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A REVIEW OF HEART FAILURE IN ADULTS WITH CONGENITAL HEART DISEASE

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Introduction

The nearly one-million estimated adult congenital heart disease (ACHD) patients in the United States now outnumber children with congenital heart disease (CHD).[1] With continued improvement in survival due to surgical and medical management of patients born with CHD, there is an overall shift in the burden of care from childhood to adulthood.[2] Due to this transitioning population, the probability of heart failure continues to increase with age[3] and represents nearly one-quarter of all mortality in ACHD.[4] Despite these sobering figures adult cardiologist and fellows continue to have limited exposure in the care of patients with congenital heart disease.

The syndrome of heart failure represents a complex derangement of neurohormones, natriuretic peptides, and cytokines leading to progressive symptoms of exercise intolerance, dyspnea, and fatigue.[5] Congenital heart patients represent a unique challenge in both categorization and protocol management of heart failure (HF). It remains unclear if the current four-stage ACC/AHA guidelines for diagnosis and treatment of HF in adults[6] can serve as a meaningful framework for congenital heart patients. Additionally, widely used conventional HF therapy of beta-blockers and angiotensin converting enzyme inhibitors (ACE-I) have not demonstrated clear survival benefit in this population. Unfortunately, adequately powered and controlled randomized studies are grossly lacking and remain challenging to conduct. Nonetheless, a review of heart failure associated with ACHD is provided.

Pathophysiology of Heart Failure in Adult Congenital Heart Disease

When myocardial injury or stress from pressure or volume overload occurs, there is a complex signaling process leading to impaired function, myocyte loss, altered gene expression, and deranged neurohormonal activation.[7] The activation of renin-angiotensin-aldosterone system, sympathetic nervous stimulation, and altered calcium handling leads to salt and fluid retention, vasoconstriction, and myocardial remodeling.[8] Pharmacological manipulation of the aforementioned derangements with b-blockers, ACEIs, and spironolactone has been shown to improve mortality in the general HF population. [9-11] Similar neurohormonal derangements have been demonstrated in a cohort of adults with varied CHD (Figure 1).[12] This included elevations in atrial natriuretic peptide, b-type natriuretic peptide, endothelin-1, norepinephrine, renin, and aldosterone related to New York Heart Association (NYHA) functional class, ventricular function, and peak oxygen consumption.

In the CHD population, development of HF is usually a chronic process with a long asymptomatic period despite overt ventricular dysfunction and decreased measured functional capacity. Whether palliated, repaired, or unrepaired, CHD patients by definition would start at ACC/AHA Stage B Heart Failure given their structural heart defects. Many seem to have adapted to their chronic HF symptoms and insidious limitations in exercise capacity, with exercise tolerance almost universal and progressive in this cohort.[13] Thus, in many patients, NYHA status does not always correlate with peak oxygen consumption,[14] and on average mean peak oxygen consumption in ACHD is less than one-half of age-matched controls (21.7 cc/kg/min vs. 45.1 cc/kg/min).[13, 15] Furthermore, the decreased oxygen consumption is correlated with deteriorating myocardial performance index (Figure 2).[14] This asymptomatic nature of chronic HF with profound cardiopulmonary exercise limitations has led some clinicians to recommend exercise testing in all ACHD patients.[16] Additionally, chronotropic incompetence, which is common after surgical repair, leads to increased symptoms and neurohormonal imbalance and reduced exercise capacity.[17]

Classic physical findings in HF of elevated jugular venous pressure, S3 gallop, hepatomegaly, peripheral edema, tachycardia, and tachypnea may also be identified in ACHD patients and improve the specificity of the diagnosis. However, a significant number of patients remain in chronic, compensated HF without many classic findings; some studies found only 49% sensitivity for using clinical judgment alone.[18]

Diastolic HF with preserved ejection fraction (EF) remains an important entity occurring in 20 to 60% of adults,[19] but limited data in the ACHD population make estimates unreliable. Echocardiographic measures of diastolic dysfunction, including left atrial volume, mitral flow indices, and strain imaging are frequently utilized, but risk stratification based on these data remains unproven. Cardiac magnetic resonance imaging (CMR) may also show some diagnostic promise, with a recent study showing that myocardial fibrosis was highest in patients with systemic right ventricles.[20]

