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Review

Rethinking Stem Cell Therapy for Cardiomyopathy in View of Mammalian Cardiac Regeneration Limits

Melvin E. Klegerman

Department of Internal Medicine, Division of Cardiovascular Medicine, University of Texas Health Science Center at Houston, Houston, TX 77054, USA; melvin.e.klegerman@uth.tmc.edu

Abstract

Stem cell transplantation represents a promising approach to regenerative medical therapies for many disorders, including neurodegenerative, rheumatologic, digestive, orthopedic, hematologic and cardiovascular diseases. In the case of stem cell therapy for ischemic cardiomyopathy, this promise has been blunted by a lack of understanding of critical factors governing regeneration of adult human heart muscle. This review aims to (1) summarize the characteristics and types of stem cells used to treat cardiomyopathies; (2) to survey the results of clinical trials conducted with stem cells used to treat cardiomyopathies; and (3) to understand limitations of and obstacles to effective stem cell therapies for cardiomyopathies. Stem cells contribute both constitutive and paracrine functions, exemplified by their ability to replace damaged and destroyed cells and to secrete cytokines and chemokines, respectively. Cardiac regenerative capacity, while high in most fish, amphibians and newborn mammals, is extremely limited in adult mammals. Alterations in physiologic functions necessary to prevent destructive oxidation in endotherms forced a trade-off with tissue regenerative capacity in these animals. A review of 15 stem cell trials for ischemic cardiomyopathies supports conclusions based on these considerations and underscores the need to maximize stem cell delivery efficiency. Experimental approaches to achieve this objective are reviewed.

Keywords: stem cells; ischemic cardiomyopathy; heart failure; tissue regeneration; wound healing; cardiomyocytes; myocardium

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1. Tissue Regeneration

One of the most enduring conundrums in biology is the profound variability in regenerative capacity among the members of the animal kingdom. Invertebrates are legendary for their ability to regenerate entire body parts—starfish limbs and planaria worms that can be bisected, with each half regenerating the other. Among vertebrates, amphibians are known for regenerative capacity among adults—limb regrowth among frogs, salamanders and newts. This regenerative capacity extends to heart repair. Function of this organ can be readily restored in these species after injury as it is for any other organ or tissue. However, among adult mammals, tissue regeneration is mainly limited to wound healing. To gain insight into the tissue regenerative capacity of these organisms, exploration of wound healing processes is instructive.

1.1. Wound Healing Programs

The first major event of wounding is bleeding, which triggers the clotting cascade and consequent clot formation, consisting primarily of a fibrin matrix and aggregated

platelets, with entrapped erythrocytes. Thrombin, which triggers both fibrin formation from fibrinogen and platelet activation, is also a key component of the protease-activated receptor (PAR) regulatory system, which coordinates the wound healing response, particularly inflammatory processes [1]. During resolution of the wound, the clot is liquidated by dissolution of the fibrin matrix through the action of plasmin, which is generated from plasminogen by tissue plasminogen activator [2].

The function of inflammation is to enable tissue remodeling by liquefaction of the extracellular matrix and destruction of pre-existing cells. The classic characteristics of the inflammatory process were summarized by the first century Roman physician Celsus as "rubor, calor, dolor, tumor" or redness, heat, pain and swelling [3]. All of these effects result from the actions of neutrophils, whose massive infiltration of the wound area can be considered the first major event of wound healing. Rubor is caused by extravasation of red blood cells from capillaries due to increased vascular permeability, induced by agents such as histamine and thrombin, which bind to endothelial G-protein-coupled receptors [4,5], leading to intracellular Ca^{++} release and protein kinase C (PKC) activation, ultimately resulting in endothelial hyperpermeability [6]. Histamine is secreted by mast cells in response to IL-1, a major cytokine released by neutrophils [7,8].

A major cause of both rubor and calor is increased blood flow to the wound, caused by the same mechanisms that contribute to increased vascular permeability. Nitric oxide (NO) generation in endothelial cells, a central event in these pathways, also causes cyclic GMP (cGMP) production in adjacent vascular smooth muscle cells (VSMC), resulting in VSMC relaxation and vessel dilation, increasing the local blood flow and fostering neutrophil migration to the site [9]. Neutrophils also follow a temperature gradient [10]. Catabolic processes carried out by neutrophils that cause the cell destruction required for tissue remodeling also generate heat [11].

Dolor is a consequence of nerve endings embedded in liquifying tissue, where degradative processes cause cells to die. The pain of inflammation, however, also serves to immobilize the wounded area, decreasing the probability of further injuring the wound. It is likely that immobilization is not simply incidental to the harsh conditions of tissue rearrangement, since inflammatory mediators decrease the thresholds of neuronal excitability and increase the sensitivity of firing rates, thereby causing peripheral and central sensitization [12], so that pain is an adaptive characteristic of the inflammatory process that is meant to influence the behavior of the organism.

Tumor is produced by some of the same processes that bring about rubor and calor—increased blood flow due to vascular dilation, favoring an influx of neutrophils to the wound site. The consequences of this influx—release of proteins and accumulation of their degradation products—contribute to the edematous influx of fluid that causes the swelling, which also serves to immobilize the wound area [13]. Monocytes and macrophages are central to the termination of inflammation, with macrophages phagocytosing apoptotic neutrophils [14].

To accomplish this, intermediate monocytes (IMs), which have pro-inflammatory characteristics [15], enter the wound site, developing into pro-inflammatory M1 macrophages [16]. After about 4 days, circulating IMs convert to non-classical monocytes (NCMs), which have anti-inflammatory characteristics [17], while macrophages at the wound site transition to an anti-inflammatory M2 phenotype [16]. Among other factors that will be reviewed in the next section, M2 macrophages secrete transforming growth factor-β (TGF-β), which causes fibroblasts to transform into collagen-producing myofibroblasts as part of a fibrotic process [18]. Collagen is the main component of scar formation, the last stage of wound healing.

The cells and growth factors involved in wound healing (Table 1) are indicative of the tissue rearrangements and restoration occurring during the process, the stages of which are summarized in Figure 1. Neutrophil and macrophage contributions have been summarized. Fibroblasts are the main cellular components of connective tissue, and their proliferation is promoted by fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF) [19]. Their conversion to myofibroblasts, induced by transforming growth factor-β (TGF-β), is the critical step in fibrosis, resulting in scar formation [20]. Endothelial cells and vascular smooth muscle cells are the major components of angiogenesis, a vital aspect of tissue regeneration governed by vascular endothelial growth factor (VEGF) [21]. Skin regeneration mainly involves epithelial cells and keratinocytes, stimulated by epidermal growth factor (EGF) and keratinocyte growth factor (KGF) [22,23].

