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Review

The imminent epidemic of atrial fibrillation and its concomitant diseases – Myocardial infarction and heart failure - A cause for concern

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ABSTRACT

Atrial fibrillation (AF) is increasingly common in the general population. It often coincides with myocardial infarction (MI) and heart failure (HF) which are also diseases in older adults. All three conditions share common cardiovascular risk factors. While hypertension and obesity are central risk factors for all three diseases, smoking and diabetes appear to have less impact on AF. To date, age is the single most important risk factor for AF in the general population. Further, epidemiological studies suggest a strong association of AF to MI and HF. The underlying pathophysiological mechanisms are complex and not fully understood. Both MI and HF can trigger development of AF, mainly by promoting structural and electrical atrial remodeling. On the other hand, AF facilitates HF and MI development via multiple mechanisms, resulting in a vicious circle of cardiac impairment and adverse cardiovascular prognosis. Consequently, to prevent and treat the coincidence of AF and HF or MI a strict optimization of cardiovascular risk factors is required.

1. Introduction

Atrial fibrillation (AF) is increasingly common in the general population and is associated with a significant morbidity and mortality. At the community level, the risk of developing AF is related to classical cardiovascular risk factors and often AF coincides with common cardiac diseases such as myocardial infarction (MI) and heart failure (HF). Whereas cardiovascular risk factors play a role in the pathogenesis of all three diseases, risk factor associations and temporal relations of disease occurrence differ. In this review we discuss the epidemiological background, shared risk factors and interdependence in disease development of AF and concomitant MI and HF.

2. Atrial fibrillation, myocardial infarction, heart failure and cardiovascular risk factors

All three diseases, AF, MI and HF are frequent in the community with increasing prevalence in older adults. As complex diseases their occurrence usually cannot be explained by the presence of a single risk factor. On the one hand, the pathophysiological mechanisms of AF, HF and MI are different. A key role in development of AF has been attributed to structural and electrophysiological remodeling of the atrial myocardium. The most prominent conditions underlying MI are atherosclerosis and coronary artery disease. The phenotype of HF is the result of multiple conditions and only partly explained by coronary heart disease. On the other hand, the incidence of all three diseases has been related to classical cardiovascular risk factors, as displayed in Fig. 2, and an aggressive risk factor management can improve clinical outcome [1–8].

2.1. Age and sex

AF, MI and HF are diseases with a steep incline in incidence with older age. They are not frequent before the age of 60 years. In the ATRIA Study, a cross-sectional study of 1.89 million U.S. inhabitants aged 20 years or older, the prevalence of AF was 0.95% overall and increased from 0.1% among adults younger than 55 years to 9.0% in participants 80 years and older [9]. A large, prospective European population-based study showed comparable results, AF prevalence increased from 0.7% in the age group between 55 and 59 years to 17.8% in the age group 85 years and above [10]. Similarly, the prevalence of HF rises from 0.7% in individuals between 45 and 54 years to 8.4% in those aged 75 years and older [11]. Likewise, MI prevalence increases with age. MI prevalence in individuals older than 80 years is approximately five-fold higher compared to individuals between 40 and 59 years [12].

Notably, men suffer from AF, MI and HF more often than women [8,9,13,14]. Regarding AF, incidence in women lags behind incidence

Abbreviations: AF, atrial fibrillation; BMI, body mass index; DCM, dilated cardiomyopathy; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular; MI, myocardial infarction; NSTEMI, non-ST segment elevation myocardial infarction; OSA, obstructive sleep apnea; PAR, population-attributable risk; RAAS, renin-angiotensin-aldosterone-system; SCD, sudden cardiac death; STEMI, ST segment elevation myocardial infarction; TIC, tachycardia-induced cardiomyopathy; TGF, transforming growth factor.

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in men by 10 years [9,10,13,15]. On the contrary, women have a higher risk for developing heart failure with preserved ejection fraction (HFpEF) [16] and represent the majority of patients with MI after the age of 75 [17].

The Framingham Heart Study and many other investigations showed that age is the single most important risk factor for AF compared to all other classical cardiovascular risk factors as well as alcohol consumption, left ventricular (LV) hypertrophy, heart murmur, but also HF and MI [18]. Taking into account the ageing world population, the number of patients with AF is estimated to increase 2.5-fold during the next 50 years [9]. Likewise, the prevalence of HF is projected to increase by 25% over the next 20 years although the risk factor age is not as important as for AF [19,20]. By contrast, the incidence of MI decreased during the last years, largely due to better risk factor management [14,21].

