

## Atrial Fibrillation and Metabolic Syndrome: Correlation or Simple Coincidence?

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### Abstract

**Background:** The atrial fibrillation (AF) is the iperkinetic arrhythmia most frequently encountered in the general population. Metabolic Syndrome (MS) is a condition characterized by a set of cardiovascular risk factors that include: abdominal obesity, hypertension, impaired fast glucose, elevated tryglicerides and low HDL-C. We set out to analyze the impact of the MS has on our population looking to explain the reasons for the possible correlation with AF.

**Methods:** MS was defined according to the definition of the guidelines of NCEP-ATP III. 350 patients were enrolled in the Department of Cardiology of our University Polyclinic of Palermo. Among these patients, 149 (42.57%) had Paroxysmal Atrial Fibrillation (PAF) and 201 (57.42%) had Chronic Atrial Fibrillation (CAF). We had two groups, the first 170 patients (48.57%) with AF and MS, and the second 180 patients (51.42%) with AF but without MS.

**Results:** In our population, there is not a significant difference in the prevalence of hypertension between group with MS and group without MS ( $p=0.52$ ), while there is a significant difference in prevalence between the two groups in relation to other variables as overweight/obesity, hyperglycemia, hypertryglicerydemia and low HDL-C ( $p<0.0001$ ).

**Conclusions:** Our results lead us to think that metabolic and hormonal disorder may be important in the pathogenesis of the CAF and in the maintenance of the arrhythmia, although by mechanisms not yet completely known. Inflammation and oxidative stress important for the MS have been proposed as etiologic factors also implicated in the pathogenesis of AF or at least maintaining.

**Keywords:** Metabolic syndrome; Atrial fibrillation; Obesity; Hypertension

### Introduction

Atrial Fibrillation (AF) and Metabolic Syndrome (MS) are two of the most common diseases that, as we know, affect western population, but that are also a frequent finding in oriental populations, once considered immune with these conditions of so-called "welfare" [1,2]. According to the ACC / AHA / ESC guidelines AF can be distinguished in paroxysmal (first onset or recurrent), persistent (first onset or recurrent) and permanent (chronic) [3]. AF does not represent only the hyperkinetic arrhythmia most frequently encountered, but gains importance especially for its hemodynamic and thromboembolic complications that frequently are combined with this rhythm disease, and which unfortunately are the causes of the high rates of morbidity and mortality encountered, and the causes of the high costs in terms of hospitalization (50% of costs) and drug therapy (20% of costs) for the system National Health Service.

The FIRE study (Italian multicenter observational study) has shown as AF affects on health care costs: in the observation period, AF has been the cause of 1, 5% of all access to the emergency department and 3.3% of all hospitalizations; 62% of patients presenting to the emergency room was then admitted to an internal medicine or cardiology department (41.7% of subjects were hospitalized in cardiac intensive or semi-intensive care units) [4]. The AF is fascinating for its really complex etiology, that includes not only electrophysiological reasons but inflammatory too, in fact an inflammatory focus may at times, but not always, be considered the "trigger" of arrhythmogenic events [5-8].

The MS, considered at the beginning as a metabolic disease, is becoming a cardiovascular disease, with severe morbidity and mortality. Today the most important classifications to define the MS are: the 1998 working definition of WHO (World Health Organization), then revised in '99 following the redefinition of the diagnostic criteria for hypertension [9] the operational definition NCEP-ATP III (National Cholesterol Education Program-Adult Treatment Panel III) of 2001,

that is the most reliable and it is most recently reaffirmed on Circulation on May 2010 [10]; the EGIR definition (European Group for the Study of Insulin Resistance) of 1999 [11]; the AACE definition (American Association of Clinical Endocrinologists) of 2003 [12]. As for AF, even for MS we were found in recent years a remarkable increase in prevalence, especially related to age and BMI increasing. The prevalence also changes depending on the classification used, remaining generally higher comparing the ATP III criteria to WHO ones. As far as the U.S. population, about 47 million of residents are affected by MS. The prevalence increases from 6.7% in the age group between 20-29 years to 43.5% in the age group between 60-69 years. In studies conducted in Europe, the estimates are generally lower, but not systematically [13-15]. The etiology of MS is largely unknown in its molecular mechanisms, but it certainly derives from a complex interaction between genetic, metabolic and environmental factors, including diet, having the insulin-resistance as a common pathogenic mechanism.

