

Review

The relevance of health related quality of life in paced patients

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Abstract

With the tremendous advances in cardiac pacing during the past four decades, cardiac pacemaker implantation is now a common clinical procedure. In recent years, the indications for permanent pacemakers have expanded. This increase in reasons for pacing and shift in mode of pacing have been caused by the evolution of pacemaker therapy from a life-saving measure (mortality), to one aimed at improving health-related quality of life (HRQoL). Until now the efficacy of pacing therapy has predominantly been measured using “objective” criteria. However, in recent years the importance of HRQoL as an outcome measure has increasingly been recognized as patients prefer quality over quantity of life.

In this review we describe the development and testing of Aquarel, a new developed HRQoL questionnaire for pacemaker patients, composed of a generic core module with disease specific add-ons. Current and future research to improve the Aquarel questionnaire is also described.

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In the Netherlands there is an increased implantation rate of cardiac pacemakers in patients of all ages over the past decade (Fig. 1). This increase in the number of implanted pacemaker-units and leads combined with a rising population age contribute to an increase in hospitalisation, care and follow-up. Until now the efficacy of pacing therapy has predominantly been measured using clinical outcomes such as improvement of prognosis, relief of symptoms, complications, technical failures and recalls. However, to evaluate the full spectrum of outcome of pacemaker therapy patient reported outcomes as well as clinical outcomes should be measured. In recent years the importance of health-related quality of life (HRQoL) as an outcome measure has increasingly been recognized [1,2]. This has particular relevance in cardiac pacing because the goal of therapy

for most patients with chronic disease is improvement in function, not cure [3]. These measures should be incorporated as one of the primary measures of outcome in the evaluation of new therapies in chronic diseases including cardiac pacing. Doing so, clinicians, patients, policy-makers, health care providers and HRQoL researchers gain experience with these measures.

To measure HRQoL, appropriate instruments should be used and a large number of questionnaires has been developed in the past two decades. However, in the field of cardiac pacing until recently several instruments were used to measure HRQoL that were not properly validated and applied [4–17]. Consequently these HRQoL data should be interpreted cautiously. HRQoL is typically measured either in a generic or a specific way. Generic means that an instrument gives information on several dimensions and is useful for a variety of illnesses, diseases and different (patient-) populations, allowing for comparison between these (patient-) populations. Disease specific questionnaires focus on dimensions most relevant for the disease under

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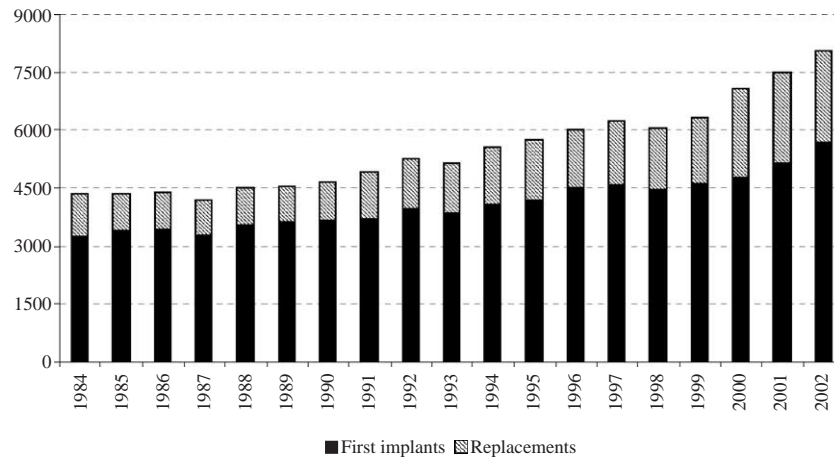


Fig. 1. Number of pacemaker implants 1984–2002 in the Netherlands, based on SPRN (Stitching Pacemaker Registratie Nederland) data.

study, or on patient characteristics frequently associated with a certain illness or disease. For proper HRQoL evaluation it is appealing to use a generic HRQoL questionnaire as a core module, with a disease specific module added to it. By doing so the advantages of generic and disease-specific questionnaires are combined [2]. In this way the measurements will be maximally valid and responsive to changes in health status of pacemaker patients. Furthermore, using a generic core comparisons can be made with other patient populations and the general public. Examples of questionnaires that have served as core module to which a disease specific module is added are the SF-36 (Short-Form-36, see below) [18], the EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, an integrated system for assessing the HRQoL of cancer patients participating in international clinical trials) [19] and the FACIT (Functional Assessment of Chronic Illness Therapy, a range of questionnaires that measure HRQoL for people with chronic illnesses) [20].

