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CURRENT OPINION

Treatment of heart failure in adult congenital heart disease: a position paper of the Working Group of Grown-Up Congenital Heart Disease and the Heart Failure Association of the European Society of Cardiology

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Heart failure in congenital heart disease: prevalence and outcome

Improved medical care of congenital heart disease patients increased survival into adulthood from 15% in the 1960s to over 85% in the current era. As a consequence, the prevalence of adult congenital heart disease (ACHD) increased rapidly,[1] which is estimated to be >1 million ACHD patients in North America and 1.2 million in Europe. The growing number and aging of ACHD patients led to an overall increase in hospitalizations over the last decade and a substantial increase in patients presenting with heart failure (HF) (~20%).[2]

The incidence of first HF-admission was 1.2 per 1000 patient-years in the Dutch national 'CONCOR' registry. Patients admitted with HF had a five-fold higher risk of death than those not admitted. From the same registry, the mortality was 2.8% during a follow-up period of 24 865 patient-years. Chronic HF (26%) and sudden death (19%) were recorded most frequently. The median age at death from HF was 51.0 years (range: 20.3–91.2 years).[3] In another ACHD cohort, sudden death (26%) was the most common cause of death, followed by progressive HF (21%) and perioperative death (18%).[4] Although patients with ACHD may not readily report symptoms, clinical HF is documented in 22.2% of patients with a Mustard repair for transposition of the great arteries (TGAs), 32.3% with congenitally corrected transposition of the great arteries (ccTGA), and 40% of patients after Fontan palliation.

Pathophysiology of heart failure in adult congenital heart disease

Heart failure with impaired systolic ventricular function

The aetiology and triggers of impaired systolic ventricular function in ACHD patients are summarized in *Table 1*.

Heart failure with preserved systolic ventricular function

This occurs less often in ACHD patients, but is associated with specific conditions such as Shone complex and restrictive right ventricular (RV) physiology in the context of pulmonary atresia, ventricular septal defect (VSD), and major aorto-pulmonary collateral arteries.

Genetic and neurohormonal background

Heart failure in ACHD is the result not only of a structural defect but also of defective contractility or conduction. An intriguing and emerging hypothesis is that genes involved in morphogenesis during

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Table 1 Pathophysiology of heart failure with impaired systolic function: triggers (examples)

1. Systolic dysfunction of the systemic morphological left ventricle
   - Pressure overload (sub-, supravalvular or valvular aortic stenosis, coarctation of the aorta)
   - Volume overload (aortic valve regurgitation, VSD, patent ductus arteriosus, or mitral regurgitation)
   - Myocardial injury (limited myocardial protection during bypass, ventriculotomy)
   - Altered myocardial architecture (non-compaction)
   - Altered geometry of the sub-pulmonary ventricle interfering with diastolic filling of the systemic ventricle (severe pulmonary regurgitation in ToF)
2. Systolic dysfunction of the sub-pulmonary morphological right ventricle
   - Volume overload (severe pulmonary regurgitation in ToF, atrial septal defect with large left-to-right shunt)
   - Pressure overload (severe RV outflow tract obstruction)
3. Systolic dysfunction of the morphological systemic right ventricle
   - Pressure overload [congenitally corrected transposition of the great arteries, dextro-transposition of the great arteries after atrial switch repair (Mustard or Senning)]
   - Myocardial injury by functional ischaemia (single right coronary artery)
4. Systolic dysfunction of the systemic single ventricle
   - Volume under-load after initial volume overload (Fontan repair)
   - Myocardial injury (limited myocardial protection during bypass, ventriculotomy)
   - Myocardial architecture
5. Systolic dysfunction of the cyanotic systemic and/or sub-pulmonary ventricle with or without pulmonary hypertension
   - Myocardial injury by chronic hypoxia (VSD with pulmonary stenosis)
   - Pressure overload (Eisenmenger syndrome)
6. Acquired ischaemic heart disease and ventricular dysfunction
   - Cardiovascular risk factors (hypertension, hyperlipidaemia, diabetes mellitus, smoking)
   - Congenital coronary artery abnormalities (anomalous origin and/or course, extrinsic compression by a dilated pulmonary artery, coronary kinking after re-implantation of coronary arteries)
7. Systolic dysfunction of the systemic ventricle due to tachyarrhythmias

early development also play a key role in regulating myocardial function and the responses to physiological stress in both the developing and the adult heart.[9] Adult congenital heart disease patients, rather than developing HF as a result of myocyte loss (myocardial infarction) or of intrinsic abnormalities in myocardial components (inherited cardiomyopathies), may, according to this predisposing genetic model, develop easier HF due to persistent abnormal cardiac pressure, volume, tension, and flow. Furthermore, it has been shown that all types of congenital heart disease cause neurohormonal activation of the natriuretic, endothelin, sympatho-adrenergic, and renin–aldosterone systems.[5]

