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Responsiveness of AF6, a new, short, validated, atrial fibrillation-specific questionnaire—symptomatic benefit of direct current cardioversion

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Abstract
Objectives To measure the effects on symptoms of electrical cardioversion (DC) in patients with atrial fibrillation (AF) by means of a new, short, validated, AF-specific questionnaire, the AF6.
Methods One hundred eleven patients (67±12 years, 89 men) were screened before and 12±3 days after DC using AF6, covering 'breathing difficulties at rest', 'breathing difficulties on exertion', 'limitations in day-to-day life due to atrial fibrillation', 'feeling of discomfort due to atrial fibrillation', 'tiredness due to atrial fibrillation', and 'worry/anxiety due to atrial fibrillation'. A single global score was calculated. The Toronto AF Symptoms and Severity Check List (AFSS) and the generic SF-36 were also administered. Patients in sinus rhythm at 12±3 days (n=56) were defined as responders and patients in AF (n=55) as non-responders.
Results The mean single global score decreased in all patients (18±12.4 to 13±11.6, $p<0.0001$) and in responders (22±14 vs. 12±12, $p<0.01$) but not in non-responders (14±9 vs. 14±11, N.S). The AFSS frequency scores decreased from 14.5±7.7 to 9.5±7.8 in responders, p=0.001, but not in non-responders. There was a strong correlation between changes in the AF6 and the SF-36 regarding four of the six items. Effect sizes of AF6 ranged from 0 to 0.52 in all patients, in responders from 0.10 to 0.85 and in non-responders from −0.23 to 0.34, the highest figures consistently referring to 'tiredness due to atrial fibrillation'.
Conclusions The symptom scores measured by AF6 decreased significantly, especially in responders. AF6 demonstrated adequate responsiveness to change, and effect sizes were mostly moderate, in responders moderate to high.

Keywords Atrial fibrillation · AF6 · Responsiveness · Symptoms · AF specific instrument

1 Introduction

Patients with atrial fibrillation (AF) can experience anything from no to unbearable symptoms. The symptoms often have an impact on their health-related quality of life (HRQL) [1–3] and frequently cause patients to seek medical help. As symptoms in AF are so diverse, it may be difficult to estimate whether an individual patient would benefit symptomatically from a treatment attempt, e.g., cardioversion [4, 5]. No single symptom is truly AF specific, however, and almost any of the symptoms could also be caused by a concomitant condition. Evaluating the symptoms in a patient with AF may thus be a challenge, and there is still an unmet need for tools that can capture the patient-reported symptoms caused by AF.

At present, the generic Short Form 36 (SF-36) is the most frequently used tool to assess HRQL and is also used in patient populations with AF [6–10]. The AF disease-specific Toronto AF Symptoms and Severity Check List (AFSS) is frequently used to assess symptoms and covers both the frequency and the severity of AF episodes [7, 8,

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10–12]. We have previously reported the psychometric validation of a new, disease-specific, very short questionnaire, AF6, which was developed as an instrument to assess the baseline symptom burden and to be responsive to changes due to treatment [13]. The present report evaluates the ability of the AF6 to detect change following elective direct current electrical cardioversion (DC) in patients with persistent AF.

2 Patients and methods

Patients with persistent AF scheduled for DC were asked to participate in the study. There were no pre-specified exclusion criteria other than inability to understand and respond to the questions or unwillingness to participate. The patients were familiar with the term atrial fibrillation, received information about the instrument, and completed the instrument prior to any clinical examination or intervention (the day before DC and at their follow-up visit 12±3 days after DC). Neither the study nurse nor the patient knew the actual rhythm until after the questionnaire was completed. Patients were interviewed about their underlying heart diseases and other co-morbidities, and their medical and specific arrhythmia history. A 12-lead electrocardiogram (ECG) and an echocardiography were performed according to the clinical routine. The study was part of the quality assurance program of the clinic. Elective DC took place in a nurse-led outpatient clinic with physician back-up. After 4 weeks with a therapeutic international normalized ratio (INR), the patients were invited to the clinic the day before DC for a 30-min information and preparation visit with routine laboratory tests, a 12-lead ECG and blood pressure measurements. The DC was performed the following day under a short general anesthesia with propofol, using biphasic waveform shocks of 70-200J. After DC and 2-3 h of observation, the patient met their cardiologist before discharge. All patients returned to the AF nurse 12±3 days after DC for a rhythm control. Patients who were converted to sinus rhythm (SR) and had SR at the follow-up visit were defined as clinical responders, while those who were in AF at follow-up were defined as clinical non-responders.