In epidemiology it has remained difficult to dissect solely age-related changes that predispose to AF, HF and MI from an increasing risk factor burden and its effects that accumulate during a lifetime. Likewise, the underlying pathophysiological mechanism of how ageing is related to AF is not completely understood. It is known that the number of cardiomyocytes decreases during lifetime. They are partially replaced by fibrotic tissue [22], which leads to changes in cellular connectivity and variable arrhythmogenic conduction responses to premature stimuli [23]. Additionally, ageing goes along with impaired electrical coupling between the myocytes [24]. Furthermore, age-related alterations in structure and function of atrial ion channels result in a reduced calcium and, simultaneously, an increased potassium current [25]. Another mechanism that has been suggested is the reduced sinoatrial node firing and at the same time an enhanced impulse initiation from aged atrial cells in the pulmonary veins and coronary sinus [25]. Whereas some of the outlined mechanisms may also be causal for the development of HF and MI, most of them are fairly specific for changes that may increase the susceptibility for AF.

2.2. Hypertension

High blood pressure promotes the development and recurrence of AF [26,27]. Furthermore, untreated hypertension enhances stroke and bleeding risk in AF patients [27,28]. Due to the high prevalence in the general population, hypertension bears substantial relevance as a risk factor for AF development, as expressed by a population-attributable risk (PAR) of 13.5% [13,29]. The same applies to HF, where hypertension is one of the most important risk factors besides coronary artery disease [30]. In MI, hypertension is at least as important as in AF and HF development. In the INTERHEART study hypertension accounted for 18% of the PAR of a first MI [4]. A comparison of PARs of hypertension for AF, MI and HF is presented in Fig. 1.

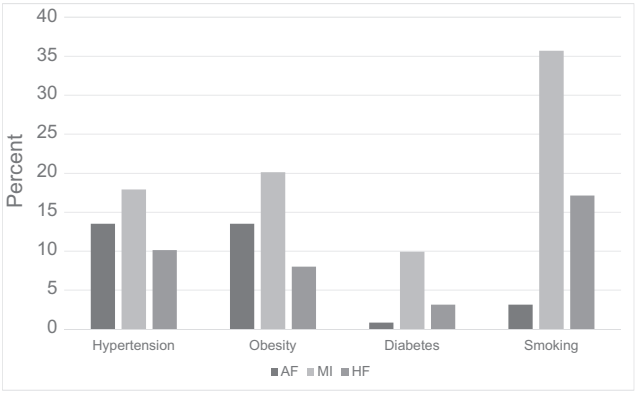

Fig. 1. Population-attributable risk of classical cardiovascular risk factors for atrial fibrillation (AF), myocardial infarction (MI) and heart failure (HF) in community studies [4,13,30].

Moreover, patients with hypertension develop cardiovascular disease five years earlier compared to normotensive individuals [31]. In individuals with AF hypertension leads to increased cardiovascular as well as all-cause mortality [32]. In general, hypertension is a well-established risk factor for adverse cardiovascular outcomes [33,34].

Pathophysiologically, hypertension leads to atrial dilation and dysfunction [35,36] as well as LV hypertrophy [37] and diastolic dysfunction [38,39] resulting in an increased risk of AF development. Besides these structural changes, atrial electrical remodeling has been discussed as a possible cause for AF related to hypertension [40]. Furthermore, it has been suggested that the activation of the renin-angiotensin-aldosterone-system (RAAS) is an important underlying pathophysiological mechanism by triggering hypertension itself as well as the above mentioned cardiac structural and electrical changes [41,42]. The pathophysiology of HF and MI due to hypertension is similar to AF. LV hypertrophy and diastolic dysfunction caused by hypertensive blood pressure are main reasons for incident HF [43,44]. LV hypertrophy and the activation of the RAAS are linked to an increased risk of MI [45,46].

2.3. Obesity

Due to its rising prevalence obesity and resulting morbidity and mortality has gained importance in the population [47]. The role of obesity in the development of AF, HF and MI is well-established.

