Medical Therapy for Chronic Right Ventricular Failure in Congenital Heart Disease

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Abstract

The clinical importance of right ventricular (RV) function has been increasingly recognised in populations with and without congenital heart disease (CHD). CHD patients most at risk of chronic RV failure are those with repaired tetralogy of Fallot (TOF), atrial baffle redirection procedures for transposition of the great arteries (TGA-baffle), congenitally corrected transposition of the great arteries (ccTGA), Ebstein anomaly of the tricuspid valve or a Fontan circulation with a dominant RV. This chapter considers medical management options that might be beneficial in these groups. It reviews current literature and guidelines, offers opinions based on clinical experience and discusses potential avenues for future research.

Keywords

Congenital heart disease • Heart failure • Right ventricle • Pharmacological therapy

Introduction

Whether there is benefit to be derived from the medical treatment of chronic heart failure (HF) in patients with congenital heart disease (CHD) remains unproven. While outcome data from HF medication studies in CHD patients have been underwhelming, anatomical, electrical and physiological dissimilarities restrict confident application of evidence or guidelines in non-CHD populations. There is particular need for pause when contemplating the use of medical therapies of known benefit in systolic left ventricular (LV) failure for CHD patients whose primary problem is a failing right ventricle (RV). A failing RV in patients with CHD may have been subject to surgical incision, decades of exposure to abnormal loading conditions and/or the effects of chronic pacing; any of which could induce significant divergence from the pathophysiological pathways seen in acquired HF. In addition, a RV has an inherently different myocardial fibre arrange-

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M.K. Friedberg, A.N. Redington (eds.), *Right Ventricular Physiology, Adaptation and Failure in Congenital and Acquired Heart Disease*, https://doi.org/10.1007/978-3-319-67096-6_16

ment and geometry from a LV and this too may affect its processes and mechanisms of failure. This chapter reviews what is known about medical therapy for chronic RV failure in patients with CHD, considers the available data and its quality and draws on the author's clinical experience of caring for these patients as children and adults. Underpinning the narrative is an assumption that potentially reversible causes of RV dysfunction (arrhythmia, valve disease, baffle leaks, volume loading due to arterial-venous collaterals, dyssynchronous pacing and the potential to improve hemodynamics by surgical revision) have been already addressed.

Medical Therapy for Symptom Control

In CHD, patients with quite severe RV dysfunction often remain well compensated for many years. Symptoms usually arise relatively late in the "natural" history and may first be recognised when something additional occurs to tip the balance: arrhythmia, inter-current infection, surgery or development of pulmonary hypertension. The symptoms and signs of chronic RV failure in CHD depend in part on the RV's position (subaortic or subpulmonary) as well as on the type of circulation (biventricular or single ventricle physiology) and perhaps also on whether the main problem is systolic or diastolic dysfunction.

Fluid overload affects most CHD patients with a failing RV, albeit to different extents and with different patterns of symptoms. Patients with a failing subpulmonary RV (TOF, Ebstein anomaly, unrepaired ASDs, Eisenmenger syndrome) or a failing single RV in a Fontan circulation tend to manifest classic features of "right-sided HF" with elevated jugular venous pressures, hepatic enlargement, peripheral edema and ascites. These symptoms and signs are less prevalent in patients with a failing systemic RV in a biventricular circulation, but so also are clasisic "left-sided HF" manifestations, at least until the later stages of disease. In patients with ccTGA or TGA-baffle and a failing RV, fluid overload can be difficult to detect clinically, existing as hemodynamic-congestion, only evident on cardiac catheterisation. Somewhat arbitarily, our group routinely performs cardiac catheterisation in ccTGA and TGA-baffle patients once they reach the age of 40 years, because we have noted elevated filling and pulmonary artery pressures are so difficult to detect by any other means.

