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Review on atrial fibrillation and coronary artery disease

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Abstract
Atrial fibrillation (AF) is a common cardiac arrhythmia, it is not considered as a benign arrhythmia as it leads to decreased quality of life, high risk of developing thromboembolism, and increase in mortality rate. There are various recognized risk factors for AF, these risk factors are also considered risk factors for developing coronary artery disease (CAD).Moreover, they also share some pathophysiological mechanisms. So, the overlapping risk factors and pathophysiology arises the need to illustrate the relation between the two grave diseases.

Keywords: atrial fibrillation, coronary artery

Introduction

Atrial fibrillation (AF) is documented as the commonest grave cardiac arrhythmia, In the United states of America (USA) it affects 2.3 million individuals (nearly 2% of individuals younger than sixty five years of age have AF, while nearly 9% of individuals aged sixty five years or older) have AF, and in the European Union (EU) 4.5 million individuals (nearly 0.12%–0.16% of people younger than forty nine years of age, 3.7%–4.2% of people aged 60–70 years, and 10%–17% of people aged eighty years or older) have AF [1,2,3].

AF is associated with diversity of symptoms, major mortality and morbidity and reduced quality of life [4,5]. The AF patients' mortality rate is nearly twice that of patients with normal sinus rhythm. Notably, this observation is attributed to the augmented cardiac death caused by associated cardiovascular disease [6–9] instead of to thromboembolism [10].

Coronary artery disease (CAD) is vastly prevalent in patients with AF and can be one of its etiologies [11]. Additionally, the lone manifestation of CAD can be AF [12]. Remarkably, epidemiological data have point out that one of the commonest underlying causes of death among patients with AF is CAD [13]. Notably, after acute myocardial infarction (MI), development of AF is related to a worse prognosis [14].

Some studies have found common cardiovascular risk factors between CAD and AF for instance hypertension, diabetes and obesity that support the association between CAD and AF. [15, 16]. The Framingham study supported that angina predisposed to AF and that the association of AF with CAD was stronger in men [7]. Despite the high prevalence of CAD in patients with AF of 18–46.5% [8, 11, 17, 19], the prevalence of AF in patients with confirmed CAD is very low, at 0.2–5% [20-23]. In contrast, a survey of historic literature by Zipes indicates that AF usually arises in patients with CAD [24].

Over the years, the incidence of cardiovascular risk factors have dramatically increased and this is anticipated to continue. [19, 25] More over, the interest in investigating patients with AF has grown owing to the probability of specific antiarrhythmic treatment for CAD and non-vitamin K oral anticoagulants (NOAC). [26-28]

Definition

Atrial fibrillation is a rapid, irregularly irregular atrial rhythm; it has been attributed to multiple wavelets with chaotic reentry in the atria. However, in several cases, firing of an ectopic focus in venous structures adjacent to the atria (usually the pulmonary veins) is responsible for initiation and may be maintenance of atrial fibrillation. [30] In AF, the atria do not contract, and the atrioventricular (AV) conduction system is attacked by several electrical stimuli, producing inconsistent impulse transmission and an irregularly irregular ventricular rate, which is usually within the tachycardia rate range. [30]

Classification

In 2014, the (AHA/ACC/HRS) published updated guidelines for the management of patients with AF. These guidelines replaced the AF guideline released in 2006 and updated in 2011. The guidelines offer the following revised classification scheme, based on duration of the episodes [2]

- **Paroxysmal AF:** Episodes of AF that self-terminate or with intervention within seven days; may return with variable frequency
- **Persistent AF:** Episodes of continuous AF lasting beyond seven days and do not end spontaneously
- **Long-standing persistent AF:** Episodes of continuous AF lasting beyond 12 months
- **Permanent AF:** after a shared physician/patient decision has been made to accept the persistence of AF and end any additional attempts to regain and/or maintain sinus rhythm (as this is a clinical acceptance instead of

an inherent pathophysiological characteristic of AF, it is understood that acceptance of AF might vary as symptoms, efficiency of interventions, and patient/physician preferences develop.