Table 1. Cells and growth factors involved in wound healing.

Cells	Growth Factors
FIBROBLASTS	EPIDERMAL GROWTH FACTOR (EGF)
MYOFIBROBLASTS	INSULIN-LIKE GROWTH FACTOR (IGF)
SMOOTH MUSCLE CELLS	FIBROBLAST GROWTH FACTOR (FGF)
ENDOTHELIAL CELLS	KERATINOCYTE GROWTH FACTOR (KGF)
KERATINOCYTES	PLATELET-DERIVED GROWTH FACTOR (PDGF)
IMMUNE CELLS Neutrophils Macrophages	TRANSFORMING GROWTH FACTOR (TGF)
EPITHELIAL CELLS	VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF)
	NERVE GROWTH FACTOR (NGF)

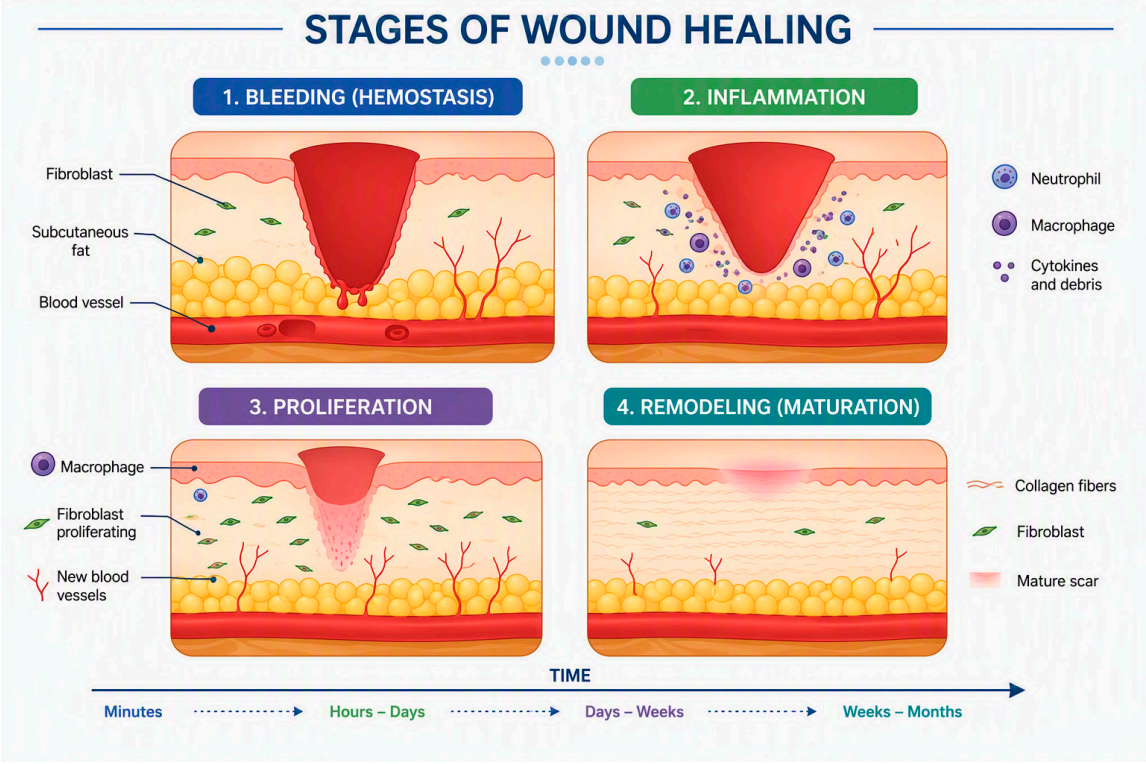


Figure 1. Schematic of major stages of normal wound healing. Image created with Microsoft 365 Copilot.

1.2. Cytokines in Wound Healing

The M1 macrophages that promote the inflammatory response secrete the pro-inflammatory cytokines TNFα, IL-1β, IL-6, IL-12 and IL-23 [24], while M2 macrophages terminate inflammation by secreting the anti-inflammatory cytokines IL-4, IL-10 and IL-13. They also secrete TGF-β, which promotes fibroblast conversion to myofibroblasts, followed by deposition of collagen and the initiation of the fibrotic program [18,24,25].

As will be seen, fibrosis in adult mammalian wound healing programs is a natural endpoint, resulting in scar formation, which is suitable for binding injured tissue. However, it is disadvantageous for other tissue regeneration, especially internally, in these animals. In addition, stem cells, considered in the next section, play a controlling role in wound healing by secreting cytokines as well.

2. Stem Cells

2.1. History

In 1868, the German biologist Ernst Haeckel coined the term *Stammzelle*, meaning stem cell, to denote both the single cell from which all multicellular organisms descended and the fertilized egg from which all cells of an organism derive [26]. Twenty-four years later, Theodor Boveri and Valentin Haecker first used the term "stem cell" in tracing embryonic germ cells that give rise to different tissues. During the following decade, Pappenheim and Neumann extended the stem cell concept to hematopoiesis, postulating the existence of a progenitor cell for all blood cells [26]. This cell was not definitively identified until 1963, by McCulloch and Till [27]. Five years prior to that, Georges Mathé achieved a practical medical application of the concept by performing the first bone marrow transplant, to treat radiation exposure [28].

In 1981, embryonic stem cells were first isolated from mouse blastocysts and cultured by British biologists Martin Evans and Matthew Kaufman [29]. Human embryonic stem cells were first isolated by James Thomson 17 years later [30]. In a major breakthrough for stem cell research and technologies based on it, Shinya Yamanaka's team in Japan converted mouse skin fibroblasts into pluripotent stem cells (iPSCs) by transduction of four defined transcription factors, Oct3/4, Sox2, Klf4, and c-Myc, in 2006 and did the same with adult human dermal fibroblasts one year later [31]. By this time, cardiac stem cell transplantation clinical trials were already underway. Highlights of stem cell history are outlined in Table 2.

Table 2. Stem cell history.

