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REVIEW ARTICLE
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Health-related quality of life in pulmonary arterial hypertension (RCD code: II)

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Abstract

Health-related QoL (HRQoL) is defined as "the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient" and is a reflection of one's health on physical, psychological, and social aspects of life. PAH is a condition associated with symptoms that may severely affect patient's QoL. Awareness of having a rare disease of poor prognosis, with limited therapeutic options and symptoms restricting daily activities may cause anxiety, panic, depression, anger, and hopelessness. Current European Society of Cardiology guidelines suggest that psychosocial support should be considered in patients with PAH (with recommendation class IIa and level of evidence C). PAH is a progressive disease, leading to a gradual reduction in exercise tolerance and significantly decreasing the HRQoL. A recent development of PAH-specific therapies has significantly improved patients' survival and rate of clinical deterioration. It may be useful to consider patient's personal outcomes in predicting treatment benefits and decision making. JRCD 2014; 2 (1): 5–8

Key words: physical activity, QoL, questionnaire, depression, CAMPHOR

Background

The years of research on pathophysiology and treatment of pulmonary arterial hypertension (PAH) resulted in various therapeutic strategies. This progress expanded treatment goals from increasing survival to improving the quality of life (QoL). Since the World Health Organization (WHO) established a definition of health as not only an absence of disease but also as a state of physical, mental, and social well-being, the investigations on QoL became more important in the clinical setting.

According to the WHO, the QoL represents individual's perception of life position in the context of the culture and value systems. It is influenced by the person's physical health, psychological state, level of independence, social relationships, and personal beliefs [1]. Health-related QoL (HRQoL) can be distinguished from QoL to emphasize the predominant influence of health care providers and health care systems on QoL [2]. HRQoL is defined as "the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient" [3] and is a reflection of one's health on physical, psychological, and social aspects of life.

Health-related quality of life as an important clinical endpoint in pulmonary arterial hypertension

HRQoL is becoming a valuable tool to define endpoints in PAH clinical trials. Current therapeutic protocols has improved survival in this disease, making QoL a complementary goal in its therapy [4]. Studies have shown that PAH, especially with coexisting systemic sclerosis, is associated with a significantly decreased HRQoL. Pharmacological treatment of PAH often requires frequent dosing and strict monitoring along with the use of specialized drug delivery systems (continuous intravenous or subcutaneous infusion, nebulization) which may lead to major adverse effects. These interventions may affect hemodynamic parameters without improvement in the QoL, especially in mental and emotional aspects [5]. Therefore, the QoL has been recommended as a tool to determine the effects of treatment [4].

Conflict of interest: none declared.

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Why do we use patient-reported outcomes?

There is a growing recognition that physiological parameters not completely correlate with patient's personal benefits [6]. Patient-reported outcomes (PROs) are patient-centered measurements of health status that allow to assess treatment effects from the patient's perspective (which may otherwise remain unrecognized). That is why PROs may be used to determine patient's benefits for which no adequate observable or physical measures exist. What is more, PROs are relatively quick and easy to assess [7]. Until now, only a few instruments assessing PROs have been precisely evaluated; however, the use of these measures continues to grow.

Effect of pulmonary arterial hypertension on patient-reported outcomes

PAH is a condition associated with symptoms that may severely affect patient's QoL. Awareness of having a rare disease of poor prognosis, with limited therapeutic options and symptoms restricting daily activities may cause anxiety, panic, depression, anger, and hopelessness [8]. Shafazand et al. [9] have found moderate or severe levels of anxiety and depression in 20.5% and 7.5% of the patients with PAH, respectively. The Hospital Anxiety and Depression Scale was used in that study. In a Heidelberg cohort, 35% of the patients with pulmonary hypertension suffered from mental disorders. The most common were major depressive disorders (15.9%) and panic disorders (10.4%), most of them were potentially treatable and their prevalence increased as the severity of disease progressed [10]. Current European Society of Cardiology guidelines suggest that psychosocial support should be considered in patients with PAH (with recommendation class IIa and level of evidence C) [2].

PAH frequently affects relatively young, professionally active people, predominantly women. Severity of symptoms, complex treatment, or psychological distress often makes it challenging to tolerate normal work conditions and responsibilities. This may result in job loss, which can lead to loss of economic independence and social isolation [8]. Work ability in PAH is determined by specific job demands, patient's health condition, and mental resources [11]. Qualifying of work ability is crucial for obtaining social security or medical disability benefits; however, many patients with PAH experience problems with qualifying their work ability status by health care providers. The main factors contributing to this situation are rare prevalence and rapid course of PAH, young age of the patients, late or missed diagnosis, and relatively normal physical examination [8].