- **Nonvalvular AF:** AF in the absence of moderate-to-severe mitral stenosis or an artificial heart valve.[29] Over time, it is noted that episodes frequently increase in frequency and duration. Furthermore, the term "lone AF" to identify AF in usually younger patients with no structural heart disease, hypertension, or diabetes mellitus is supposed potentially confusing and should not be used to guide treatment selections. [2]
- The European Society of Cardiology (ESC) uses a similar classification scheme released in its 2010 guidelines. The ESC enclosed one supplementary categorization, Silent AF (asymptomatic), which may manifest as AF-associated complications like ischemic stroke or tachycardiomyopathy, or is diagnosed incidentally on electrocardiography (ECG). Any type of AF can be silent or asymptomatic. [27]

Etiology of Atrial Fibrillation

AF is strongly related to the following risk factors**:** [31, 32, 33]

Hemodynamic stress

When the intra-atrial pressure rises it causes atrial electrical and structural remodeling and predisposes to AF. Mitral or tricuspid valve disease and left ventricular dysfunction are the commonest causes of raised atrial pressure. Systemic or pulmonary hypertension similarly usually predisposes to atrial pressure overload, and intracardiac tumors or thrombi are rare causes**.** [31]

Atrial ischemia

CAD occasionally directly causes atrial ischemia and AF. More usually, severe ventricular ischemia causes raised intra-atrial pressure and AF**.** [31]

Inflammation

Myocarditis and pericarditis may be idiopathic or can take place in association with collagen vascular diseases; viral or bacterial infections; or cardiac, esophageal, or thoracic surgery**.** [31]

Non-cardiovascular respiratory causes

Pulmonary embolism, pneumonia, lung cancer, and hypothermia have been related to AF**.** [31]

Drug and alcohol use

Stimulants, alcohol, and cocaine may initiate AF. Acute or chronic alcohol consumption (i.e., holiday or Saturday night heart, also known as alcohol-related cardiomyopathy) illicit drug use (i.e., stimulants, methamphetamines, cocaine) are found to be specifically associated with AF. Whereas the association of over moderate chronic alcohol consumption and AF has been formerly reported in multiple studies, a community-based study found a connotation between even moderate alcohol consumption and an increased risk of AF. [32, 33]

Endocrine disorders

Hyperthyroidism, diabetes, and pheochromocytoma are related to AF**.** [31]

Neurologic disorders

Intracranial processes as subarachnoid hemorrhage or stroke may precipitate AF**.** [31]

Familial AF

A history of parental AF appears to confer increased liability of AF (and occasional family pedigrees of AF are related to definite ion channel abnormalities, particularly sodium channels). [56] One cohort study suggests that familial AF is related to an increased risk of AF. This increase was not reduced by alteration for genetic variants and further AF risk factors. [34]

Advancing age

AF is strongly age-dependent, affecting 4% of persons older than sixty years of age and 8% of persons older than eighty years of age. Nearly 25% of people aged forty years and older may develop AF in their lifetime. [31]

Other

In a 15-year prospective cohort study of 132,250 Japanese subjects, Xu *et al*. found that an increased risk of new-onset AF has been related anemia and chronic kidney disease (CKD), alone and in combination. [58, 59] Throughout a mean follow-up of 13.8 years in 1232 patients with new-onset AF, multivariate analysis showed that those with an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m2 were 2.56 times more expected to develop new-onset AF compared with patients with normal kidney function; patients with lower hemoglobin levels than 13 g/dL had a 1.5 times increased risk of new-onset AF compared with patients with normal hemoglobin levels ($P < 0.0001$ for both analyses). [35, 36] Patients with both CKD and anemia had a threefold higher incidence of AF. [36]

Epidemic characteristics

Morbidity of CAD combined with AF

In the past four decades, it has been established that patients with CAD are more susceptible to develop AF than the common population, and vice versa. In the Framingham Study, CAD doubled the frequency of many types of AF among men and quadrupled the risk of transient AF among women [37]. The incidences of AF vary among different types of CAD, regions and various monitoring methods but are higher than those in normal individuals, ranging from 4.1% to 58%. [38]

