

Is medical management of paediatric heart failure evidence based?

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Treatment of paediatric heart failure is based on much less evidence when compared with corresponding treatment in adult population. Nevertheless, successful treatment methods have been adjusted or developed for paediatric patients with chronic and acute heart failure and promising future trends exist.

Key words: Heart failure – Paediatrics – Evidence base

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Léčba srdečního selhání je u dětí založena na omezených důkazech ve srovnání s odpovídající léčbou u dospělých. Přesto existují úspěšné léčebné metody přizpůsobené nebo nově vyvinuté pro dětské pacienty s chronickým nebo akutním srdečním selháním a existují i slibné nové léčebné trendy.

Klíčová slova: Srdeční selhání – Pediatrie – Důkazy

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There has been ever increasing emphasis on the use of evidence based practice in all areas of medical, surgical, and nursing care over the last decade or so. This even lead to creation of a government sponsored body reviewing the evidence for good practice and issuing recommendations in the United Kingdom.^{1,2} Moreover, large prospective trials have formed the basis of evidence based treatment in adult cardiac patients for some time now.^{3–5} We sought to review similar evidence for prevention and/or treatment of chronic and acute heart failure in paediatric population.

Causes of paediatric heart failure

Congenital heart defects (CHD) are the most common cause of heart failure in paediatric population worldwide. They are also the most common congenital anomalies. They added 10% to infant mortality and 50% to mortality from all congenital defects in the United Kingdom in 1990's.⁶ Progress in the management of CHD led to reduction in 1-year mortality in almost 5 500 children treated surgically or by catheter interventions from 8.5% in 2000–2001 to 2.7% in 2006–2007.^{7,8} This successful reduction in mortality did not take away the burden of a significant morbidity associated with treatment and prevention of congestive heart failure in children with congenital heart defects.

Additional causes of heart failure include myocarditis, cardiomyopathy, dysrhythmias, drug toxicity, and sepsis or metabolic disease.^{9–13} Therefore both acute and chronic heart failure in children still presents difficult therapeutic problem in the current era.

Prevention and treatment

Chronic heart failure

Diuretics are the most frequently used medication in the treatment of heart failure in children despite very little published evidence about their clinical effect or pharmacokinetics in this age group.^{14,15} Given their widespread use and anecdotal beneficial clinical effect, paediatric prospective, placebo-controlled study is currently inconceivable.

Limited published evidence exists on the use of vasodilators in mitral and/or aortic regurgitation in paediatric population (*Table 1*).^{16–19} Strikingly low numbers of patients were included in the so far published series not to mention the presence of a control group in only one of these.¹⁷ The only so far published prospective controlled trial on the use of enalapril in heterogeneous group of young patients with single ventricle circulation failed to show any improvement in clinical, biochemical or echocardiographic parameters.²⁰

Table 1 Published evidence on the use of vasodilators in paediatric heart failure

Author	Year	No	Age (years)	Lesion	Drug	Effect
Hsu ²⁰	2010	185	< 1.2	Single ventricle	Enalapril	None
Gisler ¹⁶	2008	18	5.4–10	AR	Captopril Enalapril	None
Mori ¹⁷	2000	24	0.3–16	AR or MR	Enalapril	Reduced LV size and LV mass
Calabro ¹⁸	1999	10	3–16	MR	Enalapril	Reduced LV size and wall stress
Alehan ¹⁹	1998	20	12–16	AR	Captopril	Reduced LV size and wall stress

AR – aortic valve regurgitation, LV – left ventricle, MR – mitral valve regurgitation

Beneficial role of beta-receptor blocking medication in children with chronic myocardial dysfunction is somewhat better documented including its pharmacokinetics when compared with the above treatment modalities (Table 2).^{21–31} However, the most promising prospective, multicentric, placebo-controlled trial to date did not show any tangible benefit in administration of carvedilol to 62 children with dilated cardiomyopathy.²⁹ Some benefit was observed in the subgroup of 17 patients with congenital heart defects and left ventricular failure.