The SF-36 has been derived from the work of the Rand at Santa Monica during the 1970's, and has become a standard for measuring HRQoL [18,21]. It comprises 36 questions to be scored on 3–6 point scales. In spite of its short length it covers eight dimensions. It may be self-administered or used in personal or telephone interviews. It is an instrument which fulfils stringent criteria of reliability and validity, and has been used in various cardiovascular settings, including in patients with angina pectoris [22], aorta valve replacement [23], intra-cardiac defibrillators [24], syncope [25], radiofrequency catheter ablation [26], heart transplant [27], cardiac rehabilitation [28], heart failure [29] hypertrophic cardiomyopathy [30] and also once in pacemaker patients [17]. To help estimate the overall HRQoL impact, summary scores have been developed for some HRQoL instruments. For example, physical and mental health composite scores for the SF-36 are available [31]. Disease specific supplements for the SF-36 have been developed for angina pectoris [22], liver disease [32], kidney disease [33],

epilepsy [34], multiple sclerosis [35], smoking cessation [36], prostate cancer [37], and duodenal ulcer patients [38].

In the area of cardiac disease, there is only one example of a generic core module plus a disease specific add-on: the APQLQ (Angina Pectoris Quality of Life Questionnaire) [22]. It consists of the SF-36 as generic core and 5 AP specific domains: physical abilities, symptoms, emotional distress, patient complaints and life satisfaction.

The SF-36 covers several domains relevant for pacemaker patients, but does not incorporate questions on cardiac symptoms, which may limit sensitivity and responsiveness in pacemaker patients. For assessment of disease specific HRQoL in pacemaker patients, questionnaires developed for other cardiovascular diagnosis (i.e. the APQLQ or the Minnesota Living with Heart failure questionnaire for congestive heart failure) cannot be used, simply because of the differences in symptomatology and the consequent lack of content validity [39]. The disease specific module should qualify the following criteria: (1) cover a broad range of symptoms often experienced by pacemaker patients, (2) items organisable in multiple scales to aid interpretation, (3) exist of no more than 20–30 items to limit patient burden, and (4) of course be valid, reliable and responsive to change in health. Development and validation of such a disease specific module for pacemaker patients, to be added to the SF-36, resulted in the Aquarel questionnaire [40,41].

1. Aquarel

The development of Aquarel consisted of several steps: a preliminary version, based on existing questionnaires [2,42] and interviews with patients, was tested for its psychometric properties (structure, reliability, validity). The first full version of Aquarel with 4 scales was then tested for sensitivity to change. Based on these results, the cognition scale was dropped. The final version of Aquarel consists of 20 short and clear formatted items, and only takes about 10 min to fill out. Aquarel comprises 3 scales: arrhythmia (5

items), dyspnea and exertion (7 items) and chest discomfort (8 items), appendix. The psychometric properties of this questionnaire were shown to be satisfactory and suggest this instrument to be valid and reliable [40,41]. The inter-scale correlations within the Aquarel questionnaire as well as with the SF-36-domains were moderate demonstrating their individual value and distinctiveness. Repeatability or test–retest reliability in stable patients was very acceptable on group level as demonstrated by various techniques (intra-class correlations from 0.8 to 0.91). However, it should be recognized that the individual difference between test and re-test without a relevant change in health can be up to 20 points, which limits the usefulness of this instrument for evaluation of HRQoL in individual patients. However, this limitation holds for many HRQoL-questionnaires as well as for seemingly objective laboratory tests. The Aquarel met the standards for internal consistency with scores varying from 0.74 to 0.92. Analysis of the floor and ceiling effect showed that the percentage of patients with the maximum score was >20% in five scales of the SF-36 and in one scale of the Aquarel, whereas two scales (role emotional and role physical of the SF-36) had a high percentage of patients attaining the minimum score, Table 1 [40].