However, AF was an independent predictor and directed a 2.2 times higher probability of new coronary events [38]. According to the REGARDS study, the rate of MI was approximately 2-fold higher in patients with AF [39] **.(** This association is mainly notable in women and black individuals [38]. To be accurate, the incidence of CAD in patients with AF was as high as 34% [38]. To make things worse, patients with CAD and AF together tend to have worse outcomes**,** including higher complication rates and mortality [38], regardless of the type of CAD and AF. It has been detected that new onset AF (NOAF) following acute MI possibly had the worst prognosis [38]

Coronary lesions and AF

The lesions and severity of CAD are also associated with the existence of AF. Some studies have found a substantial correlation between infarction or lesions within the right coronary artery (RCA) and NOAF [**40**, **41**, 42]. On the other hand, numerous studies have point out that patients with NOAF are more expected to have left main CAD [40, 43, 44].

At the same time, some studies have indicated that patients with AF are more likely to have coronary lesions [42-46]. Nucifora *et al*. [46] detected coronary atherosclerosis and obstructive CAD (≥50% luminal narrowing) more frequent in AF patients, and the lesions were more common within the left main or proximal left anterior descending artery**.** Patients with both AF and chronic coronary syndrome (CCS) are more likely to present with one-vessel lesions, which are more often detected in the RCA. However, no study has illustrated coronary lesions in patients with AF and acute coronary syndrome (ACS). [40]

Pathophysiology of CAD and AF

CAD is a class of diseases referring to the development of atherosclerotic plaques in the coronary arteries, resulting in intraluminal stenosis. According to different clinical presentations, CAD may be classified into ACS and CCS. Once the cardiac load increases, the myocardial blood supply cannot satisfy the demand owing to stenosis**,** leading to myocardial ischemia, the main cause of CCS [38]. If the plaques rupture or are eroded, plaque fragments or secondary thrombosis may partially or completely block the vessels, causing MI, that is the leading cause of ACS pathogenesis [38]. Although the precise mechanisms of AF remain uncertain, generally accepted hypotheses for pathophysiological progression are reentry and focal ectopic activity [38] **.**Reentry is favored by three factors. First, short refractory period aids cardiac myocytes to recover from depolarization and preserve activity. Second, slow conduction, resulting from fibrosis, abnormal connexins or decreased Na+ current [38] INa, contributes to the formation of circuits by creating barriers or permitting recovery [38]. Third, structural remodeling, such as atrium dilation, will increase vulnerability to AF by prolonging the conduction pathway or containing more circuits [38] **.** On the other hand, focal ectopic activity can be induced by enhanced automaticity, early after-depolarizations (EADs) caused by prolonged action potential duration (APD), and delayed after-depolarizations (DADs) triggered by diastolic calcium (Ca2+) release [47]. A review also illustrated that autonomic nervous system distribution changes can act on cardiomyocyte ion channel functions and affect electrical remodeling [48].

Common risk factors

CAD has several recognized risk factors, including hypertension, obesity, high cholesterol, diabetes mellitus (DM), smoking, age and reduced physical activity [38] Obstructive sleep apnea (OSA) is also a dependent risk factor for CAD [38]**.** Interestingly, the most frequent concomitant conditions with AF are hypertension, DM, and chronic pulmonary disease as well [38]. Additionally, there are other factors contributing to AF, such as OSA, coronary artery disease, obesity and age [38].

Hypertension

A history of hypertension will increase the risk of AF by 34% [38]. The mechanisms of AF in hypertension are very complex, associated with various underlying processes in hypertension [38]. Hypertension directly enforces the left ventricle, additionally leading to progressive thickening of the ventricular wall and left ventricular hypertrophy (LVH). Stiffness of the ventricle, as a result of LVH, will develop and progress to diastolic dysfunction, which can induce atrial enlargement and atrial cardiomyopathy [38]. Besides these structural changes, inflammation and the renin-angiotensin-aldosterone system (RAAS) are also involved in the creation of reentry [38]. For the former, various mediators of inflammation, such as tumor necrosis factor α (TNF-α), may modulate cardiac myocyte apoptosis and the activation of fibrotic pathways, which participate in structural remodeling of the atria [49, 50]. Furthermore, inflammation also changes the expression of connexins. Overexpression of TNF-α may decrease the levels of connexin in the atria, leading to heterogeneous conduction [50]. For the latter, angiotensin II (Ang II) may promote myocardial fibrosis by acting on Ang II type 1 receptor (AT1R) [50], shorten the atrial effective refractory period (AERP) and decrease INa in myocytes**,** supporting