While it forms a keystone of most HF self-care behaviour advice, in fact sodium and fluid restriction in HF remains a much-debated topic. All contemporary general adult and paediatric HF guidelines recommend some degree of fluid and sodium intake restriction (Table 16.1). These recommendations are based on population data that excessive sodium adversely affects cardiovascular outcomes [1], an understanding that maladaptive activation of the renin-angiotensin-aldosterone system leads to sodium and water retention [2] and from recognition that fluid overload is very often the stimulus for HF hospitalizations [3]. Nevertheless, the evidence available from clinical studies fails to support an aggressive approach. Travers et al. conducted the first randomised trial of fluid restriction versus free fluids in patients with acute decompensated HF in 2007 [4]. This study of 67 patients showed that fluid restriction to 1 L per day had no impact on time to discontinuation of intravenous therapy or markers of clinical and biochemical stability [4]. Paterna et al.'s 2008 study of 232 outpatients with stable chronic HF, compared the impact of a normal (120 mmol) and low (80 mmol) sodium diet [5]. During 180 days of follow-up, the low sodium diet was associated with adverse neurohormonal effects and increased risk of hospital admission [5]. In 2013, Aliti and colleagues published the results of a randomised clinical trial conducted in 75 patients with acute HF and found that at 3 days after hospital admission, aggressive sodium and fluid restriction (<800 mL and <800 mg per day) had no effect on weight loss or clinical stability [6]. This somewhat counterintuitive data has led to several reviews articles that discuss how we should counsel patients with HF about sodium and fluid restriction [7–9]. Most authorities support mild to moderate fluid and

Table 16.1 Recommendations regarding sodium and fluid restriction in heart failure

Reference	Body	Patients	Daily Na intake		Daily fluid intake	
			Amount	Class/level	Volume	Class/level
Can J Cardiol 2006;22:23–45	Canadian Cardiovascular Society	Adults	2–3 g with reduction to 1–2 g in advanced HF	Class 1 Level C	1.5–2 L in all with uncontrolled fluid overload or those with renal dysfunction or hyponatremia	Class 1 Level C
J Card Fail 2010;16:475–539	Heart failure Society of America	Adults	2–3 g and <2 g in severe HF	Level C	<2 L if Na <130 mEq/L. Should be considered when difficult to control fluid overload	Level C
Eur Heart J 2012 33:1787–847	European society of Cardiology	Adults	Na restriction may help control symptoms and signs	Not provided	1.5–2 L may be considered in severe HF. Routine restriction in all patients probably not of benefit	Not provided
Circulation 2013;128:e240–e327	American Heart Association	Adults	1.5 g for stage A&B, consider some degree (<3 g) for stage C&D	Class IIa Level C	Not discussed	–
Can J Cardiol 2013;29:1535–1552	Canadian Cardiovascular Society	Children	Not discussed	–	Restriction to 80% of basal requirements may be necessary in some patients	–
ISHLT monograph series Volume 8 published 2014	International Society of Heart and Lung Transplantation	Children with acute heart failure	Fluid restriction is reasonable for patients with acute heart failure regardless of serum sodium	Class IIa Level C	A low sodium diet is reasonable for hospitalized patients	Class IIa Level C

sodium restriction in patients with HF and suggest that stricter restriction less likely to be beneficial and may indeed carry some risk. There is no data on this subject specific to patients with CHD. Until further evidence becomes available it seems reasonable to suggest mild to moderate restriction for CHD patients with RV failure and in clinical practice this approach generally reduces symptoms.

Although their effects on disease progression and mortality remain uncertain, diuretics are the pharmacological mainstay of treatment for symptoms of HF related to hypervolemia [10, 11]. They are recommended for symptom relief in general adult and paediatric HF guidelines [12–16] and appear clinically successful at relieving symptoms and improving hemodynamics in CHD patients with RV failure. Diuretics have different mechanisms of action, but for the most part function by blocking sodium reabsorption from different parts of the renal tubules. Furosemide is the most familiar diuretic used in the management of heart failure. It is a loop diuretic, acting at the ascending limb

