THE CHANGING EPIDEMIOLOGY AND NATURAL HISTORY OF NONVALVULAR ATRIAL FIBRILLATION: CLINICAL IMPLICATIONS

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ABSTRACT

The growing "epidemic" of non-valvular atrial fibrillation (NVAF) with its associated morbidity and mortality intersects with a number of conditions including aging, thromboembolism, stroke, congestive heart failure, hypertension, and perhaps the metabolic syndrome and inflammation.

In the USA approximately 2.3 million people currently have NVAF and estimates based upon the United States census and the aging of the population suggests that this will be 3.3 million by 2020 and 5.6 million by 2050. This may be a serious underestimate since recent data from Rochester, Minnesota have demonstrated an almost threefold increase in the prevalence over the last three decades *after* adjustment for age. The explanation is probably multifactorial but the socioeconomic implications of this phenomenon are enormous and sobering.

Ongoing efforts towards understanding atrial fibrillation are driven, in part, by the concept that atrial fibrillation may in most patients be the consequence of a systemic condition, in which reduced vascular compliance, atherosclerosis, obesity, and inflammation are primary causal factors. These epidemiological investigations need to be carried out in association with studies aimed at defining the molecular genetics of atrial fibrillation which hopefully will provide more insights into the structural and electrical phenotypes resulting from genetic mutations and their interactions with the environment.

INTRODUCTION

Atrial fibrillation, an "old" arrhythmia first described in 1909, has assumed increasing importance in the 21st century, in which the global demographic tide has resulted in a rapidly expanding elderly population (1,2,3). Currently, atrial fibrillation is the most common sustained

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cardiac arrhythmia, which effects approximately 2.3 million individuals in the United States (4). In the last 15 years, hospital admissions for atrial fibrillation have increased two- to threefold based on data from the National Hospital Discharge Survey from 1985 to 1989 (5). During this period, hospitalizations increased from 154,086 to 376,487 for a first-listed diagnosis of atrial fibrillation and from 787,750 to 2,283,673 for any diagnosis. This perceived increase was most apparent in successive age groups and was higher in men than in women. Atrial fibrillation is an independent predictor of mortality and associated with an increase in the incidence of embolic stroke, accounting for perhaps 75,000 to 100,000 strokes per year (6). Not only is atrial fibrillation primarily a disease of the elderly, but advanced age is, in itself, a powerful risk factor for stroke among patients with atrial fibrillation.

Atrial fibrillation is considered as one of the three growing cardiovascular epidemics in the 21st century in conjunction with congestive heart failure and type II diabetes mellitus and the metabolic syndrome (7). In this respect, the interaction between atrial fibrillation, congestive heart failure, diabetes, hypertension, and stroke, and perhaps inflammation, places atrial fibrillation in the center of current research into some of the most topical areas of cardiovascular disease.

INCIDENCE AND PREVALENCE

Prior Studies

Multiple studies including a series from the Framingham Study and Olmsted County, Minnesota, Scotland, Holland, and Australia, have demonstrated highly consistent findings (Figure 1). Atrial fibrillation is uncommon under the age of 60 years, but the prevalence increases markedly thereafter, with a prevalence of approximately 10% by the age of 80 years. In the Framingham Study, the prevalence was considerably greater in men than in women, for reasons that are largely unexplained. Approximately one third of all patients with atrial fibrillation are age 80 years or more. Moreover, octogenarians are the fastest growing segment of our society, and it is estimated by the year 2050 that the majority of the population with atrial fibrillation will be aged 80 years or older (8).

Projections

Go, et al, performed a cross sectional study of adults age 20 years or older enrolled in a large health maintenance organization in California

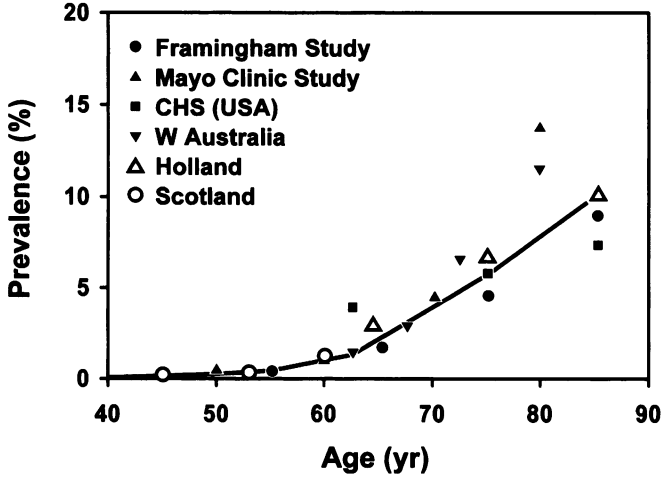

FIG. 1. Prevalence of atrial fibrillation in six natural history studies (CHS = Cardiovascular Health Study). (W.Australia = Western Australia). Modified from Feinberg WM, Blackshear JL, Laupacis A, et al: Prevalence, Age Distribution, and Gender of Patients With Atrial Fibrillation: Analysis and Implications. Archives of Internal Medicine 1995;155:469–473, Reference 4.

