Published in final edited form as:
Ped Health. 2010 ; 4(1): 45–58.

Role of β -blocker therapy in pediatric heart failure

Akash R Patel and

The Children's Hospital of Philadelphia, Department of Cardiology, 34th & Civic Center Boulevard, Philadelphia, PA 19104, USA Tel.: +1 215 590 3548 Fax: +1 215 590 5825

Robert E Shaddy[†]

The Children's Hospital of Philadelphia, Department of Cardiology, 34th & Civic Center Boulevard, Philadelphia, PA 19104, USA Tel.: +1 267 426 7518 Fax: +1 267 426 0950

Akash R Patel: patela@email.chop.edu; Robert E Shaddy: shaddy@email.chop.edu

Abstract

Heart failure is becoming an increasingly common and significant problem in the field of pediatric cardiology. The numerous types of cardiomyopathies, and more recently, long-term survival of patients with congenital heart disease, have added to a growing patient population. Over the last several decades, our knowledge base regarding mechanisms of disease and therapeutic intervention in adult patients with heart failure has drastically changed. The most recent and important breakthrough in the pharmacologic treatment of heart failure has been the particular role of β -blocker therapy. This medication has led to significant improvements in survival and symptoms in adults, with less convincing findings in limited studies in pediatrics. The ability to study the benefits of this therapy in patients has been challenging owing to the heterogeneity of the patient population and lack of large sample sizes. However, as we investigate the mechanisms behind the disease process, the differences that exist between disease conditions and ages, and the significant alterations that may exist at the molecular and genetic level, our understanding of β -blocker therapy in pediatric heart failure will improve, and ultimately may lead to patient-specific therapy.

Keywords

β -blocker; carvedilol; congenital heart disease; heart failure; pediatric

Heart failure in the pediatric population continues to be a growing problem. Current data suggest that the incidence of dilated cardiomyopathy is 0.57 cases per 100,000 pediatric patients, with 1 and 5 year rates of death or heart transplantation at 31 and 46%, respectively, despite optimal medical management [1]. The incidence is even higher – 1.24 cases per 100,000 pediatric patients – with the addition of other primary cardiomyopathies including noncompaction, restrictive and hypertrophic cardiomyopathy [2]. This is further compounded by the development of ventricular dysfunction and heart failure in the growing

© 2010 Future Medicine Ltd

[†]Author for correspondence: The Children's Hospital of Philadelphia, Department of Cardiology, 34th & Civic Center Boulevard, Philadelphia, PA 19104, USA, Tel.: +1 267 426 7518, Fax: +1 267 426 0950, shaddy@email.chop.edu.

For reprint orders, please contact: reprints@futuremedicine.com

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

population of patients with surgically corrected congenital heart disease as these children approach young adulthood. Based on the current incidence of significant congenital heart disease – six cases per 1000 live-births [3] – and the 0.1–0.2% incidence of heart failure in patients with structural heart disease [4]; the additional number of patients with heart failure could be at least another 0.6 cases per 100,000 pediatric patients. Owing to limited alternative solutions, such as cardiac transplantation and destination therapy with mechanical circulatory support, optimization of the medical management of heart failure in the pediatric population is needed [5,6].

Much of our understanding regarding this disease process and the therapeutic management strategies that exist have been derived from the adult population with heart failure. To date, the medications that have been used in adults, such as diuretics, digoxin and angiotensin-converting enzyme (ACE) inhibitors, have demonstrated clinical utility in the pediatric population [7]. Despite the apparent increased use of these medications in children with heart failure, there have been no significant changes in survival over the last two decades [6]. The advent of β -adrenergic receptor blockade (β -blocker) therapy, which has shown significant improvements in symptoms, survival, left ventricular function and reverse remodeling in adults with heart failure, has led to early optimism in its utility for management of pediatric heart failure. However, owing to the high degree of heterogeneity of diseases in the pediatric patient population as well as the small numbers of patients with heart failure, our ability to fully investigate the efficacy of this medical management strategy on outcomes in terms of mortality and surrogate end points has been difficult [8]. By understanding the pathophysiology of heart failure in the unique pediatric population and the potential differences that may exist at the genetic, molecular and cellular levels, we may be able to better understand the mechanisms and effects of β -blocker therapy in order to improve management. This review will address these issues by focusing on our current understanding of the pathophysiology of heart failure with regard to the adrenergic system and the renin–angiotensin–aldosterone system (RAAS), in addition to the current and future role that β -blocker therapy may play in the management of heart failure in the pediatric population.

Pathophysiology of heart failure

The paradigm for the pathophysiology and treatment of heart failure has changed over the last three decades owing to the improved understanding of the compensatory effects of the neurohormonal system whose role it is to preserve cardiac output at the expense of maladaptive cellular and vascular changes that can exacerbate heart failure [9–13]. The particular role of the adrenergic and RAAS systems has come under significant investigation over the last two decades, which has resulted in landmark clinical trials that have significantly altered the management of heart failure [14–32].

Our current understanding is that the normal physiology of these systems is to augment cardiac output by increasing heart rate, myocardial contractility, and myocardial relaxation by β -adrenergic receptor stimulation of the heart [10,12,13,33]. Cardiac output is further altered by the systemic effects of α -adrenergic receptor stimulation, which increases peripheral vascular tone resulting in increasing afterload and optimizing cardiac output to the most vital organs. As a consequence, there is activation of the RAAS system, which results in attempts to increase preload [13]. These combined effects initially result in increased cardiac output in the acute state; however, the chronic activation of these systems results in maladaptive changes that lead to myocardial injury over time, adverse cardiac remodeling and ventricular dysfunction that continue to worsen if left unchecked [9–12]. The understanding of the adrenergic system at the cellular signaling level has resulted in

improvements in therapy that blunt this response, resulting in the slowing, stopping and/or reversal of this process.

To date, there have been three subtypes of β -adrenergic receptors identified. The understanding of the intricate cellular signaling pathways these receptors activate has led to a deeper understanding of heart failure and has provided avenues for the development of novel therapies. Our current understanding is that β -1 and β -2 adrenergic receptors are the predominate mediators by which the neurohormonal system affects the progression of heart failure [12,34].

The β -adrenergic receptors are seven-trans-membrane guanine nucleotide (G) protein-coupled receptors, which are activated by cat-echolamine stimulation, norepinephrine and epinephrine. The G-protein receptors fall into two subgroups. The G_s (stimulatory) protein recruits and activates adenylyl cyclase and, thus, increases intracellular cAMP, a second messenger that mediates numerous downstream pathways. The G_i (inhibitory) protein deactivates adenylyl cyclase and, thus, inhibits the production of cAMP and also inhibits downstream signaling of cAMP. cAMP leads to activation of a variety of pathways including activation of protein kinase A, which regulates pathways via phosphorylation of intermediaries and results in myocardial relaxation, contraction and increased heart rate through calcium regulation [9,12].

Our current understanding is that the β -1 and β -2 adrenergic receptors are the predominant receptors found in the heart with equal distribution between the right and left ventricles [34]. The β -1 adrenergic receptor is coupled to a G_s protein receptor while the β -2 receptor is coupled to both G_s and G_i protein receptors based on the presence or absence of phosphorylation. Over time, neurohormonal homeostasis changes in the failing heart and the distribution changes. The ratio of β -1 to β -2 adrenergic receptors in the non-failing heart is 77:23, but in the setting of heart failure there is predominantly downregulation of β -1 adrenergic receptors, which results in a change in this ratio to 60:38 [34]. This down-regulation (loss of receptors) is also accompanied by desensitization (loss of signaling) over time due to chronic overstimulation. Desensitization is due to the phosphorylation of the G protein-coupled receptor via G-protein receptor kinases or protein kinase A, which results in the binding of β -arrestins that uncouple this complex [35]. Ultimately, there is internalization and loss of the G-protein-coupled receptor. Counter regulatory pathways are also activated to mitigate this response. Phosphorylation, for instance, leads to conversion of G_s proteins to G_i proteins with the net effect of decreasing cAMP and counterbalancing the effects of activated G_s proteins. The β -arrestin also directly signals counter-regulatory pathways [35]. The net overall effect in heart failure with adrenergic overstimulation is increased cytosolic calcium via these mechanisms, which results in adverse cardiac remodeling, including myocyte hypertrophy, apoptosis, fibrosis and extracellular matrix proliferation (Figure 1) [12,36].