of the loop of Henle and distal tubule, impairing reabsorption of sodium, potassium and chloride. Metolazone, a thiazide-like diuretic that works in the distal tubule, can be a useful addition in some patients, but care must be taken to monitor electrolytes for hypokalemia. Potassium-sparing aldosterone antagonists and potassium supplementation are often required. Patients with hepatic involvement may gain particular benefit from spironolactone, which is recommended, as the drug of choice in the initial treatment of ascites due to cirrhosis [17, 18]. We have noted clinical improvement after addition of high dose spironolactone (100 mg or more) to the diuretic regimen of failing adult Fontan patients or those with Ebstein anomaly, again careful monitoring of serum electrolytes is essential. When trying to make rational decisions about medical therapy for chronic RV failure in CHD, it is also important to be aware that aldosterone antagonists have been identified as drugs with potential anti-fibrotic properties [19]. Given the growing evidence that fibrosis plays an important role in the pathophysiology of HF in CHD, particularly in conditions such as TOF [20, 21] and TGA-baffle [22, 23] these drugs may have theoretical benefits beyond their role in symptom control.

Diuretic doses may need frequent adjustment in the initial stages of therapy and blood pressure and electrolytes should be monitored closely after any medication change. Further adjustments may be needed as a patient's HF progresses. The aim should be to identify and maintain a euvolaemic state in which the patient has minimal symptoms or signs of fluid overload. If patients are listed for cardiac transplant we perform frequent (3–6 monthly depending on the diagnosis) invasive hemodynamic studies and adjust diuretics according to intra-cardiac and pulmonary pressures so as to maintain optimum clinical condition for as long as possible while on the waiting list.

Without measures that improve cardiac output, it is difficult to tackle the lethargy, decreased exercise capacity and general malaise from which patients with a failing subaortic RV (ccTGA, TGA-baffle) frequently suffer. However, exercise training [21], lifestyle modification and addressing systemic issues such as anaemia [24–26] and thyroid disorders [27] may have benefit.

Potential Disease-Modifying Medications

The neurohormonal hypothesis is a key reason that HF advances, even in instances where the initial activating injury has ceased and its direct effects on the myocardium have ended. Neurohormonal activation is a maladaptive response to cardiac injury/stress that both exacerbates hemodynamic abnormalities and has independent, direct toxic effects on cardiac cells. A wealth of mechanistic evidence supports this hypothesis and therapies targeted against neurohormonal activation are proven to reduce mortality and hospital admissions in non-CHD adult HF patients with systolic dysfunction. On the strength of this evidence the 2013 American College of Cardiology Foundation/American Heart Association guideline for the management of heart failure recommends an angiotensin converting enzyme inhibitor (ACEi) and sympathetic beta-receptor antagonist (β-blocker) in all patients without contraindications who have reduced ejection fraction and current or prior symptoms of HF [12]. They recommend that patients who cannot take ACEi be prescribed an angiotensin receptor blocker (ARB) [12]. In addition, and with some additional specified criteria, these guidelines recommend aldosterone receptor antagonists in patients with New York Heart Association (NYHA) class II-IV HF and an LV ejection fraction of <35% [12]. All adult HF guidelines from other major bodies carry similar advice [13, 14, 28]. The 2013 ACC/AHA guidelines unambiguously state that they do not address HF in the setting of CHD [12]. This is not made explicit in the European Society of Cardiology [13] or Heart Failure Society of America [28] guidelines but since CHD is not included in the former's list of causes of HF or the latter's section on special populations, one can assume the documents were not intended for direct application to this patient group.