The hypothesized scale structure was supported by the data, demonstrating more impaired HRQoL with shorter distances walked on the 6-min walk test and with higher NYHA classification. The impact of cardiac pacing on HRQoL was quite strong in the major HRQoL fields: physical functioning and perceived health. A moderate impact was seen on mental health and dyspnea and exertion. The final questionnaire was composed as an eight domain general profile and a three domain specific profile. No

summary scores were calculated. It is not yet known whether Aquarel scores can be used to generate a valid single index, and this should be an item for additional testing and development. An overall score of the SF-36 with the Aquarel questionnaire is not desired because the possibility for comparison with other populations is then eliminated. During the validation process, Aquarel showed smaller standard deviations than the SF-36. This might imply that Aquarel cannot discriminate between different types of patients, as smaller standard deviations suggest a reduced spread in scores. However, in subsequent research the Aquarel discriminated between populations with different disease severity [43]. Therefore, the smaller standard deviations imply that Aquarel will be able to measure smaller increments in HRQoL than the SF-36.

2. Aquarel in trials

By using Aquarel in trials with pacemaker patients the full spectrum of relevant outcomes can be shown. This is of increasing importance since current FDA approval processes for new devices are a compromise between (a) the needs for expediency and encouraging innovation by the medical device industry but most of all (b) the need to ensure that new devices will contribute to improved patient outcomes compared to current treatment strategies [44].

A major aspect of evaluative instruments is responsiveness, i.e. the ability to detect clinically relevant change [45]. One aspect of the responsiveness of Aquarel, namely the sensitivity to change, was tested in two trials comparing different pacing modes. In the first trial (RASTAF II), preference of patients with atrial fibrillation (AF) for pacing with a novel ventricular rate stabilization (VRS) algorithm, a multi-center randomized crossover trial was tested [43]. It showed that VRS promotes ventricular rhythm regularity in AF without increasing mean heart rate. Patients with paroxysmal AF had a preference for VRS pacing, but this was not reflected by improved HRQoL scores on the SF-36 or Aquarel. A major cause for the lack of improvement in HRQoL is that the patient population under study was relatively well at baseline, leaving no or little room for improvement.

In the second trial (OASES, overdrive atrial septal stimulation multi-center trial), the effect of the pacing site on AF burden reduction, during DAO (dynamic atrial overdrive) pacing was evaluated [43]. It was shown that atrial overdrive pacing in patients with class I or II pacemaker indication and a history of atrial arrhythmia, was effective in reducing AF burden, in patients on anti-arrhythmic drugs. Lead positioning in the LAS (low right atrial septum) was more effective than in the RAA (right atrial appendage) in reducing AF burden. The reduction in burden was most pronounced in AF of short duration (less than 6 min). Baseline scores on the SF-36 and Aquarel were lower (worse) compared to the scores in the RASTAF

Table 1
Scores distribution and scales reliability of the SF-36, Aquarel and the APQLQ specific profile

	<i>n</i>	Means of scores	SD	% Floor	% Ceiling
<i>SF-36</i>					
Physical functioning	74	60.82	25.55	1.4	4.1
Social functioning	74	78.72	22.35	1.4	32.4
Role functioning, phys	74	52.03	43.15	29.7	37.8
Role functioning, emo	74	68.92	41.41	20.3	59.5
Mental health	74	71.80	20.88	0	9.5
Vitality	74	62.59	21.78	0	5.4
Pain	74	78.96	24.50	1.4	45.9
General health	74	57.83	22.21	1.4	97.0
<i>Aquarel</i>					
Chest discomfort	74	85.29	15.48	0	21.6
Dyspnea and exertion	74	64.03	20.37	0	6.8
Arrhythmia	74	80.95	16.40	0	18.9
<i>APQLQ</i>					
APQLQ Index	170	65.54	20.51	0	0.6
Sleep	168	80.06	27.16	0.2	56.5
Sexual Activity	146	62.50	38.42	15.8	41.1
Climatic conditions	166	78.92	25.07	0.1	56.8
Patients complaints	167	83.15	14.31	0	14.4

