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Electrophysiology

The Impairment of Health-Related Quality of Life in Patients With Intermittent Atrial Fibrillation: Implications for the Assessment of Investigational Therapy

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OBJECTIVES We sought to assess the impact of intermittent atrial fibrillation (AF) on health-related quality of life (QoL).

BACKGROUND Intermittent AF is a common condition with little data on health-related QoL questionnaires to guide investigational therapies.

METHODS Outpatients from four centers, with documented AF (n = 152), completed validated QoL questionnaires (Medical Outcomes Study Short Form 36 [SF-36], Specific Activity, Symptom Checklist, Illness Intrusiveness and University of Toronto AF Severity Scales). Comparison groups were made up of healthy individuals (n = 47) and four cardiac control groups: published (n = 78) and created for study (n = 69) percutaneous transluminal coronary angioplasty (PTCA); published heart failure (n = 216) and published post-myocardial infarction (MI) (n = 107).

RESULTS Across all domains of the SF-36, AF patients reported substantially worse QoL than healthy controls (1.3 to 2.0 standard deviation units), with scores of 24%, 23%, 16% and 30% lower than healthy individuals on measures of physical and social functioning, mental and general health, respectively (all $p < 0.001$). Patients with AF were either significantly worse ($p < 0.05$, published controls) or as impaired (study controls) as either PTCA or post-MI patients on all domains of the SF-36 and the same as heart failure controls on SF-36 psychological subscales. Patients with AF were as impaired or worse than study PTCA controls on measures of illness intrusiveness, activity limitations and symptoms. Associations between objective disease indexes and subjective QoL measures had poor correlations and accounted for <6% of the total variability in QoL scores.

CONCLUSIONS Quality of life is as impaired in patients with intermittent AF as in patients with significant structural heart disease. Patients' perception of QoL is not dependent on the objective measures of disease severity that are usually employed. (J Am Coll Cardiol 2000;36:1303–9)

Atrial fibrillation (AF) is the most common symptomatic arrhythmia (1,2) and results in a high rate of consumption of medical care resources (3). There is reasonable consensus with regard to the prevention of cardioembolic events from AF; the other current goals of therapy are largely based on the amelioration of symptoms and functional capacity and reduction of disability and consumption of healthcare resources.

Therapy to achieve and maintain sinus rhythm is often administered to patients, particularly to those with intermittent paroxysmal (self-terminating) or persistent (requiring therapy to terminate) AF. Such therapy is frequently ineffective and may cause adverse effects, occasionally serious (4,5). As a result, many patients with intermittent AF are referred to tertiary care referral centers for therapy, which may include investigational therapies, including device, ablative (surgical or catheter) and investigational drug approaches. Most of these investigational therapies use unambiguous physiological measures as end points to establish therapeutic efficacy. Such measures include the frequency and duration of AF episodes, underlying ventricular function, functional capacity during sinus rhythm and during AF (6,7), heart rate and maximum volume of oxygen. In a nonfatal condition such as intermittent AF, the use of physiological measures to assess therapeutic efficacy is based on an assumption that these measures reflect the health-related contributions of how patients subjectively feel (8). This belief has never been formally tested. In addition to a possibly tenuous connection between objective physiological

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Abbreviations and Acronyms

AF = atrial fibrillation
AV = atrioventricular
MI = myocardial infarction
NYHA = New York Heart Association functional classification
PTCA = percutaneous transluminal coronary angioplasty
QoL = quality of life
SAS = Goldman Specific Activity Scale
SD = standard deviation
SF-36 = Medical Outcomes Study Short Form 36

measures and patient-perceived subjective factors, there is also a growing appreciation that subjective patient-perceived dimensions of the severity of an illness are themselves important considerations in weighing the benefits versus the risks for any therapy.

To date, there has been no systematic study of subjective quality of life (QoL) in a relatively large, consecutive group of patients with AF. The lack of such health-related QoL data is usually based on a perception that such data is difficult to interpret, does not have normative or cardiac disease related controls and does not contain adequate data to allow for adequate sample size estimations.

