Quality of Life in Patients with Implantable Cardiac Devices

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7.1 Introduction

In recent years, there has been considerable development in the treatment of arrhythmias and atrioventricular (AV) conduction disturbances through the use of implantable cardiac devices (e.g., pacemakers, cardioverter defibrillators). Such devices may serve several functions, but their primary purpose is to prevent syncope and sudden cardiac death.

7.2 Single- or Dual-Chamber Pacing?

Pacemakers are classified according to the number of cardiac chambers stimulated: one, two, or three. In single-chamber stimulation, the intracardiac lead is located in the right atrium (AAI type of stimulation) or right ventricle (VVI type of stimulation). In dual-chamber stimulation (DDD type of stimulation), two leads are located in the right atrium and right ventricle. These leads preserve AV synchrony, may be more physiological, and can have a rate responsive function that is dependent upon the physical activity of the individual. Three-chamber (i.e., biventricular) stimulation constitutes a relatively new type of electrotherapy in which the third lead is responsible for stimulating the left ventricle.

The health-related quality of life (HRQoL) of subjects with cardio-stimulators is low and comparable with that of the HRQoL of subjects undergoing hemodialysis [1]. However, after implantation, HRQoL improves compared with that observed before the procedure. Gribbin et al. observed improvement in selected areas of

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HRQoL 1 month after the procedure regardless of the type of pacemaker implanted (e.g., VVI, DDD/AAI) [2]. This study used the Schedule for the Evaluation of Individual QoL (SEIQoL) questionnaire, the Short Form Health Survey (SF-36) and the Karolinska Questionnaire (KQ). Both single- and dual-chamber pacing significantly improved SEIQoL scores, cardiovascular symptoms, and the SF-36 domains of mental health, physical and social role limitations.

Młynarski et al. evaluated changes in the primary mental and physical areas of HRQoL in 198 patients 6 months after implantation of a pacemaker because of sinus-node dysfunction or AV block. The Minnesota Living With Heart Failure (MLWHF) questionnaire was used in the study. However, the MLWHF is not designed for patients after pacemaker implantation. A very high statistical improvement in mobility, everyday activity, and pain was found except one: the anxiety/depression dimension in patients with AV block worsened [3].

The question arises as to how different pacing modes influence HRQoL. In terms of hemodynamic advantages such as increasing ejection volume or decreasing pulmonary and right-atrium pressure, short- and long-term clinical studies have demonstrated the superiority of DDD pacemakers over VVI pacemakers. The influence of AV synchrony was then anticipated to include a reduction in critical endpoints and an improvement in QoL. In a study of > 4,500 patients presenting chiefly with sick sinus syndrome (SSS), Lamas, et al. [1] and Connolly, et al. [4] could not prove the advantages of dual-chamber stimulation in terms of overall mortality, cardiovascular mortality, risk of stroke, and the development of atrial fibrillation (AF). Consequently, an attempt was made to measure the greater influence of dual-chamber pacing compared with single-chamber pacing on HRQoL. With this aim, several large, randomized clinical trials were undertaken: the Pacemaker Selection in the Elderly (PASE) study [5], the Canadian Trial of Physiologic Pacing (CTOPP) study [6], and the Mode Selection Trial (MOST) [7].

The aim of the PASE study was to assess HRQoL in 407 patients aged ≥ 65 years who required a permanent pacemaker for the treatment of SSS or AV block [5]. Pacemakers were programmed randomly to ventricular or dual-chamber pacing. HRQoL was assessed using SF-36 and the Specific Activity Scale (SAS) for disease-specific cardiovascular functional status. At the start of the study, according to SF-36, no differences were noted for patients with an indication for pacemaker implantation. After 3 months of follow-up, significant improvement was noted in HRQoL regardless of age, sex, social status, baseline indication for implantation, or previous history of coronary artery disease. QoL improved significantly after pacemaker implantation, but there were no differences between the two pacing modes. No differences were noted between the two forms of stimulation. Also, after 18 months of observation, no differences were noted between ventricular and dual-chamber stimulation in any of the subscales of SF-36. However, after 9-month follow-up, significant differences were noted favoring dual-chamber pacing only in scores for

the psychological and emotional health subscale. When measured using the SAS, after 3 months and 9 months of observation, no differences were noted in the HRQoL of either group. However, after 18 months of observation, differences were noted in favor of dual-chamber pacing.