The latest receptor to be discovered to play a role in this process is the β -3 adrenergic receptor, which was discovered in the myocardium in 1996 [37]. The β -3 receptor is coupled to a G_i protein that is influenced by nitric oxide synthesis. In heart failure, there is an increased upregulation of β -3 adrenergic receptors, which increases cGMP. cGMP activates phosphodiesterases that decrease cAMP and activate protein kinases that mediate pathways that decrease the amount and effect of calcium. Both of these mechanisms counterbalance the effects of β -1 adrenergic receptor stimulation and, thus, attempt to slow the progression of heart failure [38]. An integral feature of the β -3 adrenergic receptor is the lack of phosphorylation sites, which makes the β -3 adrenergic receptor resistant to catecholamine desensitization [38,39]. The importance of this receptor is still under investigation with the aim of developing new therapies.

Unique aspects of heart failure pathophysiology in pediatrics

Cardiac pathophysiology in the setting of heart failure is well defined in adults. However, there may be additional factors in the pediatric population to consider that may contribute to, or alter the progression of, heart failure. These differences are not only due to younger age but to disease states that may affect the myocardium differently.

The first difference is the impact of younger age on the cardiovascular and neurohormonal systems. It is well-documented that the newborn heart is 'immature' and that continued development occurs through the first year of life [40–42]. This includes cardiac myocyte hyperplasia, changes in ion transporter density, development of the T-tubule system, and maturation of the sarcoplasmic reticulum. All of these changes affect calcium regulation, which results in neonatal hearts tending to be 'stiffer' [42,43]. The variability in the degrees of myocyte maturation at the cellular and molecular level leads to potential differences in baseline cardiac function. Therefore, the timing of heart failure in pediatric patients may be important, particularly under 1 year of age as there is a potential for cardiac regeneration and differences in the efficacy of downstream β -adrenergic signaling.

Specific changes can also be seen in the β -adrenergic system that may be important. Neonates tend to have higher sympathetic tone, which results in increased density of adrenergic receptors that decrease over time [43,44]. This can be further altered by the presence of congenital heart lesions at various ages, which have been demonstrated to cause downregulation of β -adrenergic receptors, preferentially β -1 adrenergic receptors, at baseline and after cardiac surgery [45–55]. This could conceivably alter the effect of β -blocker therapy and its ability to blunt the maladaptive adrenergic responses observed in heart failure in pediatric patients and in those with congenital heart disease.

The impact of abnormal cardiac development may also be important owing to the potential implications of differences in ventricular morphology (e.g., left vs right ventricle) and location (e.g., systemic vs nonsystemic ventricle). Cardiac development and β -adrenergic receptor development occur during the first trimester of pregnancy, and congenital heart disease may alter this process. In normal hearts, there has been no detectable difference in the distribution and density of β -1 and β -2 adrenergic receptors between right and left ventricles [34]. However, it has been demonstrated that there are significant differences in gene expression for hypertrophy signaling pathways between the right and left ventricle in congenital heart disease. The expression of genes for angiotensin, adrenergic receptors, G-proteins, cyto-skeleton and contractile components are lower and expression of growth factors higher in the right ventricle compared with the left ventricle in patients with congenital heart disease [56]. This leads to the hypothesis that the right ventricle may have a weaker ability to adapt to compensate for heart failure [56]. This may confer differences with regard to timing of heart failure and responsiveness to β -blocker therapy.

The etiologies of heart failure in children are vastly different and more diverse than in the adult population. This may result in significant alterations in the pathophysiology of heart failure. For instance, recent work has shown that carvedilol may have a cardioprotective effect in preventing anthracycline-induced cardiomyopathy [57]. The mechanism is unknown but may perhaps work through its antioxidant effects in preventing free radical cardiac myocyte toxicity. However, its use in other conditions such as mitochondrial cardiomyopathy is less likely to result from this cardioprotective effect and may only confer improvement owing to an alteration of the neurohormonal system. By understanding how these different disease states lead to heart failure and alter the β -adrenergic system, we may be able to better determine the clinical course of, and response to, β -blocker therapy.

The question still remains as to whether these potential differences have any clinical relevance. Currently, multiple small studies suggest that β -blockers may be efficacious in some pediatric patients with heart failure, but not all patients respond equally or at all to therapy. Investigations into these matters may result in alterations in practice management of pediatric heart failure.

β -blockers

Based on our improved understanding of the neurohormonal mechanisms involved in heart failure, the use of β -blocker therapy has drastically changed. Its use in heart failure was first investigated in 1966 [58]. Since the importance of the neurohormonal system has been elucidated over the last two decades, the use of β -blockers has become a mainstay in heart failure management in order to blunt the adrenergic stimulation, which results in the cascade of events leading to adverse cardiac remodeling and congestive heart failure [59]. The current agents used and approved for heart failure fall into two major categories: second-generation 'selective' and third-generation 'non-selective' β -blockers [60,61].

The second-generation β -blockers are designed to be preferentially β -receptor selective. The agents in increasing order of β -1 selectivity are metoprolol tartrate, metoprolol succinate, bisoprolol and nebivolol. At high doses, these agents lose their β -selectivity properties and their potential benefit may be altered [61,62]. Several of the newer agents have been shown to have additional properties, including anti-oxidant effects, as observed with nebivolol and bisoprolol, and vasodilator effects, observed with nebivolol. Currently, metoprolol succinate and bisoprolol are approved for heart failure management in adults, with only metoprolol usage being reported and investigated in pediatrics.

The third-generation β -blockers are non-selective agents that attempt to counteract the adrenergic system at multiple sites. Both carvedilol and bucindolol have β -1, β -2 and α -1 blockade. There have also been proven antioxidant, antiapoptotic, vasodilatory and myocyte energy utilization effects with carvedilol [63–67]. Bucindolol lacks these additional properties except for vasodilatation, but also has intrinsic sympathomimetic activity, which may ultimately limit its efficacy [68]. The limited impact of bucindolol can also be connected to race after the β -Blocker Evaluation of Survival Trial (BEST) demonstrated a lack of survival benefit in black patients compared with non-black patients, raising the question of whether genetic variations in these subpopulations led to disparate findings [27]. To date, the only head-to-head comparison amongst these agents has been the comparison of carvedilol to metoprolol tartrate, which demonstrated carvedilol to be superior, causing an additional reduction in all-cause mortality by 6% and an increase in median survival by 1.4 years based on extrapolation (Figure 2) [30].

As can be seen, the number of agents available is limited. The future of β -blocker therapy may need to focus on the development of harnessing these additional benefits and providing a more 'balanced' blunting of the adrenergic system by including modulation of the β -3 adrenergic receptors [69,70]. In the meantime, we will need to optimize our current armament of drugs through investigations into the pharmacogenetics and pharmacokinetics of β -blockers.

Pharmacogenomics & pharmacokinetics & heart failure

Currently, our dosing guidelines for β -blocker therapy in children were extrapolated from adult trials that have demonstrated dose-dependent effects, but this has resulted in a wide dosing range to be utilized in pediatrics [17–19,71]. However, these assumptions may not be correct. Based on a recent pharmacokinetic study of carvedilol, there appears to be a need for even higher and/or more frequent dosing in pediatrics [72,73]. Of particular interest has

been the recent finding of significant genetic variability in the CYP2D6 enzyme, the main metabolizer of β -blockers. This can result in variable enzymatic function leading to inadequate dosing and unpredictable responsiveness to therapy [74]. The role of this enzyme in pediatrics is not well established, but a single study to address this revealed no difference in carvedilol clearance based on enzyme activity [73]. Further investigation of β -blockers with regard to pharmacokinetics in our complex and heterogeneous pediatric population is needed.

The newest frontier in heart failure management is the emerging role of pharmacogenetics in understanding therapeutic variations and clinical outcomes in adults with heart failure [75]. Single nucleotide polymorphisms (SNPs) have been shown to result in functional changes in β -1 adrenergic receptors, β -2 adrenergic receptors and G-protein receptor kinase 5 [76]. These polymorphisms have racial variability and may partially explain the altered response to therapy in ethnic groups such as African-Americans. The two most studied and significant SNPs to date have been the β -1 adrenergic receptor Arg/Gly 389 and the G-protein receptor kinase 5 Gln/Leu 41 [76].