Comorbidities and heart failure in adult congenital heart disease

Liver disease occurs in patients with ACHD. Elevated systemic venous pressures might lead to liver stiffness[6] and cardiac liver cirrhosis.[7] Liver disease is mostly associated with a failing Fontan circuit.[8] Combined heart liver transplantation is in the end needed when a failing ventricle presents with liver cirrhosis.[9] Also *protein loosing enteropathy* (PLE) occurs in a failing Fontan. Elevated systemic venous filling pressures are considered to trigger PLE.[10] Diuretics[11] and fenestration[12] between the systemic venous return and the pulmonary venous atrium, allowing right-to-left shunt, might reduce PLE. Also oral steroids[12] as budesonide might improve symptoms and stabilize serum albumin levels; however, its long-term effect remains unclear. *Plastic bronchitis* is a rare complication after Fontan palliation.[13] Elevated central venous pressure and low cardiac output likely contribute to the formation of tracheobronchial casts. Haemodynamic optimization and aggressive pulmonary vasodilation might improve the clinical course. Approximately 30–50% of ACHD patients have significantly *impaired renal function*.[14] The risk of chronic kidney disease is higher in cyanotic disease, but also present in non-cyanotic diseases. As such, stringent blood pressure control and reduction of proteinuria are obligatory. Finally, some *haematological disorders* might occur, mainly in ACHD patients with chronic systemic cyanosis. Haematocrit levels are increased,[15] which leads to high blood viscosity and a low flow phenomenon. The latter might trigger thrombosis. In contrast, bone marrow dysfunction leads to a lower number and dysfunctional platelets and increases the bleeding risk. Elevated uric acid levels induce gout attacks and accelerate renal functional impairment.[16]

Diagnostic approach in heart failure

Knowing the baseline heart defect and the history of surgeries and/or percutaneous interventions is mandatory in HF ACHD patients. Diagnosing HF may be difficult as patients often fail to recognize in themselves subtle changes in functional class. Patients might have no typical HF symptoms and signs, despite reduced exercise capacity and reporting New York Heart Association (NYHA) functional class I.[17] Heart failure is therefore a clinical syndrome with a