Event	Achievement
1868—Ernst *H*aeckel	*Stammzellen*
1892—*H*aecker and *B*overi	Stem Cells
1903–1912—*P*appenheim and *N*eumann	Hematologic Precursor Cells
1958—Georges Mathé	First Bone Marrow Transplant
1963—*M*cCulloch and *T*ill	Hematopoietic Stem Cells
1981—*E*vans and *K*aufman	Isolation and Culture of Embryonic Stem Cells
2006—Shinya Yamanaka	Induced Pluripotent Stem Cells
2001	First Cardiac Stem Cell Transplant Clinical Trials

2.2. Stem Cell Properties

2.2.1. Self-Renewal

Stem cell self-renewal is the ability to undergo repeated cycles of cell division and proliferation, while maintaining an undifferentiated state. There are two types of stem cell proliferation, *asymmetric* and *stochastic*. The former refers to the ability of a stem cell to divide into one mother cell, which is identical to the original stem cell, and a daughter cell that is differentiated. The undifferentiated cell maintains its potency, as well as its proliferative potential, which requires complex control of the cell cycle [32].

Stochastic differentiation involves symmetric stem cell division into two differentiated daughter cells, while another stem cell undergoes mitosis to produce two daughter cells of identical proliferative potential and potency. Maintenance of self-renewal status requires telomerase lengthening of the 3′ end of telomeres within the stem cell after division [33]. These mechanisms enable stem cells to persist in tissues in a quiescent state to replace damaged and dead cells when needed, while also fulfilling a constituent differentiated cell replacement function.

2.2.2. Potency

Potency refers to the ability of a particular stem cell to differentiate into progeny of less potency. *Totipotent* stem cells populate the Morula, which is the first stage after division of the fertilized egg, and have the ability to create a complete multicellular organism. *Pluripotent* stem cells populate the blastocyst, which is the structure that undergoes embryogenesis, and can differentiate into all cells of the three germ layers, *endoderm*, *mesoderm*, and *ectoderm*. *Multipotent* stem cells arise during gastrulation and embryonic organogenesis. Continuing into adulthood, they can form related tissues, such as cardiovascular, neurologic or immunologic. As they divide, multipotent stem cells give rise to *oligopotent* stem cells that can differentiate into cells of a particular tissue, while *unipotent* stem cells represent the last stage of stem cell differentiation, retaining only the property of self-renewal [34]. Early and late stages of potency are summarized in Figure 2.

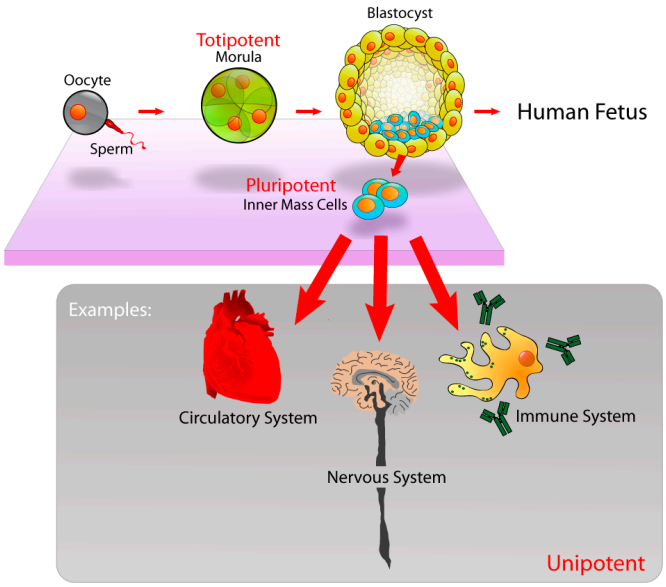


Figure 2. Overview of stem cell potency with stages of development. Figure adapted from Mike Jones, licensed under CC BY-SA 4.0 via Wikimedia Commons.

2.3. Stem Cells in Wound Healing

In many ways, stem cells appear to drive the direction of wound healing and tissue regeneration in general. They do this through two functions: *paracrine* and *constitutive*. The first involves secretion of soluble factors that impact the functions of cells involved in the various phases of wound healing, as well as establishing and maintaining the structural and functional integrity of the tissue. The second derives from stem cells' ability to strategically populate various tissues and differentiate to replenish damaged and destroyed cells, such as those of the epithelium, endothelium and extracellular matrix.

Mesenchymal stem cells (MSC), multipotent stromal progenitor cells that mainly derive from bone marrow and adipose tissue, are probably the most important stem cells involved in wound healing and tissue regeneration in general [35,36]. Serving both paracrine and constitutive roles, MSCs secrete VEGF, basic fibroblast growth factor (bFGF), keratinocyte growth factor (KGF), insulin-like growth factors (IGF-1 and IGF-2), IL-6, macrophage migration inhibitory factor (MIF), and other factors promoting angiogenesis, neutrophil and macrophage functions, and immune mechanisms [37]. Constitutively, MSCs have the potential to differentiate into cells of the mesenchymal lineage, i.e., adipocytes, osteocytes, and chondrocytes, as well as cells of skin and muscle [38,39].

Hematopoietic stem cells (HSC), which are multipotent, reside mainly in the bone marrow and differentiate into all of the mature blood cell types [40], making their role primarily constitutive. Their contribution to wound healing programs involves their ability to modulate the immune response, stimulate angiogenesis and promote tissue repair [41]. The role of endothelial progenitor cells (EPCs) is primarily paracrine. They stimulate angiogenesis by secreting thymosin β4, while muscle-derived stem cells secrete VEGF [35,42]. A major factor in wound healing is epidermal stem cells (EPSC), which are multipotent and primarily constitutive. Originating in the basal epidermal layer, regions of hair follicles and sweat glands, EPSCs can regenerate all epidermal layers, as well as hair follicles, sweat glands and sebaceous glands [43].

3. Cardiac Regeneration Potential in Vertebrates

Experimental studies of cardiac regeneration have relied on three approaches: *resection*, characterized by surgical injury of the myocardium, which favors a wound healing program, *cryoinjury*, and left anterior descending (LAD) coronary artery ligation in mammals (including a few cases of myocardial infarction in newborn humans) [44]. Based on these experimental methods (and cases), recent advances in the understanding of vertebrate cardiac regeneration mechanisms have provided insights into the inherent limitations of options for treatment of myocardial damage, particularly heart failure, including stem cell transplantation.