The β -1 Arg389 exhibits a threefold increase in adrenergic activity due to a higher affinity for coupling between the Gs protein and adenylyl cyclase. The SNP that results in Gly at position 389 results in loss of this function. This change at the molecular level has also been shown to confer clinical differences as well. Patients with heart failure who are Arg389 homozygous demonstrate higher peak oxygen consumption compared with those who were homozygous Gly389 [77]. This difference was also seen with improvements in ventricular function in patients with Arg389 who were treated with metoprolol or carvedilol [78,79]. The largest study to date to elucidate the effects of SNPs in heart failure has been a substudy on the patient cohort from the BEST trial, which originally showed no improvement in heart failure with bucindolol [27]. Re-evaluation based on DNA analysis demonstrated a clear difference in survival benefit when stratified into Arg389 versus Gly389 homozygous groups [80]. The β -1 Arg389 group treated with bucindolol had improved survival by 38% (HR: 0.62; 95% CI: 0.4–0.96; $p = 0.03$) and decreased hospitalization by 36% (HR: 0.64; 95% CI: 0.46–0.88; $p = 0.006$) compared with the Gly 389 group or the placebo group (Figure 3). Smaller studies with carvedilol and metoprolol have yet to confirm these findings [81–83]. The GRK5 Gln/Leu41 polymorphism also results in alterations in the β -adrenergic signaling pathway. The polymorphism from Gln41 to Leu41 results in a gain of function mutation leading to increased phosphorylation of β -adrenergic receptors. This results in desensitization and downregulation of the receptors, and thus diminished adrenergic signaling [76]. Ultimately, genetic polymorphisms such as these demonstrate the potential impact of these SNPs on phenotypic expression of clinical heart failure and differences in efficacy of drug therapy. The clinical utility of this new information in a prospective manner is yet to be determined.

Clinical studies of β -blockers in pediatric heart failure

The use of β -blocker therapy for the treatment of heart failure in adults with ischemic and non-ischemic cardiomyopathy has been well established. Clinical trials of adults have shown that second- and third-generation agents such as nebivolol, metoprolol succinate, bisoprolol, bucindolol and carvedilol produce improvement in symptoms, functional status, ventricular function, quality of life, hospitalizations and mortality [14–32,84]. Based on these results, the use of β -blocker therapy in adults is now incorporated into clinical practice and, with continued efficacy, has gained acceptance for investigation in pediatrics.

Early work with β -blocker therapy in pediatrics investigated the use of propranolol, a first-generation agent, in the treatment of heart failure in pediatric patients secondary to

congenital heart disease with volume overload due to left to right shunt lesions [47,52,85–87]. Children treated with propranolol showed improvement in symptoms and functional class and decreases in the neurohormonal activation as manifested by lower resting heart rates and increased heart rate variability.

Several small retrospective studies and case series using the second-generation β -blocker metoprolol in pediatric patients with a variety of etiologies for heart failure again demonstrated improvement in functional class and/or in ventricular function [88,89]. The largest cohort was a retrospective study evaluating the experience at three institutions where a total of 15 patients with heart failure were treated for an average of 2 years. The functional class in eight of the 11 patients improved and the average ejection fraction increased from 25 to 41% [90]. With the advent of third-generation agents, such as carvedilol, the investigation of this drug increased as suggestions of its superiority to previous agents and additional cardioprotective properties became known [30,31,84,91,92].

Based on the early experience and promise with carvedilol in adults, this third-generation β -blocker has become the most extensively studied β -blocker in pediatric heart failure. The initial retrospective reports suggested improvement in ventricular function and symptoms [93–97]. The largest retrospective study was conducted by Bruns *et al.* who reviewed the experience at six institutions caring for a total for 46 patients, 37 with dilated cardiomyopathy and nine with congenital heart disease [94]. After 3 months of therapy with a dose of 0.8–1.5 mg/kg/day divided twice-daily, there was a significant improvement in ejection fraction from 32 to 41%, left ventricular shortening from 16 to 19%, and modified New York Heart Association (NYHA) class in 67% of patients. There was a significant adverse outcome rate of 30%, defined as death (one patient), transplant (12 patients) and placement on a ventricular assist device (one patient). The retrospective nature of this report and the lack of a control group makes any interpretation of the beneficial effects and adverse outcomes associated with carvedilol difficult.

Several prospective studies have since been conducted to evaluate efficacy of carvedilol therapy with regard to left ventricular function, patient symptoms and/or mortality [72,98–101]. An early prospective study was performed as an open-label, prospective trial on 15 children with heart failure stabilized on conventional therapy for 1 month prior to enrolment [72]. The group consisted of ten patients with dilated cardiomyopathy and five with congenital heart disease who had an average follow-up of 5 months after being on maximal therapy of 0.7 mg/kg/day divided twice-daily. This study showed there was significant improvement in ejection fraction from 36 to 54%, left ventricular shortening from 18 to 26%, and in symptoms demonstrated by a Ross heart failure score decreasing from 4.6 to 2.8. There were no significant adverse events reported in this trial.

The first prospective, randomized, double-blinded, placebo-controlled trial was performed at a single institution on a total of 22 children with dilated cardiomyopathy with a left ventricular ejection fraction of less than 30% with heart failure despite at least 2 months of conventional therapy [98]. A total of 14 patients received therapy and eight received placebo. After an average follow-up of 19 months on 0.2 mg/kg/day divided twice-daily, there was significant improvement in ejection fraction from 18 to 35%, left ventricular shortening from 14 to 21%, and improvement in symptoms from NYHA class IV in all patients to NYHA Class I in eight patients and class II in one patient with no change in the placebo group. The adverse outcomes were notable for four deaths in the carvedilol group and two deaths in the placebo group. Of the four deaths, three occurred in the up-titration period with a mean dose of 0.04 mg/kg/day; a total of three patients from the entire cohort received a heart transplant. The study was underpowered to detect any causal relationship between death and carvedilol. Another multi-center, prospective trial was conducted on a

total of 20 patients [99]. The subgroup of 12 patients with dilated cardiomyopathy when compared with untreated historical controls after 6 months of therapy on 0.8 mg/kg/day of carvedilol revealed a significant improvement in ejection fraction from 31 to 40%, left ventricular shortening, and a trend of longer time to death and/or transplant. Of the eight patients with congenital heart disease, three showed 'improvement', three had no change, one received a transplant and one was withdrawn. The interpretation of the efficacy in this small heterogeneous group, which included patients with a variety of congenital heart disease including those with a single systemic right ventricle, was difficult.

The only multicenter, randomized, placebo-controlled trial to be performed in pediatric heart failure in a similar fashion as to the landmark adult trials was conducted over a 5-year span involving 26 centers and a total of 161 patients [100]. The study was designed to determine the effects of carvedilol on pediatric patients with symptomatic chronic heart failure who had a left ventricular ejection fraction of less than 40% or qualitative ventricular dilation and moderate systemic ventricular dysfunction in patients with a single ventricle or systemic right ventricle. The study included 95 patients with dilated cardiomyopathy and 66 with congenital heart disease who were enrolled in one of three arms: placebo, low-dose carvedilol (0.4 mg/kg/day divided twice-daily), or high-dose carvedilol (0.8 mg/kg/day divided twice-daily). The average follow-up was 6 months on goal therapy with the primary end point being a composite measure of clinical heart failure. The study showed no difference between groups in a composite clinical end point of worsened, improved or unchanged. The secondary end points of functional class, left ventricular ejection, and brain natriuretic peptide levels also showed no difference. The outcomes of this study differ from those previously seen in pediatrics as well as the numerous large adult trials. The reasons for this are almost certainly multifactorial, but may include inadequate sample size, the heterogeneity of the cohort, the unexpectedly high improvement rate seen in the patients not treated with β -blockers, the unexpectedly high enrolment of patients with only mild (class 2) heart failure symptoms and/or the duration of the study and its possible effect on the ability to detect the differences in the primary end point of composite measure of clinical failure. A recent study evaluating the pharmacokinetics of carvedilol suggested that the dosing may have been suboptimal in order to see the benefits of the medication [73]. Of note, there was a noticeable trend in improvement in ventricular remodeling in those patients with a morphologic left ventricle compared with those whose systemic ventricle was not a left ventricle, again raising the suspicion that the response to β -blocker therapy in heart failure may vary depending upon ventricular morphology (Figure 4). The challenges associated with investigating β -blocker therapy in children with heart failure are many and will undoubtedly continue due to sample size limitations and heterogeneity in this population. Thus, the likelihood of head to head trials and the investigation of newer agents will be difficult. Based on these studies, including the subanalyses of the patients with a systemic left ventricle in the multi-center, randomized, carvedilol trial, there may be benefits to the use of carvedilol in left ventricular remodeling in children with heart failure who have a systemic left ventricle.

