

## **Cardiac Repair With Autologous Bone Marrow Stem Cells**

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## CARDIOLOGY CASEBOOK

A regular feature of the *American Journal of Critical Care*, Cardiology Casebook is intended to enhance practitioners' knowledge and critical thinking. Stylized case studies are accompanied by self-assessment quizzes. We welcome letters to the editor regarding this feature.

# CARDIAC REPAIR WITH AUTOLOGOUS BONE MARROW STEM CELLS

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In a small town in northern Montana, a 64-year-old retired nurse, physically active, but moderately obese, had been having episodes of angina related to physical stress for 1 week. When a more severe attack of angina persisted, she immediately chewed and swallowed 325 mg of aspirin and called her family practitioner, who arrived at her home promptly and administered 5 mg of intravenous morphine sulfate. The chest pain was alleviated soon after, and she was given 20 mg of atorvastatin and then transported by medical air ambulance 150 miles to a tertiary hospital equipped to care for acute coronary events. The admitting electrocardiogram revealed an acute ST elevation anterolateral infarction with several multifocal ventricular premature beats and a heart rate of 100 beats/minute. The duration of the acute myocardial infarction (MI) (from onset of chest pain to arrival at the hospital emergency department) was estimated to be 3½ hours. Primary percutaneous transluminal angioplasty and drug eluting stenting of a proximal left anterior descending artery thrombotic occlusion was successfully performed. The cardiologist in attendance was a member of a national team investigating the therapeutic benefits of transplanting bone marrow–derived endothelial progenitor cells (EPCs) into the myocardium of patients with an acute MI. The patient agreed to participate in this investigation.

### QUESTIONS

1. Which of the following improve cell viability and reduce ventricular remodeling and as a result increase survival in patients with heart failure and following an MI?
  - a. pharmacological therapy
  - b. coronary artery bypass graft surgery
  - c. cardiac catheterization
  - d. mechanical assist devices
  - e. cardiac transplantation

- f. cellular cardiomyoplasty
  - g. all of the above
2. Repopulation of cardiomyocytes to regenerate new myocardium involves which of the following?
    - a. cellular replacement of injured myocardium and blood vessels
    - b. directing differentiated cells to specific organ targets
    - c. removal of dead recipient cells and infusion of new donor cells
  3. Aging may contribute to atherogenesis by which of the following?
    - a. hypertension usually seen in older patients
    - b. hardening of the arteries as an aging process
    - c. depletion and obsolescence of reparative cells
    - d. a disequilibrium between vascular injury and repair
    - e. all of the above
  4. Repopulating necrotic myocardium with donor cardiomyocytes assists in regenerating functional myocardial tissue by which of the following mechanisms?
    - a. enhancing cardiomyocyte hypertrophy and expansion
    - b. transplanted precursor cells that transform into replacement cardiomyocytes
    - c. transplanted precursor cells that facilitate neovascularization
    - d. all the above
  5. Tissue injury or inflammation activates stem cell recruitment.
    - a. True
    - b. False

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6. Donor cell types used to replace necrotic myocardium include which of the following?
  - a. fetal cardiomyocytes
  - b. embryonic stem cells
  - c. skeletal myoblasts
  - d. bone marrow–derived EPCs
  - e. adult mesenchymal stem cells
  - f. any of the above
  
7. Transplantation of cellular products has been achieved by which of the following?
  - a. intramyocardial injection
  - b. intracoronary injection
  - c. intravenous administration
  - d. percutaneous catheter–based myocardial injections
  - e. all of the above
  
8. Statins reduce cardiovascular (CV) events and death by which of the following?
  - a. preventing atherosclerosis
  - b. stabilizing atherosclerotic plaques
  - c. reducing inflammation, platelet aggregability, and thrombus deposition
  - d. promoting and accelerating neovascularization of ischemic tissue
  - e. all of the above

**Adult stem cell:** An undifferentiated cell found in differentiated adult tissue that can restore itself and can (with certain limitations) differentiate to yield all the specialized cell types of the tissue from which it originated.

**Bone marrow stem cell:** One of at least two types of multipotent stem cells: hematopoietic stem cell and mesenchymal stem cell. Easily accessible and resistant to ischemia.

**Differentiate:** The process by which an unspecialized early embryonic cell acquires the features of a specialized cell, such as a heart, liver, or muscle cell.