While cardiac regeneration potential is high in vertebrate neonates up to 7 days after birth and in most adult fish and amphibians, it is low in adult mammals, with few exceptions [44]. Examples of this are shown in Table 3. Although high cardiac regeneration potential was observed in newborn humans in cases of spontaneous MI and cardiac regeneration potential is undoubtedly low in adult humans, loss of regenerative potential in humans 2–7 days after birth, like in other mammalian species up to pigs, cannot be unambiguously confirmed. The primary mechanisms responsible for high cardiac regeneration potential in lower vertebrates and the limitations consequent to their impairment fall into 5 categories: cardiomyocyte proliferation, reversible fibrosis, angiogenesis, inflammatory and regenerative immune responses, and altered energy metabolism. These mechanisms will be summarized in the following sections.

Table 3. Cardiac regeneration in vertebrates after injury.

Class	Species	Regeneration Capacity	Time to Regeneration (Days)
Fish	Zebrafish	High	60
	Goldfish	High	60
Amphibians	Western Clawed Frog	High	60
	Axolotl	High	90
	Eastern Newt	High	70
Mammals	Spiny Mouse	High	
	Neonatal rat, rabbit, pig, sheep, human	High < P7	
	Adult rat, rabbit, pig, sheep, human	Low > P7	

P7 = postnatal day 7.

3.1. Cardiomyocyte Proliferation

When myocardial injury occurs in lower vertebrates, cardiomyocytes adjacent to damaged cells quickly enter the cell cycle and proliferate to replace the injured tissue [45–47]. This requires that the cardiomyocytes be mononucleate and diploid, allowing them to undergo mitosis readily [47,48]. In neonatal mammals, cardiomyocytes are mononucleated, diploid and able to proliferate for at least one week after birth [49–51]. After one week, in mice up to pigs, 95% of cardiomyocytes stop dividing, becoming binucleate and polyploid [44,52]. In humans, the situation is more complex.

The DNA content in the majority of cardiomyocytes increases via endoreplication and the annual cardiomyocyte turnover rate drops to around 1% by early adulthood [49,50,53]. The question of whether appreciable cardiomyocyte proliferation occurs in adult humans remains controversial, however, and is complicated by the difficulty in unequivocally assessing the identity of proliferating cells in the human heart. Vicinanza et al. have identified a small proportion of c-kit+ cardiac stem cells that appear to undergo cardiomyocyte proliferation [54].

In a very elegant study using virtually pure cardiomyocyte populations prepared by flow cytometry and analyzed for C-14 content relative to atmospheric C-14 levels due to atomic bomb tests, Bergmann et al. [53] established that about 25% of cardiomyocytes are binucleate throughout life, all of them become tetraploid between ages 9 and 10, about 1% per year turn over at age 25, and that this turnover rate declines to 0.45% by age 74. These investigators concluded that "with this turnover rate, most cardiomyocytes will never be exchanged during a normal life span," and "the limited functional recovery in humans after myocardial injury clearly demonstrates insufficient regeneration of cardiomyocytes."

The shift of cell structure to preclude cardiomyocyte proliferation coincides with a switch in energy metabolism from glycolysis to oxidative phosphorylation [55]. The inverse correlation between oxidative metabolism in adult mammals and tissue regenerative potential points to the price of mammalian evolutionary strategy, involving high mobility and endothermy, requiring a high metabolic rate and the enhanced cardiac output provided by a four-chamber heart. The oxidative conditions of mammalian physiology generate reactive oxygen species (ROS) that are particularly damaging to DNA [56,57]. Propagation of the resulting mutations during cell proliferation in critical organs, especially the heart, could be lethal. Thus, a trade-off is required between the adaptive advantages of mammals and necessary limitations of tissue regeneration.

What is left is the wound healing program, which is the most critical form of tissue regeneration required by this highly mobile animal class. Vulnerabilities in the regenerative capacity of internal organs can be tolerated on an evolutionary scale, since injuries of that magnitude would mean the sacrifice of individuals, although lung injuries due to volcanic eruptions and forest fires may become normally local extinction events. What could not be anticipated is widespread organ damage within a species due to unprecedented lifestyle aberrations.

3.2. Reversible Fibrosis

As summarized in Section 1.1, fibrosis is the last stage of the adult mammalian wound healing program, resulting in scar formation. This is sufficient for surface wounds, even if they are penetrating, within the demands for survival. However, internal organs such as the heart will not tolerate more than minimal scarring, which can seriously interfere with organ function. In the case of the heart, scarring often results in disruption of conduction pathways. It is well established that cardiac fibrosis, such as scar formation after myocardial infarction, leads to heart failure [58].

In lower vertebrates, fibrosis after cardiac injury is reversible and quickly resolved, allowing replacement of fibrotic tissue with functional tissue [59,60]. An important feature of this process is that cardiac myofibroblasts in lower vertebrates and neonatal mammals deposit collagen into a relatively pliable extracellular matrix (ECM) [61,62]. The stiffer ECM in adult mammalian hearts means that reversal of fibrosis could result in muscle weakness and cardiac rupture [62,63].

3.3. Angiogenesis, Revascularization, and Inflammatory and Regenerative Immune Responses

While the coronary circulation in adult mammals, especially humans, has adapted well to the high-energy demands of these organisms, neovascularization after myocardial infarction is insufficient to properly restore heart function, possibly related to the highly organized nature of the cardiac circulatory system [64]. In lower vertebrates characterized by high cardiac regenerative potential, the cardiac circulation is relatively disorganized, with many fish and amphibians lacking a coronary vasculature, the function of which is fulfilled by a plexus of endocardial extensions [65,66].

Revascularization after MI can be improved by available mechanisms, however. For instance, lymphangiogenesis after cardiac injury in adult mammalian hearts can be enhanced by treatment with VEGF-C isotypes [67,68]. This suggests a mechanism by which stem cell therapy could potentiate cardiac regeneration in human subjects, through stem cells' paracrine function. As noted in Section 2.3, both mesenchymal and hematopoietic stem cells secrete VEGF.

Initially, the wound healing program is followed after cardiac injury, involving neutrophil influx and inflammation. Differences between lower vertebrates and mammals begin to be seen in clearance of neutrophils and reversal of fibrosis in the former animal species, in which macrophages play a leading role [69]. Thereafter, the critical processes of cardiomyocyte proliferation and flexible ECM morphology, which are blocked in adult mammals, occur [70].