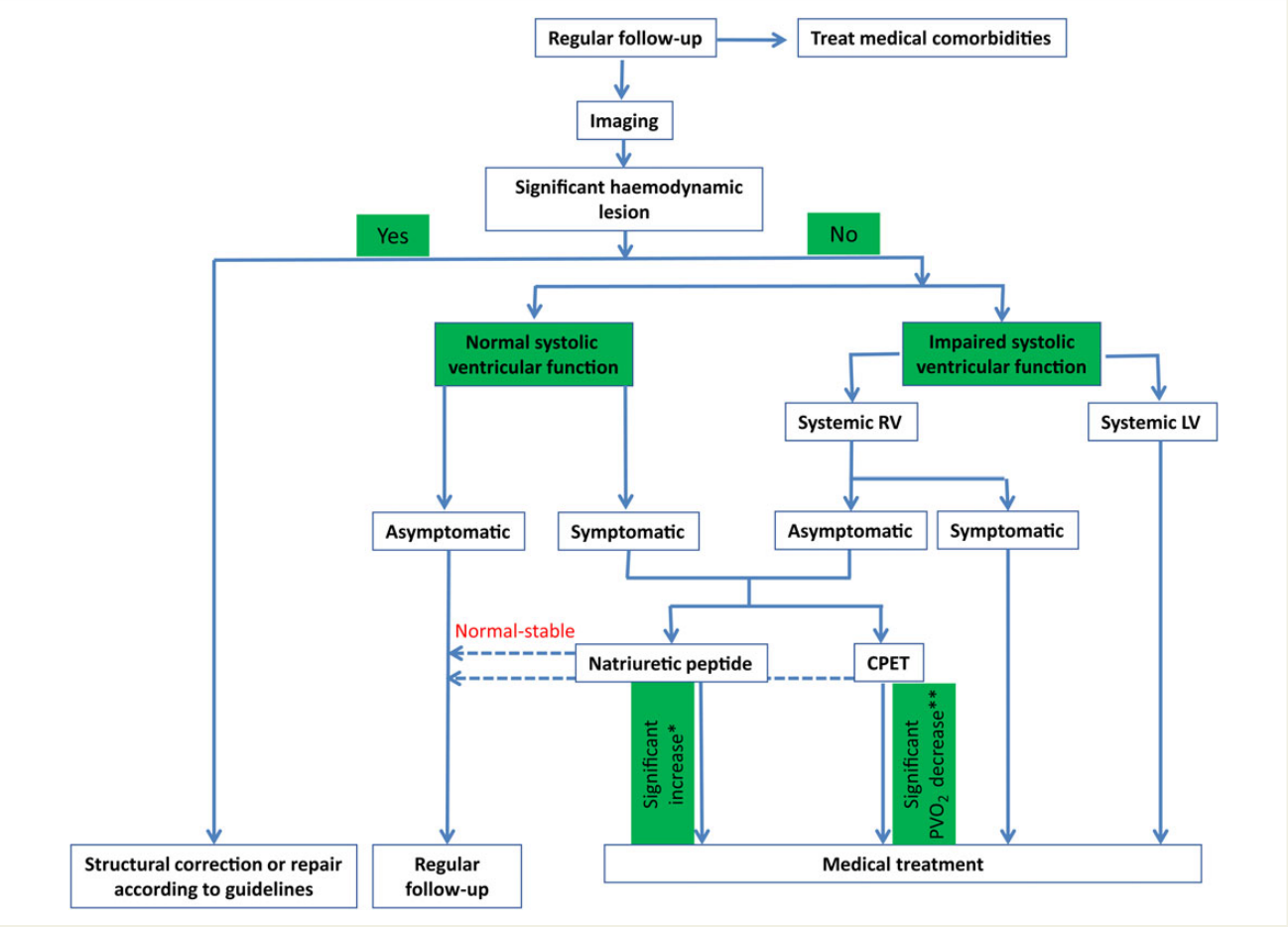

Figure 1 Diagnosis–treatment algorithm. CPET, cardiopulmonary exercise test; PVO_2, peak oxygen consumption; LV, left ventricle; RV, right ventricle. *Two-fold increase of baseline natriuretic peptide value within 6 months. **>25% decrease of peak oxygen consumption.

diagnosis based on history, examination, and investigations. Determining the cause of HF is important, as it may be reversible due to a new or worsening residual haemodynamic lesion or an another medical problem, e.g. thyroid dysfunction (*Figure 1*).

Clinical symptoms and signs

Heart failure symptoms and signs are described in the European Society of Cardiology (ESC) guidelines (*Table 2* adapted from ESC HF guidelines).[18] Some patients with complex congenital heart disease may have worsening cyanosis in the context of intra- or extracardiac shunts or fenestrations. Of note, arrhythmias are closely related to HF symptoms and may be the first clinical manifestation of HF.

Electrocardiography

Many ACHD patients have baseline abnormal electrocardiograms (ECGs) with prolonged QRS duration, other intra-ventricular conduction delay, nodal rhythm, and LV (left ventricular) or RV hypertrophy. A change in ECG morphology is therefore most relevant in the ACHD patient. However, each ECG has to be looked after atrio-ventricular (AV) conduction abnormalities (i.e. complete AV block in ccTGA) or for 'inappropriate' apparently sinus tachycardia that may mimic atypical supraventricular re-entrant tachycardia.

Imaging

A *chest X-ray* easily identifies pulmonary congestion and effusions. The position and size of the heart, size of pulmonary arteries and thoracic aorta, and concomitant lung and thorax pathology are simply obtained.

Echocardiography allows to:

- Establish or confirm the underlying congenital heart disease diagnosis
- Identify concomitant/residual lesions and sequelae
- Assess ventricular function (sub-aortic–sub-pulmonary)
- Monitor disease progression
- Detect new ± acquired lesions
- Guide further interventions

Recommendations have been recently published for tetralogy of Fallot (ToF) imaging.[19] *Three-dimensional (3D) echocardiography* is more sensitive than 2D for the assessment of ventricular function and volumes and valves. *Transoesophageal echocardiography* may

Table 2 Signs and symptoms of heart failure in congenital heart disease

Symptoms of systemic ventricular failure	Signs of systemic ventricular failure
Fatigue	Third or fourth heart sound (gallop)
Breathlessness	Laterally displaced apical impulse
Dry cough especially lying flat	Pulmonary crepitations
Reduced exercise tolerance	Absent BS and dull percussion lung bases due to pleural effusions
Orthopnoea	
Paroxysmal nocturnal dyspnea	
Wheezing	
Symptoms of sub-pulmonary ventricular failure	**Signs of sub-pulmonary ventricular failure**
Fatigue	Elevated JVP
Bloating	Hepatomegaly
Weight gain (> 2kg/week)	Ascites
Loss of appetite	Pitting leg oedema, sacral oedema, scrotal oedema
Reduced exercise tolerance	
Increased abdominal girth	
Symptoms of congestive (biventricular) failure	**Signs of congestive (biventricular) failure**
Combined systemic and sub-pulmonary symptoms	Combined systemic and sub-pulmonary signs

BS, breath sounds; JVP, jugular venous pressure.

also be indicated.[20] *Stress echocardiography* helps assessing contractile reserve[21,22] and diagnoses acquired heart disease such as coronary artery disease (CAD).

