Pathophysiology and Management of Heart Failure in Repaired Congenital Heart Disease

Paul F. Kantor, MB, BCh, DCH, FRCPC*,
Andrew N. Redington, MD, FRCP

KEYWORDS

• Heart failure • Congenital heart disease • Fontan
• Remodeling • Right ventricle

Transient myocardial dysfunction during the early postoperative course is a common sequela of open heart surgery in children, which for the vast majority seems to resolve completely. However, whether related to this perioperative insult or a more chronic effect of the disease, its treatment, or residual abnormalities, established heart failure in children with congenital heart disease may occur at any time in their postoperative course. This article details the current knowledge of congenital disease-related heart failure (CDHF), alluding to common themes in the pathophysiology of systemic ventricular dysfunction, which inform the clinician regarding treatment. These aspects are examined in the context of specific lesions, and treatment options are discussed.

PERSISTENT VENTRICULAR DYSFUNCTION FOLLOWING SURGICAL REPAIR

In the contemporary era, advances in perfusion, anesthesia, and early postoperative supportive care/drug therapy have resulted in a "new normal," in which relatively few patients manifest overt ventricular dysfunction after the first 72 postsurgical hours. However, certain high-risk lesions persist in manifesting late ventricular dysfunction, even when the primary correction is expertly done. These include

- Hypoplastic left heart syndrome during its staged repair.
- The Fontan repair for single-ventricle physiology of various sorts.
- Congenitally corrected transposition of the great arteries requiring surgical intervention.

In many respects, the substrate for late ventricular failure is evident in early childhood and is amplified over years and decades because of one or more persistent hemodynamic problems. Operative repair is frequently imperfect, but how often this actually results in symptoms that could reasonably be described as heart failure can be questioned. In a meta-analysis, Verheugt and colleagues[1] reviewed the published literature from 1980 to 2007, identifying 35 case series describing the course of 7984 patients with postoperative congenital heart disease. Although survival was generally good, they were also able to identify the prevalence of New York Heart Association (NYHA) I status for the major common diagnoses (**Fig. 1**). Overall, 93% of patients from follow-up studies commencing in the pediatric age range survived, and of these, around 80% were in NYHA I class. However, only 50% of cases with a systemic right ventricle (RV) were symptom-free at a mean age of 20 to 25 years. The importance of the solitary or

University of Toronto, Division of Cardiology, Hospital for Sick Children, 555 University Avenue, Toronto, ON M5G 1X8, Canada
* Corresponding author.
E-mail address: Paul.Kantor@sickkids.ca

Heart Failure Clin 6 (2010) 497–506
doi:10.1016/j.hfc.2010.06.002
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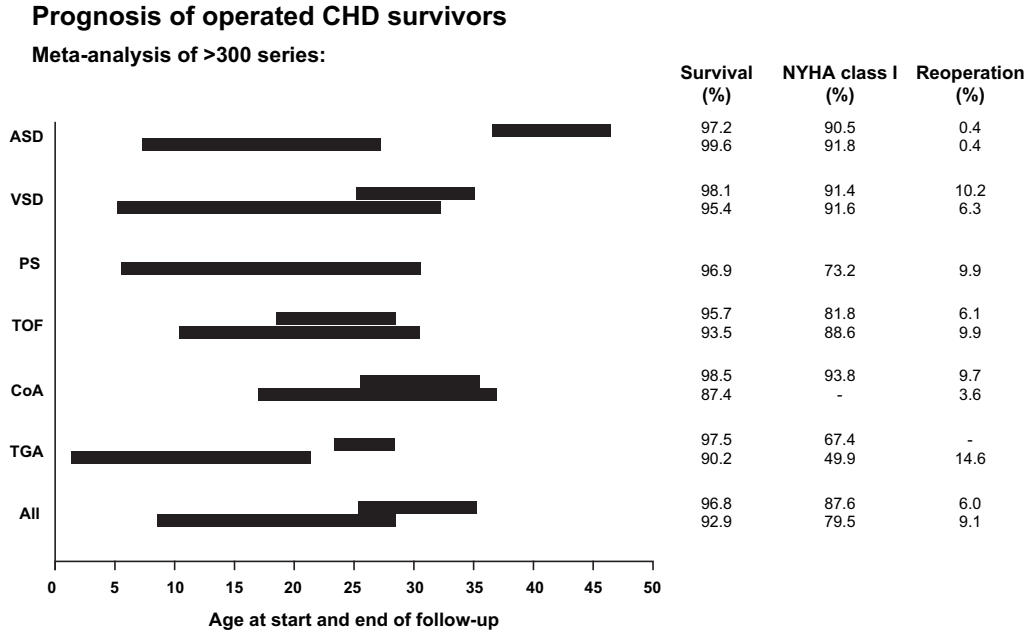