(8). In this population of approximately 1.9 million individuals, the prevalence ranged from 0.1% among adults under the age of 55 years to 9% in patients age 80 years or older. Based upon the United States Census projections for the next 50 years, these authors estimated that by the year 2020, approximately 3 million individuals will have atrial fibrillation, and approximately 5.6 million by the age 2050, with more than 50% of affected individuals being 80 years or older. Since the elderly are not only at the highest risk of stroke among the population with atrial fibrillation, but also at the highest risk of bleeding on anticoagulants, these epidemiological features point out the necessity of developing new therapeutic strategies.

Evidence for Underestimation of Atrial Fibrillation

Clinically Undetected Atrial Fibrillation

The analysis by Go, et al, is disturbing, yet for several reasons is likely to represent a substantial underestimation of the magnitude of the epidemic. Firstly, many episodes of atrial fibrillation remain undetected due to a lack of symptoms. 30% of patients in the Cardiovascular Health Study (9) and 45% of patients in the Stroke Prevention in Atrial Fibrillation Trials (10) had an incidental diagnosis of atrial fibrillation

when an electrocardiogram was performed for an unrelated reason. In another study of patients with symptomatic paroxysmal atrial fibrillation, the rates of asymptomatic to symptomatic episodes was 12:1 (11).

Changing Incidence and Prevalence

It has been generally accepted that the genesis of the epidemic of atrial fibrillation is a function of the increasing proportion of the elderly in the population. Two more recent studies from Framingham and Rochester, Minnesota, suggest that other factors, as yet poorly understood, are playing a major role in the marked increase and frequency of this disease (12,13).

In the Framingham Study of individuals age 65 to 84 years of age (12), *after* adjusting for age, the prevalence of atrial fibrillation which was 3.2% in men between 1968 to 1970, increased to 9.1% between 1987 to 1989. This was less marked in women in whom the prevalence of 2.8% increased to 4.7% respectively. Underlying explanations for these changes are unclear.

A recent matched case-control study among residents of Rochester, Minnesota, demonstrated a two- to threefold increase in age-adjusted prevalence from 1960 to 1969 compared to 1989 (13). This was noted in the control population and also among patients who had experienced an ischemic stroke. The increase in prevalence of atrial fibrillation over the period did not differ between men and women. These figures suggest that we are in the throes of an extraordinary increase in the prevalence of this disease, over and above what can be attributed to age alone. Although the analysis of multiple concurrent trends is a complex process, a clearer understanding of the causes of this rapid increase in the numbers of patients with atrial fibrillation is needed. The sheer magnitude of the population with this disease creates a major public health issue.

Factors Contributing to the Development of the Epidemic of Atrial Fibrillation

A relatively mundane explanation for the increase in numbers is that this is the result of ascertainment bias related to the increased use of the electrocardiogram in the community. This was addressed and found to be an unlikely cause in the Rochester population (13), since over the 30-year period, the utilization of the electrocardiogram increased by only 9% to 12%, in comparison to the two- to threefold increase in the prevalence of atrial fibrillation.

The Role of Established Comorbidities

One potential explanation for the increased prevalence is that today's elderly are a "sicker population," namely, survivors with a higher prevalence of comorbid conditions including hypertension, diabetes, congestive heart failure, coronary artery disease, and prior cardiac surgery. For centuries, highly selected individuals have lived to a very advanced age, providing an example of the principle of the Darwinian principle of the "survival of the fittest" (13). During the 20th century, advances in preventative medicine and increasing socioeconomic prosperity have resulted in a marked increase in the proportion of the population attaining "old age." The more recent trend, brought about by both primary and secondary prevention plus advances in the treatment of acute and chronic cardiovascular disease, may result in a population of elderly survivors who may comprise a "sicker" population in comparison with their counterparts who lived to a similar age 50 years age (14,15,16,17).

