Symptoms in Atrial Fibrillation
Why Keep Score?

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In practice, although the objective goals of therapeutic intervention in atrial fibrillation (AF) are usually framed in terms of the prevention of stroke and of heart failure, the majority of clinical decisions in AF are driven by symptoms.1 The risk of stroke among those with AF is highly heterogeneous and difficult to predict for the individual patient, but there are extensive empirical data supporting current anticoagulation algorithms. A simple awareness of the presence or absence of the arrhythmia is a factor in decisions regarding anticoagulation and cardioversion, but it correlates poorly with arrhythmic episodes.2 The pathophysiological relationship between AF and heart failure is more complex, and data linking intervention for the arrhythmia to a reduction in the incidence of heart failure are much less robust. In the absence of rigorous data on mortality benefit for most interventions in AF, evaluation of the subjective symptom burden in each patient is a central component of the risk-benefit calculation.3

Article see p 268

Symptoms in AF are notoriously variable and difficult to compare among individual patients.1-3 The clinical syndromes associated with AF run the gamut from an incidental ECG finding through acute heart failure to syncope. Nevertheless, approximately 25% to 30% of those with the arrhythmia are asymptomatic. Clinicians managing AF also must deal with the wide range in symptom severity observed in those with substantively similar physiology.2 There is also significant variation in the correlation between symptoms and objective findings for any given individual.

In the last few years, concerted efforts have been made to characterize symptoms in a number of clinical trials designed to test management strategies in AF.1,3,4 These efforts have largely relied on generic quality-of-life scales such as the SF-36 questionnaire. Such quality-of-life instruments, although time-consuming to administer, offer a multidimensional assessment of physical and mental health but often fail to capture the distinctive features of individual medical problems in complex patient populations. Disease-specific instruments such as the AF Severity Scale (AFSS) can be used to address some of these limitations but require even more sophisticated administration.4,5 As the number of medical and interventional options for AF increases and our preconceived notions of management are challenged, the need for rigorous yet efficient techniques to compare symptoms across populations and across studies grows. Although symptoms undoubtedly affect quality of life, clinical experience suggests that specific complaints affect quality of life in very different ways for each patient. It is worthwhile to consider AF symptoms in a broad context as novel comparators are developed.

Symptom Mechanisms in AF
The mechanisms of many of the symptoms in AF are poorly understood. Palpitation, or awareness of the irregularity of the heartbeat, is prominent in more than half of those with AF, but correlation with documented arrhythmia is unimpressive.2 The simple sensation of dysrhythmia may be quite debilitating. The afferents responsible for palpitations are unknown but do not appear to be interrupted by the denervation of cardiac transplantation.6 Interestingly, there is a significant correlation between the perception of arrhythmia and specific neuropsychiatric variables.7,8

Dyspnea in AF is often attributed to elevated left heart pressures, but objective hemodynamic investigation has demonstrated that the arrhythmia may be associated with normal or even low intracardiac pressures, implicating other mechanisms.9 Chest discomfort, pressure, and frank chest pain often occur during episodes of AF in the absence of coronary disease or critical valve disease. The arrhythmia is also frequent in several cardiomyopathies with well-characterized metabolic defects, and together these studies implicate primary or secondary abnormalities of specific pathways in the etiology and pathogenesis of at least some forms of AF.10 Recent functional genomics studies have buttressed such arguments revealing evidence of perturbed energetic pathways even in short-lived episodes of AF.11

AF is clearly associated with a decrease in exercise tolerance, and consistent improvements in exercise capacity tolerance are noted after conversion to sinus rhythm.5 Most clinicians will tailor their rate control regimen in an effort to optimize the physiological response, avoiding the extremes of chronotropic incompetence and inappropriate tachycardia.1

There are small studies that suggest that increased heart rate variability in AF, possibly reflecting the degree of rate control, may be associated with greater exercise tolerance, but other work has attributed such effects to the specific drugs chosen. Of note, in the rate control arm of the AFFIRM study, there was no relationship between the degree of heart rate control

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215
and any objective indices of function, including 6-minute walk tests and formal quality-of-life measures.\textsuperscript{12}

Presyncope and syncope are often reported with AF, yet in many studies the onset of the arrhythmia is not associated with major hemodynamic changes.\textsuperscript{9} Whether AF represents an "escape" rhythm after a primary bradycardic or vasomotor event is unknown, but Holter data reveal evidence of sympathovagal imbalance before the onset of AF in a substantial subset.\textsuperscript{13} The role of the autonomic nervous system in AF is extremely complex. Sympathetically driven forms of AF with particular rate triggers undoubtedly exist, yet high vagal tone is a prerequisite for the maintenance of the arrhythmia in most animal models. In acute AF, sympathetic activation, both neural and humoral, is often evident and a major determinant of the initial ventricular response. Variation in sympathovagal balance or in the gain of the autonomic nervous system may be not only a major contributor to both the genesis and hemodynamic effects of AF, but autonomic afferents also may be a source of disparate sensations of dysrhythmia. Whether the autonomic variation seen among individuals can be attributed to differences in perception or is rather a consequence of a shared disorder of multiple excitable tissues is unknown. A potential role for the Pitx2 transcription factor in the patterning atrial myocardium is emerging from human genetic studies,\textsuperscript{14} and this might also explain some associated central or autonomic neuronal contributions to the arrhythmia.\textsuperscript{15}