Fig. 1. Meta-analysis of the prognosis of congenital heart disease, including 35 series incorporating 7984 patients followed between 1980 and 2007. Horizontal bars represent studies clustered according to follow-up duration and age (either pediatric or adult range), arranged according to the major diagnostic groups. Percentage survival, NYHA I symptomatic class, and reoperation status at last follow-up are represented in the right hand columns for each diagnostic group and age stratum. (*From* Verheugt CL, Uiterwaal CS, Grobbee DE, et al. Long-term prognosis of congenital heart defects: a systematic review. Int J Cardiol 2008;131(1):25–32 [Review]; with permission.)

systemic RV as the substrate for failure is further supported by work from Norozi and colleagues[2] in a single-center series, in which more than 20% of patients with a single ventricle or a systemic RV (as well as with tetralogy of Fallot) had both a reduction in aerobic capacity and elevated B-type natriuretic peptide (BNP) levels by age 20 years. These specific situations are examined in more detail.

THE SINGLE VENTRICLE: HEART FAILURE DURING INTERSTAGE PALLIATION

Scope of the Problem

Many of the conditions that fall under the umbrella of functionally single ventricle present in the neonatal period, with some form of heart failure. Those with anatomy that limits systemic blood flow in utero (eg, double inlet left ventricle [LV] with discordant ventriculo-arterial connections, hypoplastic left heart syndrome [HLHS]) are (1) predisposed to aortic arch anomalies that render their systemic circulation duct-dependent, and (2) at risk of rapid development of preoperative heart failure symptoms because of an increasing pulmonary-to-systemic flow ratio (Qp/Qs), as the pulmonary vascular resistance falls. The key to successful treatment lies in timely surgical palliation, but preoperative management should be directed at maintenance of ductal patency, where appropriate, and manipulation of Qp/Qs. Nowadays this is achieved primarily by modification of systemic vascular resistance (SVR).

Neither strategy is effective if there is limitation of blood flow elsewhere in the circulation. For HLHS in particular, an appropriate interatrial communication is required to avoid pulmonary venous hypertension and its secondary effects on pulmonary blood flow and oxygenation. The success of fetal screening programs has made presentation with cardiovascular collapse a rare event in many units, and consequently, overt early ventricular myocardial failure has become similarly uncommon. As a result, even in the HLHS population, there is remarkably little data pointing to a correlation between preoperative ventricular performance and postoperative outcomes. However, in one study, a poor RV ejection fraction (RVEF), though not associated with early survival, was predictive of poorer late outcomes.[3] The authors' data from a cohort of patients managed

in Toronto between 1998 and 2007 suggested an adverse impact of reduced preoperative RVEF on both early and late survival after first-stage Norwood procedure.

Phenotype of the Failing Single Ventricle Palliation

It is beyond the scope of this article to discuss in detail the early postoperative management of the neonate after palliation (most often some form of Norwood palliation). The general principles of preoperative management apply equally, and perhaps more importantly, postoperatively. Residual obstruction to systemic blood flow is poorly tolerated, and in the early postoperative period, manipulation of SVR with intravenous vasodilators has become part of routine care.

