Atrial Fibrillation Susceptibility in Metabolic Syndrome
Simply the Sum of Its Parts?

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In this issue of Circulation, Watanabe et al1 demonstrate an apparent correlation between the presence of metabolic syndrome (MS) and increased susceptibility to atrial fibrillation (AF) in a relatively large (>28,000 subjects) community-based cohort in Japan. The study’s strength, apart from the size of the population, lies in its prospective assessment of free-living individuals without evidence of AF on entry into the study. As such, this report provides new insight into the prevalence of MS in Japan, and in addition, highlights an underappreciated health risk (ie, AF susceptibility) associated with the syndrome. On the other hand, applicability of the findings in the report from Watanabe et al1 is importantly constrained by several key methodologic limitations. First, both the study population as a whole and the subsets with MS features incorporated a high proportion of females (66%). The basis for the make up of the cohort, which was ≈34% male, is unclear, but the sex imbalance suggests that men in the community were less compliant with the voluntary health screening process offered by the prefecture. Second, the prevalence of MS in the study population (13% to 16% depending on the MS definition used) was substantially higher than the approximate 6% previously reported from Japan.2 The basis for this seemingly substantial difference is unknown, but it may reflect selection bias due to less healthy individuals electing to come for screening. Finally, the study protocol did not include a comprehensive effort to document AF by long-term ambulatory ECG monitoring. This failing raises concern that the frequency with which AF was identified, both at baseline and during follow-up, was imprecise. Self-reporting of arrhythmias is notoriously unreliable. Even well-intentioned patients are known to both underreport and overreport symptoms, often with poor correlation between symptoms and the presence or absence of sustained arrhythmia.3

Limitations aside, in their report, which encompassed a mean follow-up of 4.5 years, Watanabe et al observed that individuals who satisfied the criteria for MS using definitions provided by either the National Cholesterol Education Program Third Adult Treatment Panel (NCEP-ATP III)4 or the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI)5 carried an excess risk of developing AF after adjusting for age and sex (hazard ratio, 1.88 and 1.61, respectively). Furthermore, the hazard ratios for developing AF increased as more components of MS were met, suggesting a possible biological gradient. In addition, the link with AF was greater when MS was determined with the NCEP-ATP III definition of glucose intolerance (glucose ≥110 mg/dL) than with the AHA/NHLBI criteria (≥100 mg/dL), suggesting a stronger association among those with greater severity of impaired glucose tolerance (perhaps another example of biological gradient).

Metabolic Syndrome and AF Risk
Although precise definitions may differ,4,5 MS is reasonably considered a cluster of cardiovascular and/or metabolic rearrangements that are believed to be associated with greater risk of development of atherosclerotic Cardiovascular Disease. The key features of MS are abdominal obesity, dyslipidemia (high triglycerides and low high-density lipoprotein), elevated blood pressure, and glucose intolerance. The prevalence of MS in the general US population has been estimated to be approximately 20%,6 further highlighting the importance of identifying and managing potential MS-related health issues. Previously, certain individual components of MS (particularly hypertension and diabetes) have been associated with increased AF susceptibility.7,8 In terms of MS as an entity, however, an association with increased AF risk has received more limited attention, and that attention has been primarily in specific patient populations. For instance, in the recent report by Umetami et al9 from Japan, the study group was restricted to hospitalized patients. In that report, MS was present in ≈21% of enrolled patients (a number similar to that quoted above for the US population6 but much higher than previous Japan estimates3), and AF was twice as common in MS patients than in individuals without MS. Similarly, Echahidi et al10 assessed the relation of MS to AF susceptibility in patients undergoing coronary artery surgery. The MS frequency in that selected population was, perhaps not unexpectedly, relatively high (46%). Once again, MS was accompanied by increased AF risk (approximately 2-fold). Given this background, the study by Watanabe et al1 expands our understanding of MS, both in terms of its prevalence and its association (as a syndrome) with increased AF risk in a non-US/European population.

