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MINIREVIEWS

# Clinical cardiac regenerative studies in children

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## Abstract

Although the incidence of pediatric heart failure is low, the mortality is relatively high, with severe clinical symptoms requiring repeated hospitalization or intensive care treatment in the surviving patients. Cardiac biopsy specimens have revealed a higher number of resident human cardiac progenitor cells, with greater proliferation and differentiation capacity, in the neonatal period as compared with adults, demonstrating the regeneration potential of the young heart, with rising interest in cardiac regeneration therapy in critically ill pediatric patients. We review here the available literature data, searching the MEDLINE, Google Scholar and EMBASE database for completed, and www.clinicaltrials.gov homepage for ongoing studies involving pediatric cardiac regeneration reports. Because of difficulties conducting randomized blinded clinical trials in pediatric patients, mostly case reports or cohort studies with a limited number of individuals have been published in the field of pediatric regenerative cardiology. The majority of pediatric autologous cell transplantations into the cardiac tissue have been performed in critically ill children with severe or terminal heart failure. Congenital heart disease, myocarditis, and idiopathic hypertrophic or dilated cardiomyopathy leading to congestive heart failure are some possible areas of interest for pediatric cardiac regeneration therapy. Autologous bone marrow mononuclear cells, progenitor cells, or cardiospheres have been applied either intracoronary or percutaneously intramyocardially in severely ill children, leading to a reported clinical benefit of cell-based cardiac therapies. In conclusion, compassionate use of autologous stem cell administration has led to at least short-term improvement in heart function and clinical stability in the majority of the critically ill pediatric patients.

**Key words:** Congenital heart disease; Heart failure; Cardiac regeneration; Cell-based therapy; Hospitalization; Children



**Core tip:** This review summarizes the available literature data involving pediatric cardiac regeneration reports.

Due to lack of randomized blinded clinical trials in pediatric cardiology patients, mostly case reports with limited number of individuals have been published in the pediatric regenerative cardiology. The majority of pediatric autologous cell transplantations into the cardiac tissue have been performed in children with severe or terminal heart failure, and led to the conclusion, that compassionate use of autologous stem cell administration may lead to at least short-term improvement in heart function and clinical stability in the majority of the critically ill pediatric patients.

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## INTRODUCTION

### *Epidemiology of heart failure in children*

The overall prevalence of pediatric heart failure is largely unknown because of the non-unique definition and classification of this disease. According to statistical estimations and pediatric registries, 2.5 million children annually are born with congenital heart disease (CHD) worldwide, and among these children, 15%-25% eventually develop heart failure[1-4].

The incidence of pediatric dilated cardiomyopathy with consequent heart failure is low, calculated as 0.57-2.6 per 100000 children under age 18 years[5,6]. In this group, approximately two thirds of cases are idiopathic, and the remaining involve postmyocarditis syndrome or musculoskeletal diseases[7]. Dilated cardiomyopathy dominates myocardial disease-related heart failure, followed by hypertrophic cardiomyopathy, with restrictive cardiomyopathy identified least frequently[8]. The median age of the patients with dilated cardiomyopathy is approximately 1.8 years when the initial diagnosis is made[8].

The mortality of pediatric heart failure is high, and approximately one third of patients die in the first year following diagnosis[9,10]. The surviving children develop progressive heart failure requiring intensive medical care and heart transplantation[7]. For those surviving at least 2 years after the diagnosis, mortality and the need for heart transplantation are somewhat lower (13.6%)[6]. Approximately 18 of every 100000 children are hospitalized annually because of heart failure, with 0.87 new cases per 100000 children per year[11]. The hospital mortality of these pediatric patients is 7%, and numbers are much higher compared to the adult population (4%)[11,12]. After the first hospitalization, only 21% of pediatric patients remain free from serious adverse events (rehospitalization, death, or heart transplantation)[13]. The lack of sufficient numbers of young donor organs and the relatively high post-transplantation mortality limit the incidence and success of pediatric heart transplantation.

In addition, the cost of hospital treatment for pediatric heart failure is usually extremely high, exceeding 135000 USD per patient. Underlying CHD involving a single ventricle, for example, expands the costs of in-hospital treatment for heart failure to over 200000 USD[14].