Despite this, myocardial dysfunction and associated systemic atrioventricular (AV) valve regurgitation are not infrequent, particularly in HLHS but also in other forms of functionally single ventricle. For some, intrinsic abnormalities of the atrioventricular valve drive a spiral of worsening regurgitation and ventricular dysfunction. These patients may benefit from direct surgical intervention on the valve.[4] For others, the primary abnormality appears to be within the myocardium. While a clear-cut abnormality can sometimes be defined (eg, coronary ischemia in HLHS associated with mitral stenosis and aortic atresia, or LV noncompaction in the setting of pulmonary atresia with intact ventricular septum), most often this appears to reflect the outcome of "multiple hits" conspiring to cause adverse remodeling and potentially inexorable decline (**Fig. 2**). Unfortunately, the treatment options for this latter group are limited, but are discussed as follows.

Treatment Options for Heart Failure Before Fontan Completion

The prophylactic use of angiotensin-converting enzyme (ACE) inhibitors has become ubiquitous in the postoperative management of the functionally single ventricle, despite there being little data to support their use in this way. Indeed, a recent study completed by the National Institutes of Health-supported Pediatric Heart Network showed no benefit in terms of symptoms or weight gain of ACE inhibition as interstage therapy before the bidirectional Glenn procedure (D Hsu, personal communication, 2009). Proponents of this therapy identify the benefits of afterload reduction in the early postoperative period, and it has become commonplace to wean patients after stage 1 palliation from intravenous vasodilators to oral therapy in the immediate postoperative period. While intuitively attractive, superficially, this logic does not sustain close scrutiny; although many patients also receive intravenous inotropic agents, one would not consider replacing such therapy with an oral inotrope during weaning. Also, little is known of the effects of a chronically reduced afterload. In disease states (eg, vitamin B deficiency, arteriovenous malformations), a chronically reduced afterload can itself lead to high-output failure, with ventricular dilation, atrioventricular valve regurgitation, and ultimately, systolic dysfunction. At the very least, some caution

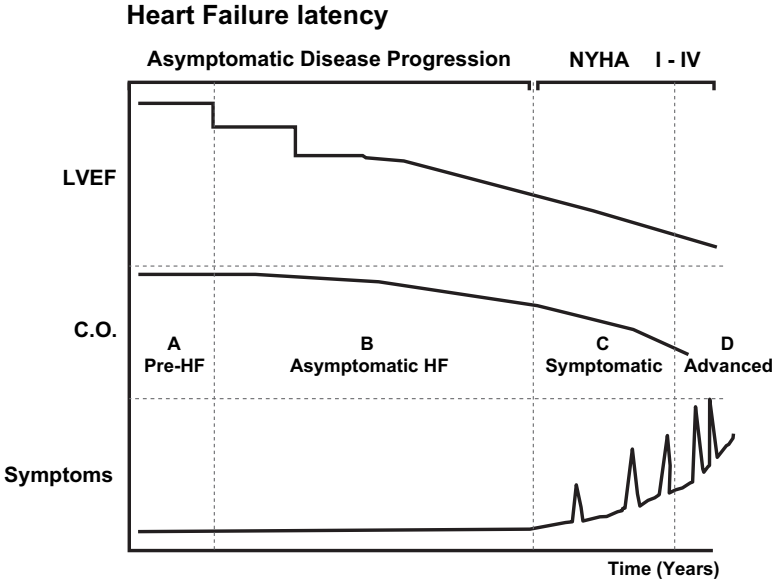

Fig. 2. Schematic depiction of the latency of clinical symptoms and functional deterioration in heart failure. The phase of deteriorating function and diminishing cardiac output greatly exceeds the duration of overt symptoms. In congenital heart disease, much of stage A and B occurs in early childhood, with overt symptoms more frequently developing in later adolescence or adult life. CO, cardiac output; HF, heart failure. (*Adapted from* Liu P, personal communication, 2009; with permission. *Courtesy of* Peter Liu, MD, Toronto, Canada.)

should be exercised in the indiscriminate use of these agents in this setting. Similarly, given the wealth of data from adult trials, the use of β-blockers to treat the ventricular dysfunction associated with congenital heart diseases appears intuitive. However, the data available suggest that such therapy may have overtly adverse effects on the systemic RV[5]; these agents, if used, should be used under strict (ideally research-driven) protocols and cannot be recommended for routine or prophylactic therapy.