Further disappointing results came from a retrospective review of the use of combined therapy with angiotensin-converting enzyme inhibitors and beta-receptor blockers in 57 children with dilated cardiomyopathy between 1976 and 2005.³¹ No added benefit was found in 5-year transplant-free survival when compared with digoxin treatment only (59% versus 68% in digoxin only treated patients, $p = \text{NS}$).

Acute heart failure

Incidence of low cardiac output state has been stable at around 25% early after surgical treatment of CHD for more than 30 years now.^{32–34} PRIMACORP study still remains a unique paediatric prospective, placebo-controlled study showing beneficial effect of inodilator Milrinone on low cardiac output state postoperatively.³⁴ With 238 patients included in the study, peroperative and postoperative administration of Milrinone reduced the incidence of low cardiac output

state by 55% ($p = 0.023$). No difference in postoperative mortality between the control and treatment group was encountered. Nevertheless, treatment with Milrinone decreased the length of postoperative artificial ventilation from 3.1 to 1.4 days ($p = 0.001$) and length of hospital stay from 11.3 to 8.9 days ($p = 0.016$). These conclusions are supported by previous smaller haemodynamic study showing increased cardiac index and reduced systemic and pulmonary vascular resistance by Milrinone bolus and continuous infusion treatment in neonates following cardiac operation.³⁵ Moreover, Milrinone was shown to have positive direct myocardial effect in infants with low cardiac output state when added to catecholamine treatment early postoperatively.³⁶

Promising results have recently been published on the use of vasopressin in paediatric patients suffering from profound vasodilatation associated with sepsis or cardiopulmonary bypass.³⁷ Vasopressin administered as a bolus or continuous infusion led to significant increase in systemic blood pressure allowing for reduction of catecholamine doses. Similar preliminary favourable results were reported on vasopressin use in paediatric cardiac arrest refractory to cardiopulmonary resuscitation and adrenalin administration.³⁸

The use of mechanical circulatory support is the best documented treatment in paediatric heart failure to date.^{39–42} Davies et al reviewed 2 535 patients younger than 19 years

Table 2 Published evidence on the use of beta-receptor blocking medication in paediatric heart failure

Author	Year	No	Age (years)	Lesion	Drug	Effect
Bruns ²³	2001	46	0.3–19	DCM/CHD	Carvedilol	Improved LVSF and NYHA class
Azeka ²⁴	2002	14	< 15	DCM	Carvedilol	Improved LVEF
Williams ²⁵	2002	12	< 15	DCM/CHD	Metoprolol or carvedilol	Improved LVEF
Buckhorn ²⁶	2003	8	< 1	CHD	Propranolol	Improved diastolic function
Rusconi ²⁷	2004	24	0.8–13	DCM	Carvedilol	Improved LVEF and NYHA class
Blume ²⁸	2006	20	0.8–17	DCM/CHD	Carvedilol	Improved LVEF
Shaddy ²⁹	2007	103	< 18	DCM/CHD	Carvedilol	No difference in outcome, improved LV contractility in CHD
Bajcetic ³⁰	2008	21	0.5–16	DCM	Carvedilol	Improved LV ejection fraction and NYHA class
Kantor ³¹	2010	57	< 15	DCM	Propranolol, metoprolol, carvedilol	No effect on transplant-free survival

CHD – congenital heart disease, DCM – dilated cardiomyopathy, LV – left ventricle, LVEF – left ventricular ejection fraction, LVSF – left ventricular shortening fraction

undergoing heart transplantation between 1995–2005.³⁹ Mechanical support was used successfully as a bridge to transplantation in 431 patients (17%) without any difference in long term survival. Moreover, recent evidence from 255 patients below 18 years of age with acute myocarditis supported by extracorporeal membrane oxygenation (ECMO) showed survival to hospital discharge in 61% of the patients.⁴⁰

Heart transplantation has been well established treatment of end-stage paediatric heart failure with satisfactory results over the last couple of decades.^{43,44} Nevertheless, both acute and chronic rejection have significant adverse impact on the medium and long-term survival in paediatric heart transplant recipients in the current era.^{45,46}

Intriguing results calling to question indications for heart transplantation in children with acute heart failure were published by O'Sullivan et al.⁴⁷ They treated 27 young patients (age 0.1–72 months) with acute severe heart failure between 1988–2005. Three patients required ECMO support in the course of their treatment. Complete recovery without heart transplantation was observed in 66% and 96% of the patients at 18 and 24 months, respectively. This experience is supported by Amabile et al who studied retrospectively 11 patients with acute myocarditis presenting between 1998 and 2003.⁴⁸ All patients received inotropic support and corticosteroids with seven patients treated by intravenous immunoglobulin as well. Long-term survival with normal left ventricular ejection fraction was observed in 10 children (90%) despite cardiopulmonary resuscitation required in five of these.

