

Atrial Fibrillation and Metabolic Syndrome: Understanding the Connection

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Abstract

Metabolic syndrome, a constellation of conditions including obesity, dyslipidemia, hypertension and insulin resistance, has increased to epidemic proportions. Metabolic syndrome has been recognized as a risk factor for cardiovascular morbidity and is likely related to the epidemic of cardiovascular diseases. Perhaps not coincidentally, its growth in incidence has paralleled that of atrial fibrillation. Various components of metabolic syndrome have been known to have a role in the pathogenesis of atrial fibrillation. With the conglomeration of components seen in the metabolic syndrome, the risk for atrial fibrillation increases greatly. Several studies have elucidated the role of metabolic syndrome in the development of atrial fibrillation. Its role on the atrial substrate makes it an important determinant of progression of disease and failure of therapeutic strategies such as catheter ablation. Control of the various components of metabolic syndrome may ultimately lead to better outcomes in atrial fibrillation patients.

Introduction

Atrial fibrillation (AF), already the most common arrhythmia worldwide, continues its growth to epidemic proportions.^{1,2} Perhaps not coincidentally, the conglomeration of insulin resistance, hypertension, dyslipidemia, and obesity known as the metabolic syndrome (MS) also has grown in prevalence to epidemic proportions, particularly in the adult U.S. population.³ The association of AF with an increased risk for stroke⁴ and mortality is well known.^{5,6} However, the association of MS with cardiovascular disease is now becoming more evident.^{7,8} The MS has been associated with increased prevalence of coronary heart disease and cerebrovascular disease.^{7,9} It has also been associated with worsened coronary heart disease outcomes and cardiovascular mortality.⁷ More recently, a body of evidence has linked the MS with both the incidence of AF and outcomes of management of AF. In this

review, we present the evidence and potential underpinnings of this convergence of epidemics.

Definition of the MS

The American Heart Association / National Heart, Lung, and Blood Institute (AHA/NHLBI) 2005 scientific statement¹⁰ defined the metabolic syndrome as the presence of at least three of the following criteria:

- Waist circumference greater than or equal to 40 inches (102 cm) in men or 35 inches (88cm) in women
- Triglycerides greater than or equal to 150 mg/dl (1.7 mmol/L) or on drug treatment for elevated triglycerides
- High density lipoprotein (HDL) cholesterol less than 40 mg/dL (1.03 mmol/L) in men or 50 mg/dL (1.3 mmol/L) in women or on drug treatment for

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reduced HDL

- Systolic blood pressure greater than or equal to 130 mmHg or diastolic blood pressure greater than or equal to 85 mmHg or on antihypertensive drug treatment in a patient with a history of hypertension
- Fasting glucose greater than or equal to 100 mg/dL or on drug treatment for elevated glucose

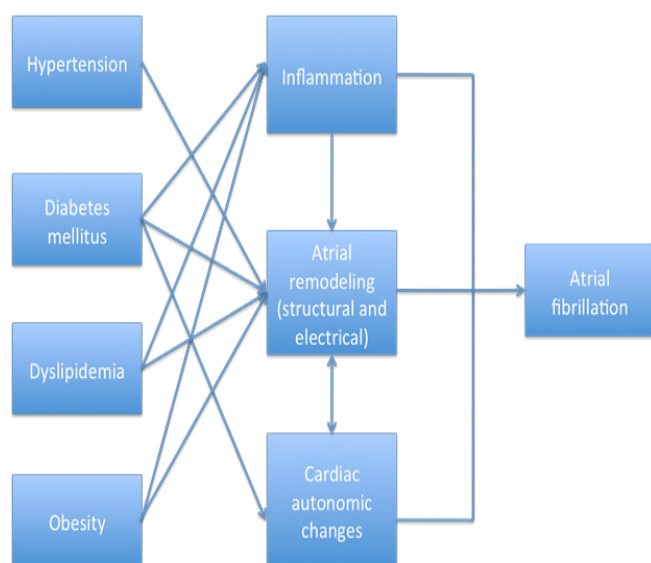
Based on the more conservative ATP III definition (fasting glucose \geq 110 mg/dL), the age-adjusted U.S. prevalence of MS was 24% with Mexican Americans having the highest prevalence overall (32%).¹¹ Prevalence increases with age such that those over 60 have an astounding 44% prevalence of MS.¹¹ Based on 2000 census data, nearly 50 million U.S. residents have the metabolic syndrome and its prevalence is only increasing with time.