New studies in congenital heart disease & pediatric cardiomyopathy

Recent investigations have focused on understanding the impact of β -blockers in congenital heart disease, particularly as pediatric patients begin to reach young adulthood [102]. The research in this area has been limited but is expanding. Several studies on the effects of β -blocker therapy on systemic right ventricular dysfunction have shown mixed results [99,103–105].

Systemic right ventricular dysfunction is well known in patients with transposition of the great arteries after atrial switch operation and in congenitally corrected transposition [106–

110]. Several retrospective analyses have suggested that β -blockers may cause functional and clinical improvement in these patients [103–105]. The largest cohort studied was a retrospective analysis of 60 patients with transposition of the great arteries who underwent an atrial switch operation [110]. A total of 31 patients were treated with metoprolol or carvedilol and 29 were used as historical controls. The baseline median clinical status of the treatment group was NYHA class II. The only difference in the baseline groups were the increased use of spironolactone and pacemakers in the treatment group. The mean follow-up was an average of 4 months and analyses showed no significant change in RV end diastolic area, RV ejection fraction or tricuspid regurgitation. The control group, however, did show a statistically significant increase in RV end diastolic area (cm^2) from 40 to 44, which could be hypothesized to be due to the lack of prevention of β -adrenergic-induced adverse cardiac remodeling. Of interest is that β -blockers showed no significant improvement in NYHA class after adjustment for pacemaker therapy. However, the patients with pacemakers showed improvement in NYHA class compared with those without a pacemaker, which is likely owing to the effects of pacemaker therapy on improving heart failure [111].

The investigation into the management of heart failure in the growing single ventricle population who have undergone the Fontan operation has been garnering more attention following the increased survival of Fontan patients and their development of chronic heart failure [106,112,113]. A case report of a patient with severe heart failure after the Fontan operation demonstrated improvement in systolic and diastolic function, symptoms and functional class after 1 year of β -blocker therapy, at which time the patient was reverted back to a total cavopulmonary connection. The role of carvedilol or other β -blockers in this disease state is yet to be determined [114].

The role of nonsystemic subpulmonary right ventricle dysfunction has also been evaluated owing to the development of significant morbidity in the population of patients with Tetralogy of Fallot [115,116]. A prospective, randomized, placebo-controlled trial to assess the effects of 6 months of bisoprolol demonstrated no difference in ventricular function in patients with asymptomatic or mildly symptomatic heart failure [115].

Investigations into the role of β -blocker therapy has also expanded into the area of heart failure prevention. Trials in children and adults have suggested possible efficacy of metoprolol and carvedilol in anthracycline-induced cardiomyopathy [88,90,117]. A recent study investigated the role of carvedilol as a cardioprotective agent against the development of anthracycline-induced cardiomyopathy [57]. In this study, 50 patients were randomized in a single-blinded, placebo-controlled manner in which 25 patients were administered carvedilol once-daily prior to and for 6 months during chemotherapy. The study demonstrated that there was no change in ejection fraction in the treatment group, but there was a significant decrease in ejection fraction from 69 to 52% in the untreated group. This suggests that carvedilol may have a cardio-protective effect that counteracts the cardiotoxic effects of this chemotherapeutic agent [118,119]. These same principles are also being applied to other disease states such as Duchenne muscular dystrophy. Currently, in Japan there is a clinical trial examining low-dose daily carvedilol in the prevention of cardiac dysfunction after previous data suggested that carvedilol may improve ventricular function after the onset of cardiomyopathy [120–122].

Current state of clinical management in pediatric heart failure

Based on our current understanding of heart failure and the clinical trials that have ensued, there is strong evidence supporting the use of β -blockers in adults with heart failure. The American Heart Association/American College of Cardiology guidelines from 2009 recommended β -blockers – bisoprolol, carvedilol and sustained-release metoprolol succinate

– for all stable patients with current or prior symptoms of congestive heart failure and a reduced left ventricular ejection fraction unless contraindicated (class 1 recommendation, level of evidence A) [123]. This includes NYHA class I to IV patients but excludes stage D refractory end-stage heart failure. Similar recommendations in heart failure management for pediatric and congenital heart disease patients are lacking owing to limited data.

The only published set of consensus guidelines for the management of pediatric heart failure comes from the International Society of Heart and Lung Transplantation in 2004 [7]. Based on limited data and expert opinion, the use of β -blockers is contraindicated in stage D heart failure. However, no recommendations are made regarding its use in patients with current or prior symptoms of heart failure and/or abnormal cardiac morphology or function. Rather, consideration should be taken into the involvement of a heart failure or heart transplantation referral center prior to initiation of β -blocker therapy in infants and children with heart failure.

Our institutional experience has been in keeping with these guidelines regarding indications for initiating therapy. In children with stable, symptomatic heart failure secondary to systemic left ventricular dysfunction, it is reasonable to provide the family with what evidence exists to support or to refute the use of β -blockers in this clinical situation. Based on trials in adults and children, and based on our experience, we believe it is also reasonable to consider the use of carvedilol or another β -blocker therapy in this group of patients. It may then be necessary to help the family decide if they would like to institute this therapy. In the presence of a systemic ventricle that is not a left ventricle, the potential benefits from this medication are much less clear. Extrapolating from adult dosing, our experience has been to start with a dose of 0.05 mg/kg/dose twice-daily. We continue to up-titrate every 2 weeks by doubling the dose until we reach a goal dose of 0.4 mg/kg/dose twice-daily. In stable patients, up-titration can occur as an outpatient, but with every dosing adjustment patients are monitored for 2 hours to assess for symptoms of hypotension or bradycardia [124]. There has been recent evidence that the dosing may need to be higher based on physiological changes that occur with aging [71–73].

Conclusion

The role of β -blocker therapy is well established and investigated in the adult population with heart failure. This has led to increased utilization in the pediatric population despite the lack of well-established studies proving its benefit in terms of mortality, hospitalizations, quality of life and progression of disease. Despite the vast heterogeneity of etiologies leading to heart failure, the common pathway appears to be the maladaptive changes that occur with chronic β -adrenergic stimulation to preserve cardiac output. The ability to blunt this signaling process with β -blockade has been shown to not only lead to measurable changes at the cellular level, but also to improve clinical outcome in adults. Ultimately, by investigating the differences between adult and pediatric heart failure as well as differences in the wide variety of disease states, we will hopefully be able to provide better and more disease-specific management strategies.

Future perspective

The use of β -blocker therapy in pediatric heart failure will continue to lag behind the advances being established in the adult population. Owing to heterogeneity and lack of patient sample sizes, there will continue to be difficulty in conducting large, randomized, placebo-controlled clinical trials to elucidate the true benefits of therapy. The development of disease-specific targeted therapy will become of greater importance in attempts to overcome these inherent difficulties. In order for this to occur, there must be a greater effort

to understand the differences in heart failure in this heterogeneous pediatric population at a genetic, molecular and cellular level. This may lead to the realization of targeted selective β -blocker therapy in the pediatric population and the utilization of pharmacogenetics to optimize management. For instance, a patient with a single systemic right ventricle such as that seen with hypoplastic left heart syndrome after a Fontan operation may benefit from a different β -blocker agent or dosage compared with a child with dilated cardiomyopathy secondary to Duchenne's muscular dystrophy. The ability to create 'designer' β -blockers with varying degrees of β -1, β -2, β -3 and α -adrenergic effects may also help re-establish a 'normal' adrenergic state that can help reverse and/or prevent the maladaptive cardiac changes evident in heart failure. The use of β -blockers may be further expanded to include patients with more severe heart failure and potentially those requiring inotropic support if novel β -antagonistic agents become available. Finally, the role of preventative therapy will likely expand as we begin to understand which disease states will have high incidences of heart failure. This may include utilization in cancer patients to prevent chemotherapy-induced cardiomyopathy. β -blockers will ultimately have an expanding role in the future as our population of heart failure patients increases and, thus, continued investigation into this area will be of critical importance.