2.1 AF6

The six items of AF6 summarize the most frequent problems named by patients in their contact with the nurse at the AF clinic. They focus on: item 1 'breathing difficulties at rest', item 2 'breathing difficulties on exertion', item 3 'limitations in day-to-day life due to atrial fibrillation', item 4 'feeling of discomfort due to atrial fibrillation', item 5 'tiredness due to atrial fibrillation' and item 6 'worry/anxiety due to atrial fibrillation'. Patients choose a number on a Likert scale from 0 to 10, where 0 means no and 10 severe symptoms or difficulties, and the scores of the six questions are added into a single global score. The recall period for the instrument is the most recent 7 days.

AF6 has undergone psychometric validation, showing adequate internal consistency reliability with a Cronbach's α of 0.81. Test-retest reliability was done in patients who failed DC and was >0.70 for three of the six items. The patients also completed the SF-36 generic quality of life instrument [6] and the AFSS [12]. Data gathered in the SF-36 were used in the validation process of the AF6, and the AFSS was chosen as a frequently used measure to provide additional information, although it has not been validated in its Swedish translation. The Pearson correlation coefficients were used to assess the convergent and discriminant validity, and items 1 and 2 correlated strongly or moderately well with four of the eight SF-36 domains, item 5 with five domains, item 7 with six and items 4 and 6 with all eight domains. All items at baseline were compared against three levels of symptom severity obtained from the AFSS. "No", "mild", "moderate" and "severe" symptoms were reflected in low to high scores showing known-groups validity. Finally, the items were tested individually in the Rasch analysis and represented one domain, their range of locations being −0.43 to +0.41 [13].

3 Statistical methods

Values are expressed as mean ± standard deviations (SD) and as median with interquartile ranges. Student's t test was used to test differences between responders and non-responders. All p values are two-tailed and considered statistically significant if below 0.05. Correlation coefficients of changes in the items of the new instrument and changes in the SF-36 domains were determined, after adjustment for Bonferroni multiplicity at a level of $p<0.0001$ statistical significance. Effect sizes and standardized response mean values were calculated overall and in responders (patients who achieved and maintained SR) and non-responders (patients who did not achieve SR or relapsed into AF after an initially successful DC) using the following formula: mean score at follow-up—mean score at baseline/standard deviation of baseline scores [14]. The effect size was characterized as small (>0.2 but <0.5), moderate (0.5-0.8) or large (>0.8) according to guidelines proposed by Cohen [15].

4 Results

In total, 137 patients were identified and eligible, 11 of whom did not wish to participate (for reasons of a lack of time and not wishing to answer questions about their symptoms). One was not included because of language problems. Fourteen patients were excluded because of non-therapeutic INR values (n=3),

Table 1 Baseline characteristics

	Responders at 12±3days		
	All	Yes	No
Number of patients	111	56	55
Men, *n* (%)	89 (80)	46 (82)	43 (78)
Age, years	67±12	66±11	67±13
Weight, kg	86±20	85±17	86±22
Length, cm	178±9	177±9	178±10
BMI	27±5	27±5	27±5
Episode duration of AF, months	5.8±8.1	4.8±5.4	6.9±10.1
First episode of AF (*n*)	36	20	16
Hypothyreosis	2 (2)	1 (2)	1 (2)
Hyperthyreosis	2 (2)	2 (4)	0 (0)
Hypertension	45 (41)	26 (46)	19 (35)
Angina pectoris	18 (16)	10 (18)	8 (15)
Previous acute myocardial infarction	17 (15)	7 (13)	10 (18)
Previous CABG	12 (11)	7 (13)	5 (9)
Previous PCI	9 (8)	3 (5)	6 (11)
Diabetes mellitus	13 (12)	5 (9)	8 (15)
Heart failure	25 (23)	13 (23)	12 (22)
Dilated CMP	11 (10)	6 (11)	5 (9)
Hypertrophic CMP	3 (3)	3 (5)	0 (0)
Stroke	6 (5)	3 (5)	3 (5)
TIA	7 (6)	0 (0)	7 (13)
Venous trombosis	1 (1)	1 (2)	0 (0)
Peripheral arterial embolism	1 (1)	0 (0)	1 (2)
Pulmonary embolism	1 (1)	1 (2)	0 (0)