3.4. Altered Energy Metabolism

Consistent with the hypothesis that oxidative metabolism in adult mammals prevents heart regeneration by proliferation of mononucleate, diploid cardiomyocytes as a guard against oxidative DNA damage and fatal degradation of myocardial function, the perinatal withdrawal of mammalian cardiomyocytes from the cell cycle coincides with a switch in energy metabolism in these cells from glycolysis to oxidative phosphorylation [55]. Subjecting adult mice to chronic severe hypoxemia resulted in reduced ROS levels, in-

creased cardiomyocyte proliferation, and improved outcome after MI [71]. Because the adult zebrafish heart is two-chambered, allowing mixing of oxygenated and deoxygenated blood, the cardiomyocytes in these animals exist in a much more hypoxic environment than that of adult mammals. Induced systemic hyperoxia in zebrafish reduced cardiomyocyte proliferation and impaired the regenerative response [72].

When the human heart is subjected to sudden episodes of severe hypoxia, as occurs in cases of reversible myocardial ischemia–reperfusion injury, it creates a condition known as *myocardial stunning*. The heart muscle function is impaired for a period of time but eventually recovers. Since cell death does not occur, cardiomyocyte regeneration is not relevant. Thus, induced hypoxia has not been considered as a therapeutic option [73].

Oxidative metabolic suppression of cardiomyocyte proliferation apparently is orchestrated by thyroid hormones. Cardiomyocyte diploidy has been linked to metabolic rate and body temperature (both thyroid-dependent), as well as thyroid hormone levels [48]. Thyroid hormone levels rise in newborn mice shortly before curtailment of cardiac regenerative potential [74]. Blocking thyroid hormone signaling decreased polyploidy in the adult mouse heart, down-regulated oxidative phosphorylation, and increased cardiomyocyte proliferation after myocardial infarction, with concomitant reduction in fibrosis and improvement of functional outcome [48].

4. Stem Cell Therapy for Heart Failure in Human Subjects

Investigators reviewing studies of stem cell therapy for heart failure have concluded that paracrine functions are more important than constitutive functions of stem cells and perhaps are exclusively responsible for the observed benefits of this approach [75,76]. As mentioned, VEGF secretion by both MSCs and HSCs could provide most of the known regenerative potential of the injured mammalian heart. Evidence for transdifferentiation of injected bone marrow-derived cells into functional cardiomyocytes is contradictory [77]. It was reported that injection of cardiosphere-derived cells into infarcted mouse hearts induced endogenous stem cells to localize in the myocardium and proliferate [78]. Bai et al. also reported that freshly isolated adipose-derived stem cells could differentiate into cardiomyocytes in vivo [79].

Major evidence in support of the paracrine hypothesis comes from recent attempts to improve cardiac function by administering extracellular vesicles and exosomes released by stem cells in preclinical heart failure models [80–82]. These vesicles contain microRNAs, proteins, lipids and growth factors that constitute much of the paracrine repertoire of stem cells and affect regenerative and pathologic mechanisms such as angiogenesis, inflammation, cell death and fibrosis. However, the ability to reconstitute the regenerative potential of stem cells with subcellular components has not yet advanced to the stage where they can be administered clinically.

Another major factor influencing the success of stem cell therapy for cardiac injury is the proportion of administered stem cells retained in heart muscle [83]. Typically, only 1–10 percent of transplanted cells are retained at the site after two hours [77]. Ott et al. reported that less than 1% of transplanted skeletal myoblasts survived in the myocardium [84]. Laflamme et al. reported that 18% of injected human embryonic stem cell-derived cardiomyocytes was retained in infarcted rat hearts, compared with 90% in uninjured hearts [85]. Transplanted cardiomyocytes derived from induced pluripotent stem cells could no longer be detected in infarcted mini pig hearts after 8 weeks [86]. VEGF dose response is another rationale for maximizing stem cell delivery to injured myocardium [87].

A major factor in determining the proportion of residual stem cells persisting in the myocardium after initial engraftment is the ability of the cells to survive the harsh inflammatory environment created by the wound healing program [88]. Thus, cell survival

strategies, as well as engraftment potentiation, have been employed for augmentation and delivery enhancement protocols summarized in Sections 4.4 and 6. In this regard, hypoxic preconditioning, while not an option in vivo, has been employed for treatment of stem cells in vitro prior to transplantation [88].

Based on these considerations, one can conclude that combinations of mesenchymal and hematopoietic stem cells will be most effective in fostering cardiac regeneration after myocardial infarction, while preventing or ameliorating heart failure. Beneficial effects should also be proportional to the number of stem cells delivered. Confirmation of these projections, as well as insight into other considerations such as delivery route and auxiliary treatment procedures, may be achieved by review of clinical trials of stem cell therapy for heart failure that have already been conducted.

The first stem cells used for heart failure therapy in clinical trials, beginning in 2004, were autologous skeletal myoblasts. Thereafter, bone marrow-derived cells consisting of hematopoietic and mesenchymal stem cells and endothelial progenitor cells, adipose-derived cells that include stromal cells and pericytes, cardiac cells, embryonic stem cells, and induced pluripotent stem cells have been used in these trials. Each will be reviewed to examine factors that could inform future directions for cardiac stem cell therapy. Considering that this is a narrative, rather than a systematic, review, it should be emphasized here that the purpose of this clinical trial review is to discern what factors may be important to eventual effectiveness of stem cell therapy for heart failure, rather than an objective review of these trials to judge their success in current practice.

Searches were conducted in ClinicalTrials.gov, using the search terms “heart failure” and “stem cells;” and in PubMed and Google, using the search terms “heart failure,” “stem cells,” and “clinical trials.” Trials showing positive results were selected from reviews of the subject [77,89] and from summaries of the clinical trials themselves. Searches in ClinicalTrials.gov and PubMed were limited to post-2000 information. “Positive results” were defined as increases in left ventricular ejection fraction (LVEF), decrease in scar tissue, improvements in cardiac functional parameters, and/or improvements in codified quality of life scores, such as that of the New York Heart Association (NYHA).

4.1. Autologous Skeletal Myoblasts

Skeletal myoblasts (SkMs), which are precursor cells of adult myofibers, were an attractive choice to begin human trials of cardiac stem cell therapy, mainly because they could be harvested from muscle biopsies of patients, obviating tissue compatibility issues, and because cells derived from these samples could be expanded by cell culture techniques [90,91]. In addition, these cells are committed to a myogenic, functionally contractile phenotype and are able to form new myotubes in scarred myocardium [90,92]. Preclinical studies in animals established that heart transplantation of these cells led to formation of new contractile tissue that improved ventricular volumes, wall motion, ejection fraction and exercise tolerance [93,94].