Table 2
Baseline SF36 scores of AF patients

Baseline SF-36	OASES ⁴³	RASTAF II ⁴³	Jessurun ³³	Bubien ³⁴	vdBerg ³⁵	Gronefeld ³⁶	Lonnerholm ³⁷	Erdogan ³⁸
Type and number of patients	PAF <i>n</i> =255	All AF <i>n</i> =184	PAF <i>n</i> =41	All AF <i>n</i> =22	PAF <i>n</i> =73	CAF <i>n</i> =252	All AF <i>n</i> =48	PAF <i>n</i> =30
Physical functioning	42.6	60.2	56.4	34.1	76.6	61	66.0	55.3
Social functioning	56.4	68.0	56.3	41.1	78.1	72	63.1	44.7
Role functioning, phys	19.2	51.2	15.3	7.2	49.7	36	29.3	37.6
Role functioning, emo	33.7	64.5	59.3	28.3	64.9	61	51.7	58.8
Mental health	55.2	70.1	63.3	58.3	72.2	65	69.7	38.8
Vitality	50.6	50.2	40.8	24.3	55.1	47	47.0	36.5
Pain	60.4	70.8	83.5	45.0	81.1	68	68.8	58.8
General health	51.0	52.9	54.4	48.0	59.6	49	54.6	45.9

PAF=paroxysmal AF, CAF=chronic AF, All AF=paroxysmal and chronic AF.

II trial. HRQoL improved on all Aquarel scales and on all scales of the SF-36 (except vitality) in both RAA and LAS patients, when the atrial overdrive pacing algorithm was enabled in spite of the elevation of the mean heart rate. The largest improvement in SF-36 domains was seen in pain, social functioning and physical functioning. However, the improvements, expressed as effect sizes, were larger for the Aquarel scales, which indicates the higher sensitivity to change of the Aquarel questionnaire compared to the SF-36.

The overall HRQoL improved after implantation of either type of pacemaker. However, no improvement in HRQoL was shown for VRS pacing in the patients of the RASTAF II trial, although patients with paroxysmal AF preferred VRS-on. In the OASES study an important improvement in HRQoL was measured during DAO, especially in the LAS patients. This might be due to inclusion of relatively different patients regarding HRQoL, also compared to other studies in patients with AF, Table 2.

Despite the fact that Aquarel discriminates between different patient populations, it does show ceiling effects. In the RASTAF II study, there was little room for improvement in HRQoL scores due to ceiling effects on the Aquarel as well as the SF-36. Still, in the Aquarel questionnaire this appears to be less outspoken, supporting the possible additive value of the Aquarel questionnaire. Patients in the OASES study showed much more impaired scores at baseline.

3. Aquarel in the future

Future research to improve the Aquarel questionnaire holds several challenges, such as the interpretation of observed change, an aspect of responsiveness. The one standard error of measurement values were calculated for each Aquarel scale; this is a proxy for clinical relevant change in health from the statistical point of view [46]. It would be interesting to know what change in HRQoL scores is clinically relevant for patients or clinicians. For instance, how many points do the HRQoL scores have to increase before the clinician registers an increase in NYHA classification, or, how much change is needed before patients regard themselves as improved or deteriorated.

Another issue is whether attempts should be made to eliminate the ceiling effects that Aquarel suffers from. This may be done by adding items to the questionnaire with particular discrimination in the higher scoring regions. However, the difference in SF-36 scores with the general population was already small in the RASTAF II population, so it questionable whether this will really attribute to a better performance of Aquarel.

Finally, current research is conducted to examine the need for forward and backward translation. Since the Aquarel questionnaire comprises mostly questions on symptoms, which are supposedly less influenced by culture, forward translation may be sufficient, without backward translation and resolving differences. In three languages (English, Serbian and French) the differences in HRQoL scores on Aquarel between single translated and forward and backward translated are tested. Furthermore, a study is on its way to assess the responsiveness of Aquarel to increased finetuning of pacemakers.

4. Conclusion

Patients with sinus node dysfunction, atrioventricular block or other bradyarrhythmias are, prior to pacemaker implantation, willing to exchange 5 years of pre-implant health for approximately 4 years in perfect health [47]. This indicates that patients prefer quality of life over quantity of life. In this perspective potential improvement in HRQoL is a critically important outcome measure in clinical trials of cardiac pacing and should be incorporated together with the more traditional outcomes of morbidity, mortality and outcomes of diagnostic test like echocardiography, or treadmill exercise capacity. Trials of interventions must show that the observed changes in these outcome measures due to these medical interventions are important and substantial enough to warrant further consideration in medical practice and policy planning [48].