Adults and children with CHD also exhibit biochemical evidence of neurohormonal activation [29, 30]; although there is much individual variation with levels highly dependent on age and underlying hemodynamic substrate [30–32]. One of the largest studies of neurohormonal activation in patients with CHD considered levels of NT-proBNP in 475 adult outpatients with a broad cross-section of repaired lesions [31]. This 2013 study by Eindhoven et al. found that NT-proBNP levels correlated with NYHA functional class and some echocardiographic parameters [31]. The investigators reported NT-proBNP levels >3 times above their laboratory upper reference range value of 14 pmol/L in 28% of Mustard patients, 55% of ccTGA and 18% of TOF patients [31]. Again in a mixed CHD population, Giannakoulas et al. found neurohormonal activation to be prevalent [33]. This was the first study to document an association between BNP level and mortality adults with CHD and of the 49 patients included 18 (37%) had TOF and 6 (12%) had a systemic RV [33]. The cut-off identified in this unselected population of consecutive patients recruited from ambulatory ACHD clinics was 78 pg/mL [33]. In our own ACHD/HF clinic, which includes only patients with identified HF or referred for transplant assessment; there are very few patients with BNP levels below this. Most patients having levels in the mid-hundreds to thousands (unpublished data) and we therefore find it challenging to apply this cut-off as means of stratifying risk. Plymen et al. investigated NT-proBNP levels and their relationship to ECG and MRI indices in 35 adults with Mustard or Senning repairs of TGA [34]. This group found modest but statistically significant correlations between NT-proBNP and QRS duration, RV volumes and ejection fraction as measured by magnetic resonance imaging (MRI) [34]. There are several other, mostly small-scale, studies looking at NT-proBNP or BNP in children and adults with repaired TOF [32–36]. In general, their findings suggest that patients with repaired TOF also exhibit neurohormonal activation and that the degree of this activation may correspond to RV size, dysfunction and exercise capacity [35–39].

The studies discussed in the preceding paragraph lend support to the hypothesis that patients with CHD including those with failing RVs exhibit neurohormonal activation and suggest that while individual variability exists, there is some correlation between this activation and worsening clinical, hemodynamic and/or RV contractile status. However in the main, investigations of RV failure in CHD have studied only BNP or NT-proBNP and it remains true that little is yet known about activation of the renin-angiotensin aldosterone or sympathetic nervous system in this patient group, or even in the wider population of RV failure without CHD [40]. Nothing is understood about the extent to which maladaptive compensatory mechanisms might control evolution of RV failure in CHD. It is entirely possible that the prominence of other issues (such as abnormal atrioventricular coupling, chronic tricuspid or pulmonary regurgitation, decades of abnormal electromechanical interaction or ventricular fibrosis) may completely eclipse neurohormonal activation as a driver of HF progression in these specific patients. If so, neurohormonal activation might simply be the wrong pathophysiological focus [41]. It is however important to review the data that exists regarding clinical uses of these agents for RV failure in CHD and what the CHD guidelines currently recommend.

There have been several small studies and randomised, controlled trials of ACEi/ARBs and β-blockers in patients with subaortic RVs, which are summarised in Table 16.2. Studies looking at the role of neurohormonally active medications in patients with a Fontan circulation or TOF are summarized in Table 16.3. The results of ACEi/ARB studies in patients with a systemic RV have thus far been disappointing with no signal these medications are likely to be of clinical benefit in this population, despite several randomised, placebo-controlled trials. Data regarding β-blockade are a little more encouraging, but the quality of these data is less impressive and those relating specifically to RV failure are smaller-scale and in the main, retrospective or observational in design. Data regarding the role

of these medications in patients with a Fontan circulation and dominant RV is sparse, but that which exists also suggests no benefit. A similar story is seen in studies regarding neurohormonal therapy in patients with TOF. One double-blind randomized, placebo-controlled trial of ramipril vs. placebo in 72 patients with repaired TOF did find improvement in RV long-axis shortening in those who were treated with ramipril for 6 months, although RVEF did not improve [42].