From 2004 to 2011, four clinical trials (Phase 1-2a), POZNAN, MAGIC, CAuSMIC and SEISMIC, were carried out using autologous skeletal myoblasts. In the POZNAN trial, ASM transplantation was performed via a percutaneous trans-coronary venous approach using the TransAccess® catheter system under fluoroscopic and intravascular ultrasound (IVUS) guidance in patients with post-infarction LV dysfunction [93]. The MAGIC trial, a multicenter, randomized, placebo-controlled, double-blind study, included patients with LV dysfunction (LVEF $\leq$ 35%), MI, and indication for coronary surgery [91]. In the CAusMIC study, 23 subjects (11 control and 12 treatment) with previous MI and HF, NYHA functional class II to IV, were enrolled [94]. In the SEISMIC trial, 40 patients (14 controls and 26 treatment) were randomized to ASM therapy vs. optimal medical treatment. The primary

safety endpoint was defined as the incidence of procedural and device-related serious adverse effects, while the efficacy endpoints were defined as the change in global LVEF by MUGA scan, change in NYHA classification of heart failure and in the distance achieved during a 6 min walk test at a 6-month follow-up [90].

Reflecting the advantage of in vitro expansion, cell numbers administered (all intracardially) ranged from 1.7×10^7 to 8×10^8. The best outcomes achieved were an 8% enhancement of left ventricular ejection fraction (LVEF) and a significant quality-of-life improvement, but outcomes did not appear to be proportional to number of cells administered. Most problematic was the tendency of skeletal myoblast cell therapy to cause ventricular tachyarrhythmias and sudden cardiac death. This arrhythmogenesis occurs because transplanted skeletal myoblasts fail to form proper electrical gap junctions with host cardiomyocytes, creating electrically isolated tissue islands that disrupt normal conduction and trigger re-entrant spiral waves [95]. The conditions and outcomes of these trials are summarized in Table 4.

Table 4. Stem cells for cardiomyopathy clinical trials: Autologous skeletal myoblasts.

Trial	Year/ Phase (n)	Pathology	Route	Endpoints	Cell No.	Results	Reference
POZNAN	2004 1 (9)	HF LVEF 25–40%	Trans-Access Catheter	NYHA Class LVEF	1.7×10^7–1.1×10^8	All NYHA Cl 1 LVEF ↑ 3–8%	[93]
MAGIC	2007 RPCDP (97)	LV Dysfunction Post MI	Peri-scar injection	6-month LVEF	3×10^8–8×10^8	NS	[91]
CAuSMIC	2008 1 (23)	CHF LVEF $\leq$ 40%	Epi-cardial Catheter	Qual. Life, Syst./Diast. Dia., volt.	3×10^7–6×10^8	QL sign. ↑ Dia. NS Volt. ↑ <0.05	[94]
SEISMIC	2011 2a (40)	CHF LVEF 20–45%	Intramyo-card. MyoCell MyoCath	6-month LVEF NYHA Cl. 6 min. walk	1.5×10^8–8×10^8	NS	[90]

Abbreviations: CHF, congestive heart failure; Cl, Class; Dia., diameter; Diast., diastolic; HF, heart failure; intramyocard., intramyocardial; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NS, not significant; NYHA, New York Heart Association; QL, quality of life; RPCDB, randomized, placebo-controlled, double-blind; Sign., significant; Syst., systolic; Volt., voltage.

4.2. Hematopoietic and Mesenchymal Stem Cells

Even before autologous skeletal myoblasts were being used in early cardiac stem cell trials, bone marrow stem cells were utilized for this therapy, which was an obvious choice since bone marrow transplantation was an established practice by then. It was known that bone marrow contained both HSC and MSC and, thus, this approach could be considered a good test of the hypothesis that both types of stem cells may be optimal for myocardial regeneration in adult humans. By 2009, suitable stem cell markers and GMP (Good Manufacturing Practices)-compliant methods to isolate and expand cells expressing them were known. Thus, clinical trials utilizing relatively pure stem cell populations could be conducted.

Clinical trials utilizing BMSC (BOOST, REPAIR-AMI and TIME) achieved LVEF enhancement of 2.8–6.0% with the increased cell numbers characteristic of bone marrow transplants [96–99], while comparable results were obtained with lower numbers of stromal and autologous MSC in the MSC-HF and POSEIDON trials (Table 5) [100,101]. Improvements were less impressive with $CD133^+$ HSC in the PERFECT trial [102], but the number of cells administered was an order of magnitude lower than in the MSC trials, reflecting the specific subpopulation of stem cells isolated for administration.

Table 5. Stem cells for cardiomyopathy clinical trials: HSC and MSC.

Trial	Year/ Phase (n)	Pathol.	Stem Cell Type	Route	Endpoints	Cell No.	Results	Ref.
PERFECT	2009–16 3 (82)	Post-MI LVEF 25–50%	HSC $CD133^+$	Intramyocard. w/CABG revasc.	Net LVEF	0.5×10^6–5×10^6	LVEF ↑ 2.6% NS	[102]
REPAIR-AMI	2004–05 RPC (204)	Post MI LVEF ≤ 45%	BMC (HSC + MSC)	Culprit Artery Catheter	4-month LVEF, CVE	$2.4 \times 10^8 \pm 1.7 \times 10^8$	LVEF ↑ 3.9% ($p = 0.02$) CVE $p = 0.03$	[96]
BOOST	2002–03 RPC (60)	Post MI LVEF = 50%	BMC (HSC + MSC)	Culprit Artery Catheter	6-month LVEF	$2.5 \times 10^9 \pm 9.4 \times 10^8$	LVEF ↑ 6.0 ($p = 0.0026$)	[99]
TIME	2008–11 1/2 (85)	Post MI LVEF ≤ 45%	BMC (HSC + MSC)	Intracoronary catheter	LVEF LVEDV, LVESV	1.5×10^8	LVEF ↑ 2.8% NS Vols. NS	[97,98]
MSC-HF	2009–13 2 (60)	HF LVEF < 45%	MSC Stromal	Intramyocard. Catheter	12-month LVESV LVEF	$7.8 \times 10^7 \pm 6.8 \times 10^7$	LVESV ↑ 17 mL ($p < 0.0002$) LVEF ↑ 6.2 ($p < 0.0001$)	[100]
POSEIDON	2010–11 1/2 (15)	HF NYHA Cl 2,3	MSC Autol.	Trans-endocardial	12-month 6mwlk MLHFQ score LV vols., EF	2×10^7–2×10^8	6mwlk $p = 0.02$ MLHFQ $p = 0.009$ LV vols, EF NS	[101]

Additional abbreviations: Autol., autologous; BMC, bone marrow cells; CABG, coronary arterial bypass graft; CVE, cardiovascular event; HSC, hematopoietic stem cell; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; MLHFQ, Minnesota Living with Heart Failure Questionnaire; MSC, mesenchymal stem cell; revasc, revascularization; vols., volumes; 6mwlk, 6 min walk.