Bibliography

Papers of special note have been highlighted as:

- of interest

1. Towbin JA, Lowe AM, Colan SD, Sleeper LA, et al. Incidence, causes and outcomes of dilated cardiomyopathy in children: findings from the Pediatric Cardiomyopathy Registry. *JAMA*. 2006; 296(15):1867–1876. [PubMed: 17047217]
2. Nugent AW, Daubeney PE, Chondros P, et al. The epidemiology of childhood cardiomyopathy in Australia. *N Engl J Med*. 2003; (348):1639–1646. [PubMed: 12711738]
3. Hoffman J, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol*. 2002; 39(12): 1890–1900. [PubMed: 12084585]
4. Kay JD, Colan SD, Graham TP. Congestive heart failure in pediatric patients. *Am Heart J*. 2001; 142(5):923–928. [PubMed: 11685182]
5. Kirk R, Edwards LB, Aurora P, et al. Registry of the International Society of Heart and Lung Transplantation: Eleventh Official Pediatric Heart Transplantation Report – 2008. *J Heart Lung Transplant*. 2008; 27(9):970–977. [PubMed: 18765188]
6. Harmon WG, Sleeper LA, Cuniberti L, et al. Treating children with idiopathic dilated cardiomyopathy (from the Pediatric Cardiomyopathy Registry). *Am J Cardiol*. 2009; 104(2):281–286. [PubMed: 19576361]
7. Rosenthal D, Chrisant M, Eden E, et al. International Society for Heart and Lung Transplantation: Practice guidelines for management of heart failure in children. *J Heart Lung Transplant*. 2004; 23(12):1313–1333. The only published consensus guidelines on the management of pediatric heart failure that are based on expert opinion and limited pediatric data. [PubMed: 15607659]
8. Shaddy RE. Paediatric heart failure trials.. and tribulations. *Cardiol Young*. 2007; 17:354–355. [PubMed: 17572938]
9. Bristow MR. Mechanisms of action of β -blocking agents in heart failure. *Am J Cardiol*. 1997; 80(11A):26L–40L.
10. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling—concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. behalf of an International Forum on Cardiac Remodeling. *J Am Coll Cardiol*. 2000; 35(3):569–582. [PubMed: 10716457]
11. Colucci WS, Sawyer DB, Singh K, Communal C. Adrenergic overload and apoptosis in heart failure: implications for therapy. *J Card Fail*. 2000; 6(2 Suppl 1):1–7. [PubMed: 10908092]
12. Port JD, Bristow MR. Altered β -adrenergic receptor gene regulation and signaling in chronic heart failure. *J Mol Cell Cardiol*. 2001; 33(5):887–905. [PubMed: 11343413]

13. Floras J. Sympathetic nervous system activation in human heart failure: clinical implications of an updated model. *J Am Coll Cardiol.* 2009; 54(5):375–385. [PubMed: 19628111]
14. Gilbert EM, Anderson JL, Deitchman D, et al. Long-term β blocker vasodilator therapy improves cardiac function idiopathic dilated cardiomyopathy: a double-blinded randomized study of bucindolol vs placebo. *Am J Med.* 1990; 88(3):223–228. [PubMed: 1968710]
15. Waagstein F, Bristow MR, Swedberg K, et al. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy Metoprolol in Dilated Cardiomyopathy (MDC) Trial. *Lancet.* 1993; 342(8885): 1441–1446. [PubMed: 7902479]
16. CIBIS Investigators. A randomized trial of β -blockers in heart failure The Cardiac Insufficiency Bisoprolol Study. *Circulation.* 1994; 90:1765–1773. [PubMed: 7923660]
17. Bristow MR, Gilbert EM, Abraham WT. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure MOCHA Investigators. *Circulation.* 1996; 94(11):2807–2816. [PubMed: 8941106]
18. Colucci WS, Packer M, Bristow MR, et al. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure US Carvedilol Heart Failure Study Group. *Circulation.* 1996; 94(11):2800–2806. [PubMed: 8941105]
19. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med.* 1996; 334(21):1349–1355. [PubMed: 8614419]
20. Packer M, Colluci WS, Sankner-Bernstein JD, et al. Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure The PRECISE Trial Prospective randomized evaluation of carvedilol on symptoms and exercise. *Circulation.* 1996; 94(11):2793–2799. [PubMed: 8941104]
21. Lechat P, Escolano S, Golmard JL, et al. Prognostic value of bisoprolol-induced hemodynamic effects in heart failure during the Cardiac Insufficiency Bisoprolol study (CIBIS). *Circulation.* 1997; 96:2197–2205. [PubMed: 9337190]
22. CIBIS II Investigators. The Cardiac Insufficiency Bisoprolol study (CIBIS-II). *Lancet.* 1999; 353:9–13. [PubMed: 10023943]
23. Hjalmarson A, Goldstein S, Fagerberg B, et al. Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL randomized intervention trial in congestive heart failure. *Lancet.* 1999; 353:2001–2007. [PubMed: 10376614]
24. Hjalmarson A, Goldstein S, Fagerberg B, et al. Effect of controlled-release metoprolol on total mortality, hospitalization and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure MERIT-HF Study Group. *JAMA.* 2000; 283:1295–1302. [PubMed: 10714728]
25. Fowler MB, Vera-Lluch M, Oster G, et al. Influence of carvedilol on hospitalizations in heart failure: incidence, resource utilization and costs U.S Carvedilol Heart Failure Study Group. *J Am Coll Cardiol.* 2001; 37:1692–1699. [PubMed: 11345386]
26. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure Carvedilol Prospective Randomized Cumulative Survival study group. *N Engl J Med.* 2001; 344(22):1651–1658. [PubMed: 11386263]
27. BEST Trial Investigators. A trial of the β -blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med.* 2001; 344(22):1659–1667. [PubMed: 11386264]
28. Leizorovicz A, Lechat P, Cucherat M, et al. Bisoprolol for the treatment of chronic heart failure: a meta-analysis on individual data of two placebo-controlled studies – CIBIS and CIBIS II Cardiac Insufficiency Bisoprolol Study. *Am Heart J.* 2002; 143:301–307. [PubMed: 11835035]
29. Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study group. *Circulation.* 2002; 106:2194–2199. [PubMed: 12390947]
30. Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomized control trial. *Lancet.* 2003; 362:7–13. A total of 3029 patients with heart failure (NYHA II–IV), a prior admission for cardiovascular reasons, and a left ventricular ejection fraction of less than 35% were randomized to metoprolol tartrate or carvedilol and

showed a reduction in all-cause mortality in the carvedilol group; 34% (512 of 1511) for carvedilol and 40% (600 of 1518) for metoprolol. [PubMed: 12853193]

