STATE OF THE ART OF STEM CELL THERAPY FOR ISCHAEMIC CARDIOMYOPATHY PART 1

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Ischemic cardiomyopathy is becoming a leading cause of morbidity and mortality in the whole world. Stem cell-based therapy is emerging as a promising option for treatment of ischemic cardiomyopathy. Several stem cell types, including cardiac-derived stem cells, bone marrow-derived stem cells, mesenchymal stem cells, skeletal myoblasts, CD34+ and CD133+ stem cells have been used in clinical trials. Clinical effects mostly depend on transdifferentiation and paracrine factors. One important issue is that a low survival and residential rate of transferred stem cells blocks the effective advances in cardiac improvement. Many other factors associated with the efficacy of cell replacement therapy for ischemic cardiomyopathy mainly including the route of delivery, the type and number of stem cell infusion, the timing of injection, patient's physical conditions, the particular microenvironment onto which the cells are delivered, and clinical conditions remain to be addressed. Here we provide an overview of modern methods of stem cell delivery, types of stem cells and discuss the current state of their therapeutic potential.

Key words: *mesenchymal stem cells, cardiac-derived stem cells, skeletal myoblasts, bone marrow-derived stem cells, intramyocardial injection, transvascular cell delivery.*

INTRODUCTION

Reduced blood flow in a myocardial infarction affected area is the leading cause of morbidity and mortality in patients with ischemic cardiomyopathy [1, 2]. Although averagely 1% of adult cardiomyocytes appear to possess the ability of self-renewal, they cannot provide recovery of heart tissue after an infarction or some serious heart damage [3–5]. Thus, ischemia-induced apoptosis and necrosis of cardiomyocytes damage the geometry of the left ventricle undergoing progressive remodeling, hypertrophy and proliferation of fibroblasts, which results in cicatrization and poor contractility of the left ventricle [6–8]. Such common treatment strategies as pharmacotherapy, coronary artery bypass grafting and coronary artery stenting allow the recovery of blood supply to the ischemic regions and relative pain relief, but they fail to treat pathophysiological changes after ischemic injuries, and regenerate the muscle tissue of the heart. Therefore, the essential effect of treatment is to enable regeneration of myocardial cells using cardiac progenitor cells or other exogenous multipotent stem cells [9]. Stem cell implantation for the treatment of ischemic cardiomyopathy brought a new age to patients, and at the same time it faces numerous challenges. A lot of evidence suggests that the stem cells perform regeneration of the damaged part of the heart by differentiating into cardiac muscle cells, promoting angiogenesis, proliferation of endogenous cardiac stem cells and secretion of cytokines, chemokines and growth factors that activate endogenous reparative responses, inhibit cellular apoptosis and fibrosis, and improve myocardial contractility [10]. In the last decade, many clinical trials have been conducted to assess the safety, feasibility and efficacy of stem cell administration in patients with ischemic cardiomyopathy. Different types of cells, including bone marrow-derived stem cells, mesenchymal stem cells, cardiac-derived stem cells, skeletal myoblasts and hematopoietic stem cells, have been used to evaluate the potential therapy based on the stem cells. However, promising results from numerous clinical studies, in improvement of functional parameters, have shown several ineffective treatments. Cell transport modes and their doses, cell isolation procedures and transplantation time can determine effects on improving heart function. This paper presents the status of previous clinical trials and future perspectives for the use of stem cell therapy in patients with ischemic cardiomyopathy.

ISCHEMIC CARDIOMYOPATHY

Cardiomyopathies are myocardial degenerative diseases (Fig. 1), which develop independently under the influence of a series of known or unknown factors or occur as a side effect of other heart conditions. These

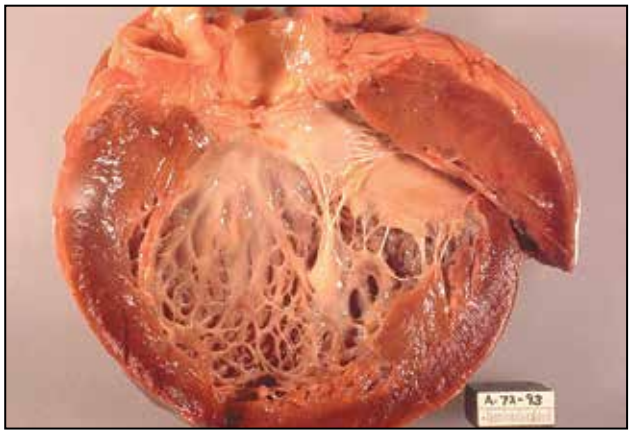

Fig. 1. Cross section through the left heart chamber, with signs of subendocardial fibrosis [12]