Future trends in paediatric heart failure treatment

There is emerging evidence that paediatric heart transplantation candidates with pulmonary vascular resistance previously considered too high for successful orthotopic heart transplantation may benefit from treatment with various pulmonary vasodilators.⁴⁹ Combined therapy including sildenafil, bosentan, inhaled nitric oxide, and iloprost has been used in 7 patients with pre-transplantation calculated total pulmonary vascular resistance between 6–20 Wood's units. Successful heart transplantation was carried out following pre-treatment with bosentan or sildenafil and inhaled nitric oxide was used in all patients in the early postoperative period. Inhaled iloprost was required in one patient long-term. All patients survived one year after heart transplantation.

The use of novel calcium sensitizer and peripheral vasodilator Levosimendan has shown promising preliminary results in the treatment of myocardial failure in patients with cardiomyopathy or congenital heart disease in total of 41 paediatric patients published so far and in our institutional experience with further 11 patients.^{50–53}

Synthetic brain natriuretic peptide (Nesiritide) combines systemic venous and arterial vasodilating effect with myocardial lusitropic effect. Its administration to 17 neonates and 30 infants in postoperative low cardiac output state as an adjunct to conventional treatment had

neutral directly monitored haemodynamic effect but led to improved urine output.⁵⁴

Concept of remote ischaemic pre- and per-conditioning is based on temporary ischaemia of one organ having protective effect against subsequent or concomitant ischaemia and reperfusion injury of other organs.⁵⁵ It is likely to be at least partly related to generalised suppression of transcription of pro-inflammatory genes in leukocytes and to upregulating cardioprotective genes in myocytes by primary organ ischaemia.⁵⁶ In paediatric clinical study, repeat mild lower limb ischaemia by blood pressure cuff inflation (4-times for 5 min) before cardiac surgery in children led to lower troponin levels and inotrope score when compared with a control group postoperatively.⁵⁷ Similar protocol involving 30 infants undergoing cardiac surgery led to upregulation of genes involved in protection against oxidative stress and suppression of pro-inflammatory genes.⁵⁸

Ischaemic and reperfusion injury has been extensively studied both in myocardial infarction and after cardiac arrest.^{59,60} It is widely accepted that cellular and mitochondrial calcium overload is an important mechanism of injury and apoptosis.⁶¹ Cyclosporin A appears a promising medication limiting cellular injury in experimental setting.⁶² It has stabilising effect on mitochondrial permeability transition pores in oxidative stress and protects against mitochondrial calcium overload at the time of reperfusion injury. Cyclosporin A has protective effect on central nervous system in paediatric heart transplant recipients following cardiac arrest.⁶³ Moreover, experimental studies showed its protective effect on central nervous system within 24 hours of ischaemic and reperfusion injury.⁶⁴ There are first reports on similar protective effect of cyclosporin A in transient myocardial ischaemia in experimental and adult clinical studies.^{65,66}

There is also emerging evidence that stem cell transplantation may have its role even in the treatment of paediatric end-stage heart failure.⁶⁷

Conclusions

Like with many other paediatric treatment protocols, evidence for medical management of paediatric heart failure is inevitably limited in comparison with corresponding adult interventions. Cause of this limitation is multifactorial and spans from ethical issues related to trials conducted in neonates, infants or children to restricted availability of resources given much smaller market for and revenues from any new and successful treatment modality. Nevertheless, marked improvement in the results of congenital and acquired paediatric heart disease treatment has been achieved over the past decade. There also exist promising new avenues to explore be it on much smaller scale than in adult population in future.

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