The simultaneous epidemic of AF in the U.S. and worldwide populations prompts one to consider whether the two may be linked. There are several hypothetical reasons why this may be the case.

Why Could MS Lead to AF?

Various components of the MS are known risk factors for AF. These factors have been hypothesized to be involved in the pathogenesis of AF by various mechanisms (Figure 1). However, recent stud-

Figure: Factors Involved in the Pathogenesis of Atrial Fibrillation



This figure summarizes the pathogenetic mechanisms for atrial fibrillation of the various components of the metabolic syndrome. Note the multiple effects of each component of metabolic syndrome.

ies have shown that all these components of the MS together may have an additive effect on the risk for AF.¹²

According to our current understanding, the pathogenesis of AF involves a complex interplay of AF triggers and abnormal atrial substrate required to sustain the arrhythmia. Various components of the MS may act as risk factors for AF by their effect on AF triggers or the atrial substrate. Below we review the potential mechanisms for the MS components in the causation of AF.

Hypertension

Hypertension is the commonest modifiable risk factor for AF.¹³ It is seen in almost 60% of patients with AF.¹⁴⁻¹⁶ Hypertension leads to left ventricular hypertrophy and diastolic dysfunction resulting in pathological remodeling of the left atrium predisposing to AF. Diastolic dysfunction results in left atrial stretching or enlargement,¹⁷ important to the pathogenesis of AF.¹⁸ In animal models, hypertension has also been shown to induce structural changes including interstitial fibrosis.¹⁹⁻²¹ In addition to mechanical remodeling and left atrial enlargement, electrical remodeling of the left atrium is known to occur with longstanding hypertension.²² Global and regional conduction delays are seen in patients with longstanding systemic hypertension.²² Moreover, changes in angiotensin II level leads to electrophysiological changes in the left atrial myocardium causing left atrial conduction delay.²³

Insulin Resistance / Diabetes

Insulin resistance and diabetes are another risk factor associated with the development of AF. The Framingham Heart Study clearly established diabetes mellitus and glucose intolerance as a potential risk factor for AF.¹³ Mechanistically diabetes mellitus predisposes to AF in a way similar to hypertension. Diabetes mellitus leads to left ventricular hypertrophy and diastolic dysfunction,²⁴ leading to mechanical and electrical remodeling of the atrium.²⁵ Apart from left ventricular hypertrophy and diastolic function, many other mechanisms of atrial remodeling in diabetes mellitus have been suggested based on animal experiments. Advanced glycation end-products (AGEs) and receptors for AGEs (RAGE) have been known to cause

interstitial scarring in the left atrium.^{26,27} Angiotensin II blockers are known to prevent anatomic and electrical remodeling likely by blocking AGE-RAGE.²⁸ In addition to structural remodeling, the atria of diabetic animals also demonstrate increased intra-atrial conduction time providing the electrical substrate for AF. Diabetes mellitus and the MS affect the cardiac autonomic system, which may contribute to arrhythmogenicity.^{29,30} Finally, diabetes mellitus may lead to ischemic or non-ischemic cardiomyopathy also predisposing to AF through the resultant left atrial enlargement.

Dyslipidemia

Hypertriglyceridemia and low HDL-cholesterolemia are the lipid disorders seen with metabolic syndrome. Low HDL-cholesterol, has been found to increase the risk of AF by 20-40%.^{15,31,32} However, data for hypertriglyceridemia are inconsistent. Proposed mechanisms of predisposition to AF due to the dyslipidemia are arrhythmogenicity due to altered membrane composition leading to altered excitability³³ as well as pro-inflammatory effects.³⁴