Dyssynchrony from chronic right ventricular pacing can lead to exercise intolerance and progressive ventricular dysfunction. Atrial arrhythmias are common after the arterial switch or Fontan single ventricle procedures, and atrial arrhythmias resulting from marked atrial enlargement late after the Fontan operation are at increased risk for developing HF compared to those without.[21] Additionally, atrial arrhythmias are also associated with the development of HF and with death late after the Mustard operation.[22, 23]

Heart Failure by Anatomy

Heart failure in ACHD is a result of many myocardial insults

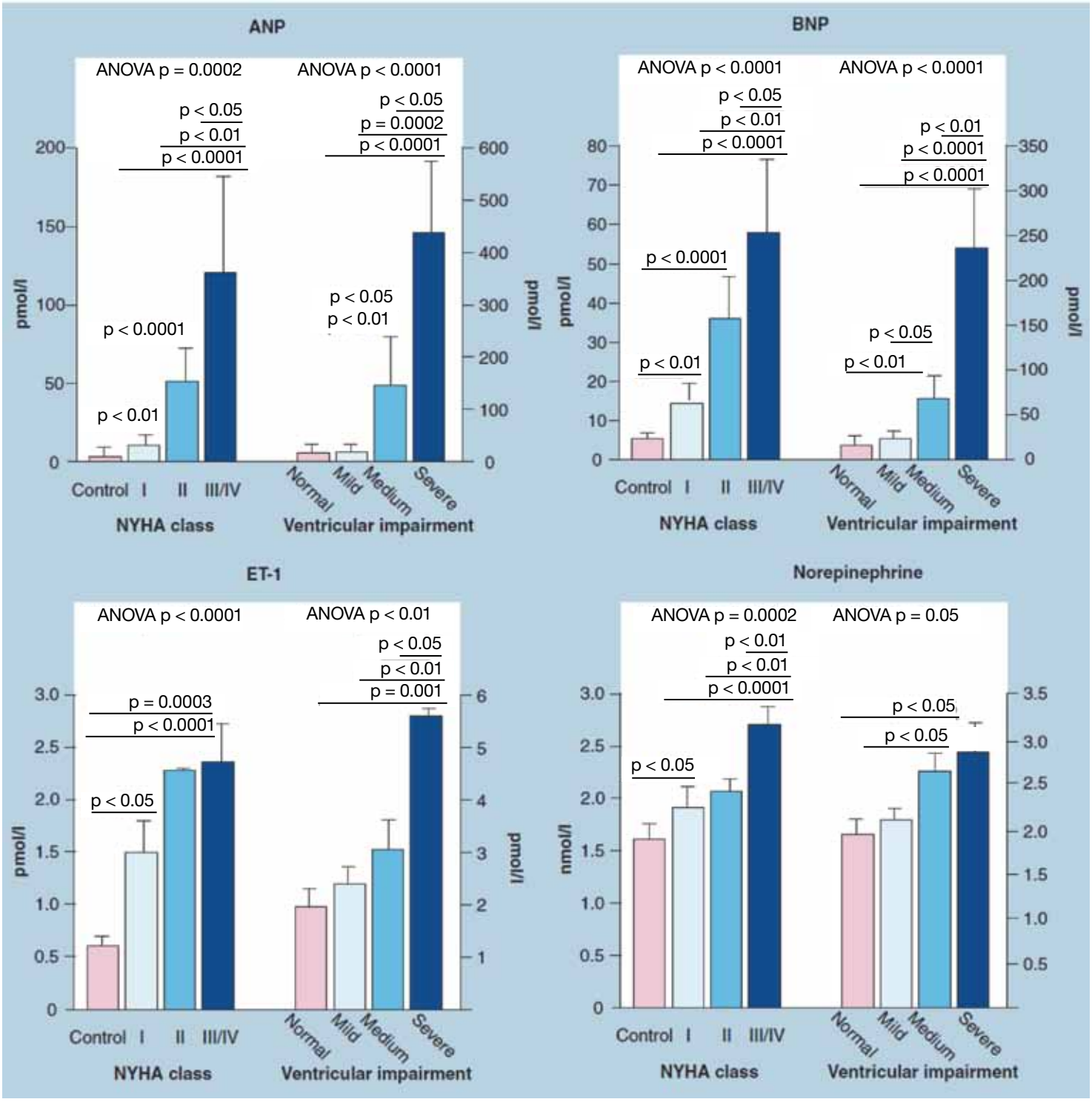

Figure 1. Neurohormonal derangements in a cohort of adults with varied CHD. Figure shows neurohormone levels in all subjects according to NYHA functional class, and in adults with congenital heart disease according to systemic ventricular function. Note differing y-scales for each measure. ANOVA: analysis of variance; ANP: atrial natriuretic peptide; BNP: b-type natriuretic peptide; ET: endothelin; NYHA: New York Heart Association.[12]

including chronic pressure and/or volume overload, cyanosis, cardiopulmonary bypass,[24, 25] coronary injury, and ventriculotomy during tetralogy of Fallot repair. Many patients with residual intra- or extracardiac shunting (i.e., ventricular septal defect, atrial septal defect, or patent ductus arteriosus) who present with volume overload, chamber enlargement, and subsequent ventricular dysfunction can be repaired surgically or percutaneously. Additionally, volume load caused by chronic pulmonary regurgitation after transannular repair of tetralogy of Fallot are now routinely addressed by placing a competent pulmonary valve in the operating room or catheterization laboratory. Hemodynamically significant outflow tract obstruction of the right or left ventricle (i.e., pulmonary or aortic stenosis, or coarctation of aorta) should be addressed accordingly as per the ACC/AHA guidelines on management of adults with CHD.