THE FONTAN CIRCULATION

Introduced in the 1970s[6] as a means of increasing pulmonary blood flow in adults without a distinct RV circulation, this palliation has undergone several iterations, taking a routine place in the staged palliation of children with a single ventricle. Early failure of the Fontan operation and associated takedown have become an uncommon event (<2%) in the current era because of more cautious patient selection, transplantation emerging as a viable option, and, to some extent, improved perioperative techniques. Patients operated on before 1985 predominantly using an atriopulmonary or atrioventricular anastomosis technique had a mortality of 30% at a median of 12 years, with a high degree of risk for reintervention. Most of these deaths occurred in the perioperative phase.[7] In contrast, more recent series suggest survival exceeding 90% at 10 years.[8] While early surgical mortality (now also <2%) has therefore declined dramatically,[9] 10-year mortality has also decreased from around 20% to less than 10%.

Ventricular Morphology

The substrate upon which a Fontan operation is constructed matters, perhaps as much as the construction itself. The prelude to a Fontan operation involves a volume-loaded ventricle and, in some cases, a pressure load as well because of pulmonary arterial (PA) banding in infancy. This is especially true for patients from the previous era who were not subject to staging via an early cavopulmonary shunt and takedown of the initial palliative Blalock-Taussig shunt.[10] As a result, the substrate of the Fontan operation is an imperfect ventricle, often hypertrophied and dilated. The subsequent reduction in inflow after the Fontan operation results in an underfilled and hypertrophied heart. Also, there is good evidence from the Pediatric Heart Network multicentre study[11] that RV morphology of the single ventricle is closely related to late ventricular dysfunction and, predictably, to AV valve failure as well. However, these are not the only mechanisms of Fontan failure and death. Most series describe a spectrum of overlapping risks for these patients, including arrhythmic events and sudden death, thromboembolism, and heart failure, occurring in about 6% in the historic series.[7] These investigators described independent predictors of heart-failure death as being protein-losing enteropathy (hazard ratio [HR], 7.1; $P = .0043$), single morphologically RV (HR, 10.5; $P = .0429$), and higher right atrial pressure (HR, 1.3 per 1 mm Hg; $P = .0016$).

Traditional Measures of Heart Failure

Are these features then a hallmark of all patients with this circulation, or only those from an earlier era? A recent report from Rotterdam suggests that many patients (32%) do not maintain sinus rhythm and that ventricular ejection fraction at rest is lower than in controls but still in the normal range.[12] Aerobic exercise capacity is well known to be reduced in these patients,[13] with both cardiopulmonary and peripheral muscle factors implicated. Ventricular function is difficult to characterize in this setting. Simple measures, such as ejection fraction, suggest normal range cavity displacement in about three-quarters of patients, with diastolic dysfunction being far more pervasive and detectable in about 70% of patients.[11] Many have stated that the Fontan circulation is preload-limited, and it is clear that the transpulmonary pressure gradient that determines this preload is precarious. With an age-related increment in systemic ventricular diastolic pressure, one can anticipate that diastolic function of the systemic ventricle becomes the weakest link in the chain for Fontan-circulation patients.

The Phenotype of a Failing Fontan

There is unfortunately no simple definition of Fontan failure, and indeed, it and may not overlap completely with obvious ventricular function problems: protein losing enteropathy, plastic bronchitis, intrapulmonary arteriovenous malformations, and atrial arrhythmias are all well described in the presence of normal ventricular function in these patients. Hence, some have argued that ventricular and cavopulmonary failure are separate entities and distinguishable by BNP levels, which remain normal in the latter[14] but are moderately elevated in Fontan patients with ventricular dysfunction.

