Progress in Pediatric Cardiology 38 (2014) 9–15

Contents lists available at ScienceDirect

Progress in Pediatric Cardiology

journal homepage: www.elsevier.com/locate/ppedcard

Review

Heart failure in adult congenital heart disease: How big is the problem?

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ARTICLE INFO

Available online 16 December 2014

Keywords:
Heart failure
Congenital heart disease
Prognosis
Tetralogy of Fallot
Transposition of the great arteries

ABSTRACT

Over the past several decades, the total number of adult patients with congenital heart disease has rapidly risen due to advances in early surgery and medical management. The current prevalence of adult congenital heart disease is now approximately 3000 per million adults. With these successes, new challenges also emerge. In this heterogeneous group of patients, several factors can contribute to the development of heart failure. For instance, longstanding right ventricular volume overload in the tetralogy of Fallot patients can lead to heart failure, while patients with a Mustard or Senning repair of transposition of the great arteries may develop heart failure after systemic right ventricle deterioration due to pressure overload. Heart failure in adult congenital heart disease is a continuum from mild ventricular dysfunction and modest neurohormonal activation to hospitalization for symptomatic heart failure and is associated with a decreased life expectancy depending on the severity.
In this review, we discuss the prevalence and etiology of heart failure in adult patients with congenital heart disease. More in detail, we discuss whether several well-established markers in acquired heart failure have a (potential) role in the diagnosis and risk stratification of heart failure in adult congenital heart disease patients. Finally, opportunities in prevention and treatment are discussed as well as future perspectives on the problem of heart failure in adult congenital heart disease.

1. Introduction

Adult congenital heart disease (ACHD) patients have an increased risk of developing heart failure due to hemodynamic compromise caused by their cardiac defects or due to previous surgery for these defects [1–4]. In this review, we will define ACHD heart failure and discuss challenges in its assessment in this population as compared with acquired heart failure. In addition, we will provide an overview of available data on prevalence and discuss some pathways of progression into ACHD heart failure. Furthermore, several well-established diagnostic markers of acquired heart failure are discussed and their prevalence and potential role in the diagnosis of ACHD heart failure as well as their correlations and prognostic implications. Finally, available data on opportunities for prevention and treatment of ACHD heart failure and future perspectives will be discussed.

2. Definition of ACHD heart failure

Heart failure is defined as a combination of symptoms (e.g., dyspnea, peripheral edema) and typical signs (e.g., pulmonary rales, increased central venous pressure) and is caused by an inability of the heart to deliver a sufficient amount of oxygen to organs and tissues [5]. Identification of an underlying cardiac cause for these signs and symptoms is essential for the diagnosis [5]. The 2012 European Society of Cardiology guidelines subdivide heart failure into heart failure with reduced ejection fraction and heart failure with preserved ejection fraction. Signs and symptoms of heart failure are essential for both diagnoses, but a reduction in left ventricular ejection fraction has to be present in the former while ejection fraction has to be preserved in the presence of other relevant cardiac disease (e.g., left ventricular hypertrophy, left atrial dilation or diastolic dysfunction) in the latter [5].

In the ACHD population, signs and symptoms of heart failure are non-sensitive or non-specific. For instance, some patients will not complain of dyspnea as their exercise capacity has declined gradually over the course of many years [6]. Moreover, ACHD patients may also have a limited exercise capacity due to non-cardiac causes such as a sedentary lifestyle, pulmonary hypertension or other comorbidity [6,7]. Distinction between heart failure with reduced or preserved ejection fraction is difficult in ACHD because factors such as subpulmonary ventricular dysfunction, shunts and valvular regurgitation may contribute to heart failure as well [8–10]. In addition, these factors influence cardiac ejection fraction and make its assessment and interpretation challenging. Bolger et al. [11,12] previously defined ACHD as a heart failure syndrome in which all pathophysiological criteria to develop heart failure are present. The authors suggested to define heart failure

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http://dx.doi.org/10.1016/j.ppedcard.2014.12.007
1058-9813/

as a continuum from mild asymptomatic ventricular dysfunction with modest neurohormonal activation to severe ventricular dysfunction with symptoms at rest and marked neurohormonal activation. In this review, we will adhere to this definition, and we will view ACHD heart failure as a continuum in which assessment of several markers may be useful to classify severity, provide prognostic information and assist in timing of interventions or treatment.

3. Epidemiology of ACHD heart failure

Aging of the general population and prolongation of the lives of cardiac patients by therapeutic interventions has led to an increasing prevalence of heart failure with now an estimated 5 million people living with chronic heart failure in the United States and 23 million worldwide [13,14]. The lifetime risk for developing symptomatic heart failure is approximately 20% [15], with a mean age of 62 years at onset of acquired heart failure [16].