Magnetic resonance imaging (MRI) is the golden standard for volumetric measurements, ventricular function, assessment of vessels, and detection of myocardial fibrosis. European Society of Cardiology recommendations for the use of MRI in ACHD patients have been published.[23]

Computed tomography is particularly good for imaging stented valves and coarctation stents along with the epicardial coronary arteries, for collateral arteries, and for parenchymal lung disease.[19]

Cardiac catheterization provides detailed haemodynamic data for calculating pulmonary vascular resistance and for proceeding to structural interventions.[24] Other indications include assessment of LV and RV diastolic function, pressure gradients, and shunt quantification. Coronary angiography and the evaluation of extra-cardiac vessels such as aorto-pulmonary collateral arteries may be indicated.[25]

Cardiopulmonary exercise and lung function test

Cardiopulmonary exercise test is a valuable tool with prognostic implications.[26] The exercise capacity is reduced in ACHD patients.[17] The expected peak oxygen consumption varies between different types of ACHD lesions, and reference values for exercise limitations have been published.[27] There is a good correlation between exercise test results and mortality that seems to be increased in patients with peak oxygen consumption (VO_2) values <15 mL/min/kg. Other prognostic parameters such as ventilator response[28] and oscillatory patterns[29] provide important clinical information. *Lung function test* is needed to detect concomitant broncho-pulmonary disease.

Laboratory testing

Adult congenital heart disease patients suspected for HF should undergo basic laboratory testing including full blood count, renal function, liver function, protein and albumin, iron, and thyroid function. Laboratory testing may reveal treatable conditions. Anaemia, renal and liver dysfunction, hypoalbuminemia, hyponatremia, and iron depletion have prognostic significance.[32–36]

Natriuretic peptides

B-type natriuretic peptide (BNP) and N-terminal pro–BNP (NT-proBNP) are related to disease severity and prognosis in HF patients with acquired heart disease.[30] Natriuretic peptides might be also clinically important in congenital heart disease.[5,31,32] A recent cross-sectional study showed that BNP correlated with age was higher in women than in men, and differed per diagnosis.[33] Disease-specific correlations were also observed.[34,35]

Septal defects

B-type natriuretic peptide levels are mildly increased in patients with unrepaired and repaired atrial septal defect or VSD.[34] Shunt severity and pulmonary artery pressures correlate strongly with BNP levels.[36,37] A clear association between BNP and functional class is demonstrated.

Tetralogy of Fallot

Studies in ToF patients showed correlations between plasma BNP, RV dilation, and severity of pulmonary valve regurgitation.[38,39] Also correlations between BNP and exercise capacity were found.[39,40] Most studies to date present only cross-sectional data.[41–50] B-type natriuretic peptide levels before pulmonary valve

replacement were found elevated and decrease afterwards; however, the results of individual BNP measurements differed widely so that the use of BNP changes as marker for outcome remains unclear.[35]

Systemic morphological right ventricle

A clear correlation was found between BNP and systemic RV function.[35] One study showed a correlation between RV ejection fraction and atrial natriuretic peptide (ANP).[51] Extensive atrial scarring in Mustard and Senning patients may contribute to elevated ANP levels. Moreover, a strong correlation was observed between plasma BNP and the severity of tricuspid regurgitation (TR).[52–59] One longitudinal study described adult patients after atrial switch surgery for TGA.[60] They found that BNP was the most prominent predictor for HF, transplantation, and death (hazard ratio of 21). B-type natriuretic peptide might therefore be useful for risk assessment.

Hypoxia and single ventricle

Most studies found no correlation between oxygen saturation and BNP.[61–64] B-type natriuretic peptide levels in asymptomatic Fontan patients were comparable with those of healthy controls. However, in symptomatic patients, there was a strong correlation between BNP and the severity of HF. One study found significantly higher levels of BNP in five patients who died from HF,[62] while another found no prognostic value of BNP.[65] B-type natriuretic peptide measurement may be useful in symptomatic patients.

Medical treatment

Systolic failure of the morphological systemic left ventricle

Trials with hard clinical endpoints have not been done in ACHD patients. The current ESC guidelines for HF[18] suggest that diuretics, renin–angiotensin–aldosterone system (RAAS) blockers, β-blockers, and mineralocorticoid receptor antagonists can be used in the congenital heart disease population, mainly when neurohormonal and cardiac autonomic activity is increased.[66–68]

There is theoretical evidence to support the use of angiotensin-converting enzyme inhibitors (ACEIs) and, if not tolerated, angiotensin receptor blockers (ARB) in the treatment of *asymptomatic or symptomatic* HF ACHD patients. Similarly, the evidence for using β-blockers, such as carvedilol, metoprolol, bisoprolol, and nebivolol, may also be extrapolated to the ACHD population. Preliminary data suggest a favourable effect of these drugs in HF secondary to aortic[69,70] or mitral valve disease.[71]

Many of these medications are prescribed for other indications, such as high blood pressure or arrhythmias, and this allows initiating drug treatment despite missing evidence in ACHD. Any treatment should serve one of two purposes: to improve prognosis or to alleviate symptoms. Loop diuretics never showed improved survival in chronic HF patients[18] but relief symptoms such as dyspnoea and peripheral oedema. Digoxin, once widely used in HF, now has a more limited role, as there is no mortality benefit when compared with placebo.