Treatment of the Failing Fontan

Some of the elements alluded to earlier and others not discussed (persistent shunts, leaks, and veno-venous collateral connections) are treatable lesions. AV valve repair and Fontan conversion

are well recognized to improve symptoms and reduce the arrhythmia burden, which is one of the major drivers of symptoms. The treatment of protein-losing enteropathy, plastic bronchitis, and AV malformations is less well established, with long-term success proving to be elusive in many. In these situations, cardiac transplantation should be considered. Medical therapy for ventricular failure in the Fontan circulation is often attempted and seldom successful in the authors' experience. Diuretics, including aldosterone antagonists, have a sound theoretical basis and are indicated. ACE inhibitors and β-adrenoceptor blockers have a lesser role and cannot be endorsed at this time. It is possible that vasodilation may worsen symptoms for many patients.

CONGENITALLY CORRECTED TRANSPOSITION AND THE ATRIAL SWITCH OPERATION

Few situations are as enigmatic and vexing from a therapeutic point of view as the RV in the systemic position, either by virtue of nature or surgical design. Congenitally corrected transposition of the great arteries (CCTGA) exists within a range of disorders of AV connections, and it is characterized by discordance of AV connections, with ventriculoarterial discordance. Hence, the circulation is physiologically corrected, but as observed by Van Praagh, little else is correct, and these hearts are at high risk of ventricular failure for many reasons.

Natural History and Surgical Options for CCTGA

The natural history of unoperated CCTGA is unfavorable, reported to be a survival of 72.3% at age 3 years in a recent Eastern European series[15] and 64% at 10 years of follow-up in a institution-based historic cohort reported by Huhta and colleagues.[16]

There are several reasons for symptoms and death in these patients, especially in those with associated lesions. The tricuspid valve subjected to systemic pressures is prone to failure, and tricuspid regurgitation alone can account for much of the excess mortality seen in CCTGA.[17] In addition, the presence of a ventricular septal defect (VSD) and subpulmonary stenosis may also result in oxygen desaturation, and, because the conduction axis passes anteriorly along the free wall of the LV and is elongated and susceptible, complete AV block is reported in about 2% of patients per year, reaching up to 45% in long-term follow-up.[18] For all symptomatic patients, especially those with associated lesions, surgery remains the first and possibly the only meaningful strategy.

Surgical remediation of this disorder is typically undertaken by one of the 2 approaches:

1. Closing the existing VSD and addressing subpulmonary obstruction by placing an LV-to-PA conduit without correcting anatomic relations (a classic or physiologic repair); the tricuspid valve remains in the systemic circulation and may also be repaired or replaced.
2. Restoration of functional connections along morphologic grounds: restoring the LV from a subpulmonary to a subaortic position and rerouting atrial inflow to the appropriate morphologic ventricle; this double switch is typically accomplished by a combination of a Mustard or Senning atrial baffle and an arterial switch or interventricular tunnel connecting the accompanying VSD to the aorta and placing an RV-to-PA conduit (a variant of the Rastelli procedure).

Modifications incorporating volume unloading for the subpulmonary ventricle by a cavopulmonary anastomosis have been advocated.[19] Even the Fontan operation is an available option for surgical palliation. Other considerations include repair or replacement of the tricuspid valve, which is commonly dysplastic and regurgitant, and, most importantly, retraining of the low-pressure subpulmonary LV to regain near-systemic pressure before a switch procedure by serial PA banding in most individuals.

The success of surgery for this condition has been mixed, and although surgical survival is improving in the current era, it is still unclear whether this can be attributed to a particular surgical approach. A Toronto group have argued for the protective effect of a Rastelli-type anatomic repair by modeling data from 124 patients in a meta-analysis.[20] Others, describing single-center data acquired over decades, are able to show an improving survival with time but cannot attribute this clearly to a particular surgical strategy.[21] Regardless of surgical strategy, the tricuspid valve and the systemic RV are probably the underlying reasons for heart failure in surgical survivors.[22]

Phenotype of Heart Failure in CCTGA

Most often, patients are noticed in 1 of the 3 scenarios:

