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Health status of cardiac genetic disease patients and their at-risk relatives

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ABSTRACT

Background: Health status is an important outcome measure that incorporates multiple dimensions of health, including symptoms, functional status, and psychosocial factors. While health status has been shown to be a predictor for hospital readmission, morbidity and mortality in the heart failure setting, there are limited data in cardiac genetic disease. We examined health status in a number of cardiac genetic disease groups compared to the general Australian population.

Methods: A total of 409 individuals were assessed. Individuals with inherited cardiomyopathies [hypertrophic cardiomyopathy (HCM), familial dilated cardiomyopathy (FDC), arrhythmogenic right ventricular cardiomyopathy (ARVC)] and primary arrhythmogenic disorders [long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT)], as well as their first-degree relatives, completed the Medical Outcomes Survey Short Form-36 (SF-36). The physical and mental component scores (PCS and MCS) and SF-6D utility score were assessed.

Results: Patients with HCM ($p<0.001$), FDC ($p<0.05$), and CPVT ($p<0.05$) were found to have a significantly lower PCS, while patients with LQTS ($p<0.01$) had a lower MCS. Individuals at risk of HCM ($p<0.0001$) and genotype positive–phenotype negative HCM patients ($p<0.01$) both had a higher PCS and utility scores compared to the clinically affected HCM population. Individuals at risk of LQTS had significantly higher PCS than those with a clinical diagnosis of LQTS ($p<0.05$) and similarly individuals at risk of FDC had significantly higher PCS than FDC patients ($p<0.05$). In HCM, female gender ($p=0.002$), presence of co-morbidities ($p<0.0001$) and higher NYHA functional class ($p<0.0001$) were predictors of a lower PCS.

Conclusions: Patients with a clinical diagnosis of a genetic heart disease have an impaired health status, related to both physical and mental function. Clinical management strategies in such patient groups need to consider health status as an important outcome measure.

1. Background

There are now over 40 cardiovascular disorders in which a genetic cause has been identified. These cardiac genetic diseases include the inherited cardiomyopathies such as hypertrophic cardiomyopathy (HCM), familial dilated cardiomyopathy (FDC), arrhythmogenic right ventricular cardiomyopathy (ARVC) and primary arrhythmogenic disorders such as long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT) and Brugada syndrome (BrS). While these diseases have distinct clinical features and genetic causes, the underlying genetic counselling issues are similar. Collectively, these cardiac genetic diseases are inherited as autosomal dominant traits (meaning at-risk relatives have a 1 in 2 risk of inheriting the disease gene), show marked variability in onset and severity of symptoms, have similar limitations regarding genetic testing (sub-optimal pick-up rates, multiple mutation genotypes and limited access to testing due to high costs), and require ongoing clinical surveillance of at-risk family members [1–5].

Individuals diagnosed with a cardiac genetic disorder are confronted with a number of factors that may adversely impact on their physical and psychological wellbeing. These patients, who are typically younger than patients suffering acquired cardiovascular diseases such as coronary artery disease, are often advised to avoid high level competitive sports, may be at a higher risk of sudden cardiac death and therefore need consideration of automatic implantable cardioverter-defibrillator (ICD) therapy, and will often be concerned about genetic inheritance and the risk of disease transmission to

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children. Furthermore, a family history of sudden death is a common feature, leaving families to cope with grief as well as understanding the risk to themselves and their close relatives. Patients living with genetic diseases such as HCM frequently have lower health-related quality of life and psychosocial wellbeing [6–8]. Most recently, a new category of patient has emerged, i.e. genotype-positive phenotype-negative patients who carry a disease-causing mutation but do not express a clinical phenotype [9]. How this "gene carrier" status in cardiac genetic diseases impacts on patient wellbeing remains unclear, although a recent study suggests the health-related quality of life (HR-QoL) and emotional wellbeing of such patients is no worse than the general population [6].

Health status is a global measure that takes into account a patient's symptoms, functional status, prognosis, as well as their own perspective of their health and wellbeing [10]. Health status is increasingly recognised as an important outcome measure in cardiac diseases, with many studies finding it to be deterministic of mortality, hospital readmission and health care costs [11]. Another measure of HR-QoL is utility scores, whereby patient preferences for particular interventions and outcomes are represented [12].

2. Study aims

While health status has been assessed in more common cardiovascular diseases, there are limited data available regarding health status of patients living with cardiac genetic disorders and their at-risk relatives. This study sought to evaluate differences in health status amongst cohorts of cardiac genetic patients, compare health status between clinically affected individuals and at-risk relatives, and to identify potential clinical predictors.

3. Methods

3.1. Patient selection

From August 2007 to November 2010, patients attending two specialised cardiac genetic centres, the Hypertrophic Cardiomyopathy and Genetic Heart Disease Clinics, Royal Prince Alfred Hospital in Sydney, and the Cardiac Genetics Clinic, Royal Brisbane and Women's Hospital in Brisbane, were invited to participate. Patients were also recruited from the Australian National Genetic Heart Disease Registry (NGHD Registry) [13]. Inclusion criteria included affected individuals aged over 15 years with a diagnosis of a genetic heart disease. Diseases included the inherited cardiomyopathies (HCM, FDC, ARVC) or primary arrhythmogenic disorders (LQTS, CPVT, BrS). First-degree at-risk relatives who were clinically unaffected and not previously genotyped were also invited to participate. These at-risk relatives were at a 50% risk of having disease.