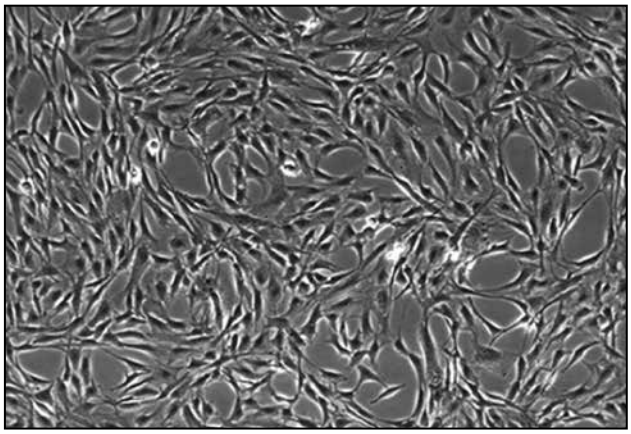

Fig. 2. Micrography of mesenchymal stem cells extracted from the umbilical cord [17]

myocardial damages are most often due to hemodynamic disorders; in systemic and pulmonary hypertension, as well as acquired and congenital heart disorders, or due to ischemia in coronary heart disease and are closely related to these disorders, making with them a whole [11].

Ischemic cardiomyopathy is the most common type of dilatative cardiomyopathy. In ischemic cardiomyopathy, the ability of the heart to pump blood is reduced, because the main heart chamber for arterial blood supply, left ventricle is enlarged, expanded and weak. This is caused by ischemia – a lack of blood supply to the heart muscle, which is induced by coronary artery disease. A study of stem cells has shown that the use of endogenous stem cells in the heart, as a regenerative approach, along with other methods of treatment, possess promising therapeutic potential [13].

STEM CELLS

Stem cells are not completely differentiated cells of different potentials, with the ability to self-replicate and generate differentiated cells. According to the simplest definition, stem cells are actively dividing cells, and on that occasion they create two daughter cells, one of which remains a stem cell, and the other gives modified, mature, differentiated offspring. This definition is understandable when it comes to fertilized egg cells and early stages of embryogenesis, but as the growth and development of embryos progress, the stem cell function also complicates. Stem cells can be functionally defined as cells that possess outstanding capacity for self-renewal and the ability to differentiate into specialized cell types [14, 15].

MESENCHYMAL STEM CELLS

Mesenchymal stem cells are found in a number of tissues in the body: in adipose tissue where they participate in the regeneration of the adipocyte population, in the bone marrow in which they have the function of bone structures renewal and in the cartilage in which they play a role in the formation of chondrocytes. They are found in pulp of the tooth, and have the possibility of proliferative formation of fibroblasts. These cells are present in the umbilical cord (Fig. 2) and in the connective tissue of the adult. They have a pyramidal structure viewed from the morphological angle [16].

SKELETAL MYOBLASTS

Skeletal myoblasts are found in muscles and have the function of creating muscle fibers in skeletal muscles. Hypertrophy and skeletal muscle hyperplasia are caused by the proliferation and differentiation of these cells. Muscle fibers are formed from the fusion of more myoblasts, as shown in Figure 3, and the subsequent differentiation of a large number of myoblasts. These cells are also pyramidal [16].

CARDIAC-DERIVED STEM CELLS

Cardiac-derived stem cells are located in the heart wall and express a series of molecules that can be reliably identified, however, taking into account the place where they are situated, i. e. the myocardium, it is usually sufficient to identify them only through four indicators (Fig. 4), which are as follows: c-kit (tyrosine kinase), preserved telomers, p53 and p16.

These stem cells have the ability to differentiate into cardiomyocytes and endothelial cells of blood vessels. Their function consists in reparation of the heart muscle and endothelium of the blood vessels, although it is known that this reparation is often insufficient in various damages and heart diseases [19].

