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A new route of transendocardial stem cell injection: from femoral vein to left ventricle through atrial septa

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Abstract. – OBJECTIVE: To evaluate the feasibility and safety of a new route of transendocardial stem cell injection.

MATERIALS AND METHODS: Atrial septal puncture was performed in six young male pigs, and then a 6F syringe was passed through the puncture to reach the left atrium. Meanwhile, a guide wire was inserted into the left ventricle through the femoral artery, and echocardiography was used to confirm the relative position of the guide wire with the syringe.

RESULTS: After atrial puncture through femoral vein, the syringe could reach the left atrium and finally the left ventricle. Echocardiography confirmed that both the guide wire and the syringe were located in the left ventricle. The diameter of atrial septa puncture and the diameter of the syringe implantation were 4.1 ± 0.5 mm and 8.4 ± 0.7 mm, respectively. But there is no difference in Left ventricle end-systolic dimension (LVES), left ventricle end-diastolic dimension (LVED) and left ventricle ejection fraction (LVEF) before surgery, after atrial septa puncture, after syringe implantation or one month after surgery.

CONCLUSIONS: It is feasible to perform transendocardial stem cell injection by 6F syringe inserted through femoral vein. The surgery may cause atrial septa tearing but does not jeopardize myocardial function.

Key Words:
Transendocardial stem cell injection, Femoral vein, Left ventricle, Atrial septa.

Introduction

In recent years, the incidence of acute myocardial infarction has increased markedly, which significantly reduces the quality of people's life worldwide. Although modern medical science and technology have made significant progress in the treatment of acute myocardial infarction, such as emergent stent implantation, ACE inhibitors and beta-blockers, how to rescue or replace damaged myocardial cells and blood vessels still remains an urgent task to be addressed[1-5].

Stem cells have the capacity to regenerate any cells and tissues and, thus, hold a great potential to cure human diseases[6-8]. Currently, the commonly used methods for stem cell transplantation include intravenous injection, intracoronary transplantation, transepicardial injection, patch graft, and transendocardial injection[9-11].

Transendocardial injection is to inject the stem cells directly into the ischemic endomyocardium determined by electric potential. This is done under the guidance of myocardial electro-mechanical mapping device, where a catheter carrying a needle is inserted retrograde into the left ventricle through the aortic valve. This technique was developed by Johnson & Johnson Company of United States in 2006 and since then has been extended to large animal and human stem cell transplantation, due to its safety, effectiveness and practicability. The system has two components: a myocardial electro-mechanical mapping device and a myocardial injection syringe[12]. It is highly efficient and effective[13]. However, since stem cell injection is carried out through the arterial system, it is hard for multiple and long-term use. In addition, each stem cell transplant needs a new surgery and a new myocardial injection syringe, so the cost is high; the femoral artery needs to be punctured every time and the possibilities of major bleeding are high; at least one week is needed between two femoral

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artery punctures, and the patients need to be bed rested for prolonged time. All these largely limited its wide application in clinical practice. It is appealing if the myocardial injection syringe can be implanted through the venous system. Currently no such study has been reported. The purpose of our study is to investigate the feasibility and safety of implanting the myocardial injection syringe to left ventricular sub-endocardium intravenously and to open a new path for stem cell engraftment.

Materials and Methods

This study was approved by the Experimental Animal Committee of Fudan University. The methods were carried out in accordance with the approved guidelines. Six one-month old male pigs were used in the study. The pigs were first injected with ketamine (6 mg/kg), diazepam (0.2 mg/kg) and scopolamine (0.3 mg) intramuscularly, then were then fixed on an operation table. Venous cannula (Size 18-20G) was placed through ear venipuncture. Diazepam (0.2 mg/kg), fentanyl (10 ug/kg), ketamine (2 mg/kg) and succinylcholine (2-3 mg/kg) were then injected intravenously. The pigs were intubated with a special long straight laryngoscope. Anesthesia was maintained with intermittent intravenous injection of fentanyl and ketamine, the dose and rate were adjusted based on the vital signs of pigs. After inguinal local anesthesia, the femoral vein was incised and atrial septal puncture (SL 0 atrial septal sheath and needle, St. Jude, USA) was carried out through femoral vein as follows: Swartz sheath was placed into superior vena cava under anteroposterior X-ray; the atrial septal puncture needle was inserted through the sheath (the tip of the needle should not exceed sheath); the indicator of the needle should point to 12 o'clock; then the needle and sheath were rotated 45 degrees clockwise while retreated synchronously. The X-ray image showed when the needle reached the oval fossa, and this is the initial point of the atrial septal puncture. The height of the puncture site was adjusted properly under posteroanterior X-ray, and the success of the puncture was determined by echocardiography (model VIVID S6, General Electronics, USA). During the experiment, echocardiography was used to confirm the relative position of the guide wire and myocardial syringe: After femoral artery puncture, the guide wire was implanted to first reach the aortic root and then reaches the left ventricle through the aortic valve.

A myocardial syringe (model 6F, Shanghai Minimally Invasive Medical Devices Co., Ltd., Shanghai, China) was inserted into the Swartz sheath and was further inserted into left atrium through femoral vein and atrial septa. The myocardial syringe was manipulated to pass through the mitral valve to reach the left ventricle, then it was further manipulated to reach every corner of the left ventricle by adjusting its angle. The diameter of atrial septa puncture and the diameter of syringe implantation in left ventricle were recorded by echocardiography. Whether there was myocardial arrhythmias, or air embolism during surgery was also recorded. LVES, LVED and LVEF were also collected by echocardiography.