Although it can be assumed that insulin- resistance is the basic defect of this condition, the assessment of insulin resistance and the hyperinsulinemia are not between ATP III diagnostic criteria. The reason for this omission is that the quantitative measurement of insulin-resistance is difficult to apply in clinical practice. The importance of environmental factors in the pathogenesis of the metabolic syndrome is well defined. Consensually with the progressive

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decrease of physical activity, there is an increase in population prevalence of the metabolic syndrome. Obesity is the main driver of the metabolic syndrome, especially the visceral one (VAT). Any excess calories, that promote obesity, end up increasing the prevalence of the metabolic syndrome.

In fact, many of deviations that characterize metabolic syndrome, which, in turn, constitute the basic conditions underlying the expression of different phenotypic traits of the same syndrome (hypertension, lipid pattern, and so on) seem to follow an increase in adipose tissue [16-18]. However, opposed to the potential primary pathogenic role of obesity, remains the realization that not all patients with the metabolic syndrome are obese. MS is a condition substantially still reversible, at least as far as most of its components (hypertension, abnormal glucose and lipid patterns, etc.) if approached at an early age and in an energetic way, although it remains the result of a residual atherosclerotic damage caused by years of unrecognized insulin resistance and subclinical inflammation. According to the NCEP-ATP guidelines III, MS is diagnosed when at least three of the following criteria are present at the same time (Joint Statement Circulation, 2009) [19,20]:

1. Waist circumference >102 cm in men and >88 in women;
2. Hypertriglyceridemia (>150 mg/dl);
3. Low levels of HDL cholesterol (<40 mg / dl for men and <50 mg/dl for women);
4. Elevated blood pressure (systolic>130 mmHg diastolic >85 mmHg and/or history of antihypertensive therapy);
- 5) Glucose intolerance (fasting glucose>100 mg/dl) or diabetes mellitus type II.

Since this risk factors appear to be important for the establishment of AF, it has been suggested in recent years the possible association between the two conditions. It is seen that MS was associated with increased size of the left atrium and also with the arrhythmogenic substrate that are conditions that may increase the risk of recurrence of AF after ablation.

Among the different studies in order to clarify the presence or absence of a real correlation between the two diseases, the most important one is the 2008 study of the Niigata Preventive Medicine, published on *Circulation*. It is a large prospective study in which 28.449 subjects were enrolled [21]. Starting from these assumptions, we set out to analyze the impact that MS has on our population, while seeking to clarify the reasons for the possible correlation with the presence of AF.

## Materials and Methods

Our observational study is based on data from A.O.U. Policlinic University of Palermo, UOC Cardiology. We studied patients aged between 28 and 90 years with paroxysmal, persistent and chronic or permanent AF (CAF), defined on the basis of the classification guidelines adopted by the ACC/AHA/ESC 2006 for the treatment of patients with atrial fibrillation [22]. We also considered patients with paroxysmal and persistent AF in a unique group defined as PAF. We have enrolled 350 patients that have been subjected to a collection of anamnesis, physical examination, blood tests, and 12-lead ECG. It was subsequently performed an echocardiogram color doppler, in order to obtain information about the size of the atria and ventricles, the wall thickness, the ejection fraction and valve function.

Among the enrolled patients, 149 (42.57%) had PAF and 201 (57.42%) had CAF. The adopted exclusion criteria included other

causes of atrial fibrillation (for example, the IMA, the thyrotoxicosis or hiatal hernia) and the previous implantation of a pacemaker. The MS was defined according to the definitions of the National Cholesterol Educational Guidelines Program Third Adult Treatment Panel (NCEP-ATP III). The population consisted of 179 males (51.14%) and 171 women (48.85%). We obtained two sets of patients: a first group of 170 patients (48.57%) with AF and MS and a second group of 180 patients (51.42%) with AF without MS. The two groups were further subdivided according to the type of AF presented at the time of the enrollment (PAF and CAF).

## Results

In patients who had only atrial fibrillation (180 subjects, 51.42%), 77 (42.7%) had episodes of PAF, 103 (57.2%) had a history of CAF. In patients with the metabolic syndrome associated with atrial fibrillation (170 subjects, 48.57%), 62 patients (36.47%) had episodes of PAF and 108 (63.52%) had a history of CAF.

