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Original article

# Challenges to success in heart failure: Cardiac cell therapies in patients with heart diseases

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ABSTRACT

Heart failure remains the leading cause of death worldwide, and is a burgeoning problem in public health due to the limited capacity of postnatal hearts to self-renew. The pathophysiological changes in injured hearts can sometimes be manifested as scar formation or myocardial degradation, rather than supplemental muscle regeneration to replenish lost tissue during the healing processes. Stem cell therapies have been investigated as a possible treatment approach for children and adults with potentially fatal cardiovascular disease that does not respond to current medical therapies. Although the heart is one of the least regenerative organs in mammals, discoveries made during the past few decades have improved our understanding of cardiac development and resident stem/progenitor pools, which may be lineage-restricted subpopulations during the post-neonatal stage of cardiac morphogenesis. Recently, investigation has specifically focused on factors that activate either endogenous progenitor cells or preexisting cardiomyocytes, to regenerate cardiovascular cells and replace the damaged heart tissues. The discovery of induced pluripotent stem cells has advanced our technological capability to direct cardiac reprogramming by essential factors that are crucial for heart field completion in each stage. Cardiac tissue engineering technology has recently shown progress in generating myocardial tissue on human native cardiac extracellular matrix scaffolds. This review summarizes recent advances in the field of cardiac cell therapies with an emphasis on cellular mechanisms, such as bone marrow stem cells and cardiac progenitor cells, which show the high potential for success in preclinical and clinical meta-analysis studies. Expanding our current understanding of mechanisms of self-renewal in the neonatal mammalian heart may lead to the development of novel cardiovascular regenerative medicines for pediatric heart diseases.



## Introduction

Despite advanced medical treatments and device-based therapies that ameliorate cardiac dysfunction resulting from the pathogenesis of heart disease, heart failure remains the leading cause of morbidity and mortality in developing countries [1]. A fundamental problem with current medical treatments for heart disease is their inability to replace lost myocardium tissue with de novo cardiovascular cells, rather than post-conditioning the remaining viable tissues within the damaged heart organ. Over the past two decades, somatic tissue-derived stem cell therapy of bone marrow, adipose tissue, and the heart, has emerged as a promising cardiac replacement therapy to treat the patients with heart failure [2]. Although cell transplantation strategies applied in patients have been extensively investigated in large animal studies, their efficacy remains unestablished in humans [3].

Early preclinical studies have investigated the efficacy of a variety of cell types, including various types of adult stem cells and progenitors. Among the somatic stem/progenitor populations, endogenous cardiac progenitor cells have been reported to be the greatest functional cell type for reducing myocardial infarction-induced adverse cardiac remodeling, via direct and indirect mechanisms [4]. However, a major limitation of somatic tissue-derived stem cells is the low cardiac differentiation efficiency. The emergence of induced pluripotent stem (iPS) cells has enabled researchers to generate highly enriched cardiomyocyte populations

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in vitro, which also differentiate into bona fide cardiomyocytes in vivo [5]. Cardiac tissue engineering technology, including stacked cell sheet patches or three-dimensional tissue surrogates, may also enhance donor cell engraftment by advancing the cell delivery method [6]. With these advancements in stem cell biology, active translational research is now expanding in various new directions, including direct cardiac reprogramming by specific transcription factors or small molecules, augmentation of endogenous progenitor cell proliferation by short, single-stranded, noncoding RNAs (miRNAs), and local modulation of intramyocardial communication through small membrane-bound vesicles, known as exosomes, that act as intercellular communicators to shuttle proteins and miRNAs that promote the therapeutic activities of stem cells in myocardial repair [7–9].

This review provides a comprehensive overview of stem/progenitor-based preclinical studies in large animals, and provides a discussion of the differing outcomes of clinical trials using cell therapies to treat human heart failure. In addition, this article examines the emergent results of progenitor cell therapy in patients with congenital heart diseases, which may provide efficacious treatment strategies for children, as an alternative to standard surgical palliation alone.