To assess HRQoL in cardiac pacing as well as possible, Aquarel can be used in addition to the SF-36. When prospective randomized trials do not show clinical improvement but do show increased HRQoL scores on this instrument, a new device or therapy may be approved based on

such results. Further research is needed to demonstrate the links among medical interventions, clinical and psychological changes and HRQoL. In this way the practising clinician can better understand the clinical implications of these measures and health care planners can use them in setting priorities. However, it should be recognized that HRQoL scores are group scores making it hard to predict on individual level which patient will profit most by a certain pacing therapy. Documentation of the possible salutary effects of pacing therapies on HRQoL, using Aquarel, will provide more evidence of the value of medical care that is increasingly demanded by sceptical payers and by the public.

Appendix A. Aquarel—final version

1. Have you felt discomfort in the chest?	11. Have you been out of breath at rest?
~ no discomfort at all	~ not out of breath
~ very mild discomfort	~ slightly out of breath
~ mild discomfort	~ moderately out of breath
~ moderate discomfort	~ very out of breath
~ great discomfort	~ extremely out of breath
2. Do you get chest discomfort while walking upstairs or uphill?	12. Do you awake when sleeping due to shortness of breath?
~ no discomfort	~ never
~ very mild discomfort	~ seldom
~ mild discomfort	~ once in awhile
~ moderate discomfort	~ often
~ severe discomfort	~ continuously
3. Do you get chest discomfort while walking quickly on level ground?	13. Did you have swollen ankles?
~ no discomfort	~ never
~ very mild discomfort	~ seldom
~ mild discomfort	~ once in awhile
~ moderate discomfort	~ often
~ severe discomfort	~ continuously
4. Do you get chest discomfort while walking on level ground at the same pace as people usually do at your age?	14. Have you suffered from an irregular heartbeat?
~ no discomfort	~ never
~ very mild discomfort	~ seldom
~ mild discomfort	~ once in awhile
~ moderate discomfort	~ often
~ severe discomfort	~ continuously
5. Have you been restricted by chest discomfort during physical exercise?	15. Have you suffered from heart pounding?
~ not restricted at all	~ never
~ slightly restricted	~ seldom
~ moderately restricted	~ once in a while
~ very restricted	~ often
~ extremely restricted	~ continuously
6. Have you experienced chest discomfort at rest?	16. Have you suffered from pounding in the neck or abdomen?
~ no discomfort	~ never
~ very mild discomfort	~ seldom
~ mild discomfort	~ once in awhile
~ moderate discomfort	~ often
~ severe discomfort	~ continuously
	17. Have you felt close to fainting?

Appendix A (continued)

7. Do you get short of breath while walking upstairs or uphill?	~ never
~ not short of breath	~ seldom
~ very mildly short of breath	~ once in awhile
~ mild short of breath	~ often
~ moderate short of breath	~ continuously
~ extreme short of breath	18. Do you feel tired and exhausted after a night's sleep?
8. Do you get short of breath while walking quickly on level ground?	~ never
~ not short of breath	~ seldom
~ very mildly short of breath	~ once in awhile
~ mild short of breath	~ often
~ moderate short of breath	~ continuously
~ extreme short of breath	19. Have you been restricted in your daily activities due to tiredness or lack of energy?
9. Do you get short of breath while walking on level ground at the same pace as people usually do at your age?	~ extremely restricted
~ not short of breath	~ very restricted
~ very mildly short of breath	~ moderately restricted
~ mild short of breath	~ slightly restricted
~ moderate short of breath	~ not restricted at all
~ extreme short of breath	20. Did you have to sit or lie down during the day to rest?
10. Have you been restricted by breathlessness during physical exercise?	~ never
~ not restricted at all	~ seldom
~ slightly restricted	~ once in a while
~ moderately restricted	~ often
~ very restricted	~ continuously
~ extremely restricted	

Scale chest discomfort: items 1, 2, 3, 4, 5, 6, 11, 12.

Scale dyspnea and exertion: items 7, 8, 9, 10, 18, 19, 20.

Scale arrhythmias: items 13, 14, 15, 16, 17.

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