31. Poole-Wilson PA. Commentary on the Carvedilol or Metoprolol European Trial (COMET). *Am J Cardiology*. 2004; 93(9A):40B–2B.
32. Flather MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J*. 2005; 26(3):215–225. [PubMed: 15642700]
33. Mann DL, Bristow MR. Mechanisms and models in heart failure: the biomechanical model and beyond. *Circulation*. 2005; 111:2837–2849. [PubMed: 15927992]
34. Bristow MR, Ginsburg R, Umans V, et al. β 1- and β 2-adrenergic-receptor subpopulations in nonfailing and failing human ventricular myocardium: coupling of both receptor subtypes in muscle contraction and selective β 1-receptor down-regulation in heart failure. *Circ Res*. 1986; 59(3):297–309. A total of 48 human hearts from recipients and donors were investigated and revealed the ratio of β 1 to β 2 adrenergic receptors to be 77:23 in the nonfailing heart and 60:38 in the failing heart. [PubMed: 2876788]
35. Patel PA, Tilley DG, Rockman HA. β -arrestin-mediated signaling in the heart. *Circ J*. 2008; 72:1725–1729. [PubMed: 18838825]
36. Pleger ST, Boucher M, Most P, Koch WJ. Targeting myocardial β -adrenergic receptor signaling and calcium cycling for heart failure gene therapy. *J Cardiac Fail*. 2007; 13:401–414.
37. Gauthier C, Tavernier GC, Langin D, Le Marec H. Functional β 3-adrenoceptor in the human heart. *Clin Invest*. 1996; 98:556–562.
38. Gauthier C, Seze-Goismier C, Rozee B. β -3 adrenoreceptors in the cardiovascular system. *Clin Hemrheol Microcirc*. 2007; 37:193–204.
39. Liggett SB, Freedman NJ, Schwinn DA, Lefkowitz RJ. Structural basis for receptor subtype-specific regulation revealed by a chimeric β -3/ β -2 adrenergic receptor. *Proc Natl Acad Sci*. 1993; 90:3665–3669. [PubMed: 8386380]
40. Hort W. Quantitative histologische untersuchungen an wachsenden herzen. *Virchows Arch*. 1953; 323:223–242. [PubMed: 13078214]
41. Zak R. Development and proliferative capacity of cardiac muscle cells. *Circ Res*. 1974; 35:17–26. [PubMed: 4276486]
42. Mahony, L. Development of myocardial structure and function. In: Allen, HD.; Driscoll, DJ.; Shaddy, RE.; Feltes, TF., editors. *Moss and Adams' Heart Disease in Infants, Children, and Adolescents*. 7. Vol. 1. Lippincott Williams & Wilkins; PA, USA: 2008. p. 573-592.
43. Wittnich C, Belanger MP, Bandali K. Are there ventricle-specific postnatal maturational differences in myocardial β -adrenoceptors? *Can J Physiol Pharmacol*. 2006; 84:859–865. [PubMed: 17111030]
44. Teitel DF, Sidi D, Chin T. Developmental changes in myocardial contractile reserve in the lamb. *Pediatr Res*. 1985; 19(9):948–955. [PubMed: 4047765]
45. Kozlik R, Kramer HH, Wicht H, Krian A, Ostermeyer J, Reinhardt D. Myocardial β -adrenoreceptor density and the distribution of β 1- and β 2-adrenoreceptor subpopulations in children with congenital heart disease. *Eur J Pediatr*. 1991; 150:388–394. A total of 26 pediatric patients with congenital heart disease undergoing surgery had assessment of myocardial β -adrenoceptor density, which revealed downregulation of the β 1-receptor and no significant change in the β 2-receptor density. [PubMed: 1645667]
46. Kozlik R, Kramer HH, Wicht H, Bircks W, Reinhardt D. β -adrenoreceptor density on mononuclear leukocytes and right atrial myocardium in infants and children with congenital heart disease. *Klin Wochenschr*. 1991; 69:910–916. [PubMed: 1665527]
47. Kozlik-Feldman R, Kramer HH, Wicht H, Feldmann R, Netz H, Reinhardt D. Distribution of myocardial β -adrenoceptor subtypes and coupling to the adenylate cyclase in children with congenital heart disease and implications for treatment. *J Clin Pharmacol*. 1993; 33(7):588–595. [PubMed: 8396157]
48. Dzimiri N, Galal O, Moorji A, et al. Regulation of sympathetic activity in children with various congenital heart diseases. *Pediatr Res*. 1995; 38(1):55–60. [PubMed: 7478797]

49. Wu JR, Chang HR, Huang TY, Chiang CH, Chen SS. Reduction in lymphocyte β -adrenergic receptor density in infants and children with heart failure secondary to congenital heart disease. *Am J Cardiol.* 1996; 77:170–174. [PubMed: 8546086]
50. Reithmann C, Reber D, Kozlik-Feldmann R, et al. A post-receptor defect of adenylyl cyclase in severely failing myocardium from children with congenital heart disease. *Eur J Pharmacol.* 1997; 330:79–86. [PubMed: 9228416]
51. Ohuchi H, Hasegawa S, Yasuda K, et al. Severly impaired cardiac autonomic nervous activity after the Fontan operation. *Circulation.* 2001; 104:1513–1518. [PubMed: 11571245]
52. Buchhorn R, Hulpke-Wette M, Ruschewski W, et al. β -receptor downregulation in congenital heart disease: a risk factor for complications after surgical repair? *Ann Thorac Surg.* 2002; 73(2):610–613. [PubMed: 11845882]
53. Davos CH, Davlouros PA, Wensel R, et al. Global impairment of cardiac autonomic nervous activity late after repair of Tetralogy of Fallot. *Circulation.* 2002; 106(12 Suppl 1):I69–75. [PubMed: 12354712]
54. Bolger AP, Sharma R, Li W, et al. Neurohormal activation and the chronic heart failure syndrome in adults with congenital heart disease. *Circulation.* 2002; 106(1):92–99. [PubMed: 12093776]
55. Davos CH, Francis DP, Leenarts MF, et al. Global impairment of cardiac autonomic nervous activity later after the Fontan operation. *Circulation.* 2003; 108(Suppl 1):II80–II85.
56. Kaufman BD, Desai M, Reddy S, et al. Genomic profiling of left and right ventricular hypertrophy in congenital heart disease. *J Cardiac Fail.* 2008; 14(9):760–767. A total of 18 pathologic specimens from patients with congenital heart disease and left ventricle and/or right ventricular hypertrophy were evaluated for 175 hypertrophy-signaling genes. This study demonstrated ventricular-specific variations in gene expression.
57. Kalay N, Basar E, Ozdogru I, et al. Protective effects of carvedilol against anthracycline-induced cardiomyopathy. *J Am Coll Cardiol.* 2006; 48:2258–2262. A total of 50 patients in whom anthracycline use was planned were randomized to carvedilol or placebo. Those receiving carvedilol demonstrated a cardioprotective effect based on preserved systolic and diastolic cardiac function assessed by echocardiography at 6 months follow-up. [PubMed: 17161256]
58. Stock JP. β adrenergic blocking drugs in the clinical management of cardiac arrhythmias. *Am J Cardiol.* 1966; 18:444–449. [PubMed: 4380738]
59. Hunt SA, Abraham W, Chin M, et al. ACC/AHA 2005 Guideline update for the diagnosis and management of chronic heart failure in the adult. *Circulation.* 2005; 112:E154–E235. [PubMed: 16160202]
60. Bruns LA, Canter CE. Should β -blockers be used for the treatment of pediatric patients with chronic heart failure? *Pediatr Drugs.* 2002; 4(12):771–778.
61. Foerster SR, Canter CE. Pediatric heart failure therapy with β -adrenoceptor antagonists. *Pediatr Drugs.* 2008; 10(2):125–134.
62. Zebrack JS, Munger M, MacGregor J, Lombardi WL, Stoddard GP, Gilbert EM. β -receptor Selectivity of Carvedilol and Metoprolol Succinate in Patients with Heart Failure (SELECT trial): a randomized dose-ranging trial. *Pharmacotherapy.* 2009; 29(8):883–890. [PubMed: 19637941]
63. Keating G, Jarvis B. Carvedilol: a review of its use in chronic heart failure. *Drugs.* 2003; 63(16):1697–1741. [PubMed: 12904089]
64. Okafor CC, Perreault-Micale C, Hajjar RJ, et al. Chronic treatment with carvedilol improves ventricular function and reduces myocyte apoptosis in an animal model of heart failure. *BMC Physiol.* 2003; 3(6):1–9. [PubMed: 12597777]
65. Gielser G, Lenihan DJ, Durand JB, et al. The update on the rationale, use and selection of β -blockers in heart failure. *Curr Opin Cardiol.* 2004; 19:250–253. [PubMed: 15096958]
66. Udelson JE. Ventricular remodeling in heart failure and the effect of β -blockade. *Am J Cardiol.* 2004; 93(9 Suppl 1):43–48.
67. Al-Hesayan A, Azevedo E, Floras J, et al. Selective versus nonselective β -adrenergic receptor blockade in chronic heart failure: differential effects on myocardial energy substrate utilization. *Eur J Heart Fail.* 2005; 7:618–623. [PubMed: 15921803]
68. Andreka P, Aiyar N, Olson LC, et al. Bucindolol displays intrinsic sympathomimetic activity in human myocardium. *Circulation.* 2002; 105:2429–2434. [PubMed: 12021232]