Next to age and hypertension, obesity represents a critical risk factor for incident AF in the general population, as the PAR amounts to 13.5% [13]. For MI development obesity also is of high relevance, as the PAR accounts for >20% [4,48]. In HF, the impact is slightly lower with a PAR of 8% [30,49]. PARs of obesity for AF, MI and HF are shown in Fig. 1.

In MI, particularly the abdominal fat mass seems to play a crucial role in the pathogenesis and appears to be an independent predictor of all-cause mortality in men and probably also in women [50]. The risk of HF and AF development correlates with extent of obesity. With an increase in body mass index (BMI), the incidence of AF rises continuously [51–53]. In a large meta-analysis of 51 studies an increase of 5 kg/m^2 in BMI was associated with an up to 29% greater excess risk of incident, post-operative, or post-ablation AF [54]. The risk of AF dynamically changes with body weight. Newly obese patients were shown to have a significantly higher risk of developing AF compared to patients who maintain normal weight. Likewise, obese patients reaching normal weight seem to be able to reduce their risk of AF [55]. In HF development, specifically morbid obesity is a strong independent risk factor [56]. Surprisingly, there is evidence that overweight and mildly obese patients have a better prognosis than do their normal weight counterparts. This observation is called the obesity paradox and applies to most cardiovascular diseases including HF, AF and MI [57,58].

There are multiple mechanisms through which obesity contributes to the development of AF, HF, MI and their co-occurrence. Major factors include hemodynamic alterations induced by high cardiac output and LV hypertrophy leading to diastolic dysfunction and elevated left atrial pressure [1,59–64]. Especially for AF development, pericardial fat, which is highly biologically active, seems to play an important role [65–68]. Furthermore, a shortened effective refractory period in the left atrium and pulmonary veins has been demonstrated in obese individuals, representing underlying electrophysiological alterations for development and maintenance of AF [63].

2.4. Diabetes

Comparing the role of diabetes in the development of AF, HF and MI, its impact is most prominent in MI with a PAR of 9.9% [4]. In HF, women seem to be particularly susceptible as diabetes is related to HF risk with twice as many cases as in men [69]. In total, the impact of diabetes on incident HF amounts to a PAR of 3.1% [30]. For AF, a PAR of diabetes of only 0.8% has been described [70]. A comparison of diabetes PARs in AF, MI and HF is presented in Fig. 1.

Even though AF often coexists with diabetes [27], the association between diabetes and incident AF was not statistically significant in some community studies like the Framingham Heart Study and other independent European cohorts after accounting for other risk factors [13,71]. Other reports however, describe an association of diabetes with an increased risk of AF development independent of sex [8,26,72]. Particularly, high levels of HbA1c, reflecting poor glycemic control, promote incident AF [73,74]. Strict glycemic control can reduce the recurrence rate after ablation [2].

The ADVANCE study revealed that the risk of all-cause mortality for diabetic patients with AF was 61% higher compared to patients without AF [75]. Likewise, diabetes is associated with a higher cardiovascular morbidity and mortality rate in patients with HF [76] and MI [77]. Although there is a decline in heart disease mortality due to better risk factor management and treatment strategies, these changes seem to be less effective for patients with diabetes [78]. Therefore an intensified, multifactorial intervention at multiple risk factors seems to be essential in patients with diabetes to reduce mortality rates substantially [79].

There are various pathophysiological pathways of cardiac impairment in diabetic patients. On the one hand, coronary artery disease and development of MI are promoted by dyslipidemia and hypertension as well as endothelial dysfunction, platelet activation and coagulation abnormalities [80–82]. On the other hand, diabetic cardiomyopathy occurs independently of coronary artery disease and hypertension [83,84]. Deposition of advanced glycation end products increasing LV stiffness, dysfunction of coronary microcirculation and autonomic neuropathy are presumed to play an important role in development of LV dysfunction [85–87]. These alterations not only build a substrate for incident HF but also lead to atrial structural remodeling as a potential basis of AF development. Accordingly, hyperglycemia and diabetic conditions have been linked to diffuse atrial interstitial fibrosis [88,89]. Advanced glycation end products and higher levels of reactive oxygen are assumed to play an essential role for these changes [90,91]. In addition, diabetes-induced increased sympathetic and decreased parasympathetic cardiac activity as well as alterations of electrical conduction in the atrium have been reported to result in a higher vulnerability for AF [92,93].