[26] The more long-term problematic issues arise when patients have only a single ventricle or systemic right ventricle due to either surgical correction (atrial switch) or naturally. Some studies suggest that the incidence of heart failure in these patients is 10 to 22%,[27] with the probability of heart failure likely increasing over time (Figure 3).[3]

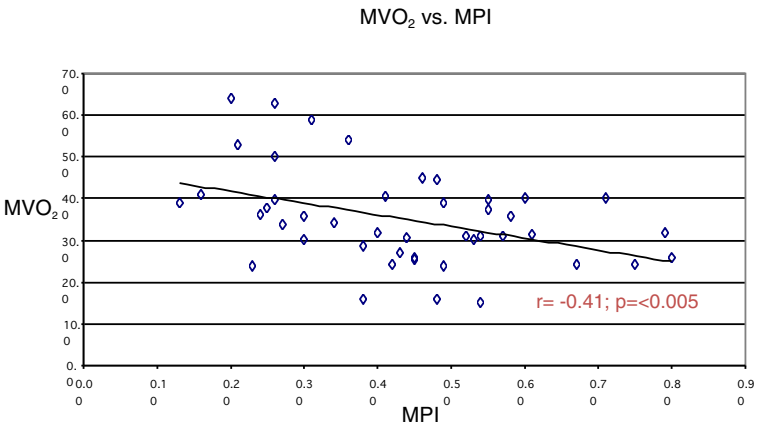

Figure 2. Correlation of peak oxygen uptake (MVO_2) and myocardial performance index.[14]

Complex patients with a single ventricle who have undergone the Fontan operation (total cavopulmonary connection) are merely palliated, and this circulation is likely to fail over ensuing decades. Complications in the so-called "failing Fontan" include atrial arrhythmias, cavopulmonary obstruction, progressive cyanosis from systemic to pulmonary venous connections, and protein-losing enteropathy, all of which are well described.[28] Prevalence of clinical HF 16 years after Fontan repair is estimated as high as 40%.[27] Despite these limitations, post-operative results have continued to improve with the utilization of lateral tunnel (LT) and extracardiac conduit (ECC) Fontan modifications. Indeed, with newer techniques, improvements in exercise capacity and late arrhythmias were reported more than 15 years after repair.[29] Currently, many patients with the classic atriopulmonary Fontan operated on in the '70s and '80s undergo evaluation for Fontan conversion to the more contemporary LT or ECC Fontan, including a right atrial MAZE for intra-atrial reentrant tachycardia.[30, 31]