## Meta-analysis results of bone marrow cell therapy for ischemic heart disease

In the past 15 years, bone marrow transplantation therapy, through either intramyocardial or intracoronary delivery, has spurred enormous excitement among clinicians as an immediate therapeutic application in patients with ischemic heart disease. Although the study designs, cell preparation methods, and delivery routes varied among trials, initial results demonstrated either modest improvement in cardiac function or no benefit, in short- and long-term observation of clinical events or left ventricular function [10–15]. Indeed, it may be challenging to achieve significant cardiac function improvements with relatively small cohort studies in patients who have received a complete revascularization procedure as an adjunctive therapy. It has also been questioned whether the functional benefits observed in short-term investigations were solely provided by cell therapies. Acute coronary occlusion may produce an initial inflammatory milieu as a healing mechanism of cardiac remodeling, which could hamper the early cell engraftment and subsequent proliferation in situ. Due to these uncertainties, optimal timing of cell delivery was carefully investigated, but failed to show any beneficial effect of bone marrow cell infusion in improving global and regional cardiac functions [16–18]. Over the past 15 years, studies of bone marrow cell therapy have indicated that both intramyocardial injection and coronary infusion of bone marrow cells are feasible and safe treatment options in patients; however, the differing outcomes of these treatments highlights the need for further trials in larger cohorts.

Meta-analysis has emerged as a comprehensive approach statistically to assess trial results obtained from public registered databases. To elucidate the negative findings from trial reports [19,20], this integrated analysis was expected to make overall interpretation relevant to cell therapy in patients with heart failure. Meta-analysis allowed the accurate assessment of the clinical efficacy of cell therapies by overcoming the limitations in statistical power associated with individual studies. The first meta-analysis report of bone marrow cell therapy combined with coronary bypass surgery appeared in 2011, included 6 trials, and reported that intramyocardial bone marrow cell injection was associated with a significant improvement of contractile function, as well as a reduction in ventricular volume [21]. In 2012, the largest comprehensive analysis, including 50 trials with 2625 patients, reported that cell transplantation improved cardiac function and infarct size, as well as reducing the incidence of cardiac death and recurrent myocardial infarction [22]. Although these findings are encouraging, a major criticism of these meta-analysis reports is this method of combining randomized and cohort trials. Furthermore, differences between individual study methods and enrolled participants, including cell preparation methods, type of heart disease, and time to transplantation, may produce considerable heterogeneity in the meta-analysis outcome.

More recently, a number of meta-analyses concerning bone marrow cell therapy in heart disease treatment have been reported. Although the study design varied among reports, overall results revealed that bone marrow cell infusion might provide functional benefits in patients with myocardial infarction or refractory angina [23–27]. The promising nature of these findings has encouraged clinicians to continue the use of cardiac cell therapies in patients, at least until any contradictory evidence is reported. As mentioned above, a major disadvantage of meta-analysis is the heterogeneity in study design and imaging modalities applied for endpoint analysis among the assessed trials. de Jong et al. were the first group to narrow down published studies of bone marrow cell therapy into 22 randomized trials that used magnetic resonance imaging as the outcome measure, but failed to demonstrate either an improvement in cardiac function or a decrease in major adverse events [28]. The ACCRUE study, a meta-analysis of cell-based cardiac studies, similarly failed to find any therapeutic benefit of bone marrow cell therapy [29]. The authors of this study aimed to overcome the problem of amplification of heterogeneity among studies associated with the study-level approach of meta-analyses, and improve the quality of data by using patient-level analysis. The ACCRUE study analyzed the results of 767 participants within 12 randomized trials, who received intracoronary infusion of bone marrow cells after infarction, and found no significant effects of cell therapy on cardiac function and adverse events.

As with the previous individual studies, the complementary findings of meta-analyses indicate the feasibility and safety of intracoronary infusion of bone marrow cells into patients with myocardial infarction or refractory angina. However, the meta-analysis also suggests that the efficacy of this treatment remains unclear. Meta-analyses have the advantage of predicting the therapeutic efficacy by collecting the endpoint results from several studies, thus eliminating problems associated with small detection power and sample size. However, despite careful interpretation of the results of these studies, e.g. stratified sampling by baseline cardiac function or imaging modality applied for endpoint assessment, a number of mixed conditions exist within the individual trials reported. Cell preparation quality, cell types, delivery route, patient background characteristics, and timing of cell infusion are all factors that could affect the interpretation of these results. Additionally, study design, data extraction, risk of bias assessment, and variability of endpoint analysis could all bias this type of comprehensive analysis. Unidentified data discrepancies detected by weighted regression analysis might be directly associated with cardiac function, resulting in the conflicting results reported by meta-analyses [30]. Infusion of functionally active cellular products in larger and well-designed phase III clinical trials with appropriate control subjects could be critical to elucidating whether bone marrow cell transplantation represents an efficacious therapy to treat the patients with ischemic heart diseases (Table 1). Of note, the preliminary findings of a study directly comparing mesenchymal stem cells and bone marrow mononuclear cells has been reported, providing a platform for definitive assessment of cell type-specific outcomes [31].

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