In this respect, in the Rochester study over a 30-year period, there were statistically significant but relatively modest increases in the prevalence of coronary artery disease, valvular heart disease, a history of prior myocardial infarction, and to a lesser extent congestive heart failure, diabetes, and a history of prior cardiac surgery. Nonetheless, when placed into perspective with the magnitude of the increase in prevalence of atrial fibrillation, the relatively small increase in the prevalence of known comorbidities, does not appear to offer more than a partial explanation.

Novel Risk Factors for Atrial Fibrillation

(a) Inflammation

C-reactive protein, a sensitive marker of inflammation, is a powerful predictor of adverse cardiac events and has recently been linked to atrial fibrillation (18,19,20). To what extent markers of inflammation should be considered risk "factors" for atrial fibrillation or as a risk "markers," and as a surrogates of other cardiovascular conditions which could predispose to atrial fibrillation, e.g., arteriosclerotic vascular disease and hypertension causing reduced arterial compliance, remains to be determined. This is currently a focus of ongoing studies in Olmsted County and other populations.

(b) Obesity, Metabolic Syndrome, and Sleep Apnea

The surge in obesity, the metabolic syndrome, and diabetes in the developed and the developing world is well documented and has reached alarming proportions. To what extent obesity is a risk factor

for atrial fibrillation, independent of its association with other cardiovascular risk factors, remains a controversial issue, in that the conclusions of different studies have been discordant (21,22,23,24). Nonetheless, given the evidence that the metabolic syndrome is proinflammatory (25,26,27) and that atrial fibrillation has been linked to an inflammatory "milieu," the relationship of these risk factors to the development of atrial fibrillation is a major focus of current investigation, including a prospective study in the Olmsted County cohort.

A relationship between obstructive sleep apnea and obesity is well documented (28,29,30,31). Moreover, the prevalence of sleep disordered breathing has been perhaps underappreciated. In one population-based study, Young, et al, estimated that 1 in 5 adults have at least mild obstructive sleep apnea with at least moderate obstructive sleep apnea present in 1 in 15 (29). Moreover, these figures were obtained in non-obese patients.

A recent study from Mayo Clinic in patients with atrial fibrillation undergoing successful cardioversion demonstrated a remarkably high recurrence of atrial fibrillation in untreated patients with obstructive sleep apnea in comparison to patients treated with continuous positive airway pressure and in two controls (32). To what extent this is the result of hypoxemia, hypercarbia, increased sympathetic and reduced vagal tone, and the increase in afterload and left ventricular wall stress, noted in patients with obstructive sleep apnea has not been clarified (31). In patients with sleep apnea, hypoxia induces pulmonary artery vasoconstriction and increased right-sided pressures which act as a stimulus for ANP release; levels of which are elevated in atrial fibrillation (33,34). Furthermore, the relationship between obstructive sleep apnea, obesity, the metabolic syndrome, hypertension, and atrial fibrillation requires further exploration—is obstructive sleep apnea a risk factor for atrial fibrillation or a risk marker of other comorbidities including inflammation, which may, in turn, predispose to atrial fibrillation (31,35)?

(c) Diastolic Dysfunction and Arterial Stiffness

Diastolic dysfunction is a common accompaniment of aging and is a precursor to hypertension, obesity, diabetes, and coronary artery disease. It is becoming increasingly evident that heart failure in older patients is frequently noted in the absence of impaired systolic function, presumably as a result of diastolic dysfunction (36). In an Olmsted County Study of patients age 65 years and older who were in sinus rhythm at the time of an echocardiographic examination, it was noted that the subsequent development of atrial fibrillation in patients with-

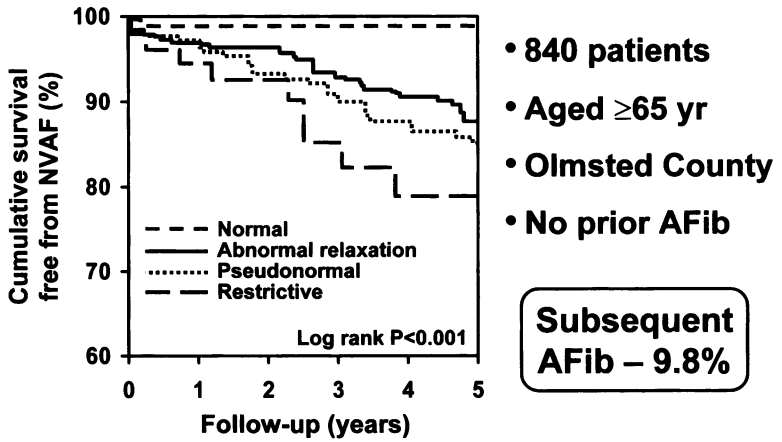

FIG. 2. Age-adjusted cumulative survival without nonvalvular atrial fibrillation (NVAF) by diastolic function profile in 960 Olmsted County patients age 65 years and older who were in sinus rhythm at the time of the echocardiographic examination. Subsequent development of atrial fibrillation was 9.8%. From: Tsang TSM, et al: Left ventricular diastolic dysfunction as predictor of a first diagnosed nonvalvular atrial fibrillation in 840 elderly men and women. JACC 2002;40:1636–1644, Reference 37.