Mean±SD percent within brackets, *BMI* body mass index, *CABG* coronary artery bypass-surgery, *CMP* cardiomyopathy, *PCI* percutaneous coronary intervention, *TIA* transient ischemic attack

pathological echocardiography (n=1), inadequate medication (n=1) or for administrative reasons (n=9). Thus, the study population consisted of 111 patients, 89 men and 22 women. At DC, 102 (92%) patients converted to SR, 93 of whom (84%) had SR at discharge and 56 (50%) who converted to SR and remained in SR at 12±3 days. Nine patients did not convert to SR at all, and nine patients relapsed within 2 h. Patient baseline characteristics are shown in Table 1. The mean duration of the ongoing AF episode was 5.8± 8.1 months. Most patients were on rhythm control agents at the time of DC, and there was no change in medication in most patients between the DC and the follow-up visit.

Table 2 Medications were stable between visits before and after DC cardioversion

	Before DC Nonresponders (n=55)	12±3days after DC Nonresponders (n=55)	Before DC Responders (n=56)	12±3days after DC Responders (n=56)
Waran	55 (100)	55 (100)	56 (100)	56 (100)
Digoxin	12 (22)	8 (15)	9 (16)	6 (11)
Amiodarone	5 (9)	5 (9)	6 (11)	6 (11)
Sotalol	15 (27)	13 (24)	12 (21)	15 (27)
β-blocker	26 (47)	31 (56)	35 (63)	32 (57)
Diuretics	22 (40)	21 (38)	13 (23)	16 (29)
Lipid-lowering drug	15 (27)	16 (29)	22 (39)	20 (36)
ARB	10 (18)	9 (16)	8 (14)	9 (16)
ACE-I	10 (18)	12 (22)	18 (32)	19 (34)
Calcium blocker	10 (18)	11 (20)	8 (14)	7 (13)
Potassium	4 (7)	5 (9)	1 (2)	2 (4)
Spironolactone	3 (5)	4 (7)	4 (7)	5 (9)
Sleep and Sedatives	9 (16)	8 (15)	6 (11)	6 (11)

Percent within brackets

ARB angiotensin II receptor antagonist, *ACE-I* angiotensin-converting enzyme inhibitor

4.1 The AF symptom burden at baseline

The mean single global score (composite of items 1-6) at baseline was 18±12.4. The items with the highest scores at baseline were 'tiredness due to atrial fibrillation' (item 5), 4.5±3.2, and 'breathing difficulties upon exertion' (item 2), 4.5±3.2. The items with the lowest scores were 'breathing difficulties at rest' (item 1), 1.0±1.6, and 'worry/anxiety due to atrial fibrillation' (item 6), 2.1±2.9 (Table 2).

No patient scored 0 in all six items before or after DC. At baseline, the most frequent symptoms were 'tiredness due to atrial fibrillation' (item 5) and 'breathing difficulties upon exertion' (item 2) and were found in 83% and 80% of the patients, respectively. The least frequent symptoms at baseline, 'breathing difficulties at rest' (item 1) and 'worry/anxiety due to atrial fibrillation' (item 6) were found in 36% and 48% of the patients, respectively. The other items, 'limitations in day-to-day life due to atrial fibrillation' (item 3) and 'feeling of discomfort due to atrial fibrillation' (item 4) were present in 65% and 64% of the patients, respectively. At baseline, the mean single global score and the mean scores per item were consistently higher in subsequent responders than in non-responders, with the exception of 'breathing difficulties at rest' (item 1). The single global score and the mean per item score decreased after conversion to SR in responders but did not change in patients remaining in or relapsing to AF.

The means and SD of each item are shown in Table 3. When the mean value of each item was calculated and included only patients with a value of ≥1 on the Likert scale (i.e., included only patients experiencing the symptom posed in the question), the figures for each item were 2.1 (item 1), 5.4 (item 2), 5.1 (item 3), 3.9 (item 4), 5.7 (item 5) and 5.7 (item 6). This analysis shows that 'worry/anxiety due to atrial fibrillation' (item 6), when present, was an important symptom, while 'breathing difficulties at rest' (item 1) was not.

4.2 Symptom reduction after DC cardioversion

The single global mean score decreased from 18±12.4 to 13±11.6, $p<0.0001$ in the total study population. There were statistically significant decreases in four of the items (Table 3). The single global mean score decreased in responders from 22±14 to 12±12, $p<0.01$, but not in non-responders, 14±9 and 14±11.