2.5. Smoking

In contrast to MI and HF, the relevance of smoking for the risk of AF development is comparably low. A meta-analysis estimated that 6.7% of the total risk of AF in men and 1.4% of the risk in women is attributable to smoking [94]. A recent analysis based on four large community-based European studies calculated a PAR of 3.1% without any sex difference for daily smoking [8]. Noteworthy, the relevance of smoking on development of MI and HF is disproportionately stronger. For MI a PAR for smoking of 35.7% and for HF of 17.1% have been reported [4,30]. A comparison of PARs of smoking for the three diseases is shown in Fig. 1.

Different pathophysiological mechanisms have been suggested to explain how smoking contributes to the development of AF. Nicotine stimulates sympathetic neurotransmission and catecholamine release [95]. Furthermore, nicotine can induce structural atrial remodeling via transforming growth factor (TGF)-β1 upregulation, providing a proarrhythmogenic substrate for the development of AF [96,97]. More prominently, mediated by various pro-atherogenic effects, smoking strongly contributes to the development of coronary heart disease explaining the high incidence of MI in smokers. The most important effects include systemic inflammation [98,99] and endothelial dysfunction [100] as well as an aggravation of dyslipidemia and insulin resistance [101,102]. Independent of coronary heart disease carbon monoxide exposure seems to impair cardiac contractility leading to hypertrophy and promoting development of HF [103].

2.6. Dyslipidemia

Paradoxically, there seems to be an inverse association of total as well as LDL-cholesterol with incident AF with a stronger risk reduction in women [13,104–107]. The PAR for incident AF resulting from lower cholesterol levels is 6.1%. Overall, blood lipids seem to play a secondary role in AF development and the same applies to HF development. In the Framingham Heart Study an elevated total cholesterol/HDL-ratio was associated with HF development [108]. However, subsequent studies showed an association for hypercholesterolemia and incident HF in men only [30] or failed to confirm an association [109]. On the contrary, high levels of LDL-cholesterol and low levels of HDL-cholesterol have a major impact on MI development. Comparing the LDL/HDL-ratio of the lowest with the top four quintiles, the PAR for the occurrence of MI amounts to 49.2% [4]. Consequently, lipid-lowering medication is successfully and broadly used in primary and secondary prevention.

The exact pathophysiology behind the paradoxical association of incident AF and lower levels of total and LDL-cholesterol remains unclear. The membrane-stabilizing effect of cholesterol might be one explanation [110]. Furthermore, increased cell membrane-cholesterol was related to action potential elongation and hereby AF occurrence [111]. Interactions of cardiac ion channels and lipid rafts in cardiomyocytes might play a role as well [112]. In contrast, the pathophysiological relation between lipid profile and MI occurrence is fairly well understood. Simply put, high levels of LDL-cholesterol induce the development of atherosclerotic lesions in the coronary arteries. Their rupture provokes acute MI [113].

2.7. Alcohol

Alcohol use is a known risk factor for incident AF. Even low alcohol intake increases the risk for AF development [114–116]. Overall, alcohol use explains only 1.4% of the PAR for incident AF und seems to play a minor role [13]. However, in the case of AF development, high alcohol intake has prognostic implications by predicting thromboembolisms and death [117]. While high alcohol intake may lead to incident HF by toxic effects [118], moderate alcohol consumption seems to have a protective effect [30,119]. This protective effect of moderate alcohol consumption was also recognized for MI occurrence. The PAR for non-alcohol drinkers was 6.7% [4]. Furthermore, low alcohol consumption is associated with reduced mortality after MI [120,121].

Attempts at explaining the protective effect of moderate alcohol consumption on MI occurrence and mortality include changes of cardiovascular biomarkers such as higher levels of HDL and adiponectin and lower levels of fibrinogen [122,123]. The pathophysiological background of alcoholic cardiomyopathy is complex. Among other factors, myocyte dysfunction and resulting HF is due to loss of myocytes, dysfunction of intracellular organelles, negative inotropic effects and an altered calcium homeostasis [124]. For AF, similar cellular effects have been reported. On the electrophysiological level, a shortened action potential and atrial effective refractory period, a decelerated intra- and inter-atrial conduction and an enhanced AV-nodal conduction have been described as possible triggers for AF due to alcohol consumption [125]. Furthermore, autonomic effects

like vagal inhibition and simultaneous sympathetic activation as well as reduced heart rate variability might play a role [125].

