with the Beck Depression Inventory (score ≥14/63). In detail, mild to moderate depression influenced prognosis (OR=1.57; 95%CI=1.20-2.07) more than the choice of the rate-rhythm-control strategy of the arrhythmia did [20]. Later, always in the same trial, it was shown that the rhythm control strategy of AF was associated to reduced cardiovascular mortality, when compared to the rate-control one (OR=0.55; 95%CI=0.32-0.95), only in those patients with high symptoms of anxiety, as evaluated with the Anxiety Sensitivity Inventory [21].

In the AF population, atrial structure undergoes a continuous remodeling process. Inflammation markers, angiotensin-II, aldosterone, endothelin-1 and the reactive oxygen species interact with the traditional arrhythmia clinical risk-factors and with obesity to change atrial myocardium and to promote AF relapse [22]. Basing on these assumptions, the "routine *vs.* aggressive risk factor driven upstream rhythm control for prevention of early AF in heart failure" (RACE 3) trial compared a conventional approach to a new, "targeted therapy", one to maintain sinus rhythm at the follow-up in patients with HF and persistent AF. In the active arm, four therapies were introduced: mineralocorticoid receptor antagonists, statins, angiotensin converting enzyme inhibitors and/or receptor blockers, and cardiac rehabilitation, including physical activity, dietary restrictions, and counselling. At the one-year follow-up, the 7-day Holter monitoring demonstrated a higher proportion of patients with sinus rhythm in the "targeted therapy" group (75 *vs.* 63%, p=0.042) [23].

The use of devices for cardiac resynchronization therapy (CRT) proved to be an effective strategy to improve left ventricular function independently of age [24]. Importantly, CRT is able to produce, after only 6 months, an increase of physical performance, as evaluated with SPPB, and a positive effect on neuro-cognition, as evaluated with the Mini-Mental State Examination [25]. However, prognosis in CRT elderly patients is negatively influenced by the presence of AF [24]. In the APAF-CRT trial, permanent AF patients with HF (mean age >70 years; mean EF: 40%) and narrow QRS were stratified to rate control strategy or to AV node ablation and CRT therapy. After 16 months of follow-up, hospitalizations for HF were significantly reduced in the group receiving the device, with an effect particularly evident in patients with an EF ≤35%. The invasive strategy had an influence also on health-related quality of life [26].

Conclusions

The interaction between AF and HF is complex. It can be responsible of some important complications of the arrhythmia, such as cognitive impairment, dementia and increased mortality. Inferring directional relationships between AF, HF and the other outcomes can be treacherous. However, the comprehension of the mechanisms linking the arrhythmia to the several related clinical conditions can greatly help to clarify patients' prognosis [27]. Subjects with AF and HF need a multifaceted treatment strategy, as patients with only HF often do [28]. In this scenario, beta-blockers and digoxin seem to lose their relevance, while treatments addressed to reduce atrial remodeling are becoming more important. Rehabilitation programs and cardiac devices, two non-pharmacological approaches, could significantly ameliorate the clinical outcomes of patients with HF and AF.

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