Patients with congenitally corrected transposition of the great arteries (often called cc-TGA, levo-TGA, or atrioventricular and ventriculoarterial discordance) and after atrial switch repair for dextro- transposition of great arteries present with unique challenges in terms of medical management. The systemic right ventricle does not behave like a normal left ventricle, and treat

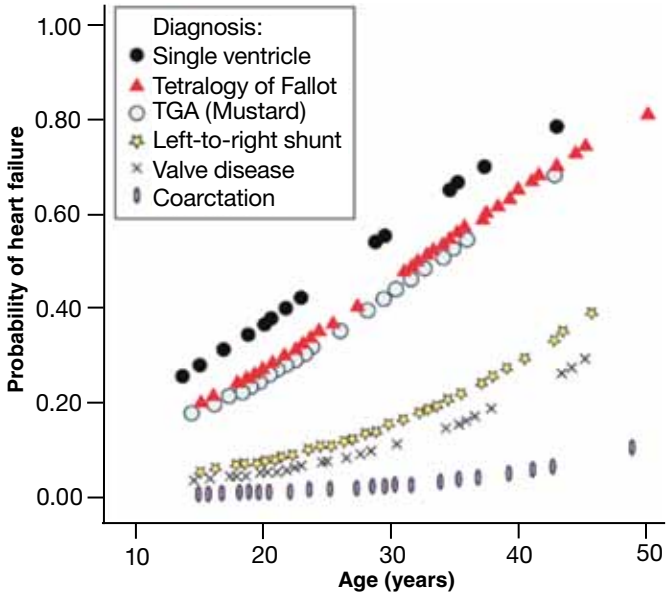

Figure 3. The probability of heart failure over age and type of heart defect.[3]

ments aimed at LV remodeling may not be appropriate. For systemic right ventricle (RV) patients, there is still unclear definition as to the normal ejection fraction, and sequential assessment by echo is technically challenging. Additionally, residual anatomic defects of systemic and/or pulmonary venous baffle obstruction after atrial switch may present with signs of left and/or right heart failure, necessitating relief of obstruction by transcatheter or surgical means. One-third to one-half of patients after a Mustard or Senning palliation have demonstrated reduced systemic RV function at 15 to 18 years follow up.[23, 32] Systemic RV patients also showed impaired increase in cardiac index and stroke volume in response to stress (exercise or dobutamine), with an inability to augment ventricular filling with tachycardia.[33] The clinical profile of these patients will change as patients with d-TGA now undergo arterial switch operation requiring coronary button reimplantation.

Adults with cc-TGA have an average systemic EF of 41%.[34] Of patients with complex cc-TGA associated with pulmonary stenosis or ventricular septal defects, 70% have systolic dysfunction[35] and 30 to 50% have symptomatic heart failure. There is a small subset of adult congenital patients with increased risk of coronary ischemia due to congenital abnormalities of the coronaries (anomalous origin or abnormal course), left-heart obstruction lesions, and coronaries that were manipulated as a result of surgical repair (e.g., arterial switch for d-TGA or Ross operation). Coronary artery complications are noted in up to 8% of patients after arterial switch repair.[36] There is evidence of early intimal proliferation by intravascular ultrasound in children after arterial switch repair.[37] Given the unknown long-term follow-up in many of these patients, continued vigilance with serial coronary artery imaging and ischemia testing (including invasive angiography) may be reasonable in these patients.[26, 38]

Surveillance and Evaluation

Echo remains the standard for initial anatomic and hemodynamic evaluation, and it continues to be the most common tool to measure ventricular systolic and diastolic function. New modalities for assessing ventricular function and diastology continue to improve and allow more advanced evaluation of ventricular performance.

