The emerging burden of heart failure in adults with congenital heart disease

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ABSTRACT

Ntiloudi et al. confirm the high burden of failure-related morbidity and mortality in adults with CHD. However, the pathways leading to heart failure in ACHD are heterogeneous and often poorly understood. Most importantly, there is a need for more randomized trials. Trials investigating effects on symptoms and surrogate measures of disease need not be large. However, much larger trials are required to investigate the effects of treatment on disease progression and prognosis, requiring collaborations at national and international levels, as is already the case for other forms of heart failure.

1. Introduction

Most (>90%) people born with congenital heart disease, even those with complex lesions, now survive well into adult life. Median survival for those with simple lesions is now >60 years and >30 years for those with complex lesions [1]. With longer survival comes a greater risk of complications, such as heart failure and arrhythmia, not only due to the effects of the congenital lesion and its repair but also due to the development of acquired cardiovascular (e.g. coronary artery disease) and non-cardiovascular diseases (e.g. diabetes, renal dysfunction and lung disease) [2]. Those with the most complex lesions, who would previously have died before reaching adulthood, constitute the most rapidly growing segment of the adult congenital heart disease (ACHD) population and are at greatest risk of developing further problems [2].

2. Main study findings

In this issue, Ntiloudi et al. report a single-center experience of the clinical characteristics and predictors of outcome in 356 people with ACHD. Over a median follow-up of 4 years, 29 (8.1%) patients died, which was due to heart failure in 14 (48% of deaths). Complications (including arrhythmias, implantation of a pacemaker or defibrillator, stroke, endocarditis, venous thromboembolism, hemoptysis, pulmonary arterial hypertension and heart failure) occurred in 58 patients (16.1%); arrhythmia (not otherwise specified) was the most common complication (9.3%) followed by hospitalization for heart failure (4.5%).

Hospitalization for heart failure was the strongest predictor of both mortality (hazard ratio [HR] 3.79 [95% confidence interval (CI) 1.27–11.30]; p = 0.017) and further complications (HR 3.38 [95% CI 1.56–7.29]; p = 0.002). Patients with a history of heart failure (n = 21) were older (median age 62 vs. 33 years; p < 0.001), had more complex congenital lesions (p = 0.02), more severe symptoms (NYHA III/IV 67% vs. 7%; p < 0.001), and more cardiac complications (p < 0.001). Other potentially important prognostic variables, including the function of the systemic ventricle and plasma concentration of natriuretic peptides were not assessed.

3. Definition and epidemiology of heart failure in ACHD

Definitions of heart failure that are used in other populations might be of little use for people with ACHD [3,4]. The 2016 AHA/ACC Scientific Statement on Chronic Heart Failure in Congenital Heart Disease defined heart failure as ‘a syndrome characterized by either or both pulmonary and systemic venous congestion and/or inadequate peripheral oxygen delivery, at rest or during stress, caused by cardiac dysfunction.’ [5] Whilst this definition might be conceptually correct, no practical method of measuring the adequacy of peripheral oxygen delivery at rest or during exercise exists. The AHA/ACC Scientific Statement classifies heart failure into four stages (A-D) (Fig. 1) [5]. From a practical point of view, only those in stage C and D might be considered to have clinical heart failure requiring treatment for symptoms and signs of congestion. Ntiloudi et al. report that more than half of patients had exertional breathlessness (Stage C), although few had severe symptoms (Stage D) or had been hospitalized for heart failure. Accordingly, the overall prevalence of heart failure in this cohort is unclear and could be more than 50%.

Recently, an international consortium proposed a universal definition of heart failure, but effectively just recapitulated many previous suggestions, defining heart failure as ‘symptoms and/or signs caused by a structural and/or functional cardiac abnormality’ [6]. However, symptoms and signs are late manifestations of congestion, there is a large subjective component to ascertaining both symptoms and signs and patients may deliberately reduce physical activity to avoid symptoms. Therefore, a universal definition based on symptoms and signs might be practical, but it is neither sensitive nor specific and does not promote...
early detection and prevention of progression. An alternative universal definition has been proposed; 'congestion due to cardiac dysfunction' with congestion defined as raised plasma concentrations of natriuretic peptides associated with atrial dilatation rather than by symptoms and signs (Fig. 2) [7]. Natriuretic peptides are one of the key defence mechanisms against water retention, the cause of congestion. Activation of such defences provides early warning of developing congestion.

The identification of heart failure symptoms in ACHD can be
challenging. Patients adapt to the restrictions imposed by their symptoms, confounding assessment of functional class [8]. Systolic and diastolic dysfunction of the systemic ventricle are common in ACHD and do not necessarily indicate the presence of heart failure. Atrial dilatation and an increase in natriuretic peptides both indicate developing congestion and are associated with worsening exercise capacity, suggesting that they might be useful guides to the presence of heart failure, even if symptoms are not overt [9]. Whether this is generally true for all types of ACHD requires further investigation.