reentry formation [48]. It has also been reported that abnormal Ca2+ handling in hypertension may generate focal ectopic activity [51]. Inflammation and RAAS are also involved in this process**.** TNF-α can regulate Ca2+ homeostasis, which contributes to the development of triggers [51]. It has been confirmed that Ang II prolongs APD and increases the frequency of spontaneous Ca2+ sparks and Ca2+ transients, increasing the frequency of automatic contractile activity in cardiac myocytes [48]. All of these pathophysiological alterations caused by Ang II are partially or completely regulated by the transcription factor ETV1 (E twenty-six variant 1) [52]. ETV1 deletion reduces the arrhythmogenic effects of Ang II. [52]

Diabetes mellitus

DM and poor glycemic control are unconventionally related to AF, which is positively correlated with HbA1c levels as well [38]. Patients with DM frequently have other associated metabolic diseases, such as hypertension and obesity. Conversely, DM is independently related to AF after adjustment, showing that hyperglycemia can directly stimulate this disease**.** [38]. In patients with DM, the leading structural alteration in AF is fibrosis induced by oxidative stress, inflammation, advanced glycation end products (AGEs) and AGE receptors (RAGEs) (the AGERAGE system) [51] ·At the same time, connexin changes, decreased INa and increased AERP dispersion have been detected, which favor reentry formation [38]. In contrast, focal ectopic activity can be created by prolonged APD and increased Ca2+ current in DM models [52]. Also, insulin resistance is the main pathological change in DM, which increases vulnerability to AF as well [51]. This process includes the down-regulation of the glucose transporter, prolonged APD and decreased INa in cardiac myocytes. Insulin therapy can decrease the susceptibility and duration of AF [51] **.**There are also autonomic dysfunction and ion channel changes in DM processing in the development of AF [38]. Notably, hyperglycemia can damage the heart and induce diabetic heart disease, which involves many pathophysiological changes, as interstitial fibrosis and cardiomyopathy [38], leading to heart dysfunction and promote AF aggravation.[38]

Dyslipidemia

Conversely, the role of dyslipidemia in the etiology of AF still indeterminate [38]. Based on the ARIC study, lower levels of low-density lipoprotein cholesterol (LDLc) and total cholesterol (TC) were related to a higher risk of AF [38]. The Framingham study revealed that high levels of high-density lipoprotein cholesterol (HDLc) and low levels of triglyceride were as well associated with lower risk of AF [**38**]. The principal mechanisms between dyslipidemia and AF are indeterminate. First, HDLc can lower the risk of AF indirectly by preventing CAD [**38**]. Furthermore, HDLc has anti-inflammatory and antioxidant properties, theoretically preventing pathophysiological changes in AF [38]. Nevertheless, thyroid hormones may explain the reverse relationship of AF with LDLc or TC. High levels of thyroid hormones are related to a high rate of AF. Thyroid hormones can up regulate the catabolism of cholesterol in the liver and stimulate LDL receptors, leading to reduced LDLc and TC levels [38]. Moreover, cholesterol modifies the distribution and function of specific ion channels in vitro, such as the Kv1.5 potassium channel, which can be involved in the existence of AF [38]. A review concluded that very LDLc might contribute to reentry formation by reducing action potentials, delaying conduction velocities and modifying gap junctions, supporting structural changes in the atrium and eventually leading to AF [38].

Obesity

Obesity and overweight are risk factors for AF, with an approximately 3% to 4% increase in AF risk per 1 kg/m2 [38]. Obesity, as a metabolic risk factor, usually has other comorbidities that may be involved in AF development [38]. In addition**,** obesity is a stage of inflammation. Inflammatory cells in obesity are in a pro-inflammatory state, secreting cytokines, such as tumor necrosis factor-α (TNF-α)**,** interleukin-6 (IL-6) and C-reactive protein (CRP) [38], which aggravate AF**.** Another mechanism underlying obesity with AF is the role of pericardial fat**.** Pericardial fat can affect the atrial myocardium, leading to fibrosis and unstable electrophysiology [53].