The medical therapy for pediatric heart failure includes the whole armamentarium used in adults; however, the benefit cannot be clearly demonstrated for all interventions in children[15]. Some established methods for adult cardiology, such as diverse regenerative therapies or left ventricular assist devices, are rarely available for young patients because of incompatibilities of implant size in growing children. Medical treatment might be insufficient because, as noted, many children end up requiring heart transplantation[16].

### *Spontaneous cardiac regeneration capacity in children*

Newborn mice can regenerate the cardiac apex after resection but only if the resection occurs within the first 7 d after birth[17]. Lineage tracing investigations have revealed that cell cycle entry of pre-existing cardiomyocytes in mice is responsible for this regeneration. Gene expression analysis indicates that neonatal cardiomyocytes maintain proliferation capacity only up to 7 d post-birth, this regeneration property is then lost[17]. Mishra *et al*[18] investigated the prevalence and proliferation capacity of different stem cell-like cells acquired from cardiac biopsy specimens of children undergoing open heart surgery. They showed that plenty of resident human cardiac progenitor cells (hCPCs, a subpopulation of cardiospheres, CDCs) can be found in the neonatal period but that the number of these cells decreases rapidly with advancing age, from 8.9% to 3.2% in the right atrium and from 0.4% to 0.1% in the right ventricle. In addition, c-kit$^+$ hCPCs were three times more frequently found in neonates than in children over age 2 years. The proliferation and differentiation potential of the hCPCs was also greater in neonates, as shown by the higher expression levels of c-kit and Ki67, as well as the expression of NKX2, NOTCH1, and NUMB, the genes responsible for proliferation and differentiation. Furthermore, heart tissue samples of children with CHD contained an increased number of c-kit$^+$ hCPCs and CD133$^+$ cells, and these cells expressed cardiac lineage and endothelial transcription factors during differentiation under *in vitro* conditions[19]. CDCs are a rich source of secreted regenerative substances, such as cytokines and growth factors, *e.g.,* vascular endothelial growth factor, hepatocyte growth factor, or insulin-like growth factor, and exert anti-apoptotic and proangiogenic effects in the myocardium[20,21]. CDCs found in infant hearts have higher telomerase activity compared with those of adults.

Together, these data suggest that the regenerative capacity of the heart in children is much greater than that of adults. Additional evidence comes from clinical observations that the younger heart can exhibit morphological changes after volume unloading by surgical correction of CHD[22]. Additionally, pressure overload from

**Table 1 Pediatric cardiac diseases treated with cells**

| Cell-based cardiac regenerative treatment | Ongoing studies |
|---|---|
| Dilated cardiomyopathy (Dil. CMP) | Dilated cardiomyopathy (Dil. CMP) |
| Idiopathic dilated CMP | |
| Cytostatics-induced dilated CMP | |
| Postmyocarditis dilated CMP | |
| Ischemic heart failure (myocardial infarction) | |
| Anomalous origin of the left coronary arteries | |
| Takayasu arteritis | |
| Congenital heart disease | |
| DORV after surgical correction | |
| Pulmonary atresia with ventricular septal defect | |
| HLHS | Hypoplastic left heart syndrome (HLHS) |

CMP: Cardiomyopathy; DORV: Double outlet right ventricle; HLHS: Hypoplastic left heart syndrome.

a single right ventricle leads to an increase in the number of cardiac stem cells (0.41% ± 0.24%) compared to dilated cardiomyopathy (0.15% ± 0.09%)[23].