The REPAIR-AMI trial was a multicenter trial in which patients with AMI were randomly assigned to receive an intracoronary infusion of BMC or placebo medium into the infarct artery 3–7 days after successful reperfusion therapy [96]. In the BOOST trial, patients who underwent successful PCI for STEMI were randomly assigned to a control group or to intracoronary transfer of BMC 4–8 days after PCI [99]. The TIME trial was designed to be the first cell therapy trial sufficiently powered to determine if timing of cell delivery following STEMI affects recovery of LV function. It was a randomized, double-blind, placebo-controlled trial involving patients with anterior STEMIs resulting in LV dysfunction. Outcomes were assessed up to 2 years after treatment [97,98].

The PERFECT trial was a Phase III multicenter, double-blinded, randomized placebo-controlled study designed to assess clinical safety and efficacy of intramyocardial $CD133^+$ bone marrow SC treatment combined with CABG for induction of cardiac repair [102]. Post-MI patients with chronic ischemia and reduced LVEF (25–50%) were randomized to receive either intramyocardial placebo or SC. The MSC-HF trial was a randomized, double-blind, placebo-controlled study in which patients were randomized 2:1 to intramyocardial injections or MSC or placebo [101]. The POSEIDON trial was a Phase 1/2 randomized comparison of allogeneic and autologous MSCs in patients with LV dysfunction due to ischemic cardiomyopathy with a 13-month follow-up. MSC were delivered by transendocardial injection into 10 LV sites [100].

4.3. Cardiac Stem Cells

Investigations of cardiac progenitor cells, which are oligopotent stem cells, demonstrated their regenerative potential in animal studies. The ability to grow these cells as cardiospheres in culture from percutaneous endomyocardial biopsies made them a promising source of stem cells for clinical trials. Two clinical trials utilizing these cells, CADUCEUS and PERSEUS, emphasized the ability of CDCs to reduce scar size. The former study was conducted in adult patients 1.5–3 months after MI with reduced LVEF, who were randomly allocated to receive CDCs or standard care. The study showed a significant reduction in scar size 6 months after CDC administration, but no significant increase of LVEF [103]. There was a question of whether MRI-measured scar size reduction was an artifact caused by contrast enhancement due to revascularization, but the method was later validated by histological studies [104].

The PERSEUS trial featured an unusual patient population, consisting of pediatric patients with congenital single ventricle physiology 4–9 weeks after surgical reconstruction [105]. This was a Phase 2 randomized controlled study to assign patients to receive intracoronary infusion of CDCs or staged reconstruction alone. In this case, also, a significant reduction of scar formation was seen 3 and 12 months after CDC administration, but the marginal LVEF increase was not significant. The cell numbers administered were fairly low (~4–25 $\times$ 10^6), arguing against the hypothesis that a stem cell population with high regenerative potential can overcome a low inoculum. These studies are summarized in Table 6.

Table 6. Stem cells for cardiomyopathy clinical trials: Cardiac stem cells.

Trial	Year/ Phase (n)	Pathology	Route	Endpoints	Cell No.	Results	Reference
CADUCEUS	2009–10 1 (25)	Post MI LVEF 25–45%	Culprit Artery Catheter	6-month scar, via. heart mass, LVEF	12.5 $\times$ 10^6 – 25 $\times$ 10^6	Scar ↓, via. HM ↑ p < 0.02 LVEF NS	[103]
PERSEUS	2013–16 2 (41)	Single ventr. physiol. w/HF risk	Coronary IA	3-month, 12-month LVEF, scar meas.	3 $\times$ 10^5/kg	LVEF ↑ 2.9, 1.1% (NS); Scar ↓ (p < 0.01, < 0.02)	[105]

Additional abbreviations: HM, heart mass; IA, intraarterially; physiol., physiology; ventr., ventricle; via., viable; w/, with.

4.4. Stem Cell Augmentation

Attempts were made to improve the efficacy of MSC transplantation using an in vitro augmentation protocol, termed cardiopoietic stem cell therapy. Autologous MSC were treated in culture for 5 days with a "cardiogenic cocktail," consisting of 5% platelet lysate-supplemented high-glucose Dulbecco's Modified Eagle's Medium containing 2.5 ng/mL TGFβ, 5 ng/mL bone morphogenetic protein 4, 5 ng/mL activin A, 10 ng/mL FGF 2, 100 ng/mL cardiotrophin, and 1 U/mL α-thrombin [106]. The C-CURE trial, utilizing this protocol and endoventricular administration of 6 $\times$ 10^8–1.2 $\times$ 10^9 cells resulted in a significant 6.5% improvement in LVEF after 6 months [106]. It was a prospective, multicenter, randomized trial in which data acquisition and analysis were performed in a blinded fashion.

CHART-1, another clinical trial utilizing the same augmentation protocol, but a lower, unspecified, number of cells, did not result in a significant improvement of LVEF [107]. This was a prospective, multicenter, randomized, sham-controlled, patient- and evaluator-blinded clinical trial that included 39 centers in Europe and Israel. The CONCERT-HF trial took another approach to MSC augmentation, adding c-kit positive cardiac progenitor cells

(CPC) to the treatment inoculum, which consisted of 1.5×10^8 MSC + 5×10^6 CPC, injected transendocardially [108]. While significant improvements were seen in the proportion of major adverse cardiac events (MACE) and quality of life (Minnesota Living with Heart Failure Questionnaire score), there were no significant improvements in LVEF, scar size, or 6 min walking distance. The improvement in both MACE and quality of life metrics was attributable to administering the combination of MSC and CPC, rather than either alone. The augmentation trials are summarized in Table 7.

Table 7. Stem cells for cardiomyopathy clinical trials: Augmentation protocols.