Analyzing the individual factors necessary for the diagnosis of metabolic syndrome related to the presence or absence of atrial fibrillation, it was observed in enrolled patients that:

- High blood pressure was found in 319 patients, of whom, 168 patients with metabolic syndrome and atrial fibrillation (93%) and 151 patients with only atrial fibrillation (88.8%). Among the 168 patients with AF and MS, 96 subjects had CAF (57%) and 72 had PAF (42.8%). Instead, in patients with AF alone, 81 presented CAF (53.6%) and 70 had PAF (46.3%).
- The hypertriglyceridemia was found in 100 patients, of whom, 87 patients with AF and MS (48.33%) and 13 patients with only atrial fibrillation (7.64%). Among the 87 patients with MS and AF, 48 presented CAF (55%) and 39 had PAF (44.8%). Instead, in patients with AF alone, 9 presented CAF (69%) and 4 had PAF (30%).
- Low HDL were found in 157 patients, of whom, 115 subjects with AF and MS (63.8%) and 42 with only AF (24.7%). Among the 115 patients with AF and MS, 65 presented CAF (56.5%), and 50 had PAF (43.4%). Instead, in patients with AF alone, 33 presented CAF (78.5%) and 9 had PAF (21.4%).
- High levels of fasting glucose or DM II were present in 190 patients, of whom, 136 patients with AF and MS (75.5%) and 54 with only atrial fibrillation (31.7%). Among the 136 patients with AF and MS, 83 presented CAF (61%) and 53 had PAF (39%). Instead, in patients with AF alone, 33 presented CAF (62%), and 21 PAF (38.8%).
- Obesity was found in 124 patients, of whom, 92 patients with AF and MS (74%) and 32 with only atrial fibrillation (25.8%). Among the 92 patients with AF and MS, 49 presented CAF (53%), and 43 had PAF (46.7%). Instead, in patients with AF alone, 21 (65%) presented CAF, and 11 had PAF (34%).

Moreover, the increase of left atrium size (>20 cmq) has been observed in 198 patients, 115 patients with atrial fibrillation and metabolic syndrome (63.8%) and 83 patients with only atrial fibrillation (48.8%). Among the 115 patients with AF and MS, 63 presented CAF (54.7%) and 52 had PAF (45%). Instead, in patients with AF alone, 54 presented CAF (65%) and 29 had PAF (35%). According to these data we can understand that type II diabetes mellitus and carbohydrate intolerance are the most common parameters, after hypertension, among the five criteria that identify the MS. Furthermore, we found a significant relationship between female sex and AF presence (in CAF

as in PAF,  $p > 0.009$ ), while the same correlation was not found in males ( $p = 0.93$ ).

The MS prevalence in patients with AF was significantly higher than the prevalence in the Italian population (32% vs. 18%,  $p < 0.0000001$ ). The analysis of our data shows that in our population there isn't a significant difference in the prevalence of hypertension between the two groups, with or without MS ( $p = 0.52$ ). However, there is a significant difference in prevalence between the two groups in relation to other considered variables as overweight/obesity, hyperglycemia, hypertriglyceridemia and low HDL cholesterol levels ( $p < 0.0001$ ).

Among the enrolled patients, we found 3 criteria of MS diagnosis in 10 subjects (70.5%), 4 criteria in 35 subjects (20.5%) and 5 criteria in 15 subjects (8.8%).

In addition it was found that the prevalence of MS appears to be significantly different between the two groups with PAF and CAF (36.47% vs. 63.52%,  $p = 0.001$ ). It was seen that the area of the left atrium was significantly higher in the group of patients with MS than in patients without MS ( $20 \pm 2$  vs.  $17 \pm 2$  cm<sup>2</sup>,  $p < 0.008$ ). Subgroup analysis showed that the area of the left atrium was also significantly higher in the group with AF and MS than in the group with AF alone, both in patients with PAF ( $20.1 \pm 2.5$  cm<sup>2</sup> vs.  $16.9 \pm 2$ , 1 cm<sup>2</sup>,  $p = 0.02$ ) and in patients with CAF ( $20 \pm 2$  cm<sup>2</sup> vs.  $16.5 \pm 2.4$  cm<sup>2</sup>,  $p = 0.03$ ).

## Discussion

In the last years the correlation between AF and SM has been investigated by several studies.