Individual MS Components and AF Risk
As noted earlier, hypertension and diabetes mellitus are widely accepted risk factors for AF. The importance of
Hypertension, Diabetes, and Obesity

Hypertension (presumably mainly due to left ventricular hypertrophy and diastolic dysfunction, but also potentially through angiotensin II effects on afterload and cardiac fibroblast proliferation) is associated with left atrial enlargement and disturbances of intraatrial conduction velocity and atrial refractoriness (so-called atrial mechanical and electrical remodeling)—all factors known to increase AF susceptibility.12,13 Because of its relation to left ventricular hypertrophy, increased cardiac mass, reduced left ventricular function, and ischemic heart disease, diabetes is similarly associated with AF-promoting structural and electrophysiological changes.14

The manner in which obesity contributes to exaggerated AF risk is less well understood but almost certainly multifactorial. Alone, obesity may alter atrial anatomy and/or intra-atrial pressure and introduce other AF predisposing factors, such as greater levels of oxidative stress, chronic inflammation, elevated circulating free-fatty acids, and disturbances of autonomic tone. By way of example, in terms of direct effects on the atria, Wang et al11 found that as body mass index increased, there was both a graded increase in left atrial size (an important determinant of AF) and an increase in risk of new-onset AF. In this context, impaired ventricular diastolic performance associated with obesity can promote both atrial remodeling and greater propensity to AF risk due to chronic elevation of intracardiac pressures with atrial enlargement.15 Conversely, weight reduction has been linked with regression of left atrial enlargement and might ultimately be expected to diminish the apparent predisposition to AF associated with obesity.16

Elevated levels of oxidative stress and chronic systemic inflammation, along with increased circulating free-fatty acids derived from abdominal fat depots, may contribute to initiation and propagation of AF in obese individuals.10,11 In this regard, certain agents with antiinflammatory properties have been reported to reduce AF susceptibility, although not with predictable effectiveness. For instance, statin administration, acting in part it is believed through an antiinflammatory effect, has been associated with a reduction in AF susceptibility both experimentally and clinically.17,18 However, the impact of antiinflammatory agents may not be adequate in postoperative AF. Statins, as well as other antiinflammatory agents such as glucocorticoids, have had variable results as prophylactic antiarrhythmic/antiinflammatory agents in postoperative AF. Finally, obesity is also strongly associated with obstructive sleep apnea, which can result in various combinations of repetitive nocturnal episodes of hypoxemia, abrupt hypervagal states associated with severe bradycardia, and catecholamine surges; any of these may contribute to atrial arrhythmogenesis.19,20 In this regard, treatment of obstructive sleep apnea with continuous positive airway pressure is associated with a fewer AF recurrences.

Glucose Intolerance, Elevated Triglycerides, and Low High-Density Lipoprotein

Although the increased risk of AF in diabetes is established, discriminating the AF-promoting effect of isolated glucose intolerance or insulin resistance (arguably a less severe stage in the diabetes continuum) poses a more difficult task. In this context, worsening glucose tolerance has been linked with increased left atrial size.21 However, others have proposed hypothetical explanations for cardiac adaptations from hyperglycemia and hyperinsulinemia via a set of complex systemic metabolic signals. These include increased cellular lipids, nonenzymatic glycation end products, altered myocardial protein degradation, insulin-like growth factor-mediated effects, altered matrix remodeling, and sympathetic activation.22,23

In the present study, Watanabe et al also demonstrated that low high-density lipoprotein (<40 mg/dL in men, <50 mg/dL in women) but not elevated triglycerides was independently related to AF risk. To our knowledge, this association has not been described previously. The potential mechanisms to explain this relationship may once again relate to inflammation and oxidative stress, but further studies are needed.

Summary

The report by Watanabe et al1 in this issue of Circulation provides support for the view that MS increases susceptibility to AF. Whether the increased AF risk in MS patients is due to the syndrome as a whole or simply the sum of the risks of its individual component parts is perhaps not unequivocally settled. Nevertheless, the observations of Watanabe et al,1 in conjunction with the disturbingly high prevalence of MS in the general population (≈20% in the United States), highlight an underappreciated but important adverse MS health risk, namely increased AF susceptibility. Furthermore, given the mounting evidence, it seems increasingly clear that physicians must, in their AF prevention and treatment strategies, focus aggressively on addressing blood pressure control, diabetes and glucose intolerance management, weight reduction, and the recognition and treatment of obstructive sleep apnea.

Disclosures

None.

References


Key Words: Editorials arrhythmia electrocardiography metabolism atrial fibrillation metabolic syndrome X
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Circulation. 2008;117:1249-1251
doi: 10.1161/CIRCULATIONAHA.107.760777
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/117/10/1249

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