### *Clinical pediatric cardiac regeneration studies*

To establish standardized therapy and guidelines for treatment of diseases, randomized double-blinded clinical studies delivering evidence-based medicine are necessary. In contrast with the huge number of adult clinical trials, in pediatric cardiology, especially for cardiac regenerative therapy, large randomized trials are lacking. In addition to the understandable ethical reasons, other factors also preclude such trials: The relative rarity of heart failure with a limited number of pediatric patients in the stable clinical condition necessary for randomization, a divergence in terminology, proprietary and often incompatible informatics platforms, and variability in data standards in growing children[24]. In 2012, the United States Food and Drug Administration Safety and Innovation Act intensified pediatric product development, also enhancing the number of pediatric clinical trials. In Europe, the Pediatric Regulation and Pediatric Therapeutics programs have strengthened the applications of new medicines in evidence-based pediatric clinical studies. In contrast with the very spare pediatric regenerative cardiology studies, pediatric cancer and HIV/AIDS treatment networks have already been successfully established and developed with standardized data validity and consistency[24]. We review here the available literature data, searching the Medline, Google Scholar and Embase database for completed, and www.clinicaltrials.gov homepage for ongoing studies involving pediatric cardiac regeneration reports.

## DISCUSSION

### *Cardiac diseases for pediatric cardiac regeneration*

In most cases, cardiac cell-based therapy has been applied in children with severe heart failure caused by diverse diseases, predominantly idiopathic dilated cardiomyopathy, post-myocarditis, or chemotherapy-induced dilated cardiomyopathy (Table 1 and Figure 1). Severe heart failure has been described also with post-myocardial infarction in cases of an anomalous origin of the left coronary artery from the pulmonary artery or Takayasu's arteritis, treated with different kinds of reparative cells. Other congenital diseases such as double outlet right ventricle, pulmonary atresia with ventricular septal defect, or hypoplastic left heart syndrome (HLHS) causing severely depressed heart function, have been considered for treatment with non-committed cells. Table 2 lists the pediatric diseases for which cardiac cell-based regenerative studies might be considered.

For the reasons described, to date, only two randomized clinical cardiac regenerative trials with a low number of included children have been conducted. Both have revealed benefits of cardiac cell-based therapy[25-29]. In addition to these currently finished trials, case reports or pilot trial results have been published, mainly based on an indication of compassionate use in severely ill pediatric patients. The majority of children receiving cardiac cell-based therapy were in a critical or terminal status of cardiac decompensation, as evidenced by the fact that some of the children had to undergo heart transplants afterwards[22].

### *Cell types and delivery modes*

Different types of cells have been used for cardiac regenerative cell therapy in children, such as bone marrow-derived mononuclear cells, cells from leukocyte apheresis, and mesenchymal stem cells. In all cases, autologous cells were used.

Most of the children received the reparative cells *via* intracoronary injections. To ensure retention of the injected cells, echocardiography-guided transcutaneous intramyocardial delivery was also used, or a transapical delivery mode was applied[30].

### *Clinical studies*

The evidence for pediatric cardiac regeneration is mostly anecdotal, deriving from case reports or cohort studies including very limited number of patients (max. nine treated children in Rupp *et al*[31]). In addition, the only comparative study, published by Ishigami *et al*[32] allocated