There has been a substantial rise in the rate of heart failure hospitalizations in people with ACHD over the last 20 years. In the Nationwide Inpatient Sample, the annual number of heart failure hospitalizations associated with ACHD in the US almost doubled between 1998 and 2011 [10]. In the CONCOR registry, of 10,808 ACHD patients followed for a median of 21 years, 274 (2.5%) were admitted for heart failure; an incidence of 1.2 per 1000 person-years [11]. Similarly, a Swedish nationwide registry of 21,982 young people with ACHD followed for a mean of 26.6 years, 729 were admitted for heart failure with an incidence of 1.25 per 1000 person-years overall, and >3.0 per 1000 person-years for complex lesions [12]. By the age of 42 years, the cumulative incidence of heart failure was 6.5%, increasing to 14.8% for complex lesions. The risk of developing heart failure in people with ACHD was 106 times higher (95% CI 38–135) than matched controls, rising to 402 times higher (95% CI 298–601) for complex lesions. In a study of older patients (>40 years) in Quebec, 12.2% of those with ACHD had a discharge diagnosis of heart failure over a median follow-up of 5 years [13]. In a small prospective single-center study, 89 of 345 patients (26%) had heart failure when defined as having both a plasma N-terminal prohormone B-type natriuretic peptide (NT-proBNP) of >100 ng/L and a peak VO2 of <25 mL/kg/min; by the age of 40 years, >60% of those with moderate or complex congenital lesions, such as patients with a univentricular circulation following Fontan palliation, transposition of the great arteries after atrial switch repair, or tetralogy of Fallot, met the above definition of heart failure [14].

4. Mechanisms of heart failure in ACHD

Several factors, in addition to the underlying structural abnormality, predispose to the development of heart failure in patients with ACHD (Fig. 3). Surgical procedures may cause myocardial scar, fibrosis or dysfunction to the ventricles or atria and damage the coronary arteries or conduction system (sometimes necessitating chronic pacing, which can cause ventricular dysynchrony) [5,15–18]. Valve disease may develop or progress. Chronic pressure and/or volume overloading of the atria and ventricles may cause systolic and diastolic dysfunction and predispose to atrial and ventricular arrhythmias. A complex array of neurohumoral systems is activated, some of which may cause water and sodium retention (i.e. renin-angiotensin-aldosterone and sympathetic nervous systems) leading to congestion, whilst others attempt to prevent it (i.e. natriuretic peptides) [19]. Only when such counterregulatory systems are overwhelmed will the symptoms and signs of heart failure develop [7]. Some mechanisms may be important for specific congenital lesions. For example, in patients with univentricular physiology, pulmonary vascular resistance acts as an important bottleneck to augmenting cardiac output during exercise and lymphatic abnormalities may contribute to impaired ventricular filling [20,21]. Finally, the functional reserve of many organs, including the heart, lungs and kidney, declines with age; biological ageing reduces the tolerance to further cardiovascular stress and injury.

Ventricular systolic dysfunction is common in ACHD and is a frequent cause of clinical heart failure (heart failure with reduced ejection fraction, HFrEF) [5], but other patients will have heart failure with preserved ejection fraction (HFpEF), although the prevalence is unknown [22]. Several congenital lesions predispose to diastolic dysfunction and HFpEF, particularly left-sided obstructive lesions, and systemic right ventricular and univentricular circulations.

5. Causes of death in ACHD

Heart failure appears to be the predominant cause of death in ACHD [23–26]. A single-center study of 6969 people with ACHD in the UK reported that heart failure accounted for 42% of 524 deaths [26]. The Dutch CONCOR registry of ACHD reported 231 (2.7%) deaths during 26,500 patient-years of follow-up; heart failure accounted for 26% of deaths [24]. A single-center Canadian study of 2609 patients reported that heart failure was the mode of death in 21% of 199 deaths [25]. The high proportion of deaths due to heart failure reported by Ntiloudi et al. may reflect their population, which was enrolled in a tertiary referral hospital with a high proportion of patients with moderate or complex CHD or the uncertainties due to the small sample size. However, classification of the mode of death in these studies was not sophisticated. Many people who develop heart failure die suddenly or from respiratory infections or from other causes that they might not have developed or been lethal had they not had heart failure; dying from heart failure is a process rather than an event [27].

6. Heart failure hospitalization as a predictor of outcomes in ACHD

Hospitalization for or with heart failure indicates a poor prognosis for both ACHD and acquired heart disease [11,28]. In the CONCOR registry, heart failure hospitalization was associated with a 5-fold increase in mortality compared with those who were not hospitalized, with 1- and 3-year mortality rates of 24% and 35%, respectively [11]. This report (Ntiloudi et al.) is consistent with these findings. The poor outcomes following hospitalization for worsening symptoms and signs of heart

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**Fig. 3.** Mechanisms of heart failure in congenital heart disease.
7. Treatment of heart failure in ACHD

Four classes of pharmacological agents, used in combination, have improved outcomes for people with acquired HFpEF substantially [29, 30]. For selected cases, cardiac resynchronization therapy, defibrillators, mitral valve repair, intravenous iron and coronary revascularization have further improved prognosis [3,4,30–32]. Recently, the concept of heart failure with mildly reduced ejection fraction (HFrEF) was introduced as a zone of uncertainty to reduce misclassification between HFrEF and HFpEF (a measurement of ejection fraction is accurate only to within 10%) and because a true normal ejection fraction is between 60 and 70% [33]. People with HFpEF have a better prognosis than HFrEF but may respond similarly to treatment. Treatment of HFpEF relies mainly on the management of co-existing problems, such as hypertension, coronary artery disease or amyloidosis [30]. However, it may not be appropriate to extrapolate evidence from trials of acquired disease to those with ACHD, especially for problems such as systemic right ventricular and uni-ventricular circulations [34,35].

8. Summary

In summary, Nitoulid et al. confirm the high burden of failure-related morbidity and mortality in adults with CHD. However, the pathways leading to heart failure in ACHD are heterogeneous and often poorly understood. Most importantly, there is a need for more randomized trials. Trials investigating effects on symptoms and surrogate measures of disease need not be large. However, much larger trials are required to investigate the effects of treatment on disease progression and prognosis, requiring collaborations at national and international levels, as is already the case for other forms of heart failure.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References


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