2.8. Obstructive sleep apnea

Sleep-disordered breathing and obstructive sleep apnea (OSA) often coincides with AF, HF and MI, which can partly be explained by overlapping risk factors like obesity and hypertension. However, there is convincing evidence suggesting an association beyond these risk factors especially for AF. The prevalence of OSA is much higher in individuals with AF compared to individuals without AF (21%–74% vs. 3%–49%) [126,127] and recurrence rates of AF after pulmonary vein isolation are significantly increased in OSA patients [128,129]. Furthermore, continuous positive airway pressure increases success rates of both, pulmonary vein isolation and cardioversion [130,131]. OSA has been described as a predictor of HF and MI even after adjustment for other risk factors although this association was not significant in women [132,133].

Besides the underlying risk factors, OSA presumably contributes to development of AF, HF and MI by direct effects triggered by the intermittent episodes of apnea and arousal. These episodes result in activation of the sympathetic nervous system, blood pressure, heart rate increase, negative intrathoracic pressure, ischemia, oxidative stress and systemic inflammation [134–138]. There may be a reciprocal relationship, as development of OSA after incident HF or MI has been described [139]. As a possible explanation an instability of ventilatory control has been suggested.

3. Atrial fibrillation and myocardial infarction

Whereas stroke has been perceived as major thromboembolic complication of AF, epidemiological studies also suggest a strong association of AF with coronary heart disease and MI. There are multiple pathophysiological interactions between the diseases as displayed in Fig. 2.

3.1. Epidemiology

In the ARIC (Atherosclerosis Risk In Communities) study AF was associated with a 63% increased risk of incident MI [140] and the REGARDS (REasons for Geographic And Racial Differences in Stroke) study demonstrated a two-fold increased risk of MI in individuals with AF [141]. In both studies the association was stronger in women than in men. Furthermore, data suggests that there are also race specific differences, as incidence of MI associated with AF was higher in African Americans. In contrast, Japanese and Taiwanese trials reported annual rates of MI between 0.2% and 0.3% in AF patients [142,143] compared to 1–2% in patients of European descent [141,144,145].

Underlying cardiovascular risk factors promoting development of both diseases seem to be the most likely explanation for the frequent coincidence of AF and MI. However, the association still remains significant after rigorous adjustment for risk factors suggesting a more direct relation. Whereas AF is associated with an elevated risk of developing MI, the event of MI also results in a significantly increased probability of new onset AF. After MI an AF incidence between 6.4% and 7.9% has been reported [146–149]. Presumably, there is an even higher incidence of subclinical AF. For a subgroup of post-MI patients with LV ejection fraction ≤40%, who received an implantable cardiac monitor, a twelve-month AF-incidence of 32% could be demonstrated [150].

3.2. Pathophysiology – AF as a possible cause of MI

There are several possible explanations of how AF may contribute to MI. Various studies have suggested that AF promotes systemic inflammation and endothelial dysfunction [151–154], eventually favoring development of coronary heart disease and MI. Furthermore, poorly controlled episodes of tachyarrhythmia in AF patients may increase myocardial oxygen demand and reduce coronary perfusion resulting in type-2 MI [155]. Another possible mechanism for MI in AF patients is a coronary thromboembolism. In a cohort of 1776 patients with acute MI, 2.9% were attributed to coronary embolism, of which 73%