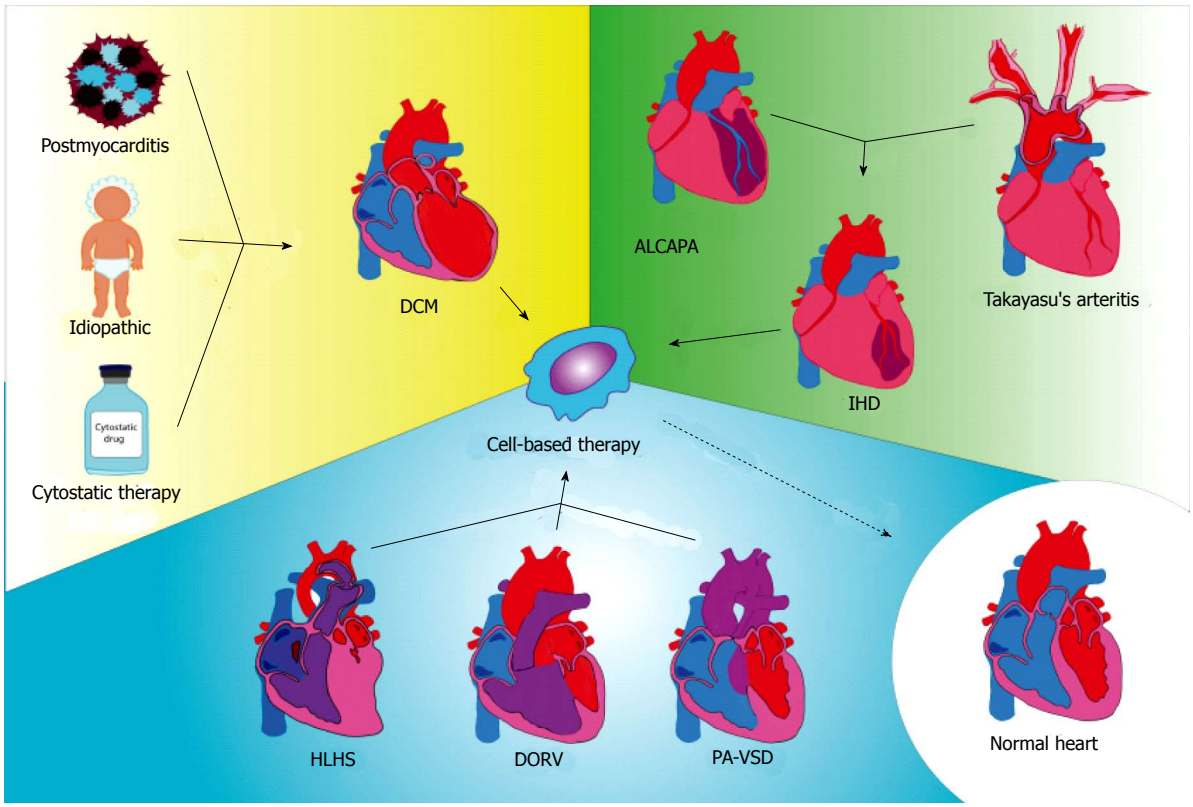


**Figure 1 Schematic display of cardiac cell-based regeneration therapies in pediatric population.** DCM: Dilated cardiomyopathy; ALCAPA: Anomalous left coronary artery from the pulmonary artery; IHD: Ischemic heart disease; HLHS: Hypoplastic left heart syndrome; DORV: Double outlet right ventricle; PA-VSD: Pulmonary atresia with ventricular septal defect.

14 children with HLHS to receive either autologous CDCs ($n$ = 7) or standard therapy ($n$ = 7) without randomization. Because of these significant limitations of the available literature, a usual review or meta-analysis of cardiac regenerative studies in children is not reasonable. Thus, this review summarizes the published cases and their conclusions.

Autologous stem cell administration has led to at least short-term improvement in heart function and clinical stability in the majority of patients. Because of the lack of randomization and control groups, an unambiguous interpretation of the results is not possible. At the least, the outcomes indicate a compassionate use of cell-based cardiac regeneration in critically ill patients.

Rupp *et al*[33,34] reported two cases of bone marrow-origin progenitor cell intracoronary injection, one involving a 2-year-old boy with dilated cardiomyopathy and the other an 11-mo-old infant with HLHS; both of them were in a critical clinical condition of heart failure. The bone marrow progenitor cells were injected into the left anterior descending and left circumflex coronary arteries in the first case and into the dominant right coronary artery in the second case, using a stop-flow technique. The cardiac cell therapy led to an increase in the left ventricular ejection fraction from 24% to 45% at 6 mo of follow-up in the first case, and to reverse remodeling and marked improvement in clinical status in the second case.

In further work, Rupp *et al*[34] published a somewhat larger cohort study of nine pediatric patients receiving intracoronary injections of autologous bone marrow mononuclear cells (BM-MNCs). The reasons for terminal heart failure in these children were anthracycline-induced dilated cardiomyopathy; post-myocarditis, idiopathic, or congenital cardiomyopathy; CHD with poor ventricular function, such as hypoplastic left heart or double outlet right ventricle; and pulmonary atresia with ventricular septal defect after surgical corrections. Three of the nine patients received a heart transplant and one patient died after cell treatment. The surviving children showed an improvement in clinical status during the 24 to 52 mo of follow-up.