Systolic failure of the morphological systemic right ventricle

A systemic RV will gradually fail.[72–74] Extrapolating the ESC HF guidelines[18] to this ACHD group is more difficult. The cut-off of impaired ejection fraction of a systemic LV at which drug treatment has clinical benefit is well defined. However, no such data exist for the systemic RV. In most adults with a systemic RV, the systolic function is abnormal with a lower ejection fraction and lower exercise performance vs. controls.[75,76]

For an *asymptomatic* patient without signs of HF, it is difficult to know if and when to initiate HF treatment. Patients with stable systemic RV function have not always an activated neurohormonal and cardiac autonomic nervous system. Therefore, blocking the RAAS does not result in better clinical outcome,[77–79] although surrogate endpoints (exercise duration, degree of systemic AV valve regurgitation) seem to be influenced positively,[78,80] Caution is required when using drugs that venodilate and reduce preload in Mustard or Senning patients. Ventricular filling is significantly compromised by concomitant baffle obstruction. β-Blockers might improve functional capacity and surrogate endpoints such as the severity of systemic AV valve regurgitation and RV remodelling.[81–83] However, patients with Mustard or Senning repair or with ccTGA are all susceptible to conduction abnormalities.

In *symptomatic* patients with neurohormonal and cardiac autonomous nervous system activation, standard HF treatment might offer theoretical benefit[84,85] and is therefore suggested to be administered as in patients with a failing LV.

Systolic failure of the morphological sub-pulmonary right ventricle

No randomized controlled trials investigated which drugs to use. The beneficial effects of RAAS blockade or β-blockers have never been studied. Lack of data on the failing sub-pulmonary RV implies only few recommendations in the ESC guidelines on HF[18] or pulmonary hypertension.[86] No medical treatment is indicated in *asymptomatic* patients. Diuretics are mainly the treatment of a *symptomatic* patient. Thiazides can be added in more resistant cases of oedema and act synergistically with loop diuretics, but then renal function and biochemical markers need close surveillance.[87] If RV failure is secondary to pulmonary arterial hypertension, drug therapy mainly focuses on the pulmonary circulation using endothelin receptor antagonists, phosphodiesterase inhibitors, or prostacyclines.

Systolic failure of the single ventricle

Phosphodiesterase inhibitors or endothelin receptor antagonists may improve ventricular function in a Fontan patient, when increasing pulmonary vascular resistance impairs ventricular filling. In patients treated with sildenafil, pulmonary vascular resistance decreases,[82] exercise performance increases,[88] and myocardial performance ameliorates.[89] The effect of bosentan in the Fontan patient is less certain. Some studies suggest a beneficial effect,[90] whereas others did not.[91] Perhaps, the combined increase in preload and reduction in afterload, which is more pronounced with sildenafil treatment, improves more the haemodynamics in the Fontan patient.[92]

Primary myocardial dysfunction in Fontan requires standard HF medication for *symptom relief* in both, morphological left and right

ventricles. However, in an *asymptomatic patient* with an impaired systemic right ventricle, the effect of medical treatment is unclear. Loop diuretics are frequently used if there is pulmonary fluid overload, but too high a dose can reduce preload and lead to the cardio-renal syndrome. Spironolactone appears to have an impact on PLE[11] and endothelial function.[93] One study showed that enalapril did not enhance exercise capacity in Fontan patients.[94] The indication for RAAS blockers in the Fontan is uncertain. Carvedilol has been shown to improve HF signs and symptoms.[95,96] In summary, reducing pulmonary vascular resistance and afterload seems to have most clinical benefit, while symptomatic treatment with diuretics should be used cautiously and judiciously.

Standard HF treatment of patients with a functional univentricular heart and intra-cardiac shunt implies a difficult balance. Peripheral or pulmonary oedema can be treated with loop diuretics. However, drugs that reduce afterload may increase right-to-left shunting and lower the systemic oxygen saturation.[97]

Heart failure with preserved ejection fraction

No treatment reduced morbidity and mortality in patients with preserved ejection fraction (ESC guidelines on HF[18]). Diuretics are used for symptom relief, and β-blockers may help by prolonging ventricular filling.

No studies in ACHD looked at ivabradine. However, in case of therapy resistance, ivabradine can be prescribed with similar indications as listed in the HF ESC guidelines.[18] The same is true for hydralazine and isosorbide dinitrate. However, both agents decrease substantially the systemic vascular resistance so that systemic oxygen saturation has to be followed meticulously (see lower). Recommendations are summarized in *Table 3*.