Many of these concerns are valid, and they led to the impetus for this study. We hypothesized that QoL in patients with intermittent AF would be significantly impaired compared with normal age-matched controls and would be similar to those who have significant coronary disease (with prior myocardial infarction [MI], heart failure or the need for angioplasty) but not correlate with more objective, conventional clinical parameters. To test these hypotheses, patient-perceived QoL using a variety of validated questionnaires, as well as objective measures of disease severity, was assessed in patients with intermittent AF who were referred to one of four tertiary care centers.

METHODS

AF patients. Consecutive outpatients over the age of 18 years who could read English or German and had no cognitive or sensory limitations were asked to participate in this study. To enter this study, eligible patients had to have at least one documented episode of paroxysmal (spontaneously self-terminating) or persistent (intervention required to successfully restore sinus rhythm) AF. Patients in permanent AF with continuous duration lasting longer than six months were excluded. Also excluded were patients who received an implantable cardioverter defibrillator or atrial defibrillator. Patients with AF due to secondary causes (postcardiovascular surgery, hyperthyroidism) were also excluded. Patients were referred to one of four outpatient arrhythmia clinics (St. Luke's Hospital, Milwaukee, Wisconsin; St. Michael's Hospital, University of Toronto, Toronto, Canada; St. George's Hospital, London, England and University of Bonn Hospital, Bonn, Germany).

Cardiac control patients. In an effort to acquire a control group with stable and significant coronary artery disease, consecutive patients from an outpatient postangioplasty clinic at one of the tertiary care referral centers that also entered patients into the main study (St. Michael's Hospital) were identified. These patients were seen at the time of their routine six-month postangioplasty clinic visit between June 1997 and February 1998. Those patients without cognitive deficits, who could read English, were eligible to participate. Patients with documented AF, an artificial heart valve, pacemaker or ventricular defibrillator were also excluded. In addition, other cardiac comparative groups were assessed from published data sources; an angioplasty group was obtained from a published case series that included an Medical Outcomes Study Short Form 36 (SF-36) questionnaire (n = 79) (8,9), and both post-MI (n = 107) and heart failure (n = 216) groups were available from the published SF-36 data manual (10).

Healthy subjects. A healthy individuals control group was also used for comparison. Patients scheduled for routine health examination, without any documented cardiovascular disease or other serious illness, were identified at two outpatient clinics (Toronto and London). English-speaking people over the age of 18 years without any diagnosed psychiatric illness were eligible to participate. Relevant medical history and medications were recorded to confirm health status independently.

Outcome measurements. Patient characteristics and clinical history, including age, gender, left ventricular function, antiarrhythmic medications, history of hypertension, history of heart failure, echocardiographic left atrial diameter and New York Heart Association classification (NYHA) were collected for each patient. Patients were given questionnaires evaluating QoL and symptom burden in the arrhythmia clinic and were instructed to mail them back within two weeks in postage paid envelopes.

QoL questionnaires. In addition to recording standard demographic variables, a number of validated outcome measures were used. The SF-36, a widely used generic health scale with standardized scores ranging from 0 to 100 was used to measure physical functioning, role functioning, social functioning, mental health, vitality, pain and general health perceptions (10). To measure functional capacity, the Goldman Specific Activity Scale (SAS) (11), modified using a continuous scale to increase its discriminatory power, was included. Arrhythmia-related symptom frequency and severity were assessed by the Symptom Checklist (12). Although developed to assess symptoms referable to arrhythmias, this was also offered to healthy controls and to one of the post-percutaneous transluminal coronary angioplasty (PTCA) cardiac control groups. The degree of life disruption attributable to illness was measured by the Illness Intrusiveness Ratings Scale (13). This scale was developed to measure the degree of life disruption in social, emotional, physical, affective and spiritual spheres caused by a chronic illness. The questions stem was altered to assess data from

this scale when administered to the healthy normal control group. The University of Toronto Atrial Fibrillation Severity Scale, a locally constructed, 14-item disease specific scale developed to capture subjective and objective ratings of AF disease burden, including frequency, duration and severity of episodes, was also included (14). This scale also includes a brief health care utilization component that assesses the number of emergency room visits, hospitalizations, specialist visits and cardioversions for AF in the previous year.