Trial	Year/ Phase (n)	Pathol.	SC Type/ Augmentatio	Route	Endpoints	Cell No.	Results	Ref.
C-CURE	2009–12 PR2-arm (48)	Post MI HF LVEF 15–40%	MSC Cardiogen. cocktail	Endovasc. NOGA XP catheter	6 mo. LVEF 6 min. walk	6×10^8–1.2×10^9	LVEF ↑ 6.5% ($p < 0.0001$) 6 mw $p < 0.02$	[106]
CHART-1	2012–15 PRDB (315)	HF LVEF ≤ 35%	MSC Cardiogen. cocktail	Endomyoc. inj. catheter	39 wk ACM, QL, 6 min. walk, LVEF	$>2.4 \times 10^7$	NS, LVEF Mann-Whitney 0.55 (NS)	[107]
CONCERT-HF	2016–18 2 (125)	HF LVEF = 28.6 ± 6.1% Scar = 19.4 ± 5.8% NYHA Cl 2,3	MSC ± C-kit$^+$ CPC	Trans-endocardial	12 mo MACE MLHFQ score LVEF, scar	1.5×10^8 MSC ± 5×10^6 CPC	MACE ↓ 22% (MSC p = 0.043), MLHFQ (MSC p = 0.05) (+CPC 0.023 LVEF, scar NS	[108]

Additional abbreviations: ACM, all-cause mortality; cardiogen., cardiogenic; CPC, cardiac progenitor cells; endomyoc., endomyocardial; endovasc., endovascular; inj., injection; MACE, major adverse cardiac events; PR, prospective, randomized; PRDB, prospective, randomized, double-blind.

5. The Critical Factor: Number of Stem Cells Delivered to the Myocardium

The results of the stem cell trials reviewed suggest that MSC may be the most effective in improving LVEF in cases of ischemic cardiomyopathy, perhaps because it is possible to administer larger numbers of these cells. Examination of clinical trial outcomes reviewed here suggest that LVEF increases ≥6.0% may have resulted from administration of $\geq 6 \times 10^8$ MSC. This corresponds to myocardial delivery of 6×10^6–6×10^7 cells based on a 1–10% localization estimate.

In an elegant study, Liu et al. assessed the efficiency of stem cell delivery by transfecting human CPC with a herpes simplex virus thymidine kinase (TK) PET reporter gene. After transplantation into murine myocardial infarction models, the cells were localized by injection of a ^{18}F-labeled TK substrate and positron emission tomography (PET) imaging, enabling the investigators to monitor the myocardial engraftment efficiency of the CPC [83]. They found that the PET signal correlated well (r = 0.64–0.80, $p < 0.0001$) with LV function expressed as percent fractional shortening. LV function was significantly higher in a high cell engraftment group, defined as PET signal ≥ 0.23% injected dose of PET tracer per gram of heart tissue, than in the low cell engraftment group (≤0.21%ID/g).

6. Experimental Attempts to Enhance Stem Cell Delivery to Injured Myocardium

Several investigators attempted to utilize the endogenous chemokine homing mechanism to promote localization of stem cells to injured myocardium. The major cardiac homing mechanism is through the chemokine SDF-1, which binds to CXCR4 on HSC and directs them to ischemic myocardium. Using a murine MI model, Zaruba et al. demonstrated that enhancement of this mechanism resulted in a significant increase of survival after induced MI, with less scar formation, inhibition of LV wall thinning, a reduction in apoptosis, and improved vascularization [109]. In another study, MSCs were preconditioned with SDF-1 in culture. The cells were then transplanted into rats following induced MI, resulting in increased cell proliferation within the injured myocardium, reduction in infarct size and fibrosis, and significant improvement in cardiac function compared to controls [110].

A variety of natural and synthetic biomaterials have been used as matrices for implantation and transplantation of stem cells into dysfunctional myocardial models, all with promising results. The former include collagen hydrogels, gelatin, alginate hydrogels, and extracellular matrix (ECM) scaffolds. The latter include polycaprolactone, polylactic/polyglycolic acid, polyurethane, methacrylated gelatin, and polyethylene glycol diacrylate [111].

Several groups explored physical methods of enhancing epicardial stem cell engraftment. Ichihara et al. coated ischemic epicardium with MSCs embedded in a hydrogel matrix in a rat heart failure model [112]. They found a 20% MSC engraftment efficiency after 28 days and a 13% improvement in LVEF by the treatment. More recently, allografts of 4–20 $\times$ 10^7 iPSC-derived cardiomyocytes embedded in epicardial engineered heart muscle (EHM) were delivered to structurally and functionally remuscularize the chronically failing heart in a rhesus macaque model. A stable 6% improvement in LVEF and inhibition of LV wall thinning was observed after 6 months [113].

All approaches involving iPSCs confront 3 major drawbacks: (1) the risk of teratoma formation and expression of embryonic antigens that can be immunogenic [114]; (2) electrophysiologically immature cells that can cause arrhythmias when transplanted into myocardial tissue, requiring expensive manufacturing techniques that are difficult to validate [115]; and (3) variability of iPSC cardiomyocyte properties among batches, complicating clinical administration parameters [116].

In an approach similar to delivery of HSCs to atherosclerotic endothelium with bifunctionally targeted echogenic liposomes (BF-ELIP) [117], $CD90^+$ adipose-derived stem cells (ASCs) were delivered to infarcted myocardium in a rat AMI model using microbubbles targeted to both CD90 and ICAM-1 [118]. The ASCs persisted in the infarcted area at least 35 days after administration and resulted in significant improvements of fractional shortening, stroke volume and posterior wall thickness.

7. Limitations of the Analysis

Quantitative estimates of critical stem cell numbers required to produce positive outcomes are derived from a relatively qualitative, cross-trial comparison of studies that differ substantially in patient population, pathology stage, delivery route, and endpoint definitions, rather than from formal pooled or meta-regression analyses. In addition, the trials examined are a selection of studies meant to gain some insight into relevant factors influencing the success of stem cell therapy for heart failure. As such, cell numbers administered as a controlling factor emerges as a testable hypothesis.

8. Conclusions

The inconsistent and unpredictable outcomes of cardiac stem cell therapy trials can be better understood in light of the inherent limitations of cardiac regenerative capacity, due to the oxidative nature of mammalian metabolism. Although the main potential of stem cell therapy may lie in the paracrine functions of these cells rather than their ability to reconstitute cardiomyocytes, efficacy appears to correlate with the number of stem cells engrafted, especially for MSCs. A threshold for significant LVEF improvement of about 1×10^8 cells administered, assuming 1% engraftment, is proposed.

Strategies to improve engraftment efficiency, either by physical means or by targeted delivery approaches, are most promising. Future clinical trials of stem cell therapy for heart failure should incorporate methods for increasing the engraftment efficiency and for quantitating that property. Engraftment enhancement protocols should show consistent effectiveness in appropriate animal models before clinical trials are attempted.

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