PROCUREMENT AND DELIVERY OF STEM CELLS

The main goal of any of the stem cell transport methods is to achieve the ideal concentration of cells needed to recover a damaged part of the myocardium, with the lowest risk to patients. Therefore, cell transport strategies have to take into account the clinical environment and the local environment, because

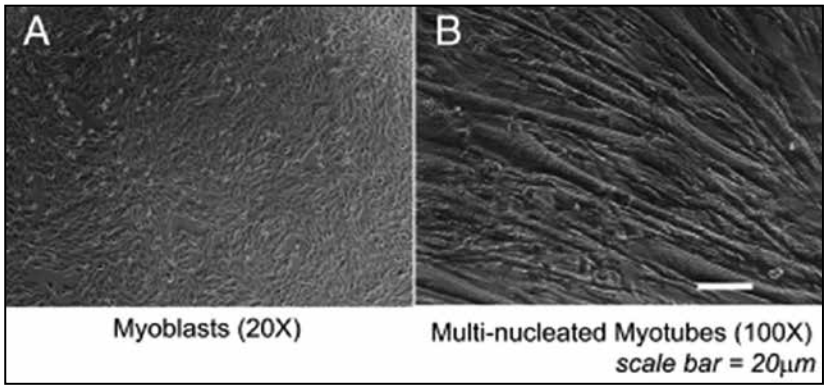

Fig. 3. Myoblasts create muscle structure through fusion [18]

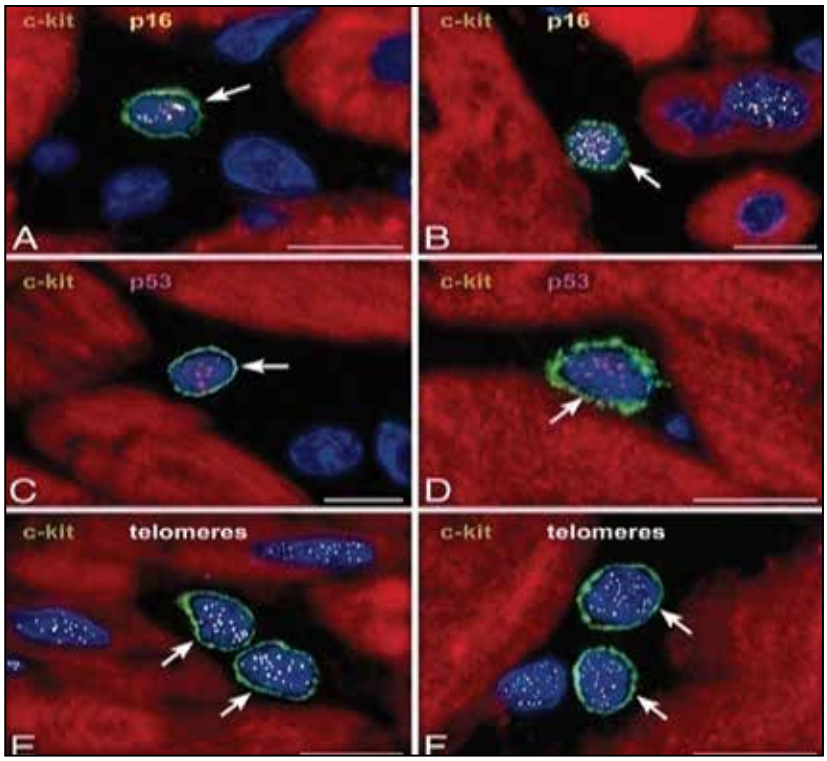

Fig. 4. Identification of c-kit positive cardiac stem cells, c-kit - tyrosine kinase, telomeres – chromosome ends, p53 and p16 – tumor suppressor proteins [20]

the stem cells can react differently, depending on the local signaling systems. A heart surrounding can help determine the level of cell retention. Stem cells can be injected through coronary arteries, coronary veins or peripheral veins (Fig. 5). Alternatively, direct intramyocardial injection can be performed using surgical, transendocardial and transvenous approaches. Each technique has its own features, and thus the choice of modality should be based on the clinical scenario in which we find ourselves [21]. The cell transport strategy may include the mobilization of stem cells from the bone marrow using cytokine therapy, with or without peripheral results [21].

There are different cell transmission modalities in the case of stem cell-based therapy. Cells can be injected by direct surgical injection, intracoronary infusion, retrograde venous infusion, transendocardial injection, and peripheral infusion.