**Embryonic stem cell:** An undifferentiated cell from an embryo that has the potential to become a wide variety of specialized cell types.

**Endothelial progenitor cell:** Found in bone marrow and peripheral blood autologous transplantation.

**Fetal cardiomyocytes:** Have short survival and limited supply and require immunosuppression.

**Inner cell mass:** The cluster of cells inside a blastocyst. Later these cells develop into the embryonic disk of the embryo and ultimately the fetus. They are the source of embryonic stem cells.

**Stem cell:** A cell that can divide for indefinite periods in culture and can develop into specialized cells.

## ANSWERS

1. g. all of the above

Emerging research in cardiac therapy is destined to enhance the rate of survival in cardiac patients. The current therapeutic options continue to be effective and are not replaced by the recent introduction of stem cells in cardiac treatment. Current therapy in acute MI is aimed at limiting the volume of injured and dead myocardium. In contrast, stem cell therapy adds new myocardium to replace infarcted muscle.

Pharmacological therapies timely administered have favorable effects on reducing complications and prognosis in acute MI and heart failure. Early cardiac catheterization of the culprit artery and the use of drug-eluting stents have often replaced coronary bypass surgery, with time being the critical factor in making a decision. Mechanical assist devices are effective in maintaining blood pressure and supporting the left ventricle in refractory congestive heart failure. Cardiac transplantation is a last resort when therapy has failed. Currently cellular cardiomyoplasty is evolving as effective therapy following an acute MI. Adult bone marrow contains EPCs, which are mobilized from the bone marrow following endogenous stimuli, enter the peripheral circulation, and incorporate into sites of injury and repair. EPCs are the origin of cell types that can differentiate into arterial wall cells (endothelium and small muscle cells) and myocardial cells (cardiomyocytes). Bone marrow–derived EPCs are harvested from the patient’s own bone marrow and can be delivered to the infarcted area of the myocardium by several methods.

2. a. cellular replacement of injured myocardium and blood vessels  
b. directing differentiated cells to specific organ targets

A wide variety of potential donor cells arise postnatally, not only from stem cells, but also from the adult bone marrow, circulating mononuclear cells, and cord blood. These vascular EPCs have endothelium-specific cell-surface marker characteristics and endothelial properties.<sup>1,2</sup> Following endogenous stimuli, EPCs mobilize from the bone marrow to the peripheral circulation and are incorporated into sites of injury and repair.

3. c. depletion and obsolescence of reparative cells  
d. by a disequilibrium between vascular injury and repair

Atherosclerosis is attributed to chronic vascular injury, which occurs with hyperlipidemia, hypertension, or tobacco use. These CV risk factors contribute to

atherogenesis by inducing endothelial cell injury, leading to endothelial dysfunction. Advancing age is a known additional factor in the incidence of atherosclerosis. Subsequent endothelial cell damage, which occurs by direct injury or incurred dysfunction, is the stimulus for the development of the atherosclerotic plaque.<sup>3</sup> In aging, there is exhaustion or obsolescence of cells that are responsible for repair and rejuvenation of CV tissues. Continuous endothelial damage or dysfunction leads to depletion or exhaustion of a presumed finite supply of EPCs. In studies of patients with CV disease, there was an inverse correlation between the number of circulating EPCs and CV risk factors. The number of EPCs was also associated with the level of endothelial function (measured by brachial artery reactivity).<sup>4</sup> As a result of aging, the supply of bone marrow cells capable of vascular and myocardial repair is probably exhausted, which would result in a disequilibrium between vascular injury and vascular repair, promoting atherosclerosis. The initiation and progression of atherosclerotic disease has been attributed to deficient vascular repair that results from obsolescence of bone marrow–derived EPCs. Reduced vascular progenitor cell content in aging bone marrow may cause the disequilibrium between reparative endothelial cells and inflammatory leukocytes, tipping the balance of injurious over reparative potentials.<sup>5</sup> Low levels of circulating progenitor cells have been noted in high-risk CV patients and are considered to be the result of a combination of factors. CV risk factors can direct the function and life span of EPCs by modulating levels of oxidative stress, nitric oxide activity, or other physiological processes. Since EPCs have a role in maintaining vascular homeostasis, the impaired mobilization, exhaustion, or depletion of these progenitor cells can contribute to the perpetuation of endothelial dysfunction, reduce atheroprotection, and reduce progression of CV disease and other diseases that are age-related.<sup>6</sup> EPCs from high-risk subjects are both fewer in number and become senescent more rapidly than do EPCs from low-risk subjects.<sup>6</sup> Thus, levels of EPCs in healthy individuals may become a surrogate biological marker for vascular health and cumulative CV risk.<sup>6</sup> Signs of senescence in endothelial cells that line atherosclerotic arteries suggest that cells from youthful bone marrow may help to modify the natural course of aging protective cells and thus, atherosclerosis.<sup>2</sup> Further associations have been noted between coronary artery risk factors, aged or low circulating levels of bone marrow–derived EPCs and the development of atherosclerosis. The reduced atheroprotective effect of old bone marrow–derived EPCs suggests that loss of cells with repair capacity occurs with aging.