Published guidelines addressing the management of pediatric HF have been published and sections relevant to this discussion. The 2014 Canadian Cardiovascular Society guidelines on presentation, diagnosis and management of heart failure in children suggest use of an ACEi is indicated in children with primary heart muscle disease of a systemic LV and that β-blockers might be indicated in treatment of moderate to severe systolic LV dysfunction [15], but the role of these medications in children with primary RV failure is not directly addressed [15]. The International Society of Heart and Lung Transplantation's (ISHLT) monograph series includes the 2014 publication: ISHLT Guidelines for the Management of Pediatric Heart Failure [16]. Chapter 6: Pharmacological treatment of chronic heart failure with reduced systolic ejection fraction, provides recommendations regarding neurohormonally active medications that are similar to those of general adult HF guidelines, but specifies these relate only to patients with systemic LV systolic failure [16]. Chapter 12 of the monograph discusses special pediatric HF populations and specifically addresses RV failure in the setting of CHD [16]. The section on systemic RV failure in a biventricular circulation (which in children will almost always mean ccTGA) states that there is no evidence to support prophylactic use of ACEi or ARBs but these medications might be reasonably considered once RV dysfunction is evident (Class IIa, level of evidence C) [16]. No recommendations are made either for or against use of β-blockers [16]. The section relating to chronic single ventricle failure cites data from the Pediatric Heart Network Infant Single Ventricle Trial [43] and makes a Class IIb recommendation against routine use of ACEi in single ventricle patients with preserved ejection fraction but again states that ACEi can reasonably be considered in those with systemic ventricular dysfunction [16]. Here no reference is made to ventricular morphology. They state there is not enough data to make a recommendation regarding use of β-blockers in children with failing single ventricles [16].

Physicians must thus make therapeutic decisions on an individual patient basis, reflecting on the potential benefits and risks of medication and reasonable arguments and experience rather than definite evidence. ACHD patients with chronic RV failure often experience coexisting complications of atrial or ventricular tachyarrhythmia [44–43] and sudden cardiac death is a particular concern for patients with failing subaortic RVs or with RV failure after TOF repair [44–48]. With this in mind, it is reasonable to develop an argument in favour of prescribing β-blockers to patients with severe subaortic RV dysfunction or RV dysfunction in the setting of repaired TOF, especially if there is evidence of biventricular failure. If prescribing a β-blocker, it seems sensible to choose one with demonstrated mortality efficacy in general adult systolic HF trials (bisoprolol, sustained release metoprolol or carvedilol) as data suggest benefit from β-blockade in HF cannot be considered a class effect [12]. For patients with a failing subpulmonary RV with any suggestion of coexisting subaortic LV failure or evidence that chronic ischemia might be a contributor, arguments in favor of ACEi/ARB prescription carry significant sway. The role of these medications in patients with a subaortic RV is much less certain and in fact the evidence summarized in Table 16.2 suggests ACEi/ARB may have no benefit at all in this population. It is the author's observation that adult Mustard, Senning and ccTGA patients with severe, symptomatic RV dysfunction are often hypotensive, with systolic blood pressure in the 80–95 mmHg range and associated dizziness and pre-syncope. By the time they are referred to our ACHD/HF clinic these patients have usually been taking an ACEi or ARB for a number of years. In most cases, gradually reducing and then stopping these

Table 16.2 Studies of neurohormonal modulation in patients with a subaortic right Ventricle

Reference	Population	Drug	Study Design	N	Therapy duration	Outcome
Am J Cardiol 2001;88:1314–16	Mustard or Senning patients aged >13 years. who had never taken ACEi	Losartan	Randomized placebo controlled crossover	7	8 weeks	Improved exercise duration, reduced TR
Am J Cardiol 2001;87:660–663	Mustard adults	ACEi	Observational retrospective	14	2 years	No difference in exercise capacity or MRI measured ejection fraction
Circulation 2005;112:2411–2416	Adults with subaortic RV (Mustard/ Senning/ccTGA)	Losartan	Multicenter randomized double-blind placebo-controlled	29	15 weeks	No improvement in exercise capacity or NT-proBNP levels
Inj J Cardiol 2008;129:187–192	Mustard or Senning adults	Ramipril	Randomized double-blind placebo-controlled	17	1 year	No benefit in RV function as assessed by MRI or exercise capacity
Circulation 2013;127:322–330	Adults with subaortic RV (Mustard/ Senning/ccTGA)	Valsartan	Multicenter randomized double-blind placebo-controlled	88	3 years	No benefit in RV function assessed by MRI, exercise capacity, TR, Q of L or neurohormonal activation
Can J Cardiol 2006;22;769–772	Mustard or Senning adults with impaired RV function who were taking a β-blocker	Any β-blocker	Case series	8	3 years	Drugs well-tolerated and associated with a trend towards improved symptoms, less TR and improved functional status
Int J Cardiol 2007;114:241–246	Adults with subaortic RV (Mustard/ Senning/cc/TGA) and RV dysfunction, no pacemakers	Carvedilol	Prospective with patients studied before and after treatment	8	12 months	Drug safe and target dose achieved in 5/8 patients. RVEF and LVEF improved, exercise duration increased, VO_{2peak} unchanged