The CTOPP study involved > 2,700 patients randomly divided into "physiologic" (DDD/AAI) or ventricular (VVI) pacing [6]. HRQoL was assessed as a secondary endpoint and measured 6 months after the procedure using the generic scales SF-36, and SAS. As a pacemaker-specific QoL instrument, the Quality of Life Assessment Package (QLAP) was developed on the basis of four domains: physical and psychological health, social functioning, and general activity. The second specific questionnaire used in the study, the Pacemaker Syndrome Scale (PSS), is an instrument measuring "pacemaker syndrome". Pacemaker syndrome refers to symptoms (e.g., dizziness, fatigue) that are potentially attributable to a loss of AV synchrony in patients with ventricular pacing. This study found that VVI and "physiologic" pacing resulted in the same relative magnitude of benefit that was associated with the commencement of pacing. In contrast to the significant effects of receiving a pacemaker, no significant differences in HRQoL could be ascribed to the randomly allocated pacing mode. The authors noted that, in patients with ventricular pacing, pacemaker syndrome was observed less frequently than found in other studies, and that the symptoms of pacemaker syndrome were present less often than in patients with dual-chamber pacing.

The MOST was designed in a similar manner to the CTOPP Trial, in which 2,000 patients with SSS were evaluated after pacemaker implantation programmed for VVI or DDD/AAI pacing [7]. They were then followed up for 2 years, with HRQoL being analyzed using SF-36 and SAS. A comparison of these two groups found no statistical differences in QoL. However, 18.3% of 996 randomly selected patients tolerated ventricular pacing poorly due to AV asynchrony. Symptoms included palpitations, syncope, and dizziness. HRQoL improved across all dimensions after reprogramming to dual-chamber pacing.

Chudzik et al. [8] also offered interesting data from a group of 55 patients with stable AF treated using an implanted pacemaker in which VVI stimulation frequencies of 80 per min and 40 per min were compared. The HRQoL of each participant was measured at baseline and after 7 days of observation using a trial-developed questionnaire. A frequency of 80 per min was found to be more advantageous, allowing not only for improved hemodynamic parameters, but also improved HRQoL by decreasing the symptoms connected with fast and irregular heart rate.

7.3 Pacemakers with Rate-Response Functions

In the 1980s, pacemakers with a rate response function began to be used. These

adapted the frequency of cardiac stimulation to the physical activity of the patient. These pacemakers allowed for more physiologic pacing, and their hemodynamic benefits were well documented [9]. Compared with pacemakers without this option, HRQoL improved in patients in VVIR and DDDR pacing groups. Though cross-sectional and involving a small sample group, these studies offered valuable insights [9–12]. Patients with rate-responsive pacemakers had a decreased feeling of illness, less shortness of breath, and fewer palpitations [10]. Lau et al. also confirmed a significantly decreased prevalence in shortness of breath and increased energy for everyday activities [9]. Unfortunately, these studies used only generic questionnaires, and their period of observation was limited to only a few weeks.

New tools are being developed to measure more objectively the HRQoL of patients with cardiac diseases treated using implanted devices. Burns et al. administered the Florida Patient Acceptance Survey (FPAS) to 200 patients with a pacemaker, implantable cardioverter-defibrillator (ICD), or implantable atrioverter-defibrillator (ICD-AT) [13]. The FPAS comprises 15 items with four consistent dimensions: return to function; device-related distress; positive appraisal; and body image concerns. This initial investigation of the FPAS suggests that it may be comparable with other methods of measuring HRQoL in patients with implantable devices. Another instrument administered to patients with pacemakers was the MacNew Heart Disease Health-related Quality of Life (MacNew) questionnaire, which was used in the Pacemaker Patients Quality of Life (PAPQoL) study [14]. The MacNew was comparable with the well-known and standardized SF-36, showing its value in measuring HRQoL in patients with implantable devices (see Appendix).