1. No prior surgical intervention, with progressive cyanosis indicating a VSD and subpulmonary stenosis
2. Previous surgical palliation leaving the tricuspid valve in the systemic position, with RV failure

3. Previous surgical palliation with secondary LV dysfunction and frequently combined ventricular dysfunction.

Recently, Szymanski and colleagues[23] attempted to codify the features of systemic RV failure in symptomatic and asymptomatic patients with a systemic RV. These investigators found that 54.2% of their patients had no RV systolic dysfunction, 23.8 % had asymptomatic RV dysfunction, and the remainder had dysfunction and symptoms; conversely, 11.9% of patients had heart failure symptoms with normal (preserved) systolic RV function, frequently in the presence of tricuspid regurgitation. They found that normal BNP levels were a good predictor of normal RV function in all patients. Other investigators reported that amino-terminal proBNP (NT-proBNP) was significantly elevated in all patients with a systemic RV, correlating with magnetic resonance imaging (MRI)-derived RVEF and with tissue Doppler-derived annular velocity, even in asymptomatic patients. MRI assessment of the systemic RV has further revealed a significant prevalence of fibrosis, as indicated by late Gadolinium enhancement (of the right ventricle in several recent studies).

The Treatment of Heart Failure in CCTGA

The best answer to what can be done to manage the failing systemic RV is also likely to address the underlying cause; because there are several surgically remediable issues, this is always a logical first step. Hence, the unoperated patient requires careful assessment to determine the most appropriate repair strategy. In those who have undergone a classic/physiologic repair, tricuspid valve regurgitation may respond to PA banding, with the attendant shift in the septal position and volume unloading of the morphologic RV that results. Similarly, tricuspid valve repair may be attempted. There is good experiential evidence that PA banding may be a preemptive therapy to systemic RV deterioration in young patients and that it may constitute a destination therapy in older patients, reducing symptoms substantially.[24] However, later data from a Birmingham group portray a pessimistic view of staged LV retraining toward completion of an arterial switch, with 45% of patients subjected to complete morphologic LV retraining developing moderate-to-severe LV dysfunction and/or requiring cardiac transplantation.[25] Medical therapy on failure of the systemic RV has so far proven unpersuasive. There are few reports of β-blocker therapy having any beneficial effect in these patients; however, one small series in adults, most of whom had undergone an atrial repair for simple TGA,[26] demonstrated a short-term benefit for the use of carvedilol, with reverse remodeling of RV volume and improvement in RVEF and LVEF while aerobic capacity remained unaltered. No controlled trials are available to assess this strategy. Similarly, the value of inhibiting the pathway of angiotensin production or cardiac binding has proven to be questionable at best. Several small studies of ACE inhibitors (see Winter and colleagues,[27] for a review of this topic), including one well-conducted placebo-controlled trial of losartan,[28] have failed to show any benefit to function of the systemic RV. The authors' current practice is to use diuretics and aldosterone (as a means to preempt cardiac fibrosis), with no routine indication for β-adrenoceptor blockers or ACE antagonists.

NOVEL APPROACHES TO HEART FAILURE IN CONGENITAL HEART DISEASE

If the foregoing portrays the limitations of conventional wisdom in dealing with heart failure following congenital heart disease repair, perhaps alternative approaches are required.

Resynchronization Therapy

In 1992, Gibson and colleagues[29] reported that a reduction in the AV coupling interval by AV sequential pacing in patients with dilated cardiomyopathy had marked effects on cardiac index and exercise tolerance. Few could have predicted the ramifications of this finding. Later, it became clear that septal pacing and, eventually, 4-chamber pacing had similar effects; shortly thereafter, Blanc and colleagues[30] offered the first analysis of the effects of multisite pacing on ventricular performance. Over the subsequent decade, the concepts of electrical and mechanical ventricular dyssynchrony have been refined, and biventricular pacing has become a proven therapy for heart failure, primarily of nonischemic cause, in adult patients.