The study was approved by each institution's local ethics review board.

Statistical analyses. The sample of 152 patients was adequately powered to detect at least a 10-point difference between patients with AF and control patients on most SF-36 subscales using a two-tailed test with 80% power (15). This difference is considered moderate in size and is within half of a standard deviation (SD) of most subscales of the SF-36 in normative populations.

Quality of life outcomes are expressed as means ± SD. To determine differences in the various QoL responses by group, continuous response variables were compared using analysis of variance. Since it has been previously shown that QoL is dependent on age and gender (15), these variables were included as possible explanatory variables. Bonferoni correction was used for multiple comparisons where appropriate. P values <0.05 associated with the group variable were considered statistically significant. Preliminary analyses showed no significant QoL differences between patients at the four centers, so data were pooled for analysis.

RESULTS

Of the 194 patients with AF consecutively referred to one of the four participating centers, 175 met entry criteria. From these, 152 (87%) had complete data for analyses (8%, 35%, 23% and 35% from Milwaukee, Toronto, London and Bonn, respectively). The mean age of the group was 58 ± 12 years, and 73% were men; AF was paroxysmal in 60.5% and persistent in 39.5%.

Ninety-nine percent of the entire AF group was NYHA class I or II with respect to exercise capacity when patients perceived themselves to be in sinus rhythm. This is similar to the NYHA status of the post-PTCA study-created control group who were all NYHA class I or II. During perceived or documented AF, exercise function was poorer with only 38% in NYHA class I. A minority of patients had other cardiac arrhythmias such as a history of Wolff-Parkinson-White syndrome (2%), atrioventricular (AV) nodal reentrant tachycardia (2%), other supraventricular tachycardias (5%) or atrial flutter (16%). Five percent had had prior PTCA, 4% bypass surgery and 4% heart valve replacement. The mean left ventricular ejection fraction in the 57% in whom it was available was 61 ± 16%; mean LA diameter was 42 ± 6 mm (Table 1).

Seventy-six percent of the patients were on anticoagulants at the time of assessment, 61% were receiving some antiarrhythmic therapy, and 42% were taking AV nodal blocking drugs. Whether patients were on any antiarrhythmic drugs or AV nodal blocking drugs was not related to any QoL outcome measured. Most patients (90%) had some symptoms during AF, including palpitations in 68%, fatigue in 62% and shortness of breath in 60%.

Table 1. Demographic Characteristics for Groups Established for This Study

	AF Patients (n = 152)	PTCA Patients (n = 69)	Healthy Subjects (n = 47)
Age (yrs)	58 ± 12	62 ± 9*	54 ± 14
Gender (% male)	73%	79%	44%*
Left atrial size (mm)	(n = 56), 42 ± 6		
Left ventricular ejection fraction (%)	(n = 86), 61 ± 16	(n = 47), 54 ± 12*	

*$p < 0.05$ compared with AF group. All values are mean ± SD.

AF = atrial fibrillation; Healthy Subjects = individuals without serious illness or cardiac history from St. Michael's Hospital, Canada; PTCA = percutaneous transluminal coronary angioplasty; PTCA Patients = Patients 6 months after percutaneous transluminal coronary angioplasty.

More than half the patients (60%) had AF episodes, subjectively, more often than once per week; 22% had episodes between once per week and once per month; and 18% had episodes less often than once per month. The average duration of the episodes, as judged by the patients, was 23% lasting <1 h, 39% lasting between 1 h and the whole day and 39% lasting more than a day at a time (University of Toronto Arrhythmia Scale).

Fifty-one percent had been cardioverted on at least one occasion in the past, with a mean of 1.2 ± 1.4 cardioversions overall. Nearly half of all patients (44.6%) had been to the emergency room at least once in the previous year, and 51% had been hospitalized for their AF at least once in the previous year. Most patients had been to visit their specialist on at least one occasion (89.8%) with a median of three visits per year for each patient. A third of all patients (33.1%) had five or more specialist visits in the previous year (University of Toronto Arrhythmia Scale).