In summary, one can observe improved QoL in patients after pacemaker implantation. However, dual-chamber pacing has not been demonstrated to be significantly more effective than single-chamber pacing. This issue is expected to be tackled in large-scale trials with long-term observation in which HRQoL is measured using reliable instruments.

7.4 Cardiac Resynchronization Therapy (CRT) and HRQoL

CRT is a relatively new type of electrotherapy. This biventricular stimulation works by returning inter- and intra-ventricular synchrony. In 2002, this method became recognized as an accepted means of electrostimulation and to be a beneficial treatment option for patients with end-stage heart failure. At present, biventricular pacing (BVP) constitutes the most dynamically developed form of cardiac electrostimulation [15].

Studies examining the value of simultaneous biventricular stimulation in cases of congestive heart failure (CHF) have been ongoing for many years. Several multicenter studies have taken place: Multi-Sensor Monitoring in Congestive Heart

Table 7.1 Studies examining health-related quality of life in subjects undergoing cardiac resynchronization therapy

Study (year)	NYHA class	Number of patients	Influence on HRQoL
MUSTIC (2001)	III	67	Significant improvement
PATH-CHF I (2002)	III–IV	42	Significant improvement
PATH-CHF II (2003)	II–IV	101	Significant improvement
MIRACLE (2002)	III–IV	453	Significant improvement
InSync ICD (2002)	II–IV	84	Significant improvement
MIRACLE ICD (2003)	III–IV	369	Significant improvement
CONTAK CD (2003)	II–IV	490	Trend towards improvement, lacking statistical significance; significant improvement only in subgroups of NYHA class III–IV patients
COMPANION (2004)	III–IV	1,520	Significant improvement
CARE-HF (2005)	III–IV	813	Significant improvement

NYHA, New York Heart Association; *HRQoL*, health-related quality of life.

Failure (MUSTIC) [16]; Pacing Therapies for Congestive Heart Failure (PATH-CHF I) [17]; PATH-CHF II [18]; Multicenter InSync Randomized Clinical Evaluation (MIRACLE) [19]; InSync ICD [20]; Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE ICD) [21]; CONTAK CD [22]; Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) [23]; and Cardiac Resynchronization Heart Failure (CARE-HF) [24]. These studies took place among patients with advanced CHF (i.e., classes III and IV according to the New York Heart Association (NYHA) scale), left ventricular dysfunction (i.e., ejection fraction < 35%), and wide QRS waves on electrocardiography. In all patients, symptoms of CHF were present despite optimal pharmacotherapy (i.e., angiotensin-converting enzyme inhibitors, beta-blockers, loop diuretics, spironolactone, digoxin).

These studies confirmed the effectiveness of BVP expressed through improved tolerance and NYHA functional class. In 2003, CRT was first confirmed to reduce mortality in CHF patients (COMPANION study) [25] and, through a meta-analysis of published randomized studies, mortality related to CHF [26].

The studies that also measured HRQoL as a primary or secondary endpoint are given in Table 7.1. MUSTIC was the first study to confirm long-term advantages after the use of CRT. The HRQoL of NYHA class-III patients, be they in AF or sinus rhythm, was measured using two questionnaires: Minnesota Living with Health Failure (MLHF) questionnaire (which was designed specifically for CHF patients)

and KQ (used widely among patients with pacemakers). Significant improvement in the measured dimensions of HRQoL was noted after 3 months and 12 months of observation, with a simultaneous decrease in CHF symptoms and better tolerance of physical activity. Improvement was also noted in the HRQoL of AF patients, but not as significantly as in patients in sinus rhythm [16].