What of the congenital heart disease population? Bundle branch block is present in most patients who have had a ventriculotomy, and hence, one would expect that clear signal of mechanical dyssynchrony could also easily be demonstrated. Vogel and colleagues[31] showed greater QRS duration and dispersion as well as systolic and diastolic velocity reversal in the RV free wall of patients with repaired Fallot tetralogy (TOF). Others have further explored this phenomenon and have implicated biventricular dyssynchrony as being present and possibly important in patients with repaired TOF.[32,33] Although

sudden death appears to be associated with QRS duration,[34] a clear and progressive link between interventricular mechanoelectrical dyssynchrony and an eventual decline in systemic ventricular function is yet to be demonstrated. However, encouraging results have been noted from the use of resynchronization therapy in a wide variety of children with congenital heart disease and prolonged QRS duration with ventricular dysfunction.[35] Recently, a small but carefully executed study measured the effects of resynchronization on young patients with systemic RV (surgically or congenitally corrected), heart failure, and QRS duration of 160 ± 30 millisecond.[36] The investigators reported that after 19.4 ± 8.1 months of cardiac resynchronization therapy (CRT), mean QRS duration decreased from 160 ± 31 to 120 ± 28 millisecond ($P = .03$); intraventricular delay, from 104 ± 27 to 14 ± 15 millisecond ($P = .01$); and NYHA functional class, from 3.0 to 1.57 ($P = .01$) with peak oxygen consumption increasing from 13.8 ± 2.5 to 22.8 ± 6.7 mL/kg/min ($P = .03$). While systematic studies identifying patients with congenital heart disease and heart failure who should receive CRT are still awaited, current intuitive guidelines suggest that the presence of RV or LV dysfunction with a prolonged QRS duration would be grounds for a trial of multisite pacing. Unfortunately, the technical challenges in patients with atrial baffles, multiple prior surgeries, and abnormal native conduction pathways are still formidable.

Diastolic Heart Failure

While the understanding of systolic dysfunction in postoperative congenital heart disease is maturing, the understanding of diastolic dysfunction (as a driver of symptoms and a cause of heart failure) is very much in its infancy. Nonetheless, there is good evidence that diastolic dysfunction is an important element of the circulatory disturbance characteristic of the exemplars discussed earlier. Some have long recognized that abnormal diastolic function is the most obvious myocardial functional abnormality detectable during staged palliation of functionally single ventricles. The acute preload reduction associated with conversion from parallel systemic and pulmonary circulations to the series bidirectional Glenn or Fontan circulation is associated with major changes in ventricular geometry and diastolic function, originally demonstrated in patients transitioning directly to a Fontan circulation.[37,38] This abrupt reduction in preload and therefore ventricular end-diastolic volume, in the setting of maintained systolic shortening and unchanged ventricular mass, was associated with an acute increase in ventricular wall thickness. The same phenomenon is seen in those transitioning to a bidirectional Glenn procedure as part of 3-stage palliation.[39] The end-effect is profound ventricular incoordination leading to early relaxation abnormalities, with prolongation of the time constant of relaxation and the isovolumic relaxation period and reduced early rapid filling. The functional importance of these abnormalities was not examined in the early studies, but recently it has been shown that patients with greater degrees of diastolic function have more postoperative complications and longer postoperative stay.[40,41] Furthermore, these relaxation abnormalities persist in long-term follow-up, and there is emerging evidence that a gradual reduction in ventricular compliance also occurs at the same time.[11,42] The functional consequences of this shift are not yet well defined; however, reduced early rapid filling with insidious reduction in late diastolic filling because of increasing ventricular stiffness could be a cause of reduced cardiac output and declining circulatory performance in this tenuous circulation and, ultimately, of Fontan failure. This area deserves more research.