Atrial fibrillation (AF) and chronic coronary syndrome

AF and Chronic coronary syndrome (CCS) share common risk factors. [53] In addition**,** inflammation plays a causative role in those diseases. [38] Atrial fibrosis due to atrial ischemia and elevated left atrial filling pressures also link AF and CCS. [38] Moreover, CCS accompanied by unhealthy lifestyle and risk factors may lead to atrial remodeling / cardiomyopathy and AF. However, it is unclear whether coronary artery disease is the precursor for AF, or whether they have the same causal pathway. [38]

Patients with angina and non-obstructive coronary lesions seem to have an increased risk of adverse clinical events. [38] They also tend to be underdiagnosed and undertreated. Moreover**,** they undergo numerous diagnostic tests with repeated coronary computed tomography angiography (CTA) or invasive coronary angiography (ICA), which may contribute to elevated healthcare costs. [38] Unfortunately, some difficulties with qualifying AF patients for invasive evaluation of CCS are evident. A significant discrepancy between findings associated with coronary anatomy, the results of noninvasive tests and chest pain accompanied by ST-segment depression and marginally elevated biomarkers of myocardial injury may mimic coronary artery disease.[38] Suboptimal ventricular rate control during AF may worsen symptoms of myocardial ischemia.[38] However, no strong association was showed between transient ischemic-type ST-segment depression during episodes of AF and underlying occult CCS.[53]

Some studies [54-57] demonstrated that AF episode induces an increase in coronary flow inadequate to meet myocardial oxygen demand, as well as an exaggerated drop in coronary vascular resistance. In addition, coronary vasoconstriction may be responsible for obstruction of coronary blood flow. [54]

In one study,[56] patients older than 40 years with AF of recent onset and temporary ischemic-type ST-segment depression who had no history of coronary artery disease, other cardiac disorders or severe comorbidities were assessed. Intima-media thickness of 0.93 mm or greater and high-sensitivity C-reactive protein of 4.65 mg/l or greater were predictors of obstructive coronary artery disease in those patients**.** [55]

In the issue of Polish Archives of Internal Medicine (Pol Arch Intern Med), Tomaszuk-Kazberuk *et al.* showed findings regarding whether a history of AF is related to the absence of significant coronary lesions on coronary angiography. **[56]**

The authors presented data from one tertiary center and analyzed retrospectively data of 8288 patients admitted for coronary angiography because of exacerbated angina from 2007 to 2016. They concluded that in patients qualified for invasive CCS diagnostic workup, AF was associated with the absence of significant coronary lesions on angiography and less common need of revascularization. Diagnostic difficulties included multiple factors, such as: symptoms of AF imitate CCS, ischemic changes on electrocardiogram during AF suboptimally predict obstructive CCS**,** stress tests are infrequently performed in AF patients**,** and rapid rhythm is associated with difficulties in the interpretation of coronary CTA findings**.** [56]

In one study, [57] coronary artery calcium tended to be highly prevalent in patients with AF, irrespective of major cardiovascular risk factors and gender. The innovative program to evaluate the coronary artery calcium from CTA, which was used in the above study, provided optimal image quality for coronary artery calcium assessment in 96% of the cases. This method also reduced the need for additional imaging and minimized the radiation hazard for patients. [57]

The available common noninvasive methods evaluating ischemia rely on detection of substantial regional differences in wall motion in epicardial perfusion territories or left ventricular perfusion (i.e., dobutamine stress echocardiography. (If ischemia is associated with the whole left ventricle**,** these techniques are ineffective. [38] Despite the constant progress in medicine, there is no method which allows a direct anatomical imaging of the coronary microcirculation *in vivo* in humans. As a consequence, patients with AF and CAD may be sometimes not correctly diagnosed which, in turn, may lead to repeated hospitalizations and unnecessary coronary angiography. [38]

Conclusion

AF and CAD are strongly related, as they have many common risk factors such as, hypertension, diabetes mellitus, heart failure, obesity, obstructive sleep apnea, renal failure and thyroid disease. They also have common pathophysiological mechanisms. farther more they aggravate each other and can form a vicious circle of significant morbidities and mortalities. Special care of the patients with these diseases should be established.

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