Obesity

Obesity is an important component of the MS and is known to be associated with an increased risk for AF. Data from the Framingham heart study showed an increased risk of new-onset AF for obesity (BMI \geq 30) with an adjusted hazard ratio of 1.52 and 1.46 for men and women respectively compared to subjects with normal BMI.³⁵ A meta-analysis of 16 studies found a 49% increased risk of obese patients developing AF as compared to non-obese patients.³⁶ The role of obesity has been explained by multiple mechanisms. Obesity is a risk factor for insulin resistance and diabetes mellitus and hence is a potential pathway for predisposition to AF. A direct correlation has been seen between increasing BMI and left atrial size.³⁷ Left atrial enlargement may be the most important mechanism through which obesity increases the risk of AF, since after adjusting for left atrial enlargement obesity is no longer a risk factor for atrial fibrillation in the Framingham Heart Study cohort.³⁵ However, other mechanisms which have been suggested include the systemic inflam-

matory state seen with obesity. Inflammation is known to be a risk factor for AF³⁸ and obese patients are known to have elevated hsCRP levels, a marker of systemic inflammation.³⁹ Another factor which may predispose to AF in patients with obesity is obstructive sleep apnea, a well described risk factor for AF.⁴⁰⁻⁴²

All Together is Worse?

It is apparent that various components of MS predispose to AF in isolation. However, the combination of these components seen in the metabolic syndrome may act in a synergistic manner (Figure 1). The final common pathway in the pathogenesis of AF can be grouped as atrial structural and electrical remodeling, inflammatory processes, and cardiac autonomic changes.

Atrial structural and electrical remodeling is of paramount importance in providing the substrate for initiation and maintenance of AF. As described above, various components of MS cause atrial remodeling. Structural remodeling with interstitial fibrosis leads to heterogeneous electrical substrate with differences in conduction velocities promoting AF.⁴³ Fibroblasts in these areas of interstitial fibrosis may couple with cardiomyocytes electrically and promote reentry and ectopic activity.⁴⁴ Electrical remodeling alters ion channel function and calcium handling of the cells and promotes initiation and maintenance of atrial fibrillation.⁴⁵

The cardiac autonomic nervous system is important in the pathogenesis of AF.⁴⁶ Vagal discharge,⁴⁷ beta-adrenoceptor activation⁴⁸ and atrial sympathetic hyperinnervation⁴⁹ have been implicated in the arrhythmogenesis of AF. Autonomic dysfunction is known to be associated with metabolic syndrome and has been shown to get worse with increasing number of MS factors present.⁵⁰

Inflammation is considered one of the basic pathophysiological substrates in the causation and progression of AF. Atrial inflammation has been seen in the histological specimens of lone AF patients as opposed to patients with sinus rhythm.⁵¹ Inflammation provides an anatomic and electrical substrate for AF. A vast body of evidence supporting the inflammation hypothesis of atrial fibrillation comes from studies of inflammatory biomarkers.³⁸

Moreover, inflammation has a role in early recurrence of atrial fibrillation after catheter ablation.⁵² As previously discussed, several components of the MS (obesity, insulin resistance, dyslipidemia) have been shown to be proinflammatory.

Thus, various components of MS are known to affect these pathogenetic factors of AF. As these factors are affected by multiple components of MS, their role in the pathogenesis of AF becomes additive and complex. Recent studies have looked at the MS as a whole and the risk of AF.⁵³⁻⁵⁶ It has been shown that as the number of components of AF increases, the risk of development of AF goes up.^{53, 57} The fact that AF is one of the important cardiovascular effects of metabolic syndrome has more recently been brought to notice by the studies detailed below.

Increased Incidence of AF with MS

Several population-based studies have demonstrated the increased risk of incident AF among patients with the metabolic syndrome (Table 1). Umetani et al analyzed 592 hospitalized patients without structural heart disease. Among 21% of patients with metabolic syndrome, AF occurred in 9% compared with 4% of those without metabolic syndrome. In multivariable analyses, the OR for AF with metabolic syndrome was 2.8.⁵⁴ Watanabe et al studied 28,449 participants with-