Healthy control group. The group of 47 healthy subjects was 45% men with a mean age of 54 ± 14 years (Table 1). There was a significantly greater proportion of men in the AF group compared with the group of healthy subjects ($p = 0.0025$), and AF patients were significantly older than healthy subjects ($p = 0.0329$). Ventricular function information was unavailable from the healthy individuals although their exercise tolerance as measured by the SAS was excellent (92 ± 14, range 58 to 100).

Cardiac control patients. The clinical characteristics of the control groups are listed in Table 1. Cardiac controls, all of whom had coronary disease with prior angioplasty, were significantly older ($p = 0.001$) and had worse left ventricular function ($p = 0.004$) than patients with AF.

Health-related QoL. The scores for the generic SF-36 instrument for which data is available in all control groups are presented in Table 2. The data for the Illness Intrusive-

Table 2. SF-36 Quality of Life Scores Across AF and All Control Groups*

SF-36 Scale	AF Patients (n = 152)	PTCA Patients‖ (n = 69)	PTCA Patients¶ (n = 78)	CHF Patients (n = 216)	Post MI Patients (n = 69)	Healthy Subjects (n = 47)
General health	54 ± 21	51 ± 23	65 ± 22†	47 ± 24†	59 ± 19‡	78 ± 17†
Physical functioning	68 ± 27	60 ± 29	76 ± 25‡	48 ± 31†	70 ± 26	88 ± 19†
Role physical	47 ± 42	47 ± 45	71 ± 39†	34 ± 40†	51 ± 39	89 ± 28†
Vitality	47 ± 21	48 ± 26	60 ± 20†	44 ± 24	58 ± 19†	71 ± 14†
Mental health	68 ± 18	74 ± 18	75 ± 16†	75 ± 21†	76 ± 16†	81 ± 11†
Role emotional	65 ± 41	64 ± 44	83 ± 35†	64 ± 43	73 ± 38	92 ± 25†
Social functioning	71 ± 28	74 ± 29	87 ± 21†	71 ± 33	85 ± 21†	92 ± 14†
Bodily pain	69 ± 19	68 ± 17	73 ± 27	63 ± 31‡	73 ± 25	77 ± 15‡

*$p < 0.05$, compared with AF patients; †$p < 0.001$, compared with AF patients; ‡All values represent raw mean scores ± SD, higher scores represent better quality of life.

AF = atrial fibrillation patients; CHF = congestive heart failure patients, from Ware, JE, Jr. (15); Post-MI = patients with recent myocardial infarction, from Ware, JE, Jr. (15); PTCA Patients‖ = patients 6 months after percutaneous transluminal coronary angioplasty, from St. Michael's Hospital, Toronto, Canada; PTCA Patients¶ = patients after percutaneous transluminal coronary angioplasty from Krumholz et al. (9); SF-36 = Medical Outcomes Study Short Form 36.

ness Scale (a measure of general health and well being), the Symptom Activity Scale (a measure of physical functioning) and Symptom Burden (based on symptom frequency and symptom severity from a symptom checklist) are presented for the study group and the control populations created particularly for this study in Table 3.

QoL in AF patients compared with healthy controls. Across all scales, both the disease specific and generic QoL was significantly worse in the AF patients compared with the controls. The magnitude of these differences was approximately a full standard deviation unit in almost all cases. Using a modified stem to reflect their normal status, the healthy control group provides an estimation of "ceiling" effects when these disease-based scales were applied with scores on illness intrusiveness of 28 ± 19 (maximum 30), global life satisfaction of 80 ± 12 (maximum 100) and symptom checklist frequency of 10 ± 6 (minimum 0) and 8 ± 5 on severity (minimum 0). All of these numbers are significantly elevated in the AF patients with, for example, illness intrusiveness rising to 35 ± 15 and symptom severity rising to 19 ± 8 and symptom frequency rising to 22 ± 10. Similarly, the Goldman Specific Activity Scale, a measure of functional capacity was 93 ± 11 in healthy controls, falling to 75 ± 20 in AF patients. There were similar profound (1.3 to 2.0 SD unit) differences on measures on SF-36 instruments subscales in AF patients compared with healthy controls (Table 2).