(continued)

Table 16.2 (continued)

Reference	Population	Drug	Study Design	N	Therapy duration	Outcome
Am J Cardiol 2007;99:704–706	Mustard or Senning adults	Any β-blocker: Carvedilol n = 15 Metoprolol n = 16	Retrospective chart review	60	4 months	Significant improvement in NYHA functional class if treated with β-blocker but effect seen only in those with pacemakers
JAMA 2007;298:1171–1179	Children and adolescents with symptomatic systolic heart failure. 43 patients with a subaortic ventricle that was not an LV	Carvedilol	Multicenter, randomized, double-blind, placebo controlled trial	161	8 months	No difference in composite endpoint Non-beneficial trend in those CHD patients whose subaortic ventricle was not an LV (included Fontan)
Cardiol Young 2010;20:615–619	Adults with subaortic RV (Mustard/ Senning/ccTGA)	Bisoprolo n = 13 Carvedilol n = 1	Prospective with patients studied before and after treatment	14	13 months	RNA measured RVEF improved but change in RVEF as measured by MRI not significant, NYHA class improved, No change VO_{2peak} or NT-proBNP

Table 16.3 Studies of neurohormonal modulation in patients with Fontan palliation or Tetralogy of Fallot

Reference	Population	N	Number with RV dominant anatomy	Drug	Study design	Therapy duration	Outcome
Circulation 1997;96:1507–1512	Children and young adults after a Fontan procedure	18	Not clear but probably only 2	Enalapril	Randomized, double-blind, placebo-controlled crossover trial	10 weeks	No benefit in exercise performance, systemic vascular resistance or resting cardiac index
Circulation 2010;122:333–340	Infants <45 days old with single ventricle physiology	230	Not provided but 127 had hypoplastic left heart syndrome	Enalapril	Multicenter, randomized, double-blind, placebo-conrtrolled trial	Followed until 14 months of age	No improvement in growth, ventricular function or heart failure severity
Cardiol Young 2007;17:372–379	Adults with repaired tetralology of Fallot	33		Bisoprolol	Randomized, double-blind, placebo-controlled trial	6 months	No beneficial effect on NT-proBNP exercise capacity or ventricular function as measured by MRI
Int J Cardiol 2012;154:299–305	Adults with repaired tetralology of Fallot	64		Ramipril	Randomized, double-blind, placebo-controlled trial	6 months	No difference in MRI-measured RV ejection function. RV and LV long axis shortening improved in treatment group. No changes in NT-proBNP or exercise capacity

medications seems to improve blood pressure and alleviates dizziness. This strategy usually permits up-titration of a β-blocker, which as already discussed, is of value in these patients to reduce their poorly tolerated intermittent atrial and ventricular arrhythmias.