The number of adult patients living with congenital heart disease (CHD) is increasing due to advances in treatment. The current prevalence of ACHD patients is now approximately 3000 per million adults [17]. Patients can be divided into different classes depending on the severity of the congenital defect [18]. The severe class comprises transposition complexes, double outlet ventricle, single ventricle physiology, pulmonary atresia, and truncus arteriosus. Moderate CHD includes the tetralogy of Fallot (TOF), anomalous pulmonary venous connection, aortic coarctation, Ebstein malformation, atrioventricular septal defects (ASD), and large ventricular septal defects (VSD), severe pulmonary stenosis (PS), aortic stenosis (AS), and some ASDs (e.g., sinus venosus defect). The mild class contains uncomplicated or repaired PDA, VSD, ASD, PS, and AS. Verheugt et al. [19] revealed heart failure as the cause of death in approximately 25% of deceased ACHD patients. However, previous studies focusing on heart failure in ACHD have used different criteria to define heart failure, resulting in different prevalence numbers. Zomer et al. [2] reported the incidence of heart failure admissions to be 1.2 per 1000 patient-years and found a higher incidence in patients with right-sided and multiple lesions. Mean age at ACHD heart failure admission was 46 years. These numbers only reflect the tip of the iceberg of heart failure in ACHD as most patients with stable chronic heart failure are not likely to get admitted. On the other hand, in a large cross-sectional study by Eindhoven et al, 53% of 475 consecutive patients had an elevated N-terminal–pro-brain natriuretic peptide ($\geq$14 pmol/L or $\geq$118 ng/L). Norozi et al. [3] defined heart failure as decreased aerobic capacity ($\leq$25 ml/kg/min) and increased N-terminal–pro-brain natriuretic peptide ($\geq$100 pg/ml or $\geq$186 ng/L). In their study, heart failure was present in 89 (26%) of 345 of consecutive ACHD patients. Heart failure was most common in right-sided lesions, especially in the tetralogy of Fallot (TOF) patients when a transannular patch was used or a pulmonary valve replacement was performed. Piran et al. [1] evaluated 188 patients with transposition of the great arteries (TGA) and defined heart failure by signs and symptoms which were present in 27% of patients. The overall mortality rate during 15 years postoperative follow-up in asymptomatic patients was 5% compared with 47% in the heart failure group. Systemic right ventricular (RV) function was markedly depressed in patients with heart failure symptoms. In a clinical trial by van der Bom et al. [20], 13% of patients with TGA and a systemic RV developed symptomatic heart failure (increase of diuretics or deterioration of NYHA class or hospitalization) during 3.1 years of follow-up. The total lifetime risk of developing symptomatic heart failure in ACHD patients remains unknown as their average age is still rising. Conclusively, prevalence and incidence of ACHD heart failure is variable depending on its definition which ranges from isolated elevated natriuretic peptides (prevalence of 53% [21]) to a combination of decreased exercise capacity and elevated natriuretic peptides (prevalence of 26%[3] or hospitalization for symptomatic heart failure (1.2 per 1000 patient-years[2]).

4. Etiology of ACHD heart failure

Sixty percent of patients with heart failure with reduced ejection fraction have ischemic heart disease as the main cause [22]. Other causes are idiopathic dilated cardiomyopathy, hypertension, and valvular disease [22]. Risk factors for acquiring these predisposing conditions, include cigarette smoking, hypertension, overweight, and diabetes [15]. The same risk factors contribute to the development of diastolic dysfunction, although patients admitted for heart failure with preserved ejection fraction are older, more likely to be female but ischemic heart disease is less common [23].

In ACHD patients, progression to heart failure may result from the hemodynamic burden of their primary defect or be a result of residual lesions after correction of this defect [1,2,9]. Most of these lesions adversely affect cardiac function therewith contributing to the development and progression of heart failure [9,24]. It is important to view ACHD patients as a heterogeneous group, since outcomes after extensive surgery and comorbidity vary widely, even between patients with the same initial cardiac defect [25]. In general, mild lesions such as a small uncomplicated ASD are unlikely to cause heart failure at an early age. In contrast, severe lesions likely to cause a major hemodynamic burden are associated with extensive comorbidity, and the correction of these lesions is often accompanied by residual abnormalities. Several (i) hemodynamic, (ii) electrical, (iii) myocardial, (iv) comorbid, (v) non-related acquired, and (vi) neurohormonal factors can play a role in the development of ACHD heart failure. An overview of these factors is provided in Table 1. (i) Hemodynamic factors that cause a volume or pressure overload include residual pulmonary regurgitation after surgical correction of pulmonary stenosis, volume overload due to shunting in uncorrected ASD, or acquired aortic stenosis in predisposed patients with a bicuspid aortic valve [26,27]. (ii) Electrical factors such as a right bundle branch block after ventricular septal defect repair or single-site lead pacing can cause ventricular dyssynchrony, which reduces ventricular efficacy and leads to deleterious remodeling [28,29]. (iii) A wide range of myocardial conditions predispose patients for the occurrence of heart failure. Patients with TGA after atrial switch have a systemic RV which is physiologically not adapted to perform under systemic pressures [1], while in other ACHD patients, extensive myocardial fibrosis develops after previous surgery, longstanding cyanosis or (subendocardial) ischemia and has detrimental effects on cardiac function [30]. (iv) Pulmonary vascular remodeling after left to right shunting leads to comorbid pulmonary arterial hypertension which eventually may cause RV failure [10]. Patients after repair for coarctation of the aorta often develop systemic hypertension which may cause left ventricular hypertrophy [31]. (v) In addition, ACHD patients can also develop acquired heart disease such as coronary artery disease, and the number of patients with such a combination of congenital and acquired heart disease will rise as the ACHD population ages. (vi) Neurohormonal activation is a compensatory mechanism in patients with reduced cardiac output and is common in ACHD patients. In the short term, neurohormonal increases cardiac output by various mechanisms at the long-term cost of detrimental effects on myocardial function and clinical well-being [12,32]. In many ACHD patients, a combination of multiple acquired, residual and congenital factors is present simultaneously and predispose them to develop heart failure.

5. Prognostic markers of ACHD heart failure

As in acquired heart failure, several markers have the potential to be used to identify ACHD patients at risk to develop heart failure, to classify disease severity or to evaluate progress of heart failure or treatment response. In addition, several markers provide valuable information for risk stratification in ACHD patients. In this review, we will discuss a wide range of well-established markers of acquired heart failure and their potential role in diagnosis of heart failure and risk stratification in ACHD patients. Prognostic heart failure markers we will discuss in