The PATH-CHF I study also measured HRQoL using the MLHF questionnaire, with scores ranging from 0 points (best) to 105 points (worst). Prior to implantation of a biventricular pacemaker, patients rated their HRQoL to a mean value of 48.6 points. After implantation, this score dropped to 20 points ($p < 0.001$) [17]. Similar results were obtained in the PATH-CHF II study, which used the same questionnaire to measure QoL in a larger group of patients [18].

In contrast to the studies mentioned above, MIRACLE was the first randomized, prospective study with a double-blind sample involving a larger number of patients. This allowed for a wider measure of HRQoL in CHF patients with CRT, in which significant improvement was noted in QoL using the MLHF questionnaire (25).

The MLHF questionnaire was also used in the prospective InSync ICD study (26). Participants in NYHA classes II–IV had a low baseline HRQoL (mean, 53 points). CRT led to significant improvement in HRQoL after 1 month of treatment (mean, 31 points). This improvement was sustained after 3 (33 points), 6 (31 points), and 12 (31 points) months of observation. Similar to the studies mentioned above, simultaneous improvement was also noted in CHF symptoms.

MIRACLE ICD, a randomized, double-blind study, compared patients who received devices (i.e., with combined CRT and ICD capabilities) and controls (i.e., ICD activated, but CRT off). Similar to other studies, the MLHF questionnaire was used to measure QoL, and improvement was noted in both groups. However, compared with ICD patients, a significantly greater improvement in the MLHF questionnaire was noted in the CRT + ICD group at 6 months [21].

Only the CONTAK CD study did not find differences in the HRQoL of patients undergoing CRT alone versus CRT + ICD versus ICD alone. This study also used the MLHF questionnaire. Patients with symptomatic CHF (i.e., NYHA classes II–IV) were included in this study. After analyses, significant improvement in HRQoL was noted only in symptomatic CHF patients (i.e., NYHA classes III and IV) [22].

The most important trial was the COMPANION study [23]. This study encompassed 1,520 patients who were randomized into one of three groups: CRT, CRT + ICD, or pharmacotherapy alone. Using the MLHF questionnaire, significant improvement in HRQoL was noted in the groups undergoing CRT as opposed to pharmacotherapy alone. CRT improved the HRQoL of patients with significant left ventricular dysfunction and those with advanced CHF symptoms undergoing optimal pharmacotherapy. In the CARE-HF study, HRQoL measured by the MLHF questionnaire as well as EuroQoL-5D (EQ-5D) improved at 90 days [24].

The question is “which factors might be associated with improvement of HRQoL

after CRT? Associations with age, sex, heart failure etiology, QRS width, and ejection fraction before CRT implantation were not found [27]. The only factor that predicted improvement after CRT was functional status (evaluated by NYHA classification). That is, patients with more symptoms of advanced heart failure at baseline responded better to CRT [28, 29].

Evidence that CRT does not "automatically" improve the subjective perception of being "healthier" came from randomized studies in which the device was switched off randomly in some patients whereas in others it remained switched on. After the observation period, an improvement in HRQoL was determined among the patients in whom CRT was switched on [30]. Kloch-Badelek et al. observed significant improvement in HRQoL after CRT implementation but only in a group of "responders" (defined as an increase in walking distance in the 6-minute Walk Test > 10% of baseline values). This finding may mean that patients with advanced heart failure perceive improvement in HRQoL after CRT if their physical ability improves [29].

Mechanical dyssynchrony may also have a role in the identification of subjects who may respond better to CRT. However, recent large clinical trials have challenged this concept. The role of CRT in heart-failure patients with narrow QRS (< 120 ms) is evolving. Such a group of patients was randomly assigned to CRT or optimal pharmacological treatment in the RESPOND study to evaluate clinical responses. HRQoL was assessed by the MLHF questionnaire. Six months after implantation, CRT led to an improvement in HRQoL scores and a reduction of NYHA class. However, no differences in total or cardiovascular mortality emerged between two groups [31].