Medical Treatment of Pulmonary Hypertension

Pulmonary hypertension should be considered as both a potential cause of and an adverse effect from chronic RV failure in patients with CHD. The medical treatment of pulmonary vascular disease may play an important role when it is a cause of subpulmonary RV failure. It is important to appreciate that patients with TGA are particularly vulnerable to the development of pulmonary hypertension and pulmonary vascular disease. This is an increasing problem for Mustard and Senning patients who have developed subaortic RV failure and subsequent elevation of left atrial pressure. In many instances this complication has been considered a contraindication to heart-only transplantation, resulting in referral for heart-lung transplantation, which has inferior long-term outcomes. Our group has found that aggressive diuresis in TGA-baffle patients with failing subaortic RVs and pulmonary hypertension can significantly improve baseline hemodynamics, even in patients without overt clinical signs of fluid overload. In some cases, with careful progressive and carefully monitored increases in diuretic doses, we have been able to reduce previously highly elevated pulmonary artery pressures and trans-pulmonary gradients into a range acceptable for heart-only transplantation. This usually takes several weeks, requires the addition of potassium sparing diuretics or supplements and weekly (sometimes more frequent) follow-up visits to our ACHD/HF clinic. It remains to be seen how long this improvement can be maintained and it seems likely that if we are to continue to pursue heart-only transplant, some of our patients will require subaortic RV assist devices to support them during the wait for a suitable donor organ.

Future Directions: RV Specific Therapies

Although they are interlinked, from the earliest stages of fetal development there are also fundamental differences between the right and left ventricles of the heart [49]. The orientation of RV myofibrils is unlike the arrangement seen in the LV [50] and this produces differences in RV [51, 52] and LV [53] contractile properties which are essential for efficient movement of blood through two such geometrically distinct chambers. The two ventricles have different myocardial oxygen demand/supply balances [54] and responses to ischemia [55–57] and other stressors. In a subpulmonary position, the RV usually operates against a low resistance system and it tolerates rapid increases in afterload poorly. However, in a subaortic position, the RV can function against a chronically high afterload. It seems to adapt through hypertrophy, dilatation and with increased circumferential shortening [58–60]. However, in the absence of a middle circular layer of muscle fibres [50] a subaortic RV remains unable to produce the highly efficient smooth wringing/unwringing motion that would be generated by a subaortic LV [58, 60]. Given these distinctions, and the growing suspicion that drugs successful in treating LV systolic dysfunction may not be effective (or as effective) in chronic RV failure in CHD, we perhaps ought to seek more specific RV therapies.

The ideal RV specific drug might have the following properties: Increase RV inotropy, reduce RV fibrosis, promote RV reverse remodelling and dilate the pulmonary vasculature while having few effects on the systemic circulation. Ideally, this drug's efficacy could be monitored noninvasively, since it would cause an improvement in RV ejection fraction, reduce RV size and diminish tricuspid regurgitation and these positive effects would lead to measurable improvements in exercise capacity, clinical status and reduce the risk of both arrhythmia and mortality. Sadly, at the moment no such drug exists. However, there are some interesting potential candidates.

Phosphodiesterase type 5 (PDE5) inhibitors, typically known for their vascular smooth muscle relaxation properties, have to date primarily been

used in situations where this is the desired effect (pulmonary arterial hypertension, erectile dysfunction). In 1999 an expert consensus document stated that due to absence of PDE5 expression in cardiac myocytes, sildenafil lacked direct effects on the myocardium; although it did mention the drug had not been extensively studied in patients with heart failure [61] As it turns out, PDE5 can be expressed by cardiac myocytes, but only in hypertrophied myocardium, something which could potentially be turned to therapeutic advantage [62] In 2007, Nagendran et al. studied surgical specimens from nine patients, seven of whom had RV hypertrophy (three as a result of TOF and one with hypoplastic left heart syndrome), one with LV hypertrophy and one without any ventricular hypertrophy [62]. PDE5 expression was markedly up-regulated in the hypertrophied RV and LV myocardium but not seen in the normal ventricles [62]. In the patient with a hypertrophied LV but normal RV, PED5 was only expressed in the LV [62]. These investigators also studied the isolated perfused hearts and cardiomyocytes from an animal model of RV hypertrophy [62]. They found significant PDE5 expression occurred in only in the hypertrophied RV chambers and that PDE5 inhibition increased RV contractility in those specimens [62]. The authors hypothesised that PDE5 inhibitors might have an important role in cardiac conditions where RV hypertrophy and failure predominate, both for their direct myocardial and pulmonary vasculature effects [62].