QoL in AF patients compared with cardiac controls. The published PTCA control group had better QoL scores than the PTCA control group created for the study. The PTCA study-created cohort were all derived from the one Canadian center (which entered 35% of the AF study group) and perhaps reflects a significantly greater symptom burden before intervention in patients referred for tertiary care services in Canada (16). Nonetheless, across all domains of the SF-36, AF patients scored either worse than (published group) or the same as study-created PTCA patients, despite the fact that PTCA patients were older, had worse left ventricular function and required a major procedural intervention. The relative impairment of QoL in AF patients compared with angioplasty control groups was similar in both physical and psychological domains of the generic SF-36 scale.

In the congestive heart failure comparator group, physical functioning scores were all worse than the AF group, with the exception of vitality, which was as impaired in the AF group as in patients with heart failure (47 ± 21 vs. 44 ± 24, p = NS). In contrast, psychological and social scales were either significantly better (mental health 68 ± 18 vs. 75 ± 21, $p < 0.01$) or the same (role emotional, social) in congestive heart failure patients compared with the AF group. Similarly, AF patients, despite younger age and better left ventricular function, were either significantly more impaired (general health, vitality, mental health, social

Table 3. Quality of Life Scores Across AF and Study Specific Control Groups

Domains	Scale	AF Patients (n = 152)	PTCA Patients‖ (n = 69)	Healthy Subjects (n = 47)
General Health and Well-Being	Global Life Satisfaction*	62 ± 20	68 ± 18‡	80 ± 12†
	Illness Intrusiveness	35 ± 15	39 ± 17	28 ± 19‡
Functional Capacity (SAS)	Functional Capacity (SAS)*	75 ± 20	72 ± 22	93 ± 11†
Symptom Burden	Symptom Frequency (SCL)	22 ± 10	16 ± 10‡§	10 ± 6†
	Symptom Severity (SCL)	19 ± 8	13 ± 9§	8 ± 5†

All values represent raw mean scores ± SD; *Higher scores represent better QoL; †$p < 0.001$, compared with AF patients; ‡$p < 0.05$, compared with AF patients; §$p < 0.01$, compared with AF patients.

AF = atrial fibrillation; PTCA Patients‖ = patients 6 months after percutaneous transluminal coronary angioplasty, from St. Michael's Hospital, Toronto, Canada; SAS = Specific Activity Scale; SCL = symptom checklist.

Table 4. Relationship Between "Objective" Indexes of Disease Burden and "Subjective" Quality of Life Measures*

	Left Atrial Dimension	Left Ventricular Ejection Fraction	NYHA Class	AF Frequency	AF Duration
General health (SF-36)	0.06†	0.01	0.00	0.05†	0.00
Mental health (SF-36)	0.00	0.02	0.03†	0.00	0.00
Physical function (SF-36)	0.04†	0.01	0.02	0.04†	0.02
Social function (SF-36)	0.02	0.00	0.01	0.03†	0.01
Functional capacity (SAS)	0.05†	0.00	0.04†	0.04†	0.04†
Cardiac symptom frequency (SCL)	0.00	0.00	0.03	0.05†	0.01
Cardiac symptom severity (SCL)	0.00	0.00	0.05†	0.05†	0.00

*Correlation coefficients between objective and subjective indexes. Despite statistical significance, the highest correlation accounts for no more than 6% of variance in the general health domain. See text for further discussion. †$p < 0.05$.
AF = atrial fibrillation; NYHA = New York Heart Association; SF-36 = Medical Outcomes Study Short Form 36.

function) or equivalently impaired (physical function, role physical, role emotional and bodily pain) as post-MI patients.