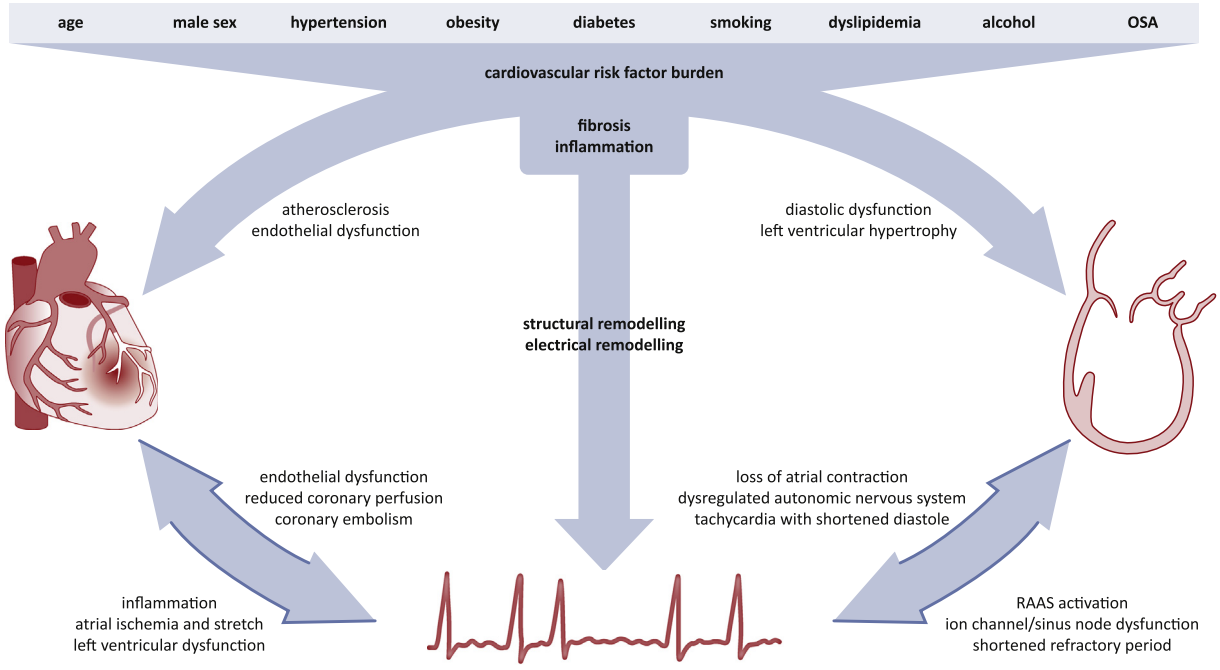

Fig. 2. Possible pathophysiologic interactions of cardiovascular risk factors in atrial fibrillation (AF), myocardial infarction (MI) and heart failure (HF). Incidence of AF, MI and HF has been related to classical cardiovascular risk factors. These risk factors generate a pro- inflammatory environment and fibrosis which are a common basis of all three diseases. Furthermore, there are disease specific changes that increase the susceptibility for AF, MI or HF. While AF facilitates development of MI and HF, both also result in an increased risk of AF. Their co-occurrence leads to progressive cardiac impairment and an adverse cardiovascular prognosis.

were caused by AF [156]. As a coronary embolism is likely to result in a sudden, complete coronary obstruction, it would presumably result in ST segment elevation MI (STEMI). However, in the ARIC study the association of AF to MI could only be confirmed for non-ST segment elevation MI (NSTEMI). Accordingly, this data suggests, that coronary thromboembolism is a rare reason of MI in AF patients [140].

3.3. Pathophysiology – MI as a possible cause of AF

Elevated admission heart rate, LV dysfunction, and LV hypertrophy, have all been identified as risk factors for the development of AF in the acute phase after MI [157,158]. The underlying pathophysiology comprises different mechanisms. Atrial ischemia during MI directly promotes development of AF and provides a possible substrate in particular for early onset AF after MI [159,160]. Another important factor is the inflammatory process induced by MI. The ischemic stimulus and oxidative stress trigger cytokine release and local as well as systemic inflammation [161–163]. Subsequently, the process of inflammation causes atrial remodeling and fibrosis [164–166] and thus promotes development of AF. A Japanese study suggested a direct correlation between plasma inflammatory markers and incidence of AF [147]. Moreover, an infarction-related pericarditis is known to trigger AF [167]. A prominent role in development of AF after MI is also attributed to atrial stretching caused by HF and resulting in an increased atrial excitability [168,169].

3.4. Clinical outcome

AF in MI patients is associated with an adverse prognosis. Increased mortality has been described in MI patients with new onset of AF as well as prior AF [170–173]. A meta-analysis showed a 1.5-fold increased mortality of MI patients with AF [170]. Particularly, new onset of AF after MI is related to an adverse outcome. Compared to individuals with permanent AF the risk of death is 87% higher [174].

An increased myocardial oxygen demand, which aggravates ischemia has been suggested to explain the increased mortality of MI patients developing AF. Another possible reason is hemodynamic alterations resulting in further reduction of cardiac output [175]. Furthermore, the rate of sudden cardiac death (SCD) is elevated in MI patients developing AF [176,177], possibly indicating an increased vulnerability for ventricular tachycardia.