STEM CELL MOBILIZATION

In humans, the mobilization of progenitor cells from the bone marrow occurs after acute myocardial infarction and indicates a natural attempt to recover the heart [22, 23]. Therapeutic mobilization of progenitor stem cells of the bone marrow after an acute myocardial infarction will, in theory, enhance the existing response to treatment. Mobilization of these progenitors is an attractive option because it is simple and eliminates the need for invasive results or cell transplant procedures. However, safety issues have been enhanced by the "off-label" application, due to the possibility of unsuitable outcomes in different patient populations, as well as theoretical problems with tumorigenesis [24]. In addition, in one clinical attempt to transfer bone marrow cells after an acute myocardial infarction, an increase in restenosis has been observed, which may be associated with increased availability of inflammatory cells in recently damaged coronary arteries [25].

TRANSVASCULAR DELIVERY OF CELLS

Peripheral (intravenous) stem cell infusion, as shown in bone marrow transplantation, could be a suitable method for transplanting stem cells. A study on mouse models has confirmed that, when injected into the peripheral circulation, human bone marrow cells are located in the peri-infarct region [26]. In addition, stem cells injected peripherally inhabit in infarct-affected areas only if injected a few days after acute myocardial infarction, this method of infusion of stem cells is less useful for the treatment of chronic myocardial ischemia. The main disadvantage of intravenous injection of the cells is the failure to reach the desired destination, due to cell loss in microvascularization of the lung, liver or lymphatic tissue [27]. Infusion of stem cells through the coronary vein system under additional high pressure was successfully achieved in in-vivo experimental models [28]. In this procedure, the coronary sinus is cannulated and the angioplasty balloon is placed in a large heart

vein. The balloon is positioned in the selected heart vein, depending on the surface to be treated. After inflation of the balloon, which is carried out with the interruption of blood flow in the coronary venous system, the cell infusion is brought under great pressure through the lumen of the catheter balloon [28]. This method of cell injection provides a wide and even distribution of cells. Its limitations include the inability to specifically direct the myocardial surface, as well as the diversity and correlation of the coronary venous system, which can make access to certain myocardial veins difficult or impossible.

Intracoronary infusion is the most popular way of transporting cells in clinical trials, especially after acute myocardial infarction [29–31]. Stem cells injected 4–9 days after acute myocardial infarction are associated with a good safety profile. The technique is similar to that in which coronary angioplasty is used, which includes the over-the-wire position of angioplasty balloon in one of the coronary arteries. The coronary blood flow is then stopped for about 2–4 minutes while stem cells are injected under pressure. This allows better contact between stem cells and microvascularization in the infarction affected artery.

This technique would be suitable only in the case of acute ischemia, after adequate adhesions and cytokine signals were temporarily increased. Although intracoronary infusion is widely used, this method lacks a strong experimental background, with a view to safety and efficacy [32].

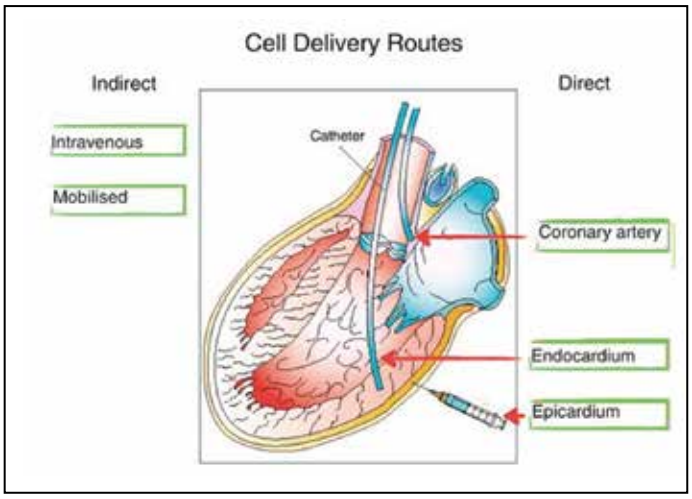

Fig. 5. Potential pathways for the transport of stem cells [22]

