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Analysis of associations between congenital heart defect complexity and health-related quality of life using a meta-analytic strategy

Peter C. Kahr *, Robert M. Radke, Stefan Orwat, Helmut Baumgartner, Gerhard-Paul Diller

Division of Adult Congenital and Valvular Heart Disease, Department of Cardiovascular Medicine, University Hospital Muenster, Münster, Germany

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ABSTRACT

Background: As a consequence of heterogeneous results of relatively small individual trials, the impact of congenital heart defects (CHD) and the effect of disease severity on patient reported outcome measures (PROs) of quality of life (QoL) remains uncertain. We aimed to systematically summarize QoL data in CHD patients using meta-analytic methods.

Methods and results: We performed a systematic review of the literature focusing on QoL in CHD. The search yielded 234 publications meeting the inclusion criteria, with a median of 88 patients per study (46% females, average age 24 years). In total, QoL was reported using PROs in 47,471 CHD-patients. More than 95 different PROs were used to evaluate QoL. The most commonly used tool was the SF36 form (69 publications). Analysis of available quantitative QoL data from SF36 publications (n = 4217 CHD patients) showed that QoL was reduced in patients with moderate or complex cardiac disease (e.g. relative physical functioning scores 0.96 [0.93–0.99] and 0.91 [0.88–0.95] compared with controls), while no such effect was evident in those patients with simple cardiac lesions. Similar results were found for the general health domain of the SF36 domain.

Conclusions: Despite the proliferation of QoL-studies in CHD no standardized approach for measuring and reporting QoL has emerged and the published results are heterogeneous. In aggregation, however, the results of this study suggest that QoL is impaired in moderate or complex CHD, while no such impact of CHD on QoL could be established — on average — in patients with simple defects.

1. Introduction

In the current era, over 90% of children born with congenital heart disease (CHD) in developed countries survive to adulthood, most of them living relatively normal lives with good long-term survival prospects [1,2]. With improving survival rates the focus of attention has shifted from mortality to morbidity, functional capacity and ultimately quality of life (QoL). Anticipating this move, Joseph Perloff argued in 1973 that "our ultimate goal … should focus on the quality of long-term survival … [and] to bring the individual to the peak of his[/her] physical capability" [3]. Testimony to this trend is a growing number of publications addressing functional aspects of patients' lives such as symptoms and objective exercise capacity. In addition, an increasing number of studies have been aiming to assess health-related QoL directly in CHD cohorts by applying patient-reported outcome measures (PROs), mostly questionnaires quantifying different aspects of QoL. As there is currently no consensus regarding the definition of QoL, many researchers have employed the World Health Organization's definition of health to investigate health-related QoL based on the five domains physical and mental health, level of independence, social relationships and environmental factors [4]. Unfortunately, the available primary evidence on health-related QoL in CHD is heterogeneous, sometimes even contradicting. This can partially be explained by differences in employed methods. After application of vigorous selection criteria, previous reviews have been able to describe these differences, [5–8] but a quantitative meta-analysis of the existing data has not been achieved so far. Despite a large number of studies investigating QoL across the full spectrum of CHD patients, the effect of defect complexity on QoL is uncertain.

The aim of the current study was to systematically review the currently available literature on QoL in CHD with a particular focus on quantitative methods aiming to combine the results comparable with studies to overcome the limitations of small patient numbers and provide aggregate estimates on the association between CHD and CHD-sub-groups on different dimensions of QoL.

2. Methods

2.1. Search strategy

The PubMed online library was searched on April 25th 2014 for a combination of the phrases "quality of life" or "QoL" and a set of terms relating to all forms of congenital heart

* Corresponding author at: Division of Adult Congenital and Valvular Heart Disease, Department of Cardiovascular Medicine, University Hospital of Münster, Albert-Schweitzer-Str. 33, 48149 Münster, Germany.
E-mail address: pckahr@gmail.com (P.C. Kahr).

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disease (Suppl. Table 1). After removal of duplicate results, studies were excluded based on language criteria (n = 66, Suppl. Fig. 1). All papers were screened by one author (PCK) and further papers were excluded if they met the following criteria: i) studies not including CHD patients (n = 213), ii) studies on relatives of CHD patients (n = 10), iii) basic laboratory work and studies that did not involve human CHD patients (n = 16) and iv) secondary literature including reviews, editorials, comments (n = 276). Finally, publications were excluded if they only commented on QoL rather than measuring QoL with a PRO (questionnaires, visual analogue scales, etc., n = 200). For example, studies that would discuss the patients' QoL solely on NYHA functional class, would be excluded from further analysis. Subsequently, 234 studies were subjected to data extraction and data analysis.

2.2. Data extraction and analysis

Data on demographics, the type of CHD and PRO utilized in the study, and the country of origin were extracted manually from the full text manuscripts. Furthermore, cardiac defects were categorized based on the consensus statement of the 32nd Bethesda Conference into simple, moderate and complex defects [9]. Because the SF36 (36-item short-form healthy survey) questionnaire was the most widely used PRO in the current literature, we aimed at combining the results of the SF36 in a quantitative way. The SF36 has been established as a tool to investigate the health-related QoL of patients with various conditions [10] and normative data for many countries have been published (for a copy of the questionnaire, translations and user manuals see the website of the RAND corporation: http://www.rand.org/health/surveys_tools/mos/mos_core_36item.html). It is comprised of 36 items that confer to 8 domains of health-related QoL. Average scores (mean or median) and distribution measures (standard deviation, interquartile range) for each sub-domain of the SF36 were extracted from the manuscripts. If quantitative absolute scores on the SF36 were only given in graphs, plot digitizer software (http://plotdigitizer.sourceforge.net/) was applied to estimate these numbers from digital copies of the graphs.