4. Atrial fibrillation and heart failure

AF and HF are closely related conditions, sharing common risk factors, and each contributing to the development of the other as shown in Fig. 2. The coexistence of both diseases leads to a substantial increase in morbidity and mortality, which particularly applies to the subset of HF patients with reduced ejection fraction (HFrEF) [178]. Though, HF with preserved ejection fraction (HFpEF) is associated with a higher relative risk of developing AF [179,180].

4.1. Epidemiology

Both AF and HF have similarities in their epidemiology with overall an increasing prevalence and an almost exponential increase in incidence after the age of 60 [19,181]. The causal relationship appears to be bidirectional. In the Framingham Heart Study the incidence of HF in AF patients was 3.3% per year. The incidence of AF in HF patients was 5.4% per year. Among those participants, who were diagnosed with both AF and HF, 38% had AF first, 41% had HF first, and 21% had both conditions diagnosed at the same time [182].

Notably, the prevalence of AF in HF patients correlates with the severity of HF. In HF patients with NYHA class I AF occurs in <10% of patients while in patients NYHA class IV an AF prevalence of up to 50% has been described [183–187]. As mentioned earlier, HFpEF more often coincides with AF. Two third of patients with HFpEF develop AF prior to or after the diagnosis [180]. Atrial remodeling has been suggested as a hallmark pathophysiological feature connecting the two diseases [188].

HF increases the risk of AF for both sexes, but the magnitude seems to be considerably higher in women [26]. For HFpEF the incidence of AF is higher in women compared to men [16]. On the other hand, women with AF have a lower risk of developing HF compared to men one year after AF diagnosis [189]. In the male population AF often manifests at a younger age [189] and has a stronger association to HFrEF. Coronary heart disease and MI have been suggested as important underlying substrate for the development of HFrEF and AF providing a possible explanation for the higher incidence in men [179].

4.2. Pathophysiology - AF as a potential cause of HF

Several reports describe a modest decline in cardiac output with the onset of AF. This direct effect is fully reversible after cardioversion [190–192]. The most prominent reasons are the loss of atrial contraction, the irregular heart rate and a shortened diastole [190].

The atrial contraction contributes approximately 25% to ventricular filling [193]. In patients with diastolic dysfunction the importance of atrial contraction becomes more pronounced, as ventricular filling shifts to the later part of the diastole. The importance of a physiological atrial contraction is underlined by a study comparing pulmonary vein isolation to AV-node ablation with biventricular pacing in AF patients with HF. Restoration of sinus rhythm after pulmonary vein isolation resulted in an improved cardiac outcome [194].

Irrespective of heart rate an irregular ventricular contraction independently contributes to reduction of cardiac output for reasons not yet completely understood [175,195]. Beat-to-beat changes in ventricular filling can result in reduction of LV ejection fraction as described by the Frank-Starling mechanism. Furthermore, myocardial contractility can be negatively influenced by length of the preceding RR intervals [196]. Additionally, irregular ventricular contraction increases sympathetic nerve activity [197], which further increases afterload and eventually aggravates HF.

On the other hand, there are also long term effects of AF contributing to HF development. Persistent tachycardia can result in LV dysfunction referred to as tachycardia-induced cardiomyopathy (TIC), which resembles dilated cardiomyopathy (DCM). Poorly controlled AF is the most common underlying condition [198] and the severity of TIC correlates to duration and frequency of the tachyarrhythmia [199]. As a pathophysiological substrate various structural and hemodynamic changes have been described in animal models of rapid atrial or ventricular pacing. Increase in LV filling pressure, LV wall stress and systemic vascular resistance eventually results in LV cavity dilation, impaired ventricular contractility and consecutive mitral regurgitation [200–203]. A recent study characterizing histomorphological changes of TIC in humans showed similar changes in cardiomyocyte morphology compared to DCM [204]. Notably, TIC samples featured less fibrosis and a macrophage-dominated myocardial inflammation differing significantly from DCM.

