Medical Therapy in Adults with Congenital Heart Disease

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KEYWORDS

• Heart failure • Congenital heart disease • Medical therapy • β-blockers
• Angiotensin-converting enzyme inhibitor

KEY POINTS

- Clinical heart failure is associated with increased morbidity and mortality in adults with congenital heart disease.
- The onset of clinical heart failure should prompt the treating physician to look for residual hemodynamically important anatomic defects that may be amenable to intervention.
- Because of heterogeneity and insufficient patients number for randomized controlled trials, extrapolation and expert opinion guide medical therapy.

INTRODUCTION

The development of heart failure (HF) is a clinically important event in patients with adult congenital heart disease (ACHD). Hospitalization for HF identifies a population of ACHD patients at risk for subsequent hospitalizations and mortality over the next 3 years. In a recent study, incidence for first HF admission in young patients with congenital heart disease (CHD) was 1.2 per 1000 patient-years, more than 10-fold higher than that in the general population of the same age. Following a first admission for HF, mortality was high, 24% at 1 year and 35% at 3 years, and primarily of cardiovascular causes,[1] emphasizing the importance of the onset of HF in an ACHD patient. Despite the significant contribution of HF to premature morbidity and mortality in the ACHD population, no adequately powered clinical trials have been done to understand the role of medical therapies in ACHD patients with clinical HF.

Although many patients with ACHD meet the clinical definition of HF,[2] patients with ACHD have been excluded from clinical trials of medical therapy in HF and, because of consequently limited specific data, from the HF guidelines.

Patients with ACHD are at risk for complications related to the original defect and/or subsequent repairs. In addition, some patients with univentricular circulations or Eisenmenger syndrome develop dysfunction involving multiple organ systems. Therefore ACHD patients with evidence of clinical signs and symptoms of HF need evaluation for residual hemodynamically significant defects, including valvular dysfunction, shunts, pulmonary vascular disease, obstruction of conduits and baffles, and other potentially correctable anatomic lesions.

In conjunction with correction of residual anatomic lesions, medical therapy may be of benefit for the management of ventricular dysfunction in the ACHD patient. This article reviews the

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applicability of the current HF guidelines to an ACHD population, and reviews medical therapies for HF in specific patient populations, including biventricular repair with normal connections, subaortic right ventricle in a two-ventricle circulation, and single-ventricle (SV) circulations.

THE HF GUIDELINES: RATIONALE FOR MEDICAL THERAPY

Similarities in clinical presentation make it tempting to broadly extrapolate the HF guidelines to patients with ACHD. Challenges in extrapolating heart guidelines to a heterogeneous ACHD population range from difficulties in recognizing exercise intolerance, quantifying ventricular dysfunction, lack of diagnostic criteria, and lack of consensus recommendations on management.

Neurohormonal activation may also be seen in ACHD patients with a variety of surgically repaired and unrepaired heart defects,[3] similar to that described in a population with acquired HF.[3–8] Therefore the use of therapies that are known to improve outcomes in acquired left ventricular (LV) systolic dysfunction (HF with reduced ejection fraction, or HFrEF) may be of benefit in carefully selected patients with ACHD.

Cardiac remodeling is the final common pathway by which an initial injury or stressor to the ventricle leads to progressive structural changes of the ventricle, which is driven by a variety of neurohormonal stimuli,[9,10] cytokines,[11] changes in calcium handling,[12,13] signaling pathways,[14] extracellular matrix,[15] autoimmunity,[16] oxidative stress, and substrate utilization.[17]

The clinical importance of neurohormonal pathways, particularly the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS), has been demonstrated in numerous clinical trials in HFrEF, demonstrating survival benefit with blockade of these pathways. Therapies that reverse or slow the remodeling process improve survival in patients with HFrEF.[18–26] Similarly, the Studies of Left Ventricular Dysfunction (SOLVD) investigators demonstrated a significant delay in the time to development of clinical HF and hospitalization in patients with asymptomatic LV systolic dysfunction treated with the angiotensin-converting enzyme inhibitor (ACEI) enalapril.[27]

However, as has been learned from the HF experience, these benefits may not be realized in populations of patients with HF of differing etiology, such as HF with preserved ejection fraction (HFpEF), despite a similar clinical event rate.[28–32] The recent observation that 24 weeks of sildenafil did not improve quality of life (QOL) or exercise capacity in patents with HFpEF, despite prior studies suggesting a hemodynamic benefit,[33] serves as a cautionary tale for clinical application of medications in a population based on small single-center studies focused on acute hemodynamic benefit, without study of long-term effectiveness. **Table 1** outlines current knowledge about the use of HF medications in different populations.

PREVENTING HF: RISK-FACTOR MODIFICATION

Identification of patients with modifiable risk factors may delay or prevent HF in certain at-risk populations. Application of basic cardiology practices to the ACHD population makes sense given the prevalence of modifiable risk factors (eg, hypertension, diabetes mellitus, obesity, atherosclerosis, sedentary lifestyle) in our contemporary population. The recently updated HF guidelines also recommend exercise training or regular physical activity, education focusing on self-care, and identification and discontinuation of cardiotoxins.[2] Early intervention in those at risk should also include patients with ACHD.

EXTRAPOLATION FROM THE HF GUIDELINES: INITIAL ASSESSMENT OF THE SYMPTOMATIC PATIENT

In addition to evaluation for important residual anatomic lesions, assessment of patients with ACHD and signs of clinical HF should include the same thorough history and physical examination described in the HF guidelines.[2] Recommendations for assessment of functional class, volume status, changes in orthostatic blood pressure, weight, body mass index, laboratory studies, 12-lead electrocardiogram, chest radiograph, and 2-dimensional echocardiography with Doppler[2] are generally applicable to an ACHD population.

DIURETICS

Diuretics should be considered for all patients with signs of fluid retention. Patients unresponsive to oral loop diuretics should be given intravenous diuretics to relieve congestion. Aldosterone antagonists can be considered in patients with systolic LV dysfunction and a prior hospitalization for congestive HF, or symptoms of New York Heart Association functional class III to IV, who are appropriate candidates (estimated glomerular filtration rate >30 mL/min/1.73 m^2 and serum potassium <5 mEq/L).[2] Baseline laboratory studies and routine monitoring of renal function and electrolytes should be performed for all patients on diuretics.