out baseline AF in the Niigata preventive medicine community-based study. The metabolic syndrome was present in 13% of participants. During a mean follow-up of 4.5 years, AF developed in 265 participants. The HR for AF among participants with MS, compared to those without MS, was 1.78.⁵⁵ Chamberlain et al analyzed the risk of AF in the Atherosclerosis Risk in Communities (ARIC) Study. Among 15,094 participants over a mean follow-up of 15.4 years, there were 1238 cases of incident AF. At baseline, 46% of black and 40% of white participants had the metabolic syndrome. The HR for AF among participants with, compared to those without, the metabolic syndrome was 1.67 and did not differ by race. In addition, the risk for incident AF increased with increasing number of MS components such that those with all 5 components had a HR of 4.4 compared to those with no components.¹² Echahidi et al analyzed the risk of post-operative AF after coronary artery bypass surgery among 5085 patients. Metabolic syndrome was present in 46% of patients and post-operative AF occurred in 27%. Among patients ≤ 50 years old, MS was associated with a RR of 2.4 with development of post-operative AF.⁵⁸ Vyssoulis et al studied a population of over 15,000 patients with hypertension. The prevalence of MS ranged from 32% to 48%, depending on the definition used. The odds of having AF in those with MS ranged from 1.61 to 1.99. Importantly, the prevalence of AF increased with each additional component of the MS. Altieri et al

Table 1 Studies Showing Association of Atrial Fibrillation with Metabolic Syndrome

Author, year	No. of patients	Findings
Umetani et al., 2007 ⁷¹	592	21% of hospitalized patients with MS; incident AF occurred more frequently in patients with MS (9% vs. 4%, OR 2.8)
Watanabe et al., 2008 ⁷²	28,449	13% had MS. After a follow up of 4.5 years, subjects with MS at baseline were more likely to develop AF (HR 1.78)
Chamberlain et al, (ARIC study) ³¹	15,094	41% of participants had MS at baseline, HR for development of AF was 1.67 with MS. Risk for incidence of AF increased with increasing number of components of MS
Echahidi et al, ⁵⁸	5085	MS was present in 46% of patients post CABG and 27% developed post-operative AF. RR of AF 2.4 with MS
Vyssoulis et al, ⁵⁷	15,075	MS associated with presence of AF in patients with hypertension (odds ratio 1.61 to 1.99 depending on the definition of MS used). Prevalence of AF increased with number components of MS
Altieri et al, ⁵⁹	173	MS was present in 16% of patients with metabolic syndrome
Liu et al, ⁷³	972	Higher incidence of AF in hypertensive patients with MS than in them without MS (OR 1.853, 12.84% vs. 6.93%)
Tang et al, ⁷⁴	741	46.3% of patients without structural heart disease coming for catheter ablation of AF had MS

demonstrated a high incidence of AF (16%) in a population of Hispanic patients with metabolic syndrome.⁵⁹ The authors suggested mechanisms of this association may include sinus node remodeling, atrial fibrosis, and older age which are all seen in a population with MS.

Worsened Outcomes of AF Treatment with MS

Atrial fibrillation is a progressive disease and various etiological factors provide substrate for its initiation as well as maintenance and progression. Hence patients with MS continue to develop substrate for AF even after treatment and are likely to have worsened outcomes (Table 2). Multiple studies have suggested that MS may influence the outcome of catheter ablation therapy. In a large prospective study of catheter ablation of AF, 1496 patients were followed up for a mean of 21 months. Patients with MS had a 39% recurrence rate compared to 32% for patients without MS ($p = 0.005$).⁶⁰ A study by Chang et al.⁶¹ from Taiwan enrolled 282 patients undergoing catheter ablation for AF. The authors found a higher incidence of recurrent AF in patients with MS (55% vs. 24%, $p < 0.001$). Notably, it was more common to see recurrent atrial fibrillation originating from non-pulmonary vein sites in patients with MS (45% vs. 20%, $p=0.037$), suggesting an effect of MS on left atrial substrate. In an analysis of predictors of late recurrence of AF after catheter ablation by Cai et al., MS was an independent predictor of late recurrence (OR = 4.41, 95% CI 1.56-12.46, $p = 0.005$).⁶² Berkowitsch et al reported the results of pulmonary vein isolation in patients with AF

with either cryo-balloon or by circumferential pulmonary vein isolation with radiofrequency catheter ablation in 702 consecutive patients with AF. The presence of MS was independently associated with a higher risk of recurrent AF (46.4% in patients with MS vs. 56.8% among patients without MS, $p = 0.006$) over 15.6 (inter-quartile range 12.7-42.3) months.⁶³

What Can be Done?