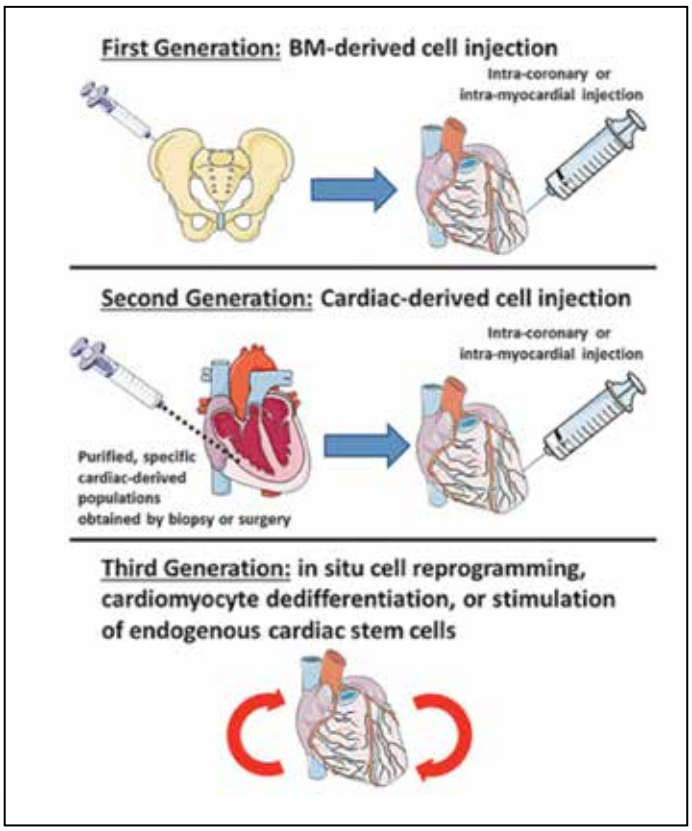

Fig. 6. The current status of a cell therapy study for the treatment of a damaged heart [37]

INTRAMYOCARDIAL INJECTION

Intramyocardial injection (Fig. 6 and 7), carried out through the epicardium, endocardium or coronary vein, is performed in chronic myocardial ischemia [33–35]. In this technique, the cell preparation is introduced into the myocardium under high pressure, using a hollow needle. This is preferential path for the stem cell transport in patients with the chronic occlusion of coronary arteries and in clinical trials which includes weaker homing signals, such as chronic congestive heart disease. Theoretically, this should be the most convenient way for transporting larger cells, such as skeletal myoblasts and mesenchymal stem cells, which could clog the capillaries [36].

TRANSEPICARDIAL INJECTION

Transepicardial stem cell transport is the most commonly used technique in cardiac stem cell therapy. It is performed during open surgical revascularization, when the cells are inserted into the damaged area of the heart or the area affected by the infarct, under CT-guided direct visualization [33–35]. This approach requires sternotomy and, with regard to invasiveness, is associated with significant surgical morbidity. However, in the case of elective open-heart surgery, the auxiliary transport of cell therapy may be justified. One important advantage of this technique is that it can provide a large number of cells per unit of area on which they are injected. In addition, not all parts of the myocardium (e. g., septum) can be reached using a direct external access [37].

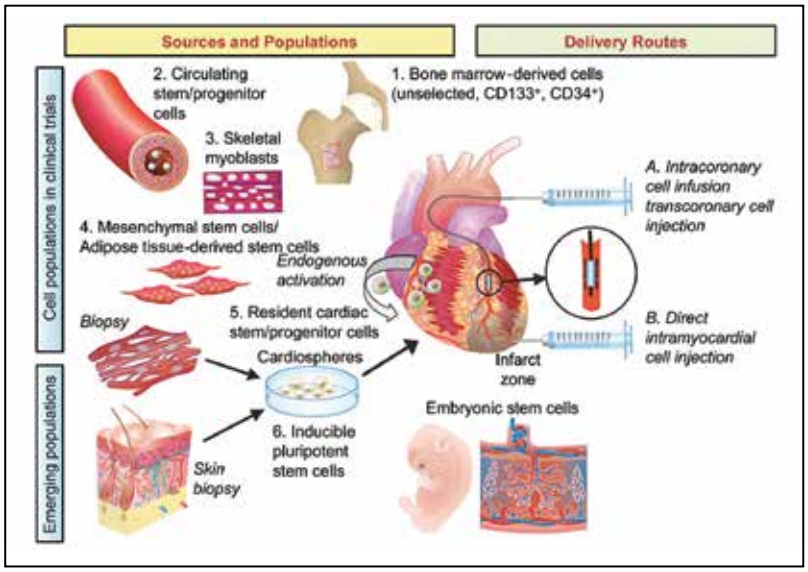

Fig. 7. Population of stem cells and pathways for transplantation [37]

TRANSENDOCARDIAL INJECTION

Transendocardial injection is performed using percutaneous access to the femoral artery. Once a catheter with a needle is progressed retrograde through aortic valve and placed opposite the endocardial surface, cells can be injected directly into any part of the wall of the left ventricle. Two catheter systems are currently available for cell transendocardial transport: the Stiletto™ and MyoStar™ [38].