out diastolic dysfunction was only 1% versus approximately 12% in patients with moderate degrees of diastolic dysfunction and 20% in those with restrictive physiology, which is the most severe manifestation of diastolic dysfunction (Figure 2). In addition, the assessment of diastolic function provided incremental predictive information over and above that obtained from the clinical risk factors (37). Moreover, increased left atrial volume is associated with an incremental deterioration of diastolic function and provides further predictive information in regard to the development of atrial fibrillation and stroke (Figure 3) (38). Since it is well established that atrial stretch and dilatation increases the vulnerability of the atrium to the development of atrial fibrillation (39), a logical focus of further investigation into the causes of atrial fibrillation will involve an understanding of the relationship between arterial compliance, diastolic function, atrial volume, and inflammation. In this respect, left atrial volume may be a surrogate or marker of multiple other processes that lead to the development of atrial fibrillation (38), and in turn left atrial volume may be a surrogate for arteriosclerotic vascular disease (40).

Conclusions

Atrial fibrillation, a "simple" arrhythmia characterized by "irregularly irregular heart beats" is now accepted as a common and rapidly

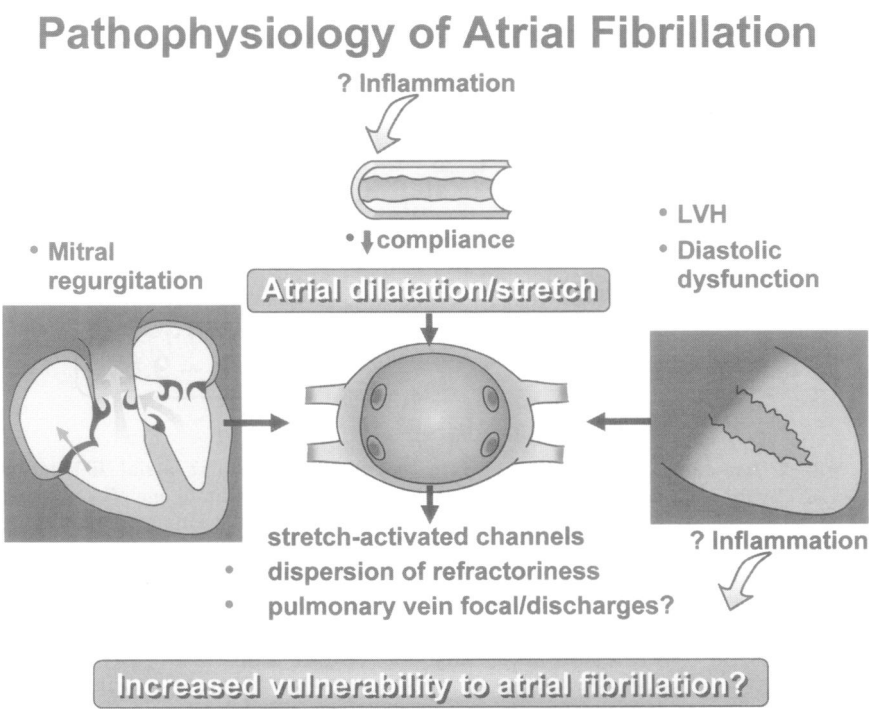

FIG. 3. Hypothetical construct of the pathophysiology of atrial fibrillation. In this schematic atrial dilatation and atrial stretch act a common denominator in increasing the vulnerability to atrial fibrillation. To what extent inflammation plays a role is under investigation, but in this substrate the etiologic role of diastolic dysfunction, hypertension, and mitral regurgitation is understandable. It is possible that conditions predisposing to increased arterial stiffness may also lead to left atrial dilatation by increasing the impedence to left ventricular ejection. It is possible that conditions predisposing to increased arterial stiffness may also lead to left atrial dilatation by increasing the impedance to left ventricular ejection.

growing clinical problem and disease entity. An emerging and sophisticated invasive and pharmacologic therapeutic armamentarium has increasingly required the expertise of an electrophysiologist. Nonetheless, our understanding of the mechanisms leading to atrial fibrillation and the ultimate role of prevention which may involve drugs such as angiotensin-converting inhibitors and aldosterone antagonists, among others, emphasizes the multidisciplinary approach that is needed.