4.3 Responsiveness of AF6

The mean changes in individual AF6 item scores ranged from −0.01 to 1.7 (statistically significant in four items, $p<0.005$), while the mean changes in individual items in responders were 0.2 to 2.8 (statistically significant in five items $p<0.005$) versus none in non-responders. The effect

Table 3 Mean scores per item at baseline and after 12±3 days. Scores refer to a 10-point Likert scale

	All, $n=111$					Responders, $n=56$					Non-responders, $n=55$				
	Baseline	SD	12± 3days	SD	p	Baseline	SD	12± 3days	SD	p	Baseline	SD	12± 3days	SD	p
Breathing difficulties at rest	1.0	1.6	1.0	1.7	0.91	1.2	1.8	1.0	1.8	0.31	0.8	1.4	0.9	1.5	0.32
Breathing difficulties upon exertion	4.5	3.2	3.4	3.0	0.0002	5.0	3.4	3.2	3.0	0.0001	3.9	2.8	3.6	3.0	0.16
Limitations in day-to-day life due to atrial fibrillation	3.3	3.1	2.5	2.6	0.0091	4.4	3.3	1.5	2.3	<0.0001	2.3	2.6	2.9	2.7	0.20
Feeling of discomfort due to atrial fibrillation	2.5	2.9	1.7	2.4	0.0031	3.4	3.3	1.5	2.3	<0.0001	1.7	2.1	1.9	2.5	0.66
Tiredness due to atrial fibrillation	4.5	3.2	2.8	2.9	<0.0001	5.3	3.3	2.5	3.0	<0.0001	3.7	2.9	3.1	2.9	0.11
Worry/anxiety due to atrial fibrillation	2.1	2.9	1.7	2.3	0.08	2.7	3.2	1.8	2.4	0.01	1.5	2.3	1.6	2.1	0.91

size (ES) ranged from 0 ('breathing difficulties at rest', item 1) to 0.52 ('tiredness due to atrial fibrillation', item 5), and the SRM ranged from 0 ('breathing difficulties at rest', item 1) to 0.53 ('tiredness due to atrial fibrillation', item 5; Table 4). ES in responders were between 0.10 ('breathing difficulties at rest', item 1) and 0.85 ('tiredness due to atrial fibrillation', item 5) with corresponding SRMs of 0.09 and 0.83, respectively (Table 4). ES in non-responders were small and ranged between −0.23 and 0.34.

4.4 Toronto AF symptoms and severity check list

At baseline, all patients reported some symptoms according to the AFSS. The most frequently reported symptoms were tiredness, irregular heart rhythm and dyspnea on exertion. The patients who reported symptoms "always" and "frequently" were those with a notable reduction after DC, while those with symptoms "sometimes", "relatively rarely" or "never" were largely unchanged. At baseline, responders had a higher frequency score than non-responders, 14.5±7.7 versus 10.8±7.3, and a higher severity score, 12.2±7.3 versus 8.6±5.8, respectively. Most symptoms were mild to moderate. At the 12±3-day follow-up, the frequency score of the responders had decreased from 14.5±7.7 to 9.5±7.8, p=0.0011, and the severity score from 12.2±7.3 to 7.7±7.1, p=0.0013. There was no change in frequency in non-responders, 10.8±7.3 versus 11.5±8.0, N.S., or in severity score, 8.6±5.8 versus 8.7±5.7, N.S.

4.5 SF-36

The correlation coefficients between changes in the AF6 instrument and changes in the SF-36 domains are shown in Table 4. There was a strong correlation between the two instruments regarding four of the six remaining items in the AF6: between 'breathing difficulties upon exertion' (item 2) and physical functioning and vitality; between 'limitation in day-to-day life due to atrial fibrillation' (item 3) and physical functioning, role physical and vitality; between 'feeling of discomfort due to atrial fibrillation' (item 4) and physical functioning and vitality; and between 'tiredness due to AF' (item 5) and physical functioning, vitality and role-emotional. There was no correlation between changes in 'breathing difficulties at rest' (item 1) and 'worry/anxiety due to atrial fibrillation' (item 6) and changes in any of the domains of the SF-36.

5 Discussion

The AF6 showed adequate responsiveness to the changes in symptoms caused by restoration and maintenance of SR after successful DC cardioversion. In addition, our analyses showed that the results of AF6 may be presented as a mean single global score including all six items. The mean single global score decreased significantly, as did the mean scores of four of the six items. The importance of SR at 12±3 days was evident in that the mean scores of five of six items decreased in responders as compared to no change among non-responders.