It is not clear whether one cell type is responsible for vascular restoration and that the exhaustion of this cell line occurs with aging. Multiple cell types may be involved in the repair process. The identification and restoration of potential age-related qualitative deficiencies in bone marrow cell function, could, in the future, facilitate atheroprotection without the need for actual cell transfer.<sup>5</sup> Scientists, using a murine model of atherosclerosis, have established that there is, in fact, an atheroprotective property of bone marrow–derived EPCs that become exhausted with aging and prolonged exposure to risk factors. As the restorative abilities diminish, aged bone marrow–derived EPCs allow several pathophysiological processes to occur; alterations in cholesterol metabolism or blood vessel wall biochemistries, cytokine expression by immune-competent cells, or the acquisition of certain immune cells that exacerbate atherosclerosis. The postulated process of aging is similar to the observations in patients with muscular dystrophy, where continuous cycles of damage and repair ultimately exhaust their supply of resident progenitor cells (termed satellite cells in skeletal muscle). The few cells that do remain, demonstrate signs of accelerated aging. In another murine model, the transfer of cells propagated from the bone marrow of young donor mice limited the evolution of experimental atherosclerosis in older, recipient mice. Signs of cell aging were noted in the cells lining the atherosclerotic vessel of the recipient; in addition, the induction of youthful bone marrow–derived cells attenuated the aging process.<sup>2</sup>

4. b. transplanted precursor cells that transform into replacement cardiomyocytes
- c. transplanted precursor cells that facilitate neovascularization

Stem cells are precursor cells that can proliferate, differentiate, and self-renew. Although specific cellular and genetic mechanisms are not well understood, it is thought that environmental and stimulating factors transform these cells into specialized tissues and organs, including cardiomyocytes. Transplanted precursor cells can potentially salvage myocardial tissue by replacing necrotic myocardium and promoting neovascularization in the injured area.

5. a. True

An injury or inflammatory event is a prerequisite to recruitment of circulating stem cells, which contribute to cellular repair, replacement, and regeneration. Once triggered, circulating stem cells begin the long journey toward the repair of tissue function and structure. The intense inflammatory cascade that follows acute MI

triggers circulating cells to home in or migrate toward the sites of injury where differentiation to the appropriate cell type begins. Cell homing is a process of cell-to-cell matrix/interactions mediated by a variety of cell-adhesion molecules that leads to the anchoring of circulating cells to specific sites in the recipient tissue. Chemical signals (such as granulocyte colony stimulating factor or stem cell factor) that promote mobilization of stem cells from the bone marrow and increase homing also increase vascular permeability and expression of adhesion molecules. The activation of homing receptors that direct the circulating cells to the injury site also augments attachment and engraftment to the injured site. Growth factors such as insulin-like and hepatic growth factors also serve to enhance the endogenous repair process by further stimulating cardiomyocyte replication and attraction of cardiac resident stem cells.<sup>7</sup> In chronic disease, however, the homing process that is upregulated in MI due to increased vascular endothelial growth factor (VEGF) levels, may be less intense and less conducive to cell engraftment.<sup>7</sup> For maximal clinical benefit, transplanted stem cells must engraft and proliferate quickly and efficiently. Newly formed cardiomyocyte cells must attain physical and electrical coupling with the existing cells. Intracellular coupling with recipient cardiomyocytes is achieved through the formation of connexin, a membrane protein that constitutes gap junctions.<sup>7</sup> Newly recruited stem cells require immediate neovascularization in order to survive and in order to keep up with the metabolic demands of the newly transplanted cells that carry out the contractile workload. The mechanism of organ specific differentiation, migration, signaling, and homing behaviors are not clearly understood, but may be related to several factors; microenvironmental, adhesion molecules, homing receptors, ischemia, and expression of VEGF.<sup>8</sup> VEGF and stromal derived factor-1 are highly upregulated in hypoxic tissue, which may signal the recruitment of circulating progenitor cells to assist in the repair of injured tissue.<sup>7</sup> Cell transplantation for treating CV disease opens a great potential for developing new therapeutic strategies to replace injured myocardium and blood vessels. Many questions remain regarding the use of stem cells and progenitor cells for myocardial and vascular repair, for example, the life span and long-term behavior of these cells after engraftment. Can these cells form detrimental cell types? How many cells are needed for transplantation? What is the best method of delivery?<sup>9</sup>