CMR is a tool increasingly utilized in ACHD as it allows for detailed functional and anatomic evaluation; this is especially useful when many times the acoustic windows are poor, and a proper assessment of detailed anatomy and the right ventricle can be extremely challenging by echo. CMR is now routinely used to assess for RV volume, function, and degree of pulmonary regurgitation in tetralogy of Fallot patients, and its use is mainly limited by availability, time, occasional need for sedation, and pacemaker incompatibility.

Invariably, the final common pathway of evaluation includes a cardiac catheterization. This allows for the most reliable hemodynamic measurements and can incorporate pulmonary vasoreactivity testing in addition to interventional procedures.

Management

A uniform and regimented treatment plan is not plausible for a patient with heterotaxy and a single ventricle or corrected TGA as it is with an ischemic patient who has a two-ventricular physiology. Currently, we extrapolate data from adult patients with acquired heart disease, and we use limited evidence and anecdotal experience to manage the neurohormonal dysfunction inherent in all heart failure syndromes. However, special attention is given to any anatomic and hemodynamic corrections that may lead to improved hemodynamics and symptomatology. Additionally, ACHD patients should be screened for hypertension, atherosclerosis, diabetes, obesity, and metabolic syndrome. There is evidence of ACHD patients having increased incidence of certain cardiovascular risk factors

compared to healthy age-matched controls.[39]

Diuretics for chronic volume overload and pulmonary congestion remain a mainstay of therapy. Caution should be used in cases of Fontan palliation since these patients are dependent on passive, nonpulsatile filling for preload of the systemic chamber. Additionally, shunt-dependent patients (e.g., Blalock-Taussig, Waterston, Potts) require a certain "driving" pressure and volume to allow for appropriate pulmonary artery flow. The balance between adequate volume status and pulmonary perfusion often requires tedious manipulation of the medical regimen.

Due to their effect on combating increased sympathetic tone and demonstrated improvement in mortality in the adult heart failure population, beta-blockers remain a mainstay in treatment of heart failure in CHD.[9, 40, 41] The additional benefits of quieting arrhythmias and reducing the risk of sudden death are also useful.[40, 42] Beta-Blocker usage in adults is associated with fewer hospitalizations, heart failure symptoms, and recurrent myocardial infarctions and reduced one-year mortality on average by 36%.[9, 40-43] Although some studies have reported a possible benefit of beta-blockers in ACHD and systemic RV dysfunction, large-scale studies are lacking.[44, 45] Anecdotal experience continues to be the mainstay of many clinicians.

Many well-designed adult studies have shown the benefit of afterload reduction with angiotensin-converting enzyme inhibitors (ACEIs)[10, 46, 47] and angiotensin II receptor antagonists[48] (ARBs) in left ventricular dysfunction, leading to improved EF and positive ventricular remodeling. On average, a 16% reduction in one-year mortality was noted in these patients with varied causes of heart failure.[9] Again, we often apply these data in our decision to use ACEI therapy in the ACHD cohort. While this extrapolation is appealing, significant obvious differences are noted in the two groups. Adult studies report higher mortality ranges (from 7 to 52%) for placebo groups due to older age at time of study and underlying ischemic coronary disease. ACHD patients do not frequently have ischemic coronary disease and are generally a much younger cohort with lower mortality rates. Of the reported studies on the use of ARBs and ACEIs in ACHD, there is no convincing evidence of improved symptoms or survival.[49-52] It would be useful to include more ACHD patients in clinical trials to determine drug efficacy on single and systemic right ventricles.

Aldosterone agonists are recommended in advanced heart failure and have shown improved survival.[11, 53] No data exist on the use of these agents in ACHD patients with HF. In addition, though digoxin is used for symptomatic benefit in HF, it is not used routinely in ACHD patients.