The QoL instruments for which study-created comparator groups only can be used show similar trends. Atrial fibrillation patients were the same as the PTCA group on illness intrusiveness and the Specific Activity Scale and significantly worse than the PTCA group on global life satisfaction (62 ± 20 vs. 68 ± 18, $p < 0.05$). The AF group was also significantly worse on measures of symptom frequency and severity than the PTCA group (22 ± 10 vs. 16 ± 10 and 19 ± 8 vs. 13 ± 9, both $p < 0.01$).

Relationship between objective measures of disease and subjective illness states. In a separate analysis, we examined potentially confounding variables that may also affect QoL. Variables such as left ventricle grade on echocardiography, ejection fraction, frequency and duration of AF episodes (from the University of Toronto AF Severity Scale), number of prior cardioversions, NYHA class and antiarrhythmic medications were examined by univariate analyses to determine if these variables were related to measures of physical functioning (SF-36), mental health (SF-36) or global well being. Significant variables identified by univariate analyses were entered into a hierarchical regression analysis controlling for age and gender. New York Heart Association class and AF episode frequency were significantly related to SF-36 physical function scores ($p < 0.02$ and $p < 0.04$ for regression coefficients, respectively) but together accounted for only <6% of total variability in scores ($r^2 = 0.03$ to 0.02). Similarly, both variables also predicted global well being ($p < 0.01$, $p = 0.05$, respectively) but accounted for only 8% of variability in total well being scores. Table 4 provides all independent correlation coefficients for each measure and QoL domains and shows the relatively poor correlation of QoL scores with 'objective' indexes.

DISCUSSION

The main result of this trial is that health related QoL, in an unselected consecutive population of tertiary care referred, symptomatic, relatively young patients with intermittent AF, is markedly impaired compared with a healthy index population and is similar on most scales to the health impairment seen in four different cardiac control groups (after angioplasty [published or study-created], heart failure and postinfarction), all of whom have a greater degree of structural heart disease. As well, we have found that the extent of subjective QoL impairment is poorly related to traditional objective measures of illness severity, such as frequency, duration, cardiac dysfunction and NYHA class. Furthermore, the other more disease-related impairments in AF patients (illness intrusiveness, physical activity and specific symptoms) were as poor or worse than that seen in the study-created post-PTCA comparator group.

Objective versus subjective measures. The most commonly employed methods to evaluate the success of therapies in AF are the time to first recurrence of documented AF or other measures focused around the frequency or duration of events. Although such end points are unambiguous, their use implies that it is the frequency and duration of the arrhythmia per se that determines the extent of patient suffering. Our data suggests that from the patient's subjective perspective, this may not be so.

Although it may seem counterintuitive that physical dimensions of QoL are poorly related to exercise capacity and measures of left ventricular function, this result is consistent with previous findings that demonstrate that formal measures of left ventricular dysfunction are poorly related to NYHA class and exercise capacity in a population of heart failure patients (17). Our results suggest that the subjective patient-perceived effects of AF on QoL not only extend to the physical and somatic dimensions but also impact on the social and emotional aspects of life and overall health quality. Such global impairment of life quality may be characteristic of many other chronic relapsing illnesses with an unpredictable clinical course. Our results suggest that, like many chronic conditions, AF leads to impairment of all domains of QoL independent of the objective severity of the underlying disease.

Perhaps surprisingly, patients with recent PTCA, had similar or greater QoL impairment compared with the AF patients. This was despite the fact that they were significantly older and tended to have worse left ventricular function. The AF population in this study had QoL scores

similar to those post-MI (15), and, at least on the Illness Intrusiveness Scale, AF patients perceived their illness to be as intrusive in their everyday lives as patients on chronic hemodialysis (13).