2.3. Meta-analysis of response ratio

To summarize the results of studies employing the SF36 PRO, a ratio of means meta-analytic method was used. This method utilizes the ratio between variables measured in the patient and the control group. The performance of this method compared with other meta-analytic methods has been established [11] and the method is now implemented as part of statistical software packages. We included, both, studies reporting means and medians. For studies where standard deviations were missing, these were imputed based on a regression of log-transformed standard deviation vs. log-transformed means. Also, some studies did not report the number of control subjects included or used normative values based on published age-specific sub-groups. In these cases the number of control subjects was assumed to be equal to that of the CHD patients assessed (representing a conservative approach, especially for studies using published normative data — usually based on hundreds of subjects). This approach was taken to overcome the limitation that the exact number of individuals in each age group of the normative data is often not available. All meta-analyses were based on random-effects models with inclusion of possible moderator variables such as average age, country of origin and complexity of underlying disease, using the *metafor* package [12] for R 3.0.2. A two-sided p-value of <0.05 was considered statistically significant.

3. Results

3.1. Systematic search of the PubMed online library

Our systematic search resulted in a total list of 1015 publications, published between 1974 and 2014, that included the phrase "quality of life" in addition to a reference to CHD. After exclusion, 234 studies remained and were included in the further analyses (Suppl. Fig. 1). We found that the publication of studies that apply PROs in the setting of CHD showed an exponential increase over time (Fig. 1), with the maximum of published studies in 2013 (n = 45) and with ≈90% of studies being published after 2000. During the last decade (2005–2014), the proportion of studies that use PROs in relation to all studies that comment on QoL (included plus excluded studies) has been relatively constant at ≈25%.

3.2. Characteristics of PRO-based studies measuring QoL in CHD patients

We found that QoL-studies in CHD were widely heterogeneous in many aspects (Fig. 2). Studies varied significantly in size: overall, data on 47,471 patient assessments was reported, which, however, may overestimate the actual number of studied CHD patients, as we were not able to reliably exclude duplicate patients. While the largest single cohort reported came from Finland (a mixed cohort of 2686 adults [13]), the average cohort size was 202 ± 324 patients (median: 88). Across all studies, females constituted 46.2% of patients and the average age of patients was 24 years. The majority of studies involved adult patients (57.8%), with 84% of these studies reporting exclusively on adult patients. Based on the geographic origin of patients, more than half of the studies came from European centers (n = 147; 63%), followed by publications from North America (USA and Canada, n = 62; 26%) and Asia (n = 15; 6%). Published studies varied in the absolute number of PROs utilized: a substantial number of studies assessed QoL using two (n = 55) or more (n = 35) PROs, while more than 60% of studies report results of only a single PRO (n = 144; 61.5%). 27 of these studies applied a questionnaire that was designed by the investigators themselves (as opposed to using standardized, validated questionnaires like the SF36), with the majority of those studies, however, being published before the year 2000. 14 studies reported QoL solely on the basis of interviews (unstructured or [semi-]structured) without providing quantitative results. The maximum number of PROs reported in a single publication was seven [14]. Overall, 96 different PROs were applied, of

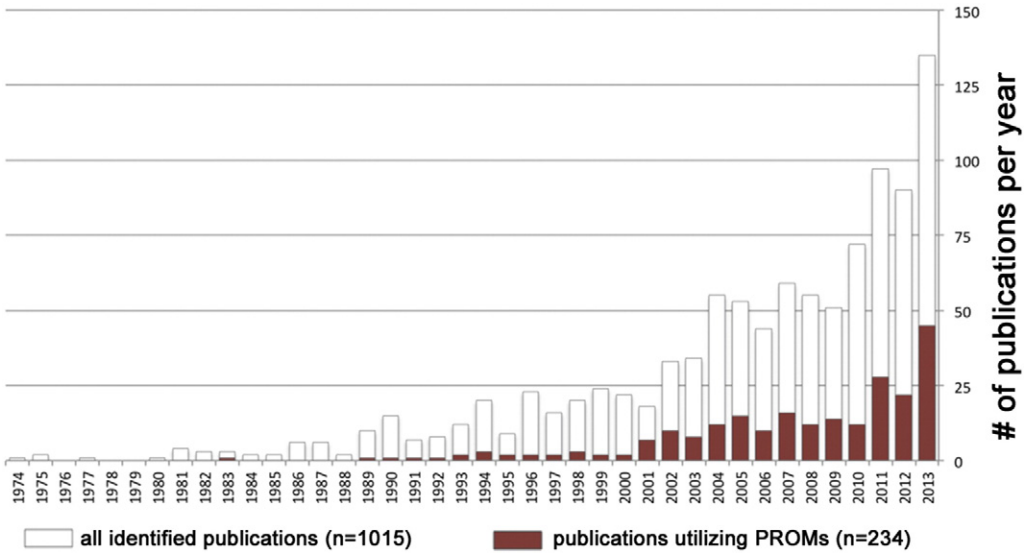

Fig. 1. Temporal trend for publications on quality of life (QoL) in the congenital heart disease (CHD) population. The annual number of publications that reported QoL has increased exponentially over the last decades. This was accompanied by a trend to use more standardized tools in the recent years, generally referred to as patient reported outcome measures (PROs).