Inotropic agents and phosphodiesterase inhibitors should be included in the armamentarium of acute decompensated HF. Since their complete discussion is beyond the scope of this article, it should be noted that most of their use is inferred from adult studies. Agents for pulmonary arterial hypertension and elevated pulmonary resistance can be used in select circumstances to improve pulmonary blood flow, preload, and possibly RV function.[54, 55]

In adult patients with prolonged QRS duration, LV dysfunction, in NYHA class III-IV, and under maximal medical management, cardiac resynchronization therapy (CRT) has been shown to be beneficial in improving symptoms, functional class, and survival.[56] Similar studies showing mortality benefit for the ACHD population are not available. Many patients have a systemic right ventricle with right bundle branch block and RV dysfunction rather than the left bundle branch block and left ventricular dysfunction. Limited studies of children and ACHD patients have shown mixed results with an overall benefit from CRT, yet ideal candidates for CRT need to be further delineated.[57, 58] A more aggressive earlier usage of CRT prior to significant decrease in ventricular function may be indicated. Often anatomic considerations prevent placing transvenous systems. These include patients with intracardiac shunting who are at increased risk for systemic emboli and those with extracardiac Fontan, atrial switch and single ventricle who may have their coronary sinus drain abnormally or into the systemic atrium, which prohibits lead placement. At times, CRT therapy with multi-site epicardial lead placements is performed in the operating room.

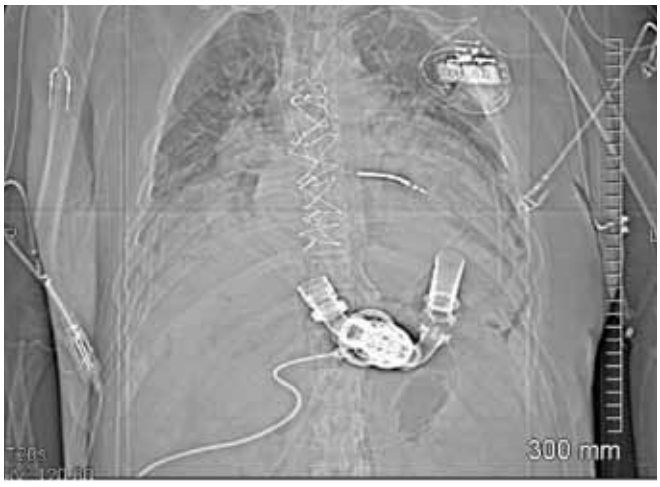

Figure 4. Patient with d-TGA after Heartmate II ventricular assist device from systemic RV to aorta.

The Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) showed the benefit of implantable cardioverter defibrillators (ICDs) in patients with ischemic cardiomyopathy and severe LV dysfunction.[59] CHD patients with dysfunctional systemic RVs, single ventricles, valvar aortic stenosis, and those who have undergone ventriculotomy are likely at increased risk for sudden cardiac death.[60] Consideration should be given to correcting any underlying residual pathology, as seen in patients after tetralogy of Fallot repair who require a pulmonary valve replacement. CHD patients with clinical symptoms, nonsustained ventricular tachycardia, and ventricular dysfunction should be referred to an eletrophysiologist. Nevertheless, it should be noted that the rate of sudden death in the younger CHD population is lower when compared to older adult ischemic patients, and the overall mortality benefit of ICDs with respect to their chronic morbidity is unclear.[60] However, there is no debate that ICD placement for secondary prevention of sudden cardiac death is indicated.

With rapid deterioration of cardiac function in patients on transplant lists, use of ventricular assist devices (VADs) may be the only option (Figure 4). Complex anatomic variants associated with CHD require a thoughtful approach to device implantation. There are case reports and anecdotal evidence of varying success in using a VAD in systemic right ventricles and single ventricle Fontan palliations.[61-64] Advances in fluid dynamics and pump technology will allow progress and continued improvement in assist devices for this complex cohort.[65, 66]

Ultimately, heart or combined heart-lung transplantation may be the only treatment option for specific lesions. Though it remains a small percentage, CHD represents an increasing primary diagnosis in heart transplant recipients,[67] and some estimate that 10 to 20% of ACHD patients will ultimately require a transplantation.[68] ACHD patients have a higher post-transplant mortality and retransplantation rate with an early hazard phase compared to adults transplant recipients.[49] However, after the initial 30 days, the 5- and 10-year survival rate is not statistically different from adult recipients.[69]