Iron deficiency has been reported in stable HF patients and in patients hospitalized for worsening HF.[98,99] In the non-congenital population, iron replacement improves functional capacity,

Table 3 Medical treatment for heart failure related to intrinsic myocardial dysfunction

Systolic HF		
Systemic ventricle		
Morphological left ventricle (EF < 40%)	Asymptomatic or symptomatic	RAAS blockers β-Blockers Mineralocorticoid receptor antagonists Diuretics (loop and thiazide) Digoxin
Morphological right ventricle (EF < 40%)	Asymptomatic Symptomatic	No medical treatment RAAS blockers Beta-blockers Mineralocorticoid receptor antagonists Diuretics (loop and thiazide) Digoxin
Sub-pulmonary ventricle		
Morphological left or right ventricle (EF < 40%)	Asymptomatic Symptomatic	No medical treatment Diuretics (loop and thiazide) Mineralocorticoid receptor antagonists Pulmonary vasodilators (PAH)
Single ventricle		
Fontan circulation (EF < 40%) Morphological left ventricle	Asymptomatic	RAAS blockers β-Blockers Mineralocorticoid receptor antagonists Digoxin
Morphological right ventricle	Asymptomatic	No medical treatment
Morphological left and right ventricle	Symptomatic	RAAS blockers β-Blockers Mineralocorticoid receptor antagonists Diuretics (loop and thiazide) Digoxin
Persistent right-to-left shunt	Asymptomatic Symptomatic	No medical treatment Diuretics (loop and thiazide) Agents reducing afterload
HF with preserved EF		
	Asymptomatic	No medical treatment
	Symptomatic	Diuretics (loop and thiazide) β-Blockers Rate-limiting calcium channel blocker

EF, ejection fraction; PAH, pulmonary arterial hypertension; PAP, pulmonary arterial pressure.

symptoms, and quality of life (QoL) and reduces the number of HF hospitalizations.[100] Although no specific trials on iron replacement exist in HF ACHD patients, a similar beneficial effect might be expected. Indeed, iron deficiency is not uncommon in ACHD patients,[101,102] and replacement might improve functional capacity.[103] In contrast, vitamin B_{12} and folate deficiency are relatively rare in patients with chronic HF,[104] and the effect of replacement on outcome, including HF ACHD patients, needs further investigation. Some data suggest that the use of anti-platelet therapy or oral anticoagulants may improve outcome in advanced HF.[105] This has never been investigated in HF ACHD patients, but it might be considered beneficial in HF secondary to ischaemic heart disease or atrial arrhythmia.

Acute heart failure in adult congenital heart disease patients

There are no scientific trials to guide clinicians on specifically managing ACHD patients with acute HF. Nevertheless, most of the ESC guidelines for managing acute HF[18] can be applied in this context, taking into account the greater complexity and varied comorbidities on a case-by-case basis. For example, in patients with pulmonary hypertension and/or persistent intra- or extra-cardiac shunts, the balance between pulmonary vascular resistance and systemic vascular resistance must be borne in mind and is a crucial consideration when prescribing pharmacotherapy.[106] Any increase in pulmonary vascular resistance will decrease cardiac output, and, in the presence of an intra-cardiac shunt, any decrease in systemic vascular resistance will increase the likelihood of right-to-left shunting and systemic desaturation. Triggers that increase pulmonary vascular resistance (hypoxia, hypercapnia, high haematocrit, positive pressure ventilation, cold, metabolic acidosis, and alpha-adrenergic stimulation) and those that decrease systemic vascular resistance (vasodilators, general anaesthesia, and hyperthermia) must therefore be avoided where possible.[106] Moreover, if there is a persistent right-to-left shunt, there is a risk of paradoxical air or thromboemboli and intravenous lines must be meticulously managed preferably with bubble filters attached. Patients with cyanosis have a secondary erythrocytosis and both an increased bleeding and thrombosis risk, which is generally more pronounced in the setting of acute HF. Coagulation factors and platelets should therefore be monitored, iron deficiency corrected, and venesection considered if the haematocrit exceeds 65%.

Cardiac monitoring of the ACHD patient in acute HF must also take into account the underlying congenital lesion, e.g. the patient with a subclavian flap repair of coarctation of the aorta should have blood pressure measured in the right arm as the left subclavian has been used for the repair, or placement of a central line in a Fontan patient, which sits in the pulmonary artery, and is therefore not a reliable measure of systemic venous filling pressure.[106]

Finally, if maximal medical treatment fails to stabilize the haemodynamics, then extra-corporal membrane oxygenation (ECMO) and or ventricular assist device (VAD) therapy should be considered as bridging therapy to transplantation.

Cardiopulmonary and physical rehabilitation in adult congenital heart disease patients with heart failure

Cardiopulmonary rehabilitation is since long time recommended in patients with chronic HF.[18,107] Indeed, exercise training is safe and tends to benefit clinical outcome.[108,109] In HF ACHD patients, no specific studies have been conducted to evaluate clinical outcome. However, exercise training seems to improve safely exercise-related and haemodynamic variables in complex congenital heart disease.[110–112] Moreover, cardiac rehabilitation programmes improve QoL in ACHD; however, none of them suffered from HF.[113] Cardiac rehabilitation is probably safe and beneficial. However, further research is needed. A recent position paper recommends individualized exercise prescription to improve long-term health behaviour, and includes also advice for HF ACHD patients.[114]