6. f. any of the above

Potential donor cells that have been cultivated and observed in the laboratory setting for transplantation

include fetal cardiomyocytes, embryonic stem cells, skeletal myoblasts, bone marrow-derived EPCs, and adult mesenchymal stem cells.

### **Fetal Cardiomyocytes**

Transplanted human fetal cardiomyocytes can survive, proliferate, couple with host myocardium, form new cardiac tissue, and increase blood flow through the induction of blood vessel formation. In murine model experiments, transplanted fetal cardiomyocytes formed new cardiac tissue and improved cardiac function when transplanted into a myocardial scar. The major disadvantages to the use of human fetal cardiomyocytes are related to several factors. Fetal cells are difficult to obtain, are limited in their ability to divide in culture, requiring in vitro expansion, and are sensitive to immunological and ischemic injury. Unresolved ethical, political, and practical constraints have further precluded the use of human fetal cardiomyocytes in routine clinical experimentation.

### **Embryonic Stem Cells**

Embryonic stem cells are the most primitive of all stem cells. Embryonic stem cells serve not only as a resource for basic research, but also as starting material for developing cell-based therapy. The derivation of murine (mouse) embryonic stem cells were first reported in 1981.<sup>10</sup> Murine embryonic stem cells have provided much of the material that is known about cell differentiation and the processes leading to the development of the mammalian heart. Cultivation of human embryonic stem cells was first reported in 1998.<sup>10</sup> In culture, embryonic stem cells retain the potential for unlimited, undifferentiated growth, although the differentiation of human embryonic stem cells occurs with a much lower efficiency than differentiation of murine cells. Human embryonic stem cells are derived from the inner cell mass of blastocyst-stage embryos, the preimplantation stage (day 5) at which the developing mammalian embryo implants in the uterine endometrium. As a pluripotent cell type, a human embryonic stem cell is capable of forming all adult cell types, including cardiomyocytes. Harnessing this potential may provide individuals a source of cells to replace those that are lost or impaired as a result of disease. Embryonic stem cells possess significant developmental potential and are the most versatile of all stem cells. Embryonic stem cells are immortal as they have the ability to undergo an infinite number of cell doublings and differentiations. Since embryonic stem cells can differentiate into cardiomyocytes, human embryonic stem cells may furnish the basis to study human cardiomyocyte physiology and may one day provide an

unlimited supply of cells for the repopulation of damaged myocardium.<sup>9,11</sup> The proliferative properties of stem cells increase the chances of having sufficient number of cells for treatment, and their pluripotent nature makes it possible to tailor the transplant to the required tissue type, which can result in the future cure of type I diabetes and Parkinson's disease.<sup>12</sup>

Advocates of stem cell research argue that unnecessary suffering can be remediated through the therapeutic use of embryonic stem cells. The moral majority, however, considers blastocysts to have a "potential for life" and that harvesting stem cells from blastocysts end their viability. Ethical and political issues surround the use of embryonic stem cells, and as a result United States federal funding for research on embryonic stem cells was restricted to the existing cell lines, which vary in their qualities and utility. Recently, 17 new embryonic stem cells lines derived from frozen blastocyst-stage embryos produced by in vitro fertilization have been developed.<sup>11,12</sup> However, this development is now academic since human embryonic stem cells can now be derived from the patient's own bone marrow, thus eliminating any debate over political and immunological issues. In several studies, using specific culture and transforming growth factors, human embryonic stem cells were transformed into myocytes with properties of the cardiomyocyte, complete with a rod-shaped morphology, myofibrillar bundles, and intercalated discs. Embryonic stem cells demonstrated the ability to engraft into the host, reduce infarct size, and improve ventricular function and contractility following MI in a rat model 6 weeks after cell transplant.<sup>7,8</sup>