Continued efforts are needed to identify the ideal transplant

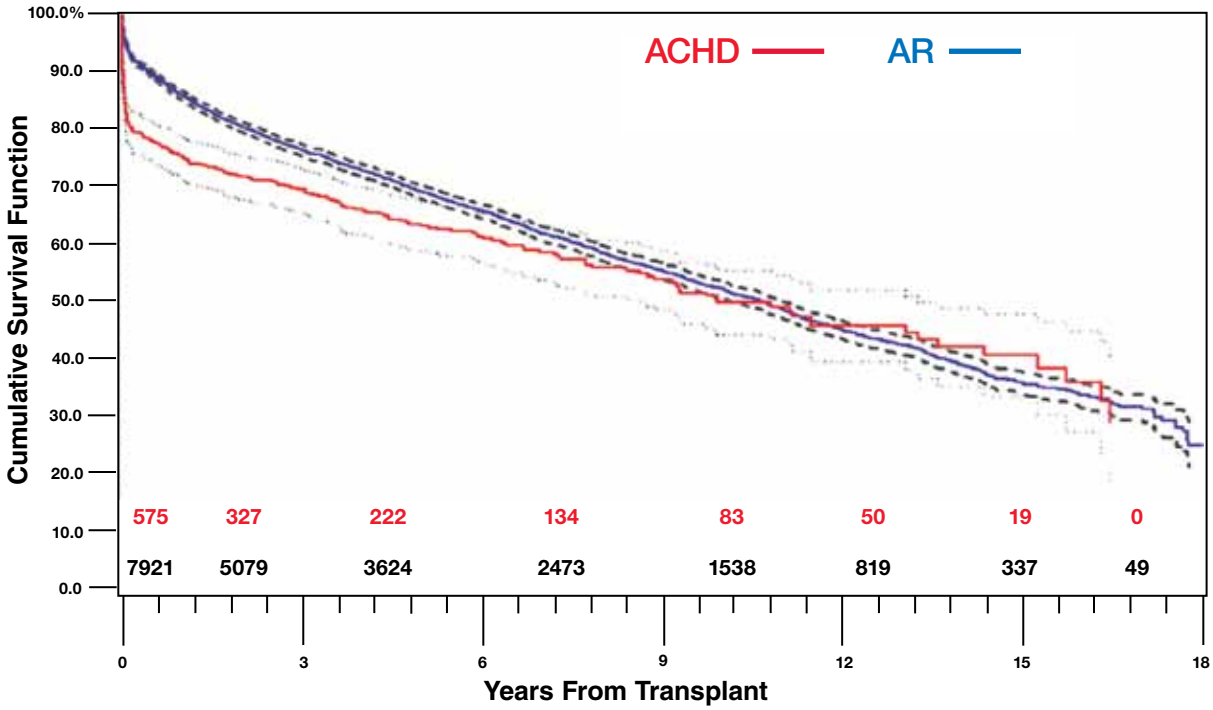

Figure 5. Risk-unadjusted freedom from death stratified by underlying diagnosis for either patients with adult congenital heart disease (ACHD) or adult recipients (ARs). The blue line depicts ARs, and the red line depicts patients with ACHD. Survival is significantly better for ARs than for patients with ACHD, mainly because of an early hazard phase representing increased postoperative mortality for patients with ACHD that persists to 2.5 years after transplantation. Numbers at inset show the patients remaining at risk. Dashed lines enclose 95% confidence intervals.[67]

candidate, hospital venue and surgical background/expertise required for transplanting adults with congenital heart disease.

Conclusion

The cohort of adults with congenital heart disease continues to grow, but the clinical and academic infancy of the field results in limited evidence-based applications in clinical practice. Extrapolation from adult studies is necessary for those caring for ACHD patients with heart failure. Nonetheless, as more research continues to move into the forefront, ACHD care should continue to improve.

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