Device therapy in adult congenital heart disease patients with heart failure

Indications for implantable cardioverter defibrillator therapy

The incidence of sudden cardiac death (SCD) in the congenital heart disease population is low (<0.1% per year) and 5–10 times lower than in the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II population.[115] However, SCD accounts for 20–25% of late deaths in ACHD patients.[4,116] There are subgroups of congenital heart disease patients carrying a slightly higher SCD risk such as patients after surgical repair of ToF, d-TGA with Mustard or Senning repairs, ccTGA, Eisenmenger syndrome, and Ebstein anomaly of the tricuspid valve.[116] In ACHD patients, consensus exists on *implantable cardioverter defibrillator (ICD) therapy for secondary prevention of SCD*.[115] Implantable cardioverter defibrillator therapy is recommended in survivors of SCD due to ventricular fibrillation (VF) or unstable ventricular tachycardia (VT) without reversible cause, patients with documented spontaneous sustained VT (sVT) that is not amenable to ablation or surgery, and syncope of unknown origin with inducible sVT/ VF at electrophysiology (EP) study or a high suspicion of ventricular arrhythmias being the cause of syncope.

Selection of *ICD candidates for primary prevention of SCD* still remains challenging. In general, prophylactic ICD therapy is also indicated in those patients who meet the same standard criteria as patients with ischaemic or non-ischaemic cardiomyopathy, i.e. the presence of biventricular physiology with a systemic LV ejection fraction <35% and NYHA class II or III symptoms.[117–122]

Non-sVT (nsVT) in ToF patients is significantly associated with inducible sVT by programmed ventricular stimulation and that inducible sVT carries a five-fold higher rate of clinical VT or SCD.[123] Moreover, a weighted risk score to predict appropriate ICD shocks in ToF patients with prophylactic ICD implantation has been developed, implementing additive factors of risk stratification such as left

ventricle end-diastolic pressures, nsVT, inducible sVT, prior shunt, prior ventriculotomy, and QRS duration.[124] According to this risk score, prophylactic ICD therapy should be recommended in selected adults after ToF repair classified in the high-risk category. However, the management of inappropriate shocks due to supraventricular arrhythmias is still challenging and has an important impact on the subjective QoL in these patients.[125]

In contrast, the predictive value of EP testing in other ACHD subgroups is limited or not known. In patients with an atrial switch repair, inducible sVT/VF does not predict clinical events.[126] However, in this subgroup of patients, a reduced ejection fraction of the systemic right ventricle has been associated with a higher incidence of ventricular tachyarrhythmias and SCD.[127] For patients with univentricular hearts and a Fontan palliation, no recommendations for ICD indications exist. Nevertheless, ICD therapy may be reasonable in adults with an impaired single or systemic RV ejection fraction and the presence of additional risk factors such as complex ventricular arrhythmias, unexplained syncope, NYHA functional class II and III symptoms, long QRS duration, or severe AV valve regurgitation. Implantable cardioverter defibrillator therapy is not recommended in ACHD patients and in patients with advanced pulmonary vascular disease (Eisenmenger syndrome),[128,129] drug-refractory NYHA class IV who are not candidates for heart transplantation (HT), significant psychiatric illness, incessant VT/VF, or a life expectancy <1 year.[117]

Indications for cardiac resynchronisation therapy

Cardiac resynchronization therapy (CRT) is an established treatment option in LV electromechanical dyssynchrony. If response to CRT is positive, reverse remodelling of the LV, functional improvement, and a reduction in HF associated morbidity and mortality can be seen.[130,131] In ACHD patients, the morphological heterogeneity of the underlying heart defects makes it far more difficult to define the role of CRT. Most of the studies available are retrospective in nature and follow-up time in all trials is limited to a few months (4.8–8.4 months); hence, the impact of CRT on long-term morbidity and mortality is not known. Surrogate parameters such as metrics of systemic ventricular function or functional parameters such as NYHA class were used to define CRT response. Despite these limitations, the following observations were made: (i) the majority of congenital heart disease patients included (58%) were in NYHA class II when compared with NYHA class III or IV patients with ischaemic or idiopathic dilated cardiomyopathy; (ii) the presence of a systemic LV predicted a better CRT response than a systemic RV[132]; (iii) the best CRT response was seen in patients with a systemic LV which were converted to CRT from conventional RV pacing[133,134]; (iv) the proportion of non-responders to CRT was ~10–14% in congenital heart disease patients and lower than in patients with ischaemic or idiopathic dilated cardiomyopathy; and (v) patients with single ventricle morphology may benefit from CRT using optimized pacing sites.[132,135] In general, CRT can be recommended in ACHD patients and patients with NYHA class II–IV symptoms, an impaired systemic ventricular ejection fraction, systemic ventricular dilation, and prolonged QRS duration. Moreover, upgrading to CRT should be considered in congenital heart disease patients with systemic LV and permanent RV pacing resulting in LV dyssynchrony and dysfunction. Cardiac resynchronisation therapy should also be considered in NYHA class IV patients as a bridge/delay to mechanical assist device therapy or HT. Remote monitoring of devices has been shown to reduce adverse outcomes in ICD patients with acquired heart disease,[136] but may also be beneficial in ACHD patients for the early detection and treatment of tachyarrhythmias.[137]