Altered anatomic and electrical substrate is a major factor in the progression of AF and has an adverse effect on outcomes of medical and catheter ablation therapy. Atrial fibrillation is known to promote the structural and electrical remodeling of the atria and control of AF by medical therapy or catheter ablation should have a favorable effect on the substrate. However, evidence suggests that risk factors for AF such as MS have a direct effect on the creation and promotion of the arrhythmogenic substrate. Hence, control of these risk factors by optimum intervention may potentially slow the progression of the remodeling process. Data suggests that optimal control of blood pressure, maintenance of ideal body weight, control of lipid disorders and intervention for insulin resistance would help to control the arrhythmogenic substrate.

Reduction in the risk of atrial fibrillation with treatment of hypertension has been well documented in various studies of antihypertensive therapy for hypertension. A meta-analysis of treatment of hypertension using renin-angiotensin system inhibitors showed a reduction in the relative risk of

Table 2 Studies Showing Increased Risk of Recurrent Atrial Fibrillation after Catheter Ablation in patients with Metabolic Syndrome

Author, year	No of patients	Findings
Mohanty et al., 2012 ⁶⁰	1496; 485 with MS	Higher recurrence rate of AF after catheter ablation in patients with MS (39% vs. 32%, $p=0.005$; mean follow up 21 months). No difference in subgroup with paroxysmal AF
Tang et al., 2009 ⁷⁵	654; 323 with MS	Patients with MS post catheter ablation had higher rate of recurrence (43.7% vs. 30.5%, $p<0.001$; mean follow up of 470 days)
Chang et al., 2009 ⁶¹	282; 53 with MS	Higher rate of recurrence of AF after catheter ablation in patients with MS (45% vs. 24%, $p=0.037$)
Cai et al., 2011 ⁶²	186; 61 with MS	Metabolic syndrome was an independent predictor of late recurrence of AF (OR 4.41, 95% CI 1.56-12.46, $p=0.005$) after catheter ablation along with obesity, procedural failure and early recurrence of atrial fibrillation
Berkowitsch et al., 2012 ⁶³	702; 276 with MS	Recurrence of AF after catheter ablation higher in patients with MS (56.4% vs 46.4%)

atrial fibrillation by 15-40%, however this benefit was limited to patients with left ventricular systolic dysfunction or left ventricular hypertrophy.⁶⁴ Other meta-analyses of studies using ARBs and ACEIs showed similar reduction in new onset atrial fibrillation as well better outcome with electrical cardioversion and lower recurrence later.^{65,66}

Control of diabetes mellitus with treatment reduced the risk of atrial fibrillation in a large study.⁶⁷ Another study showed the reduction of risk of atrial fibrillation recurrence after catheter ablation in patients with diabetes mellitus and insulin resistance with the use of pioglitazone.⁶⁸ Use of lipid lowering drugs like statins has been shown to reduce the risk of atrial fibrillation.^{69,70} However, use of pioglitazone or statin may reduce the risk of atrial fibrillation through their direct effect on inflammatory process rather than their effect on insulin resistance or dyslipidemia. Similarly, control of obesity may affect atrial fibrillation indirectly by its effect on insulin resistance and obstructive sleep apnea.

The above account suggests that those factors involved in the pathogenesis of AF work in an interactive manner. Therapeutic interventions have pleiotropic effect and their action on reduction of AF risk is frequently through multiple effects. Further evidence supporting the benefit of treatment for MS as a whole in reducing AF outcomes will improve our understanding in this area.

Conclusions

Metabolic syndrome, a constellation of associated conditions, has increased to epidemic proportions. It has been recognized as a risk factor for cardiovascular morbidity and is likely related to the epidemic of cardiovascular diseases. Recently it has been recognized that atrial fibrillation may be associated with the ongoing epidemic of metabolic syndrome. Various components of metabolic syndrome have been known to have a role in pathogenesis of atrial fibrillation. Recent studies have elucidated the role of metabolic syndrome in the causation of atrial fibrillation. Its role on the atrial substrate makes it an important determinant of progression of disease and failure of therapeutic strategies such as catheter ablation. Control of the various components of

metabolic syndrome may ultimately lead to better outcomes in AF patients.

Disclosures

No disclosures relevant to this article were made by the authors.

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