CRT is mostly achieved by BVP, although it can also be provided by left ventricular pacing (LVP). However, the superiority of BVP over LVP remains uncertain. In 2011, Liang undertook a meta-analysis of randomized controlled trials to compare the effects of two modes of CRT in CHF patients. Outcomes included clinical status besides QoL. Five trials fulfilled the criteria for inclusion in the analysis, which involved 574 patients with CHF indicated for CRT. After a mid-term follow-up, pooled analyses demonstrated that LVP resulted in similar improvements in QoL, as well as other factors of clinical status (6-minute walk distance, NYHA class) [32].

7.5 ICD Therapy and HRQoL

A recognized form of ventricular arrhythmia therapy is implantation of an ICD. During the 1990s, several prospective, randomized studies broadened the indications for using ICD in the primary and secondary prevention of arrhythmia: the Antiarrhythmics Versus Implantable Defibrillators (AVID) [33]; the Canadian Implantable

Defibrillator Study (CIDS) [34]; the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) [35]; and the Multicenter Unsustained Tachycardia Trial (MUSTT) [36]. Studies focusing on the HRQoL of patients with an ICD found that they tolerated the device, but this acceptance was present only after a certain period of acclimatization to the device (≈6 months). During this period, the HRQoL of the patient (social, economic, and psychological aspects) was also lowest [37]. Unease and anxiety associated with the presence of the ICD device is often observed in patients. Should the device get discharged, increased uneasiness, anxiety, and fear of another discharge or death can be encountered. A subgroup of ICD patients experiences psychological difficulties, with the most profound manifestation being posttraumatic stress disorder [38]. Some patients may even remain in bed for extended periods of time [39]. Only one study did not find a difference in HRQoL between patients with an ICD device that discharged and patients without such an experience [40]. Compared with subjects with cardiovascular disease without an ICD device, most studies confirm a decreased HRQoL in patients after even one discharge [37, 39, 41], and this is influenced by several incidents of ICD discharge [42]. Schron et al. found that even one ICD discharge negatively affected psychological and physical health, whereas > 5 discharges significantly decreased HRQoL [43].

More recent studies have tried to identify predictors of risk of adverse psychological outcomes in subjects with an ICD. The evidence for an influence of ICD implantation and discharges on HRQoL is probably more complex than generally assumed. Symptomatic heart failure [44], younger age [45], poor social support [42], diabetes mellitus [46] and a type-D personality (patients who experience a range of negative emotions but who inhibit the expression of these emotions) [46] constitute other factors that have been associated with a risk of poorer HRQoL outcomes.

Sex has also been proposed to be a potentially important risk factor for poor HRQoL [47]. Sex disparities may be attributed to differences: in the way of dealing with stressful situations; in the acceptance of mechanical devices; in pain sensitivity [48]. Based on these findings, it would be rational to expect women to experience more psychological distress after ICD implantation than men. However, recent studies on sex differences in HRQoL have shown mixed findings. In a multicenter study with a 12-month follow-up of 718 patients, differences in HRQoL were observed for only 2 of 8 subscales of SF-36, with women reporting poorer physical functioning and vitality than men [49].

The Canadian Implantable Defibrillator Study (CIDS) found higher HRQoL in patients with an implanted ICD device compared with those receiving the antiarrhythmic drug amiodarone [50]. This study measured HRQoL in 317 patients using the Mental Health Inventory (MHI) and the Nottingham Health Profile (NHP). Self-rated physical and emotional health improved to a large degree in the ICD group, whereas self-rated emotional health remained unchanged and self-rated physical

health worsened in the amiodarone group. However, after analyzing ICD patients who reported > 5 discharges in the previous 12 months, no advantages in terms of HRQoL were noted.

7.6 Conclusions

Improvement in the QoL is observed in most patients after implantation of cardiac devices. It refers mainly to subjects treated with single- or double-chamber pacemakers accompanied with a rate-response function and to CRT. Some studies showed that CRT can improve not only HRQoL, but also the prognosis in heart-failure patients. Conversely, those treated with an ICD device who experienced > 5 discharges may have a deterioration in HRQoL. Symptomatic heart failure, younger age, poor social support, diabetes mellitus, and a type-D personality are factors related to the risk of further decreases in HRQoL.

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