Table 1. Instruments used to asses health-related quality of life in pulmonary arterial hypertension patients (modified from [8])

Questionnaire	Contents of domains
NHP	Physical mobility Pain Sleep Social isolation Emotional reactions Energy
MLHFQ	Physical Emotional
HFQ	Dyspnea Fatigue Emotional function of daily living
SF-36	Physical functioning Social functioning Role limitations due to physical problems Role limitations due to emotional problems Mental health Energy/vitality Pain General health perception
EQ-5D	Mobility Self-care Usual activity Pain/discomfort Anxiety/depression
SGRQ	Symptoms Activity Impact
AQoL	Illness Independent living Physical ability Psychological well-being Social relationships
CAMPHOR	Symptoms (energy, breathlessness, mood) Functioning QoL

AQoL – Australian Quality of Life; EQ-5D – EuroQoL questionnaire; HFQ – 16-item Heart Failure Questionnaire; MLHF – Minnesota Living with Heart Failure Questionnaire; NHP – Nottingham Health Profile; SGRQ – St George's Respiratory Questionnaire

Instruments used to assess health-related quality of life in pulmonary arterial hypertension

Instruments used to measure HRQoL are multidimensional tools designed to assess not only the level of impairment but also its impact on individual's physical, psychological, and social well-being (Table 1) [1]. Therefore they usually contain multiple number of domains to evaluate various aspects of health status. In the last years, a number of studies on HRQoL impairment in PAH has grown but

there is still no consensus on the instrument type. The available options for the assessment of HRQoL are generic measurements, designed primarily for broad spectrum of disorders or condition-specific tools dedicated to particular group of patients.

Generic measures such as the Medical Outcome Study 36-item Short Form Health Survey (SF-36) [12] and the Nottingham Health Profile (NHP) [13] may be used in a broad disease spectrum, even in healthy subjects to compare individual's outcome with population norms. EuroQol (EQ-5D) [14] and the Australian Assessment of Quality of Life (AQoL) [15] provide a multidimensional assessment of general health in addition to preference-based "utility" scores that can be applied in economic analyses. A specific type of generic instrument is a standard gamble (SG). This tool allows to gather all health state domains into a single measure [9]. SG is expressed as the willingness to die in exchange of perfect health. This value represents the QoL of patients and can be used to determine perception of disability and possible benefits from the treatment. In a recent study evaluating PAH, a mean SG value was 0.71, suggesting that patients were willing to accept 29% risk of death to become completely cured [8].

Condition-specific measures are designed for more specified group of patients. They are assessing selected health aspects, and therefore may be more sensitive to treatment changes than generic measures. Cardiac and respiratory-specific instruments are often used in patients with PAH considering the effect of dyspnea and activity limitations on individual's condition [5]. Measures such as Minnesota Living with Heart Failure Questionnaire (MLHFQ) or Chronic Heart Failure Questionnaire (CHQ) are frequently used in PAH; therefore, they are well evaluated and have been proved to have high internal consistency and good test–retest reproducibility [16].

The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) is currently the only available **PH-specific measure**. CAMPHOR consists of three scales for the assessment of symptoms, functioning, and QoL [17]. This tool has been validated in the United Kingdom and United States, where a study confirmed a good test–retest reliability and internal consistency. CAMPHOR scales correlated with the SF-36 and 6-minute walk test (6MWT), making it a promising instrument. However, its use in the clinical trial setting still has to be determined [18].

Application of health-related quality of life instruments in the assessment of patient status

Recent studies in PAH have shown that measures of physiological response and exercise capacity, such as 6MWT, account for only a portion of the observed variance in HRQoL [5,16]. A gradual reduction in exercise tolerance in PAH is usually measured by WHO functional class, 6MWT, or cardiopulmonary exercise tests. Taichman et al. [5] showed that better HRQoL scores correlated with greater 6MWT but not with hemodynamic measurements. Furthermore, they reported significantly depressed physical and mental component scores of the SF-36 in PAH patients. This was similar in patients with other debilitating and life-threatening conditions such as spinal cord injury and metastatic cancer [5]. In a study comparing the MLHFQ with the SF-36 and AQoL [19], the total scores of all three tools correlated well with 6MWT and New York Health Association (NYHA)/WHO class. As in a previous study, a correlation with hemodynamic parameters was poor. What is more, SF-36 and MLHFQ outcomes better reflected changes in 6MWT and NYHA/WHO class than AQoL, which was much less responsive.

Application of health-related quality of life instruments in clinical trials

The most frequently used generic measure in PAH trials has been the SF-36, alongside with the condition-specific MLHFQ and CHQ. Based on the available data, domains related to physical functioning appear to be the most responsive to change in the trial setting. [7] General improvement of the QoL has been shown in the following PAH-specific drugs: sildenafil [20,21], tadalafil [22], bosentan [23], ambrisentan [24], iloprost [25], treprostinil [26], and epoprostenol [27]. Despite a growing number of conducted studies, they frequently use different instruments to determine the HRQoL, thereby making it difficult to compare the outcomes. Other chronic diseases associated with PAH may also confound the outcomes when generic measures are used. Further investigations involving identification of additional factors modifying treatment responses seem to be essential to understand why some treatments, while efficacious from the physical point of view, may be ineffective from the patient's perspective.

Conclusions

PAH is a progressive disease, leading to a gradual reduction in exercise tolerance and significantly decreasing the HRQoL. A recent development of PAH-specific therapies has significantly improved patients' survival and rate of clinical deterioration. It may be useful to consider patient's personal outcomes in predicting treatment benefits and decision making. For that reason, PROs are becoming an important endpoint in clinical trials. The HRQoL can be currently assessed with a number of designed instruments. Different instruments are dedicated for different purposes. Generic measures such as the SF-36 are useful in evaluating the general outcome of intervention and in comparing results in various conditions. Condition-specific measures focus on a particular clinical group and can be sensitive tools especially in treatment modifications. CAMPHOR, the PAH-specific measure, is a relatively new instrument that appears to be promising in future clinical trials.

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