3.2. Health status evaluation

Health status was evaluated using the Medical Outcomes Survey Short Form-36 version 2 (SF-36) [14,15]. This is one of the most widely used measures of HR-QoL in the world and its validity has been shown in many populations, including Australia [16]. The SF-36 measures eight dimensions of health: physical functioning (PF), role limitations due to physical health (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitations due to emotional health (RE) and mental health (MH). The eight scales can be combined to two summary measures, providing overall estimates for physical health (physical component score, PCS) and mental health (mental component score, MCS). In addition, the SF-6D can be used to combine SF-36 scores into a single composite scale from 0.0 (dead) to 1.0 (full health) [12]. The SF-6D is an algorithm derived from preferences of the public, weighting the domains and levels of the SF-36 to construct utility weights. Clinical information relating to disease status was collected from both the NGHD Registry and available medical records.

3.3. Statistical analysis

Data were analysed using Prism (version 5.0) and PASW Statistics (version 18.0). The primary outcome measures were the PCS and MCS. SF-6D utility weights are described for each disease group and the 8 SF-36 domains of health were assessed in the HCM and LQTS populations only. MCS and PCS were converted to Australian weighted T-scores, where scores range from 0 (worst possible health) to 100 (best possible health) and 50 is the mean score for the general Australian population [17]. The majority of scores in the population will be within 1 standard deviation from the mean of 50, i.e. ±10 (range 40–60). SF-6D utility weights were calculated as previously described [12]. Australian population norm utility weights were calculated with the SF-6D from Australian Bureau of Statistics SF-36 population data [18].

Comparisons between patient groups were made using one-way ANOVA with Bonferroni's multiple comparison test. Patient groups were compared to age-matched Australian general population T-scores [17] using one-way ANOVA with Dunnett's multiple comparison test. Subscales of the SF-36 were compared between the HCM and LQTS groups and age-matched general Australian population [18] data using unpaired t-tests with Welch's correction for unequal variance. Association with clinical and demographic variables in the HCM population was assessed using normal linear regression following stepwise selection for model-fit.

4. Results

4.1. Population characteristics

The sociodemographic characteristics of the cohort are summarised in Table 1. A total of 409 individuals completed the SF-36 survey (response rate 55%). The overall mean age of the cohort was 49 ± 16 years with 196 (48%) being males. A genetic diagnosis was available in 17% of the HCM group and 21% of the LQTS group. In the groups at risk of disease, 97% had undergone clinical screening on at least one occasion. Data for 29 participants was not included due to statistically small numbers or equivocal diagnoses [individuals with Brugada syndrome (n = 2), left ventricular non-compaction (n = 1), at risk of Brugada syndrome (n = 1), at risk of ARVC (n = 6), at risk of CPVT (n = 4) and miscellaneous diagnoses (n = 15)].

4.2. HCM and LQTS patient cohort descriptions

There were 208 (51%) participants who had clinical HCM, with a mean age of 54 ± 15 years and 129 (62%) males (Table 1). Mean septal wall thickness was 20 ± 6 mm, and 26% had left ventricular outflow tract obstruction. Only 7% had suffered a previous resuscitated cardiac arrest, and 25% of the total HCM cohort had an ICD. Importantly, 61% were New York Heart Association (NYHA) functional class 1, 36% class 2 and 3% class 3.

There were 43 (11%) participants with LQTS, the mean age was 43 ± 16 years, and 8 (19%) were male. In this group, 63% had a history of a previous syncopal episode, 44% had a family history of sudden cardiac death, 68% were taking beta-blocker therapy, and 33% had an ICD in place.

4.3. PCS and MCS compared to disease and at-risk patient groups

Comparison of physical and mental component T-scores across all disease groups showed significant differences between the HCM patient groups, with both the individuals at risk of HCM ($p<0.0001$) and genotype-positive phenotype-negative HCM ($p<0.01$) groups having a higher PCS than clinically affected HCM patients (Fig. 1A). Individuals at risk of LQTS had significantly higher PCS than those with a clinical diagnosis of LQTS ($p<0.05$) and similarly individuals at risk of FDC had significantly higher PCS than the FDC disease group ($p<0.05$). No differences were observed between the other disease groups for physical component scores. MCS values were not significantly different between the different cardiac genetic diseases (Fig. 1B). In the at-risk groups, comparison of both PCS and MCS did not show a significant difference between those who underwent regular clinical surveillance and those who did not have regular follow-up.

4.4. PCS and MCS compared to the general Australian population

Comparison of physical and mental component T-scores to the general Australian population showed that PCS was significantly reduced in the HCM ($p<0.001$), FDC ($p<0.05$), and CPVT ($p<0.05$) disease groups, while the individuals at risk of LQTS scored significantly better ($p<0.05$) (Table 1). MCS was significantly lower in the LQTS