A wholly different form of diastolic dysfunction has been described in patients with surgically corrected TGA. The poor stroke volume responses to exercise and during provocative testing in these patients was often attributed to poor systemic RV function in earlier studies.[43] However, in a later study using conductance catheter assessment of ventricular responses to dobutamine stress in patients after the Mustard and Senning procedures, there seemed to be appropriate systolic (load-independent indices, ventriculo-vascular coupling) and some diastolic (time constant of relaxation, end-diastolic pressure-volume relationships) responses.[44] Despite these myocardial responses, the RV filling rate was unchanged, and consequently, the tachycardia (and reduced diastolic filling time) related to increasing doses of dobutamine was associated with a progressive decrease in stroke volume. This phenomenon is almost certainly a reflection of abnormal atrioventricular coupling resulting from the abnormal capacitance and reduced contractile function of the restrictive atrial pathways after such operations. These findings have subsequently been reproduced by others[45]; they provide for a better understanding of pathophysiology and the well-known lack of response to ACE inhibitors and angiotensin-receptor blockers, as discussed earlier, and they further endorse the fact that intuitive assumptions are often proven to be incorrect in congenital heart disease. Detailed study of

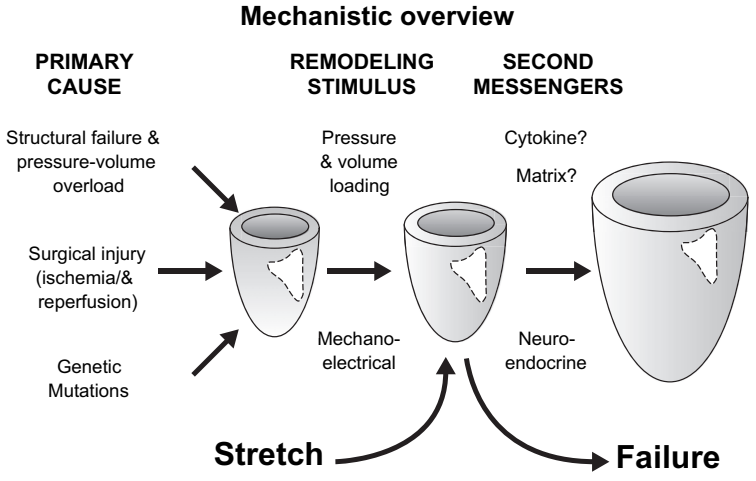

Fig. 3. Mechanistic hypothesis of the pathogenesis of heart failure in congenital heart disease. The primary mechanisms are those of structural failure resulting in hemodynamic (pressure and volume) stress, exacerbated by ischemia, and reperfusion injury. Genetic modifiers of the response are probably also important in explaining individual variation. The common pathway of structural remodeling is promoted by pressure and volume loading and by dyssynchronous mechano-electrical coupling. Lastly, second messengers of classic heart failure progression become evident; neuroendocrine activation is definitively evident, but the specific role of cytokines and matrix remodeling factors is poorly defined. (*Adapted from* Liu P, personal communication, 2009; with permission. *Courtesy of* Peter Liu, MD, Toronto, Canada.)

individual lesions and corrective procedures applied to them are likely to help develop rational and successful treatments for the heart failure that is associated with them.

SUMMARY

The overall picture that emerges regarding heart failure following congenital heart disease is that it may take years or decades to develop. As a working construct, the authors have proposed that 3 elements are necessary, as illustrated in **Fig. 3**.

1. An underlying primary cause: in most cases the lesion is the end result of an attempted palliation, leaving a residual abnormality of function; coexisiting factors, such as recurrent ischemia, and disease modifiers of a genomic nature may also play a role in determining the severity of the primary underlying cause.
2. A remodeling stimulus: typically, during the latent phase of the disease, there is a requirement for long-lasting hemodynamic remodeling to be operating in the form of a volume load (such as a regurgitant tricuspid valve) or a persistent pressure load (unrelieved LV outflow obstruction); more recognition is now given to the probable importance of mechanical and electrical dyssynchrony as a mechanism of progressive remodeling in these patients.
3. A second messenger: operating as a signaling mechanism by one of several pathways, including neurohormonal activation, matrix remodeling, or inflammatory or apoptosis-provoking stimuli; these messengers become more evident in the symptomatic phase of the disease.

Based on the above construct, it is possible to rationalize and identify the timing and role of specific therapies for each given situation.

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