69. Gan RT, Li WM, Xiu CH. Chronic blocking of β 3-adrenoreceptor ameliorates cardiac function in rat model of heart failure. *Chinese Med J*. 2007; 120(24):2250–2255.
70. Moniette S, Balligand JL. Potential use of $\beta(3)$ -adrenoreceptor antagonists in heart failure therapy. *Cardiovasc Drug Rev*. 2002; 20(1):19–26. [PubMed: 12070531]
71. Greenway SC, Benson LN. The use of carvedilol in pediatric heart failure. *Cardiovasc Hematol Disord Drug Targets*. 2006; 6:35–42. [PubMed: 16724934]
72. Laer S, Mir TS, Behn F, et al. Carvedilol therapy in pediatric patients with congestive heart failure: a study investigating clinical and pharmacokinetic parameters. *Am Heart J*. 2002; 143(5):916–922. A population pharmacokinetic model for carvedilol reveals that dosing depends on age and weight and that higher doses are required. For instance, infants require 3 mg/kg/day to assess the same drug level as an adult receiving 0.7 mg/kg/day. [PubMed: 12040358]
73. Albers S, Meibohm B, Mir T, Laer S. Population pharmacokinetics and dose simulation of carvedilol in paediatric patients with congestive heart failure. *Br J Clin Pharmacol*. 2007; 65(4): 511–522. [PubMed: 17995971]
74. Azuma J, Nonen S. Chronic heart failure: β -blockers and pharmacogenetics. *Eur J Clin Pharmacol*. 2009; 63:3–17. [PubMed: 18839161]
75. Taylor MR. Pharmacogenetics of the human β -adrenergic receptors. *Pharmacogenetics J*. 2007; 7:29–37.
76. Dorn GW, Liggett SB. Mechanisms of pharmacogenomic effects of genetic variation within the cardiac adrenergic network in heart failure. *Mol Pharm*. 2009; 76:466–480.
77. Wagoner LE, Craft LL, Zengel P. Polymorphisms of the β 1-adrenergic receptor predict exercise capacity in heart failure. *Am Heart J*. 2002; 144:840–846. [PubMed: 12422153]
78. Miallet Perez J, Rathz DA, Petrashevskaya NN. β 1-adrenergic receptor polymorphisms confer differential function and predisposition to heart failure. *Nat Med*. 2003; 9:1300–1305. [PubMed: 14502278]
79. Molenaar P, Chen L, Semmler AB, et al. Human heart β -adrenoreceptors: β 1-adrenoreceptor diversification through affinity states' and polymorphism. *Clin Exp Pharmacol Physiol*. 2007; 34:1020–1028. [PubMed: 17714089]
80. Liggett S, Miallet-Perez J, Thaneemit-Chen S. A polymorphism within a conserved β 1 adrenergic receptor motif alters cardiac function and β -blocker response in human heart failure. *Proc Natl Acad Sci*. 2006; 103:11288–11293. [PubMed: 16844790]
81. White HL, de Boer RA, Maqbool A. An evaluation of the β 1-adrenergic receptor Arg389Gly polymorphism in individuals with heart failure: a MERIT-HF sub-st. *Eur J Heart Fail*. 2003; 5:463–468. [PubMed: 12921807]
82. de Groote P, Lamblin N, Helbecque N, et al. The impact of β -adrenoreceptor gene polymorphisms on survival in patients with congestive heart failure. *Eur J Heart Fail*. 2005; 7(6):966–973. [PubMed: 16227135]
83. Sehnert AJ, Daniels SE, Elashoff M, et al. Lack of association between adrenergic receptor genotypes and survival in heart failure patients treated with carvedilol and metoprolol. *J Am Coll Cardiol*. 2008; 52:644–651. [PubMed: 18702968]
84. Packer M, Antonopoulos GV, Berlin JA, Chittams J, Konstam MA, Underlson JE. Comparative effects of carvedilol and metoprolol on left ventricular ejection fraction in heart failure: results of a meta-analysis. *Am Heart J*. 2001; 141(6):899–907. [PubMed: 11376302]
85. Buchhorn R, Bartmus D, Siekmeyer W, Hulpke-Wette M, Schulz R, Bursch J. β -blocker therapy of severe congestive heart failure in infants with left to right shunts. *Am J Cardiol*. 1998; 81(11):366–368.
86. Buchhorn R, Hulpke-Wette M, Hilgers R, Bartmus D, Wessel A, Bursch J. Propranolol treatment of congestive heart failure in infants with congenital heart disease: the CHF-PRO-INFANT Trial. Congestive heart failure in infants treated with propranolol. *Int J Cardiol*. 2001; 79:167–173. [PubMed: 11461738]
87. Buchhorn R, Hulpke-Wette M, Ruschewski W. Effects of therapeutic β blockade on myocardial function and cardiac remodeling in congenital cardiac disease. *Cardiol Young*. 2003; 13(1):36–43. [PubMed: 12691286]

88. Shaddy RE, Olsen SL, Bristow MR, et al. Efficacy and safety of metoprolol in the treatment of doxorubicin-induced cardiomyopathy in pediatric patients. *Am Heart J.* 1995; 129(1):197–199. [PubMed: 7817916]
89. Shaddy RE. β -blocker therapy in young children with congestive heart failure under consideration for heart transplantation. *Am Heart J.* 1998; 136(1):19–21. [PubMed: 9665213]
90. Shaddy RE, Tani LY, Gidding SS, et al. β -blocker treatment of dilated cardiomyopathy with congestive heart failure in children: a multi-institutional experience. *J Heart Lung Transplant.* 1999; 18(3):269–274. [PubMed: 10328154]
91. Metra M, Giubbini R, Nodari S, Boldi E, Modena MG, Dei Cas L. Differential effects of β -blockers in patients with heart failure: a prospective, randomized, double-blinded comparison of the long-term effects of metoprolol versus carvedilol. *Circulation.* 2000; 102(5):546–551. [PubMed: 10920067]
92. Sanderson JE, Chan SK, Yip G, et al. β -blockade in heart failure: a comparison of carvedilol with metoprolol. *J Am Coll Cardiol.* 1999; 34(5):1522–1528. [PubMed: 10551702]
93. Williams RV, Tani LY, Shaddy RE. Intermediate effects of treatment with metoprolol or carvedilol in children with left ventricular systolic dysfunction. *J Heart Lung Transplant.* 2002; 21(8):906–909. [PubMed: 12163092]
94. Bruns LA, Chrisant MK, Lamour JM, et al. Carvedilol as a therapy in pediatric heart failure: an initial multicenter experience. *J Pediatr.* 2001; 138(4):505–511. [PubMed: 11295713]
95. Gachara N, Prabhakaran S, Srinivas S, Farzana F, Krishan U, Shah M. Efficacy and safety of carvedilol in infants with dilated cardiomyopathy: a preliminary report. *Indian Heart J.* 2001; 53(1):74–78. [PubMed: 11456146]
96. Lee KJ. Carvedilol in heart failure management: a pediatric experience. *Can J Cardiology.* 2001; 17(Suppl C):100C.
97. Rusconi P, Gomez-Marin O, Rossique-Gonzalez M, et al. Carvedilol in children with cardiomyopathy: 3-year experience at a single institution. *J Heart Lung Transplant.* 2004; 23(7):832–838. [PubMed: 15261177]
98. Azeka E, Franchini Ramires JA, Valler C, Alcides Bocchi E. Delisting of infants and children from the heart transplantation waiting list after carvedilol treatment. *J Am Coll Cardiol.* 2002; 40(11):2034–2038. [PubMed: 12475466]
99. Blume ED, Canter CE, Spicer R, Gauvreau K, Colan S, Jenkins KJ. Prospective single-arm protocol of carvedilol in children with ventricular dysfunction. *Pediatric Cardiol.* 2006; 27(3):326–342.
100. Shaddy RE, Boucek MM, Hsu DT, et al. Carvedilol for children and adolescents with heart failure. *JAMA.* 2007; 298(10):1171–1179. The only multicenter, randomized, placebo-controlled trial to be carried out in pediatric heart failure was conducted over a 5-year span involving 26 centers and a total of 161 patients. [PubMed: 17848651]
101. Bajcetic M, Kokic A, Djukic M, et al. Effects of carvedilol on left ventricular function and oxidative stress in infants and children with idiopathic dilated cardiomyopathy: a 12-month, two-center, open-label study. *Clin Ther.* 2008; 30(4):702–714. [PubMed: 18498919]
102. Vonder Muhll I, Liu P, Webb G. Applying standard therapies to new targets: the use of ACE inhibitors and β -blockers for heart failure in adults with congenital heart disease. *Int J Cardiol.* 2004; 97(Suppl 1):25–33. [PubMed: 15590076]
103. Lindenfeld J, Keller K, Campbell D, et al. Improved systemic ventricular function after carvedilol administration in a patient with congenitally corrected transposition of the great arteries. *J Heart Lung Transplant.* 2003; 22:198–201. [PubMed: 12581770]
104. Josephson C, Howlett J, Jackson S, et al. A case series of systemic right ventricular dysfunction post atrial switch for simple D-transposition of the great arteries: the impact of β -blockade. *Can J Cardiol.* 2006; 22(9):769–772. [PubMed: 16835671]
105. Doughan AR, McConnell ME, Book WM. Effect of β -blockers (carvedilol or metoprolol XL) in patients with transposition of great Arteries and dysfunction of the systemic right ventricle. *Am J Cardiol.* 2007; 99(5):704–706. A total of 31 patients with transposition of the great arteries who underwent an atrial switch operation were treated with metoprolol or carvedilol for systemic right

ventricular dysfunction and compared with historical controls revealing echocardiographic findings suggestive of right ventricular remodeling. [PubMed: 17317376]