Heart transplantation and assist devices

According to the 2014 International Society for Heart Transplantation (ISHLT) Registry, ACHD represents ~10% of the HT indications in patients of 18–30 years.[138] Although short-term outcomes are worse in ACHD than to those with non-ACHD (20–30% at 30 days mortality in ACHD patients), late-term survival of ACHD is improved and survival at 10 years is similar between patients with ACHD and those with acquired heart disease.[139,140]

The outcomes after ACHD HT can vary according to different diagnosis and may be influenced by centre's expertise.[138] Timing of assessment for HT remains challenging, as accurate prediction of prognosis is difficult. There is no single prognostic variable to be able to provide a perfect discriminatory capacity on need for or timing of HT. Serial cardiopulmonary exercise testing and other prognostic variables such as hospitalizations, clinically relevant arrhythmia, symptomatic HF, PLE, and plastic bronchitis may help to differentiate those ACHD patients from who do not deserve to be assessed for HT.

Careful pre-transplant evaluation should be specifically done to assess pulmonary vascular resistance; the presence of disease in organ systems that could affect post-HT care and can (or cannot) be reversed with HT; the presence of chronic or previous infections that could affect both pre- and post-HT management; psychosocial evaluation of the patient and caregivers; patency of major veins and arteries; human leucocyte antigen sensitization; and surgical risk (multiple cardiac redo operations, great vessels anatomy).

Ventricular assist devices (VADs) may be used as destination therapy or bridging to HT in ACHD patients.[141] However, such patients listed for HT have less likelihood to have a VAD as a bridge to HT, longer waiting time in status 2, and higher mortality risk in the waiting list.[142] Several case reports describe successful use of LV assist devices in failing systemic right ventricles.[143,144] However, complication rates remain relatively high and are related to anatomic complexity and associated morbidities (coagulopathy, liver cirrhosis, etc.). Ventricular assist devices might be applicable in a failing Fontan circulation, however, only in these patients with systolic ventricular failure.[145,146] In case that the sub-pulmonary ventricle (as after Fallot repair) fails, an RV assist device might be useful, but clinical outcome data are lacking.[141]

Management of care, psychological issues, and nursing management

The complexity of most heart diseases leads to a systematic follow-up in specialized ACHD centres. Less complex and stable patients are frequently followed in secondary care centres. They have to

be aware of the occurrence of HF and to detect it in its early stage. Especially in complex cases or cases in which evidence-based medicine is lacking, transfer to a specialized ACHD centre is preferred. This might be important when HF becomes drug therapy resistant, and bridging to or listing for HT is needed.

Frequency of follow-up is reported in the ESC guidelines for the management of grown-up congenital heart disease.[25] Annual check-up of an HF ACHD patient, even asymptomatic, is recommended. This is important for optimizing health behaviour and treatment adherence. Follow-up visits and educational interventions contribute to persons' well-being and improve the level of patients' knowledge on the condition of their heart. Depending on the (proceeding) symptomatology and (in)stability of the disease process, more frequent follow-ups become obligatory. Routine follow-up implies focus on risk factors (as palpitations, syncope), clinical examination, and electrocardiographic and echocardiographic evaluation. Depending on the symptomatology, changes in BNP levels need to be controlled, 24 h Holter/bicycle testing is indicated, and if the patient remains unstable, invasive evaluation will be preferred.

Sexual activity is not harmful for the heart, advice for pregnancy, contraception and labour in the female subgroup, and recommendations about physical activities are discussed in the ESC guidelines on pregnancy[147] and the ESC position paper about physical activities in ACHD.[148]

Many patients with congenital heart disease deal with social and psychological concerns that may influence QoL.[149] Psychosocial condition refers to a range of issues faced by adults with congenital heart disease including the 'feeling of being different', experiences related to the living with the congenital heart disease and possible exacerbation of symptoms, emotional distress, poor illness perception, educational and behavioural issues, and compromised employability and insurability.[149,150] Psychological condition is correlated with depression, anxiety, and impaired QoL.[149,151] Possible interventions at improving illness perceptions may enhance patients' QoL, by increasing patients' knowledge regarding their disease and informing patients about treatment options, psychosocial support, cognitive behavioural therapies, and palliative care.[149]

They need life-long comprehensive care to which nurses are an integral part of the health-care team.[152–154] Nursing assessment includes physical, psychosocial, and knowledge examination.[152,153]

Conclusions

Heart failure in adult patients with congenital heart disease overshadows more and more the outcome of this patient population. No large randomized clinical trials are available to write guidelines with a certain level of evidence. However, HF strategies, effective in ischaemic and congestive heart disease, are frequently applied to patients with congenital heart defects. This position paper intends to offer a platform to parallelize HF treatment in the congenital heart disease community abroad. However, it is clear that more research is needed to reach a certain level of evidence-based medicine.

Authors' contributions

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