'Breathing difficulties at rest' (item 1) was the least frequent symptom and, when present, had low scores, indicating very low difficulties among the study population. In contrast, 'breathing difficulties upon exertion' (item 2) was the second most frequent symptom and showed high scores, indicating severe difficulties and can thus be regarded as a symptom of great clinical importance. When present, 'worry/anxiety due to atrial fibrillation' (item 6) was considered equally as important as 'tiredness due to atrial fibrillation' (item 5) and 'breathing difficulties upon exertion' (item 2). Worry/anxiety due to atrial fibrillation was most often present and improved among responders, while it remained unchanged among non-responders. The role of anxiety and depression has become more apparent in recent years [16, 17], and the results of the present study confirm their importance. In one study, higher levels of reported negative emotions were strongly associated with the reporting of a greater number of AF symptoms [18].

Table 4 Effect size and standardized response mean between baseline and 12±3 days after DC

AF6 Items	All		Responders		Non-responders	
	ES	SRM	ES	SRM	ES	SRM
Breathing difficulties at rest	0.01	0.00	0.11	0.10	−0.13	−0.13
Breathing difficulties upon exertion	0.32	0.33	0.52	0.52	0.09	0.12
Limitations in day-to-day due to atrial fibrillation	0.28	0.25	0.71	0.70	−0.24	−0.21
Feeling of discomfort due to atrial fibrillation	0.29	0.28	0.59	0.64	−0.13	−0.10
Tiredness due to atrial fibrillation	0.53	0.53	0.86	0.83	0.19	0.22
Worry/anxiety due to atrial fibrillation	0.15	0.16	0.28	0.34	−0.04	0.03

Effect sizes were characterized as small (>0.2 but <0.5), moderate (0.5-0.8) or large (>0.8)

Patients with AF may have a variety of symptoms, from none to unbearable [19–24]. Patients with few or no symptoms may not be candidates for DC, but it should be the patient who determines the level of symptoms. A simple instrument that can discriminate between patients who would benefit symptomatically from a DC and those who would not can therefore play an important role in the decision as to whether or not to cardiovert. However, it should also be kept in mind that there are indications for DC that are independent of symptoms.

While direct current DC has long been an effective treatment for terminating persistent AF [1, 4, 5], presently available pharmacological options have not been very effective in maintaining patients in long-term SR, nor have they been as safe or tolerable as would be desired. Immediately after restoration to SR, symptom relief and improvement of HRQL represent the improvements that patients expect; but with long-term maintenance of SR, signs of reverse remodeling can be observed [7–9, 21–26]. In our patients, we found a symptomatic benefit at 12± 3 days after DC. The reason for our follow-up period of 12± 3 days after DC was that little should have happened in the patient during this period except the change in rhythm. We allowed the first week for recovery after DC and applied a 7-day recall period.

In the present study, subsequent responders had higher symptom scores at baseline than subsequent non-responders, possibly a play of chance, since no selection was made at baseline. On the other hand there might be systematic differences between patients who are likely to maintain SR versus those less likely to maintain SR following cardioversion. We did not find any important differences in patient characteristics at baseline, although the AF episode duration was marginally shorter in responders. However, the patients who had most symptoms might have had the shortest AF history and/or least medical attention up to the time of DC.

In any symptom scale it is important to know the least change in score that can lead to a clinical improvement. The effect sizes of the items of the AF6 were calculated for the whole patient population together and separately for the subsequent responders and non-responders. The effect sizes were found to be moderate to low in the whole study population, consistently low in non-responders and high in one, moderate in three and low in two of the items among responders. Since patients with AF are very heterogeneous with regard to symptoms, effect sizes will change between treatments and study populations. Nevertheless, the AF6 showed an ability to detect change and was able to discriminate between more symptomatic and less symptomatic patients, indicating an ability to also detect change in populations with a more severe symptom burden.

6 Limitations

The study was carried out in a population of patients scheduled for DC who were consecutively enrolled. We do not know whether the AF6 instrument would have yielded the same information in other AF populations. Nevertheless, AF6 discriminated more symptomatic from less symptomatic patients. We compared the scores obtained the day before with those 12±3 days after DC. While this time may seem short, we wanted to be reasonably sure that the change in rhythm would be the only thing that occurred between the measurements.

7 Conclusions

The AF6 showed adequate ability to detect responsiveness to change and symptom scores measured by the AF6 decreased significantly after DC cardioversion. This was especially true in clinical responders in maintenance of SR demonstrating that SR is an important clinical anchor. Effect sizes were mostly moderate; and in responders, moderate to high.

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