### **Skeletal Myoblasts**

Skeletal muscle contains precursor cells (satellite cells, skeletal myoblasts) for new skeletal myocytes. Upon muscle injury, these cells undergo mitosis, proliferate, form syncytium and ultimately form new skeletal myocytes. Skeletal myoblasts are ideal for transplantation since they are readily available from the patient's own skeletal muscle (biopsy specimen), do not carry immunological and ethical concerns, and strongly resist ischemia, allowing these cells to engraft in hosts with areas of poor perfusion.<sup>7-9</sup> Skeletal myoblasts can be delivered to the heart by either direct intramyocardial or intra-arterial injection. In a rat model, the implantation of skeletal myoblasts resulted in the formation of viable grafts that decreased ventricular remodeling and increased cardiac function after MI. The relative ease of retrieval, culture, and production makes skeletal myoblasts readily available for clinical use.

The long-term cell outcome and terminal differentiation of skeletal myoblasts following transplanta-

tion are unknown. Limiting factors in the use of skeletal myoblasts are the need for a large quantity of cells for transplantation (which requires in vitro expansion) and the probability of arrhythmogenicity. Several patients who underwent skeletal myoblast transfer experienced ventricular tachyarrhythmias within weeks of transplantation. Due to their inability to transdifferentiate into cardiomyocytes and form cardiac-like syncytia with neighboring cells, a substrate for ventricular reentrant arrhythmias may be potentiated and thus require secondary prophylactic implantation of an implantable cardiac defibrillator. Skeletal myoblasts are not capable of forming necessary gap junctions and consequently do not form successful electromechanical coupling. Proper functioning of transplanted cells requires coupling with host cardiomyocytes to permit impulse formation a disadvantage in the use of skeletal myoblasts.

### **Endothelial Progenitor Cells**

EPCs are found in bone marrow and also circulate in the peripheral blood. As a stimulus from injured and dead myocardium following an acute MI, EPCs are mobilized from the bone marrow, promote neovascularization and generation of myocytes, which lead to myocardial regeneration. Following an MI, neovascularization can salvage hibernating myocardium, inhibit apoptosis of hypertrophied cardiomyocytes in the infarct area, and thus improve cardiac function. The autologous harvesting of EPCs obviates immunosuppression and eliminates the political hassle over stem cell research. Following in vitro expansion and intravenous administration, EPCs (in a rat model) have enhanced neovascularization and reduced left ventricular dilatation after acute MI. In another rat study, EPCs after being stimulated with granulocyte-stimulating factor, were observed to migrate to the infarct area, transdifferentiate into endothelial cells, induce neovascularization, reduce apoptosis of the hypertrophied cardiomyocytes in the peri-infarct area, limit remodeling, and as a consequence improve cardiac function. The angiogenic factors VEGF and macrophage chemoattractant protein-1, as well as statins, stimulate the proliferation of EPCs, increase collateral circulation, and thus improve cardiac function.

### **Adult Mesenchymal Stem Cells**

Stem cells are undifferentiated immature precursor cells that can proliferate, self-renew, and differentiate into one or more types of specialized cells, including cardiomyocytes. The journey from the bone marrow to vascular endothelium or myocardium is divided into stages. One or several signaling mechanisms (cytokine and/or growth factor signals) trigger the mobilization of EPCs from the bone marrow. With additional signaling these

cells differentiate into vascular cells or cardiomyocytes enter the circulation and home in on the site(s) of injury.