Other studies. This is the largest study of QoL in a series of consecutive patients with any form of AF. There is limited serial QoL data available from small, highly selected case series assessing the effects of AV junction ablation in patients with chronic AF. These studies have shown that the baseline measures of impairment in QoL are similar in magnitude to those seen in the much larger samples of this study. More importantly, these trials have generally shown very significant improvements in QoL commensurate with therapeutic interventions. These improvements suggest the inherent validity of the QoL measures. For example, in 22 patients with chronic AF assessed before and six months after ablation, QoL impairment on some of the SF-36 subscales improves, for example, on the social functioning scale, from 60.7 ± 18 to 82.1 ± 17, a return to a level similar to that of published age-matched normal controls (12,15). Other physical functioning subscales showed similar dramatic improvements. Brignole et al (18,19) showed that catheter AV junctional ablation for patients with chronic AF led to significant improvement in locally constructed, and less well validated, symptom burden scales (palpitations, dizziness, breathlessness) but not to changes in published validated instruments. Lastly, from a larger group of 107 patients selected for AV nodal ablation, general QoL improved and health care utilization decreased after ablation (20). The scale used for health care measurement in this study, however, was locally constructed and of unclear validity. Nonetheless, the data supports that QoL measurement is a bonafide end point for efficacy assessment in these intervention trials with an unknown amount of selection bias with respect to the relatively small numbers of patients entered into these trials.

Implications for research. The results of this study do not necessarily imply that eliminating AF or markedly reducing its frequency and duration is unimportant or that the latter may not contribute in any way to patient well being. Atrial fibrillation itself may independently cause worsening of left ventricular dysfunction (2), increased stroke risk (21) and increase health care resource consumption (3), apart from the subjective dimensions of illness. However, our observations emphasize that the subjective dimensions of an illness are important in the assessment of disease severity and provide data that will help enhance the use of these measures in planning the study of patients with AF. We have found that, despite relatively preserved left ventricular function, perceived symptoms during AF are significant and commensurate with symptoms in populations with more 'disease' as conventionally defined. The data also provide opportunities for the sample size estimates with respect to therapeutic interventions. The minimally appropriate effect size for interventions based on QoL is not clear. Nonetheless, in the psychometric literature, it is generally felt that changes in the order of 0.5 SD units are significant, and at least moderate in nature (22). We would emphasize that the inherent difficulty in interpreting individual QoL scales is no different than similar difficulties that are inherent in assessing biological measures with respect to individual patient symptomatology (23). Nonetheless, for a population-based viewpoint, the data provided by this larger consecutive series allows sample size estimates for intervention trials, in exactly the types of patients now typically entered into trials of investigational AF therapies.

Study limitations. Since all the data has been derived from tertiary care referral centers, there is concern over potential selection bias. However, all patients were consecutive and unselected, other than by referral to a tertiary care center. Virtually all investigational AF therapies are likely to be initiated at investigational centers in similar tertiary care referral centers. The controls used for comparative analysis in this study are important. We have used a standard, population-based normative control data for both heart failure and MI. An angioplasty population was chosen as a comparator largely on the basis that such a population marks a group of patients who have coronary artery disease and generally continue to consume medications and health care resources (24). As well, given the nature of the intervention, one may well expect significant existential concerns on the part of patients that would impact health-related QoL. To help make the PTCA comparator group more balanced with respect to selection bias via referral to a tertiary care center, two such groups were used. We found that the study-created PTCA comparator group was worse off than the published one, with commensurate impairments in QoL as the patients with AF.

Two of the scales used in our analysis (Illness Intrusiveness and Symptom Severity Scales) are designed for patients who have particular medical conditions. This, of course, is not the case with respect to the healthy control populations. Accordingly, the utility of the data from the healthy population could be considered not relevant. We would only argue that the inclusion of these scales, albeit modified for the healthy, provide further validity to the data obtained. Even though healthy patients should, by definition, have little in the way of arrhythmia-related symptoms or illness intrusiveness, their inclusion provides an opportunity to assess "ceiling" effects for scales designed for patients with actual conditions.

Conclusions. We have found that subjective health-related QoL in patients with intermittent AF is significantly impaired and commensurate with that in patients with significant cardiac disease and much worse than healthy controls. These impairments showed poor correlations with more 'objective' indexes of AF disease severity. As well, given that a host of investigational therapies for patients with intermittent AF are now being assessed from tertiary care referral centers, the data provided in this study allows for sample size estimations for health QoL end points in the assessment of therapies in AF.

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