The Stiletto™ (Fig. 8) catheter is guided fluoroscopically usually in two levels. Its basic disadvantage is that it is two-dimensional and has an "innate" lack of precision associated with fluoroscopy. The second disadvantage is that it does not show an adequate target point for the myocardium. This, in preclinical experiments, was associated with magnetic resonance imaging, which allows a three-dimensional assessment of myocardial thickness and perfusion. This technology is still being tested. Several preclinical studies have been carried out, and human safety data have not been evaluated yet [39].

However, it can be used with other recording techniques or when myocardial therapy does not have to be targeted [39].

The MyoStar™ (Fig. 9): The NOGA system is an electro-mechanical system based on the use of catheters for intramyocardial navigation and mapping. This technique uses extremely low magnetic fields, generated by a triangular backbone, which is placed below the patient. The magnetic fields are crossed with the location of the sensor proximal to catheter for mapping, which helps in determining the right location and the catheter orientation within the left ventricle [38]. The NOGA injection catheter uses the benefits of non-fluoroscopic magnetic routing. Injections are maintained in a three-dimensional electromechanical map of the left ventricle. The map was constructed by combining a number of points from several locations on the surface of the endocardium, which was separated with electrocardiogram [38].

The NOGA system uses an algorithm to calculate and analyze the movement of the catheter and/or the location of the endocardial point during the systole and diastole. Each data has a value (local linear shortening – LLS) and a voltage value. When the folder is compiled, all data is integrated with the NOGA system and presented three-dimensional. Due to the unclear involvement of myocardium in the onset of ischemic heart disease, the ability to distinguish the characteristics of the subcutaneous tissue is very important when it comes to cell transport. This technique has been widely tested on humans and animals, and proved to have an excellent safety profile [40].

TRANS-CORONARY VEIN INJECTION

Trans-coronary-vein injection is performed using a catheter system, placed percutaneously in the coronary sinus. Initial studies confirmed the feasibility and safety of this venture on pig models [27]. This cell transport method was used to inject skeletal myoblasts to the damaged myocardium in patients with cardiomyopathy [41]. It is administered by intravascular ultrasound, which allows the operator to expand the catheter and needle, far from pericardial space and coronary arteries, in the myocardium and its surroundings. To date, the feasibility

Fig. 8. The Stiletto™ catheter for intramyocardial cell transport [39]

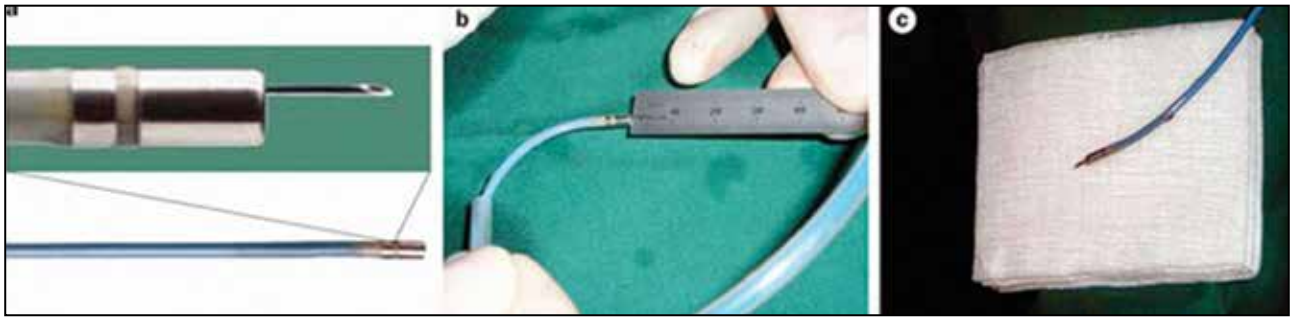

Fig. 9. NOGA® MyoStar® intramyocardial injection catheter system [41]

of studies has shown a good safety profile of this technique [27]. Preliminary data suggest that the effectiveness of acute retention (retention of cells in myocardium in the first hours after infusion), using this fluoroscopy-guided transvenic method, is superior to endovascular endpoints used in electromechanical mapping [42].

The disadvantages of this technique are similar to those mentioned above, observing the constraints associated with the coronary vein delivery. In contrast to a transendocardial technique in which the cells are injected perpendicularly into the wall of the left ventricle, the trans-coronary-vein injection allows parallel injection of the cells, which can result in greater retention of cells [41].

Conflict of interest: none declared.

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