7. e. all of the above

Several modes have been successful in the delivery of stem cells to the myocardium: intramyocardial, intracoronary, and intravenous routes. An additional method of delivery of autologous bone marrow mononuclear cells into hibernating myocardium is via percutaneous catheter guided by electromechanical mapping.<sup>7,8</sup> Intramyocardial injection requires fewer cells to achieve engraftment compared with intracoronary or venous routes, but it is invasive and associated with intraoperative and postoperative risks. Intramyocardial injection appears to be the preferred route when a surgical procedure is planned. Skeletal myocytes are better suited for intramyocardial delivery because of the potential for embolization when large quantities are implanted. Intramyocardial injection has been known to create islands of cells in the infarcted tissue, providing a substrate for electrical instability and ventricular arrhythmias. Delivery of stem cells via selective intracoronary injection to the infarct related artery is more advantageous than direct myocardial injection and intravenous administration because maximum concentration of cells can be delivered to the site of infarct and peri-infarcted tissue on the first passage. This approach allows sufficient time for the cells to home in and engraft homogeneously and may explain the absence of ventricular arrhythmias with this method. The optimal number of cells and duration of infusion must be determined, especially when coronary flow is impaired and myocardial cell necrosis is possible. Intravenous administration of stem cells is attractive, simple, and a practical mode of delivery since it does not require cardiac surgery or cardiac catheterization. The distance from point of injection to the injury site is critical for the homing of transplanted cells.<sup>7,8</sup> Non-invasive *in vivo* imaging techniques are needed to monitor and detail donor cell delivery, myocardial differentiation, integration into damaged myocardium, and contribution to cardiac function. In earlier studies, only histological confirmation was able to verify the status of the transplanted cells. Radiographic fluoroscopy is limited because it is unable to verify success of the injection. Cardiac magnetic resonance imaging is successful in the detection and characterization of stem cell engraftment following direct myocardial injection of magnetically labeled stem cells after MI.

8. e. all of the above

The lowering of plasma cholesterol levels with statin agents decreased CV events and death due to

coronary artery disease. Statins prevent development of atherosclerotic lesions, stabilize existing atherosclerotic plaques, reduce inflammation, decrease C-reactive protein levels, decrease platelet aggregability and thrombus deposition, and increase endothelium-derived nitric oxide production. Statins have been credited with the promotion, acceleration and neovascularization of ischemic tissue in normocholesterolemic animals by enhancing the mobilization of bone marrow-derived EPCs to the site of injury.<sup>13,14</sup> The potential of statins to preempt disordered vascular pathology and to augment neovascularization of ischemic tissue can be a significant factor in protecting tissue from critical ischemia. The function and life span of EPCs diminish when CV risk factors induce increases in oxidative stress levels and decreases in nitric oxide activity. EPC numbers and function increase with statin therapy.<sup>7,8</sup> The increase in progenitor cell count, homing in, and incorporation into sites of reendothelialization suggest that statin-induced vasculogenesis is related to both its ability to enhance the functional activity of EPCs (increased mobilization and differentiation) as well as its ability to increase the overall number of circulating bone marrow-derived EPCs, without correlative changes in low-density-lipoprotein cholesterol levels.<sup>13</sup> Statins (atorvastatin, simvastatin) stimulated the bone marrow's release of functional EPCs, augmenting the neovascularization process in patients with stable coronary artery disease.<sup>14</sup> Statin therapy also increased EPC levels in healthy volunteers, adding to the hypothesis that statins directly affect EPC levels.<sup>13,14</sup> Statins stimulate the protein kinase Akt, responsible for activating the enzymatic activity of endothelial nitric oxide, mediate VEGF-induced endothelial cell migration, and play an important role in mature EPCs.<sup>14</sup> Finally, it appears that statin therapy may support one of the most fundamental survival responses to maintain tissue viability in the setting of acute or chronic myocardial ischemia due to obstructive coronary artery disease.<sup>13</sup>

## Summary

All adults have stem cells in their body that can act like embryonic stem cells when given an appropriate stimulus. When VEGF is given, the bone marrow is stimulated to release stem cells, which grow new coronary arteries and also replenish damaged or dead cardiomyocytes. Transplanting autologous bone marrow stem cells into coronary arteries reduced infarct size, improved the prognosis following an acute MI and in patients with chronic congestive heart failure. Since patients are the source of their own stem cells, there would be a ready supply, with no rejection or

immunological issues, and political debate on stem cell research would end. It is worth noting that statin therapy stimulates mobilization of EPCs, which repair damaged or dead myocardial cells and stimulate growth of new coronary arteries.

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