In a time course of a few weeks after heart rate is controlled ejection fraction largely recovers [205,206]. However, the presence of cardiomyocyte apoptosis in TIC patients indicates permanent myocardial damage [204]. Echocardiographic follow-up revealed persisting changes of LV dimensions and volumes indicating lasting LV remodeling [207]. In accordance, recurrent HF with uncontrollable tachyarrhythmia and increased rate of sudden cardiac death after initial recovery from cardiac dysfunction have been observed [208]. Cardiac MRI investigations revealed a diffuse fibrosis as morphological substrate of these permanent changes [209], consistent with animal studies reporting an interstitial fibrotic response in the recovery phase of TIC [210]. Altogether, TIC usually does not result in persistent HFrEF. However, there are lasting structural myocardial transformations that may serve as an

explanation for the strong association between previous AF and the development of HFpEF [180,211].

4.3. Pathophysiology - HF as a potential cause of AF

The risk of HF patients developing AF is four to six times higher compared to the general population [26]. The most important reason appears to be a susceptibility due to structural and electrical remodeling. A canine model of HF induced by five weeks of rapid ventricular pacing resulted in sustained inducible AF. Histologically, an extensive atrial interstitial fibrosis was identified as underlying morphological substrate [212]. More recently, in a similar canine model of chronic HF changes in ion channel expression and ion currents have been demonstrated. These were accompanied by a shortening of atrial refractory period and atrial action potential duration [213]. Electrophysiological mapping in HF patients revealed correlating abnormalities of conduction, sinus node dysfunction, and increased refractoriness [214] providing a potential substrate for persistent AF.

Evidence also suggests an important role of the RAAS in the genesis of AF in HF patients. The compensatory upregulation of vasoconstrictive angiotensin II in HF contributes to maintenance of perfusion pressure [215]. However, this comes with the price of a number of negative consequences. Among others, LV afterload increases leading to further deterioration of myocardial function, adaptations can worsen coronary ischemia, and promotion of apoptosis of cardiac myocytes results in myocardial hypertrophy and fibrosis. Epidemiologic data further substantiates the contribution of angiotensin II to the development of AF in HF patients. A meta-analysis of treatment with ACE inhibitors or angiotensin receptor blockers revealed a relative risk reduction of 44% in HF patients [216]. In the SOLVD trials ACE inhibition with enalapril even resulted in a fivefold reduced risk of incident AF [217], emphasizing the importance of pharmacological treatment for this patient population.

4.4. Clinical outcome

Numerous complications are associated with AF and particularly the development of HF is frequent [218]. Both, AF and HF are risk factors for stroke [219]. In individuals with AF the modifiable risk factors including obesity, hypertension, smoking and diabetes have a major impact on the risk of developing HF. In accordance, an optimized management of these risk factors can decrease HF risk [220]. Compared to healthy individuals the manifestation of both, AF or HF, is related to a poor prognosis. The co-occurrence however, is associated with a particularly high cardiovascular and all-cause mortality [182,221]. Notably, new onset of AF in individuals suffering from HF has a stronger negative impact on prognosis than previously diagnosed AF [222–224]. All-cause mortality of AF patients with HFrEF is higher compared to patients with HFpEF [178]. However, in individuals with less-severe systolic dysfunction or preserved systolic function the occurrence of AF is also associated with an adverse prognosis [225–227]. Especially in female patients HFpEF comes with a greater risk for adverse events including hospitalizations, stroke, and death [228].

5. Conclusions

AF, MI and HF are closely related conditions that are increasingly frequent in the general population. All three diseases share common risk factors. Due to increasing life-expectancy and lifestyle-changes the prevalence of risk factors such as obesity, diabetes and hypertension and consecutively of AF, MI and HF are expected to further rise.

Individuals with AF show an increased risk of development of HF or MI, which also applies reciprocally. Furthermore, consecutive or concomitant occurrence of AF and any of the two diseases significantly reduces survival.

The pathophysiologic interactions are complex as illustrated in Fig. 2. Central to the development of AF is atrial structural and electrical remodeling as well as hemodynamic alterations, which are promoted by the cardiovascular risk factor burden but also concomitant HF or MI. On the other hand, AF contributes to the development of MI and HF in multiple ways resulting in a vicious circle of progressive cardiac impairment. But there also are significant differences in disease epidemiology, risk of developing concomitant disease, type of MI and HF in relation to AF and differential risk factor associations that need to be investigated further. At present, it can be concluded from an epidemiological perspective, that the coincidence of AF and MI or HF is associated with high morbidity and adverse prognosis that mandates rigorous risk factor targeting and treatment of the underlying conditions to prevent disease occurrence and its complications.

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