De Lezo *et al*[35] presented a case of a 5-mo-old infant with severe heart failure due to extensive myocardial infarction because of an anomalous origin of the left coronary artery. After surgical re-implantation of the left coronary artery to the aorta, the artery was occluded, then stented, then dilated after stent occlusion. Because of the critical clinical situation, during the second percutaneous procedure, autologous bone marrow-origin mononuclear cells were injected into the left main branch, which led to a gradual improvement in clinical status and allowed the discharge of the patient.

After mobilizing stem cells from the bone marrow with granulocyte colony-stimulating factor (G-CSF), Olguntürk *et al*[36] selected peripheral blood-origin stem cells and performed intracoronary injections of these cells into both the left and right coronary arteries in two patients both with dilated cardiomyopathy and severe

**Table 2 Published clinical studies with pediatric cell-based cardiac regeneration**

| Ref. | Study type | Diagnosis | No. of children | Mean age of children (m) | Sex | Type of stem cell | Cell application | FUP | Main results |
|---|---|---|---|---|---|---|---|---|---|
| Lacis *et al*[30] | Case report | Dil. CMP | 1 | 3.5 mo | F | BM-MNC | IM | 4 mo | LV EF from 20% to 41% |
| Rupp *et al*[31] | Case report | Dil. CMP | 9 | 4 mo-16 yr | NA | BM-MNCs | IC | 1-52 mo | 3 patients HTX, 1 patient died, others improved |
| Ishigami *et al*[32] (TICAP study) | Controlled study | HLHS | 7 treated and 7 controls | < 6 yr | NA | CDCs | IC | 18 mo | Increase in RV EF from 46.9% to 52.1% in treated patients |
| Rupp *et al*[33] | Case report | HLHS | 1 | 11 mo | M | BMC | IC | 14 mo | RV EF from 22% to 44% |
| Rupp *et al*[34] | Case report | Dil. CMP | 1 | 2 year | M | BMC | IC | 6 mo | EF from 24% to 45%, BNP and NYHA decreased |
| De Lezo *et al*[35] | Case Report | Post-AMI | 1 | 7 mo | NA | BM-MNCs | IC | 14 mo | LV EF from 20% to 43% |
| Olguntürk *et al*[36] | Case report | Dil. CMP | 2 | 6 and 9 yr | M, F | PBSC after GCSF treatment | IC | 8 wk, and 6 mo | 1st patient LV EF from: 16% to 39%; 2nd patient LV EF from 34% to 54% |
| Limsuwan *et al*[37] | Case report | HF post-AMI | 1 | 9 yr | F | BMC after GCSF treatment | IC | 3 mo | LV EF form 30% to 47% |
| Zeinaloo *et al*[38] | Case report | Dil. CMP | 1 | 11 yr | M | BM-MSC | IC | 1 yr | LV EF from 20% to 42% |
| Rivas *et al*[39] | Case report | Dil. CMP | 2 | 3 and 4 mo | M | PBSC after G-CSF treatment | IC | 4 mo | EF from < 30% to > 40% |
| Bergmane *et al*[40] | Case report | Dil. CMP | 7 | 4 mo-17 yr | NA | BMC | IM | 1 yr | 6 patients controlled, LV EF from 33.5% to 54% |
| Burkhart *et al*[41] | Case report | HLHS | 1 | 3 m | NA | Umbilical cord blood derived cells | IM | 3 mo | EF increased to 45% |

BMC: Bone marrow cells; CDC: Cardiosphere-derived cells; BNP: Brain natriuretic peptide; HTX: Heart transplantation; NYHA: New York Heart Association Classification; GCSF: Granulocyte-colony stimulating factor; CMP: Cardiomyopathy; LV: Left ventricle; EF: Ejection fraction; BM-MNC: Bone marrow mononuclear cell; PBSC: Peripheral blood stem cell; RV: Right ventricle; IC: Intracoronary; IM: Intramyocardial; FUP: Follow-up; NA: Data not available; HLHS: Hypoplastic left heart syndrome; F: Female; M: Male.

congestive heart failure. At the 4-mo follow-up, both children showed impressive improvement, and one of them could be removed from the heart transplantation list.