106. McAlister FA, Ezekowitz J, Hooton N, et al. Cardiac resynchronization therapy for patients with left ventricular systolic dysfunction: a systemic review. *JAMA*. 2007; 297(22):2502–2514. [PubMed: 17565085]
107. Veldtman GR, Nishimoto A, Siu S, et al. The Fontan procedure in adults. *Heart*. 2001; 86:330–335. [PubMed: 11514490]
108. Gelatt M, Hamilton RM, McCrindle BW, et al. Arrhythmia and mortality following the mustard procedure: a 30 year, single center experience. *J Am Coll Cardiol*. 1997; 29:194–201. [PubMed: 8996314]
109. Grahram TP, Bernard YD, Mellen BG, et al. Long-term outcome in congenitally corrected transposition of the great arteries: a multi-institutional study. *J Am Coll Cardiol*. 2000; 36:255–261. [PubMed: 10898443]
110. Millane T, Bernard EJ, Jaeggi E, et al. Role of ischemia and infarction in late right ventricular dysfunction after atrial repair of transposition of the great arteries. *J Am Coll Cardiol*. 2000; 35:1661–1668. [PubMed: 10807474]
111. Piran S, Veldtman G, Siu S, et al. Heart Failure and ventricular dysfunction in patients with single or systemic right ventricles. *Circulation*. 2002; 105:1189–1194. [PubMed: 11889012]
112. Rutledge JM, Nihill MR, Fraser CD, et al. Outcome of 121 patients with congenitally corrected transposition of the great arteries. *Pediatr Cardiol*. 2002; 23:137–145. [PubMed: 11889523]
113. Eicken A, Fratz S, Gutfried C, et al. Hearts late after Fontan have normal mass, normal volume, and reduced systolic function. *J Am Coll Card*. 2003; 42(6):1061–1065.
114. Ishibashi N, Park IS, Takahashi Y, et al. Effectiveness of carvedilol for congestive heart failure that developed long after modified Fontan operation. *Pediatr Cardiol*. 2006; 27(4):473–475. Case report of a 27 year old with corrected transposition of the great arteries, ventricular septal defect, pulmonary stenosis, and straddling mitral valve who underwent a atriopulmonary Fontan operation and subsequently developed severe heart failure. The patient demonstrated improvement in systolic and diastolic function, symptoms and functional class after 1 year carvedilol therapy. [PubMed: 16841268]
115. Norozi K, Bahlmann J, Raab B, et al. A prospective, randomized, double-blinded, placebo controlled trial of β -blockade in patients who have undergone surgical correction of Tetralogy of Fallot. *Cardiol Young*. 2007; 17:372–379. A total of 33 patients with Tetralogy of Fallot who have NYHA class 1 or 2 heart failure and right ventricular dysfunction were randomized to bisoprolol or placebo and demonstrated no clear benefit from therapy at 6 months. [PubMed: 17572925]
116. Norozi K, Buchhorn R, Wessel A, et al. β -blockade does not alter plasma cytokine concentrations and ventricular function in young adults with right ventricular dysfunction secondary to operated congenital heart disease. *Circ J*. 2008; 72:747–752. [PubMed: 18441454]
117. Mukai Y, Yoshida T, Nakaiake R, et al. Five cases of anthracycline-induced cardiomyopathy effectively treated with carvedilol. *Intern Med*. 2004; 43(11):1087–1088. [PubMed: 15609710]
118. Carreira RS, Monteiro LM, Goncalves LM, Providencia LA. Carvedilol: just another β -blocker or a powerful cardioprotector? *Cardiovasc Hematol Disord Drug Targets*. 2006; 6:257–266. [PubMed: 17378771]
119. Machado V, Cabral A, Monteiro P, et al. Carvedilol as a protector against the cardiotoxicity induced by anthracyclines (doxorubicin). *Revista Portuguesa de Cardiologia*. 2008; 27(10):1277–1296. [PubMed: 19178029]
120. Ishikawa Y, Bach J, Minami R. Cardioprotection for Duchenne's muscular dystrophy. *Am Heart J*. 1999; 137:895–902. [PubMed: 10220639]
121. Kajimoto H, Ishigaki K, Okumura K, et al. β -blocker therapy for cardiac dysfunction in patients with muscular dystrophy. *Circ J*. 2006; 70:991–994. [PubMed: 16864930]
122. Nishizawa T, Yasuma F. The preventive efficacy of carvedilol on cardiac dysfunction in duchenne muscular dystrophy. *clinicaltrials.gov identifier*. Current Study NCT00606775. 2007–2012

123. Hunt SA, Abraham WT, Chin MH, et al. 2009 Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2009; 119:E391–E479. [PubMed: 19324966]
124. Kaufman BD, Shaddy RE. β -adrenergic receptor blockade and pediatric dilated cardiomyopathy. *Prog Pediatr Cardiol*. 2007; 24(1):51–57.

Executive summary

- Pediatric heart failure is a growing problem with an incidence of at least 0.6 per 100,000 pediatric patients.
- Heart failure pathophysiology is well understood in adults, but variations that may exist and that may be important in pediatrics are underinvestigated.
- β -blockers have become a mainstay in adult heart failure therapy in order to blunt the adrenergic response and resultant maladaptive cardiac remodeling.
- Second- and third-generation β -blocker use has expanded into pediatric heart failure management based on strong adult evidence.
- Carvedilol and metoprolol have suggested possible efficacy in some pediatric patients with heart failure, but studies are limited.
- Current management of heart failure with β -blockers should include consideration of consultation with pediatric heart failure specialists.
- Advances in pharmacogenetics will potentially lead to improved therapeutic efficacy via targeted patient selection.
- Prevention of cardiomyopathy with β -blocker therapy in high-risk patient groups such as seen with anthracycline exposure could be of potential benefit, but will need further investigation.

Figure 1. β -adrenergic signaling pathways in cardiac myocytes

There is a complex arrangement of intracellular signaling pathways activated by the β -1, β -2 and β -3 (not shown) adrenergic receptors, which results in a net overall effect of increased cytosolic calcium in the setting of heart failure due to adrenergic overstimulation. The effect of calcium and other downstream messengers leads to adverse cardiac remodeling. Adapted from [12].

Figure 2. All-cause mortality from the Carvedilol or Metoprolol European Trial (COMET)
 Adult patients with chronic heart failure demonstrated an all-cause mortality of 34% (512 of 1511) with carvedilol and 40% (600 of 1518) with metoprolol (hazard ratio: 0.83; 95% CI: 0.74–0.93; $p = 0.0017$).
 Adapted from [30].

Figure 3. Survival analysis of the β -Blocker Evaluation of Survival Trial (BEST) patient cohort stratified by treatment (bucindolol vs placebo) and β -1 adrenergic-receptor genotype (homozygous arginine vs homozygous glycine at position 389)

Patients with the Arg389 homozygous genotype treated with bucindolol versus placebo showed decreased mortality (hazard ratio: 0.62; 95% CI: 0.4–0.96; $p = 0.03$). Patients with the Gly389 homozygous genotype treated with bucindolol versus placebo showed no change in mortality (hazard ratio: 0.90; 95% CI: 0.62–1.30; $p = 0.57$).

Adapted from [79].

Figure 4. Impact of systemic ventricular morphology on response to carvedilol therapy in pediatric patients with heart failure

There is a trend towards improvement in the systemic LV group treated with carvedilol. This is not seen in the systemic NLV group ($p = 0.02$ for interaction between drug and LV status by logistic regression).

LV: Left ventricle; NLV: Non-left ventricle; OR: Odds ratio.

Reproduced with permission from [99].