A crucial question is, to what extent are systemic cardiovascular conditions a risk factor versus a risk marker (Figure 3). This is also applicable to the role of atrial fibrillation and the left atrium as a direct cause of thromboembolic stroke, as opposed to a surrogate of other cardiovascular diseases and processes, which in themselves may lead

to stroke and thromboembolism via pro-inflammatory and prothrombotic mechanisms. Familial linkage studies are slowly starting to unravel the genetics of atrial fibrillation as an "electrical disease" particularly in younger individuals (41,42,43,44). Whether these mutations play a role in the majority of older patients with disease of the atrial substrate and in the presence of modifiers such as sleep apnea and hypertension remains to be proven.

In summary, as we are confronted with a daunting prospect of a rapidly growing epidemic of atrial fibrillation, hopefully an increased understanding of the pathophysiology and genetics of this complex condition will lead us to new approaches towards treatment and prevention.

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DISCUSSION

Wolf, Boston: As I think about Rochester, Minnesota in the winter, I wonder if the people are drinking all winter long. In this population, have you looked at the role of

alcohol which is a reported risk factor for atrial fibrillation in that population. You didn't mention that.

Gersh, Rochester: That's a good question Marshall. The reason I didn't is that we just did not have the data on alcohol consumption in our retrospective study. We also didn't have the data on our body mass index. I think that in the Framingham study however it was a weak predictor. We will be collecting that data prospectively in the study that I have just shown you. Probably in the population as a whole in Olmsted County, it will turn out that the rate of alcohol consumption is quite low, but what role it plays here I don't know. The other aspect that we are currently looking at is on the genetic component, both in relationship to the interaction of environmental factors and in young people who have no other heart disease, but it's a good point.

Ende, Philadelphia: Very interesting paper. Do you have any information from other populations, or from other nations where obesity and the metabolic syndrome are less prevalent?

Gersh: The answer is that we do not. There are five natural history studies of atrial fibrillation that show very similar results in regard to age. But the only two studies that I know of that have looked at atrial fibrillation prevalence and adjusted for age have been Framingham and ourselves, and I believe we show generally the same results. I'm just not aware of studies from areas where obesity and the metabolic syndrome are less prevalent. Certainly, we have now realized that in Europe, although the level of obesity isn't the same, the trend, I'm afraid, is in the same direction. I mean there is a growing incidence of metabolic syndrome and obesity in Europe. And the only other studies are in Australia, but that one was carried out twenty-five years ago. So we just don't know the answers, but we are looking at this prospectively.

DeSanctis, Boston: As always, Bernard, a great presentation. Two questions probably just reflects my ignorance, but what about size alone as a factor in causes left arterial enlargement and arterial fibrillation? My little brain tells me intuitively that somebody who weighs 350 pounds will have a much bigger left atrium than somebody who weighs 170 pounds.

Gersh: You know your little brain is not so little, Roman. You are absolutely right, and we are looking here at left atrium volume indexed for body surface area and left atrial volume non-indexed. I agree that this is a likely risk factor, and so that's how we are going to try and get at that.

Alexander, Atlanta: I also enjoyed that a great deal. I was really intrigued by your data about diastolic dysfunction as a risk factor associated with atrial dilatation. I really wonder if, in fact, blood pressure levels that we have traditionally regarded as "normal" are not physiologically normal. I wonder whether a lot of that diastolic dysfunction associated with left atrial enlargement and subsequently atrial fibrillation does not, in fact, reflect a huge number of people who have "a little hypertension," or systolic pressures of approximately 140 or slightly greater over decades.

Gersh: I think you've put your finger right on it. I believe that hypertension or pre-hypertension as we now call it, is playing a huge role in this. Personally I believe that the guidelines are very appropriate, and I think that although we seem to be seeing an epidemic of diastolic dysfunction it has probably always been there, but we did not recognize it, since we were unable to diagnose it. But in terms of why we are seeing so much diastolic dysfunction and heart failure, it is very likely that we are now seeing a population with mild degrees of hypertension that we previously ignored. And I'm fascinated by some of the emerging data demonstrating that the ace-inhibitors really look like they may prevent atrial fibrillation, and I'd like to know what the role is of A2 antagonist is in this. Our prospective studies will look at hypertension and arterial stiffness as a risk factor for atrial fibrillation. But I am sure you're right Wayne.