Similarly, Limsuwan *et al*[37] applied the first daily injections of G-CSF, followed by bone marrow aspiration and selection of $CD133^+/CD34^+$ cells in an 8.5-year-old girl who had had an acute extensive anterior myocardial infarction related to Takayasu arteritis one year earlier. The selected stem cells were injected into the left anterior descending artery with the stop-flow technique. The 3-mo follow-up showed an increase in ejection fraction from 30% to 47.8% by cardiac magnetic resonance imaging.

Zeinaloo *et al*[38] selected autologous bone marrow mesenchymal stem cells in an 11-year-old boy with a diagnosis of dilated cardiomyopathy and injected them into the left and right coronary arteries. The one-year clinical check-up revealed an improvement of the left ventricular ejection fraction from 20% to 42%.

Lacis *et al*[30] treated a 3-mo-old child, who was in critical clinical condition with dilated cardiomyopathy, with autologous BM-MNCs *via* echocardiography-guided transcutaneous transapical intramyocardial injections. The ejection fraction increased from 20% to 41% at the 4-mo follow-up, and the child's clinical well-being was obvious.

Rivas *et al*[39] treated two children who both had dilated cardiomyopathy and were ages 3 and 4 mo, respectively, by administering peripheral blood progenitor cells, mobilized by G-CSF treatment. One month later, both children presented improvement, but one child developed progression later. This article described a temporary effect of the cell-based cardiac regenerative therapy.

Ishigami *et al*[32] published a nonrandomized prospective cohort study comparing data for seven patients treated with intracoronary injection of cardiosphere-derived cells and seven controls treated with standard therapy. All children had HLHS with planned stage 2 or 3 surgical palliation, which allowed the collection of autologous tissue for selection of CDCs in the treated group. The intracoronary injection of CDCs proved to be safe, and the right ventricle ejection fraction increased and remained constant at the 18 mo follow-up.

Bergmane *et al*[40] treated seven children with dilated cardiomyopathy with autologous bone marrow cells administered transcutaneously and intramyocardially by subxyphoid needle puncture under echocardiographic guidance. Six of the seven patients showed dramatically

**Table 3 On-going registered clinical studies**

| Clinicaltrials.gov ID | Diagnosis | Intervention | Study design | No. of patients to enroll | Age eligible | Status |
|---|---|---|---|---|---|---|
| NCT01504594 | Dilated CMP | Intracoronary autologous stem cell infusion | Single Group Assignment | 10 | 1 to 16 | Suspended |
| NCT02256501 | CMP | Intracoronary | Randomized | 32 | 1 to 16 | Recruiting |
| NCT02398604 | HLHS | intramyocardial injection of allogeneic mesenchymal cells during the Bi-Directional Cavopulmonary Anastomosis | Randomized | 30 | to 28 d | Study is not yet open |
| NCT01883076 | HLHS | injections of autologous umbilical cord blood cells into the right ventricle of HLHS children undergoing a scheduled Glenn surgical procedure. | Safety Study | 10 | < 18 mo | Recruiting |
| NCT01829750 | HLHS | efficacy of intracoronary infusion of cardiac progenitor cells in patients with univentricular heart disease | Randomized | 34 | < 20 yr | Recruiting |

HLHS: Hypoplastic left heart syndrome; CMP: Cardiomyopathy.

increased left ventricular ejection fraction at one year after the treatment, paralleled by a decrease in N-terminal proBNP and improved clinical status.

Burkhart *et al*[41] injected autologous umbilical cord blood-derived cells directly into the right ventricle during a second palliative operation of a child with HLHS. Three months later, the ejection fraction had increased to 45% with a marked decrease in plasma pro-BNP. Ongoing registered clinical studies are listed in Table 3.

## CONCLUSION

Cell-based cardiac regeneration therapy in pediatric patients has led to at least transient improvement of heart function and improvement of heart failure symptoms in a limited number of pediatric patients included in mostly non-randomized studies or case reports.

The majority of pediatric autologous cell transplantations into the cardiac tissue have been performed in critically ill children with severe or terminal heart failure, indicating that at the moment, this treatment strategy is a supplement after standard therapies have been exhausted. Whether specific age groups or those with structural heart diseases may benefit more than others has to be elucidated.

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