There are many other complaints that have been reported with AF, including generalized fatigue, anxiety, and depression.\textsuperscript{16} Symptom assessment in persistent or permanent AF is complicated by comorbidity conditions that are considerably more likely to contribute to specific complaints and to overall quality of life. Tremendous variation in subjective symptoms over time also exists in chronic settings, but there does not appear to be a correlation between specific complaints and the conversion to persistent or permanent AF. Ultimately, it has proven difficult to demonstrate a relationship between any AF symptoms and ventricular response rates.\textsuperscript{1,3,12} Some symptoms are difficult to define, but clinical experience suggests small data sets that suggest that individuals feel better in sinus rhythm, notwithstanding the results of randomized controlled trials of management strategy.\textsuperscript{5,5} Interestingly, depressive symptoms may predict not only future quality of life but also AF recurrence after cardioversion.\textsuperscript{16,17}

Creating and Validating Objective Scoring Systems for Subjective Symptoms

The development of scoring systems for subjective symptoms is not straightforward. There are no gold standards, and, although changes in scoring systems may be reproducible, calibrating scores across cohorts or cultures is predictably difficult, and correlations with meaningful outcomes remain challenging. It is in this context that Dorian et al\textsuperscript{18} have developed a semi-objective scale of symptom severity in AF based on the work of a consensus conference of the Canadian Cardiovascular Society. The application of this symptom-based Severity in Atrial Fibrillation (SAF) scale allows the reproducible classification of the extent to which an individual is limited by AF by a range of different observers. The investigators demonstrated robust correlation of the rapidly generated SAF class with both the mental and physical domains of the formal SF-36 questionnaire.

There is considerable utility in a simple score that integrates a host of unmeasured components of the symptomatic burden of AF, but the broad acceptance of this practical scoring system should require the demonstration of exactly these attributes. As outlined above, AF symptoms are heavily conditioned by comorbid disease and by affective state, and it is important to define what if any additional information is conveyed by the SAF scale. In this regard, a direct comparison of the SAF scale with existing New York Heart Association class and a simple rhythm qualifier may be instructive. There was no linear correlation between the SAF score and subjective frequency of AF episodes or the duration of AF.\textsuperscript{18} The timing of the most recent episode of AF and the duration of AF are likely markers for discrete elements of the arrhythmic substrate and may reflect the systemic contributors to disease, a critical component for any clinical trial. Similarly, the SAF scale fails to capture the contribution of AF pattern to the AFSS. These very elements are known to play a major role in the treatment of the individual patient, in whom different components of the AF syndrome may respond very differently to various therapeutic measures. The symptom list encompassed by the current SAF scale includes the broad categories applicable to most patients but also serves to emphasize the restrictions of this approach.

Several other caveats apply in general to categorical scales. Independent observers may agree in a very specific acute setting, but it is vital to correlate SAF class with long-term subjective well-being and morbidity. It would be interesting to define correlations between SAF class and objective measures of social function such as work behavior or emerging social network analyses. It is important to demonstrate not only that the SAF scale is stable over time, but that changes in class correlate with objective changes in the frequency and duration of AF episodes. It is difficult to imagine a gold standard for subjective symptoms, but the onus remains to convince the user that the SAF scale does indeed capture the functional impact of AF rather than the impact of underlying disorders. Finally, as the authors note, there are real risks of erroneous statistical inference with any categorical scale.\textsuperscript{18}

“Orthogonal” Symptoms in AF: A Window on Biology?

A focus on symptoms is not out of place in the modern era, but rather serves to highlight the need for vibrant translational investigation. The connection between physician and patient that artful listening and inquiry bring to the clinical encounter is matched only by the unique insights that the human expression of symptoms bring to the fundamental biology of disease. The exploration of symptoms may offer orthogonal diagnostic “axes” that facilitate the identification of distinct subsets of disease.\textsuperscript{19} Are the severely symptomatic AF patients suffering from a different disorder? Can we connect the disparate range and severity of symptoms associated with AF with the known heterogeneity of etiologic mechanisms for this arrhythmia?

Perhaps the most obvious biological link is that between AF and heart failure. Recent evidence suggests that these two
syndromes not only predict each other’s future development, but in many cases also share biology.10,20 Multiple biomarkers including key reporters of the renin-angiotensin system are perturbed even after a single remote episode of AF, in many cases to a similar degree to that observed in compensated heart failure. Dyspnea might reflect perturbed intercostal or diaphragmatic afferents or a generalized subclinical metabolic myopathy as readily as it represents elevated pulmonary interstitial fluid pressure.

The correlation between certain forms of panic disorder and AF symptoms in some individuals may also reflect shared molecular mechanisms. Rare families in whom autism, seizure disorders, or other neurological syndromes cosegregate with AF suggest that at least some of these associations reflect inherited common causal defects. Similarly, systemic disease might explain the associations of AF with autonomic imbalance and the potential relationships with mood disorder or psychoactive medications.8,13,17 For example, inflammatory disorders, mitochondrial or other metabolic dysfunction, and primary defects of the patterning of cellular connectivity all might contribute to AF substrate as well as to extracardiac syndromes.

Recognizing the difficulty in quantifying symptoms in AF, we might consider approaches taken in other clinical syndromes. Subjective scales can be accompanied by objective stimulus-response measures. Parallel insights, for example, from estimating the gain of the autonomic nervous system in controlled settings, defining diaphragmatic force generation, or identifying markers of distinctive metabolic disorders, may not only resolve AF into constituent disorders for etiologic studies but also offer early prognostic or therapeutic information. One of the great promises of molecular medicine is that new phenotypes that can accommodate the multisystem nature of disease. We are remiss if we do not exploit all of the tools at our disposal in the search, including careful history taking.

Disclosures

None.

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