Goldberg et al. conducted a randomized, double-blind, placebo-controlled cross over trial looking at oral sildenafil in 28 children and young adults with a Fontan circulation [63]. Fifteen of the patients included in this study had a single ventricle of RV morphology [63]. After 6 weeks of oral sildenafil subjects demonstrated improvement in their myocardial performance index and in the product of the velocity time integral of the dominant outflow tract [64] although cardiovascular exercise performance measures (particularly in those with a dominant RV) were not improved [63]. Tunks et al. studied the hemodynamic effects of a single dose of iv sildenafil in 9 children with a Fontan (6/9 with a single RV) [65]. They found that stroke volume and cardiac output improved, with no change in heart rate and a fall in both systemic and pulmonary vascular resistance [65]. Van De Bruaene et al. performed MRIs at rest and during exercise before and after a single dose of oral sildenafil in 10 adult patients with a Fontan (2/10 had a single RV) and measured pulmonary artery pressures with a central venous catheter [66]. This group found sildenafil improved cardiac index during exercise, with an increase in stroke work index and a fall in pulmonary vascular index [66]. These studies were designed to examine whether pharmacological pulmonary vasodilation might be advantageous in a Fontan circulation and not specifically to look at the potential inotropic effects of PDE5 inhibition in patients with systemic RVs. Nonetheless they provide an interesting signal of benefit and further investigation might well prove valuable.

Metabolic modulators are another group of drugs with potential promise as an RV-specific therapy, primarily in situations that result in RV hypertrophy. Better known as anti-angina drugs, trimetazidine and ranolazine are inhibitors of fatty acid oxidation (FAO) that act within mitochondria to modify the pathways of cellular energy (ATP) generation, altering the balance of carbohydrate and fat metabolism [67, 68]. Owing to its reciprocal relationship with carbohydrate metabolism [69], inhibiting FAO results in an increase in pyruvate oxidation and shifting the balance towards glucose as the primary source of acetyl coenzyme A (and hence ATP) production. An additional effect of this switch is less reduction of pyruvate and less anaerobic glycolysis. This is relevant because hearts with RV hypertrophy demonstrate a mitochondrial metabolic adaptation favouring anaerobic glycolysis [70], which is associated with impaired RV contractility, decreased cardiac output and adverse electrical remodelling [71, 72]. In experimental models of RV hypertrophy, forcing a shift (for example by inhibiting FAO) away from anaerobic glycolysis and towards pyruvate oxidation improves RV performance [72]. In patients whose RV hypertrophy is in some part related to pulmonary vasculature disease inhibitors of FAO may prove particularly useful because these drugs also seem to beneficially affect metabolism in the pulmo-

nary arteries [73]. Thus far the RV effects of FAO inhibition have been tested only in animal models and it is likely the first human trials will be in patients with pulmonary hypertension, rather than those with CHD. However FAO inhibitors and other potential metabolic modulators remain intriguing avenues for further research into the management of chronic RV failure.

Conclusions

Medical management of fluid overload experienced by CHD patients with chronic RV failure can be achieved and is a valid endeavour. But heart failure is not a static disease; it progresses and many survivors of CHD will find themselves in dire need of treatments that interrupt their specific underlying pathophysiology. Currently, there is insufficient data to be able to recommend any medical option with confidence; which is not to say that we will never have a good treatment or that those we have now are certainly useless. It is just that presently, few signs indicate that therapies developed for treatment of systolic HF in the adult general population address targets germane to RV failure in CHD. It is self-evident that more and better research is needed. Given the lack of certainty in medication's ability to improve outcomes or slow disease progression, it is important that while treating symptoms and up-titrating heart failure medication, we keep sight of the bigger picture. This is because in CHD patients with chronic RV failure, if one exists, the window of opportunity for definitive management (usually surgical revision or transplantation) may be relatively small.

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