The study of Ken Umetani et al., published on *Circulation* in 2007, showed that in a follow-up on 592 patients, without apparent organic heart disease, the prevalence of new onset atrial fibrillation/atrial flutter was significantly higher (9%) in subjects with MS than in subjects without MS (4%) [23]. The study by Nguyen and Benditt, published on *Circulation* in 2008 and conducted in Japan on a large cohort (28,000 patients), showed a correlation between MS and an increased susceptibility to AF [24]. Hypertension and diabetes mellitus are accepted as risk factors for the AF but the role of obesity is not clear.

A recent study by Tanner et al., published on *Am J of Cardiology* in 2011, supports the hypothesis of a possible correlation between the two diseases analyzing how each component of MS, except triglycerides, is significantly associated with AF [25] (Figure 1).

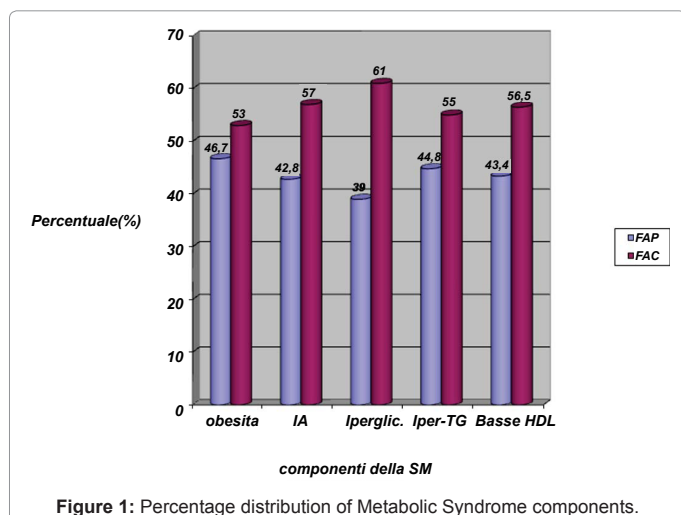


Figure 1: Percentage distribution of Metabolic Syndrome components.

Variable	All Patients	Group I SM+	Group II SM-	p
Number	350	170	180	
Male [n (%)]	179 (51.14%)	92 (51.4%)	87 (50.9%)	0.93
Female [n (%)]	171 (48.85%)	104 (60.8%)	67 (39%)	0.009
Hypertriglyceridemia [n (%)]	100 (28.57%)	87 (24.85%)	13 (3.7%)	0.17
Hypertension [n (%)]	319 (91%)	168 (52.66%)	151 (47.33%)	0.4
Low HDL-C [n (%)]	157 (44.8%)	115 (73%)	42 (26.7%)	0.0001
Obesity [n (%)]	124 (35.4%)	92 (74%)	32 (25.8%)	0.0001
DM2 o IGT [n (%)]	190 (54.2%)	136 (71.5%)	54 (28.4%)	0.0001

Table 1: Distribution of various cardiovascular risk factors in the two groups (MS+ and MS-).

Prevalence	Group I SM+	Group II SM-	P
Hypertension	49%	45%	0.52
Hypertriglyceridemia	33%	1%	0.0001
Low HDL-C	40%	19%	0.0001
DM 2 o IGT	44%	23%	0.0001
Obesity	35%	15%	0.0001
Atrium Sx enlarged	40%	31%	0.1

Table 2: Prevalence of cardiovascular risk factors in the groups in comparison.

Despite its small size (350 patients), our study has come to important conclusions, validating the existence of a real correlation between AF and MS, and it shows how the prevalence of MS in patients with AF turns out to be significantly higher than in the general population (32% vs. 18%). Moreover the prevalence of hypertension, hyperglycemia, obesity and low levels of HDL in patients with CAF is significantly higher than in patients with PAF. There was a significant relationship between female gender and AF with MS (in CAF as in PAF,  $p > 0.009$ ), while the same correlation was not found in the male gender ( $p = 0.93$ ). The area of the left atrium in patients with MS is significantly higher than in patients without MS and this correlation is also maintained in patients with PAF as in CAF. These results lead us to reflect on how the metabolic and hormonal disorder could be an important factor in AF genesis or at least in maintaining, although by mechanisms not yet fully known. Also inflammation and oxidative stress, that are important "actors" in the pathogenesis of MS, may also be involved in the complex pathogenesis of AF. Starting on this evidence, our study (still in progress) is proposing to analyze in fibrillating patients with MS the levels of the most important markers of inflammation, above all CRP and fibrinogen, to prove if these two diseases, apparently so far, are really united by an important denominator as inflammation (Tables 1 and 2).

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