Statistical Analysis

Data were presented as mean ± standard deviation. Student t test was used for comparison. $p < 0.05$ indicates statistical significance. All statistical analysis were performed using SPSS software (version 16.0, IBM, USA).

Results

The body weight of the six male pigs is 36 ± 4 kg. The atrial septal puncture under ultrasound guidance is safe and accurate, echocardiography did not show any atrial rupture.

As shown in Figure 1A, it was easy for the guide wire to pass through the atrial septal puncture site to reach the left atrium and the left ventricle. During the experiment, the 6F myocardial syringe could easily reach the left atrium through the atrial septal puncture site with Swartz sheath (shown in Figure 1B). After being adjusted for direction and angle, the syringe could smoothly reach left ventricle passing through the myocardial mitral valve (Figure 1C). Then within the left ventricle, the syringe could also be adjusted for the angle and depth to reach all parts of the left ventricle (Figure 1D). In the present study, we used a 1:1 mixture of iopamidol (370 mg/ml) with 0.9% saline to simulate stem cell transplantation (Figure 1E, F). In this study, we also used echocardiography to confirm that the syringe was placed in the left ventricle (Figure 1G). In the meantime, the femoral artery was punctured, a super-smooth guide wire was implanted through the puncture to reach the aortic root and finally reach the left ventricle through the aortic valve (Figure 1H), the guide wire and myocardial sy-

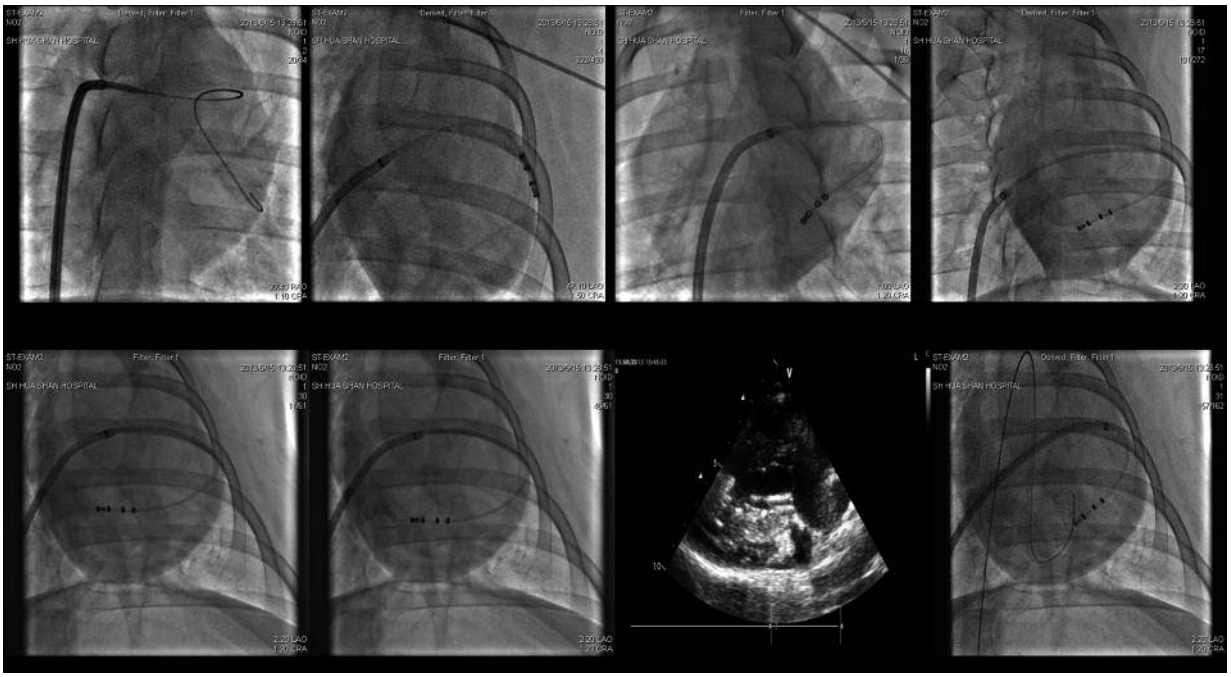

Figure 1. Anteroposterior X-ray images of various steps of the surgical procedure. **A**, Passing of the guide wire through the atrial septal puncture site to reach the left atrium and the left ventricle. **B**, Passing of the 6F myocardial syringe through the atrial septal puncture site with Swartz sheath. **C**, The syringe reaching left ventricle. **D**, Within the left ventricle, the syringe could easily be adjusted for angles and depths to reach all parts of the left ventricle, **E** and **F**, A 1:1 mixture of iopamidol with 0.9% saline was released from the syringe to simulate stem cell transplantation. **G**, Confirmation that the syringe was placed in the left ventricle by echocardiography. **H**, Relation position of the guide wire which was placed in the left ventricle through femoral artery puncture with myocardial syringe.

ringe was observed to be in the left ventricle by imaging, which further confirmed that subendocardial stem cell transplantation could be achieved by using myocardial syringe through venous system. There was no either malignant arrhythmia, air embolism, or death during the surgery.

Postoperative echocardiographic examination showed the diameters of atrial septal puncture before and after myocardial syringe passed through were 4.1 ± 0.5 mm and 8.4 ± 0.7 mm, respectively ($p < 0.01$). This may be due to a large outer diameter of the myocardial syringe (typically 7F), or the hard material which makes the myocardial syringe, or the soft part at the end of the myocardial syringe was too short. Modification is needed to fit the needs of new surgical approach in the future. Repeated echocardiographic examination one month after surgery did not show any sign of atrial septal defect. To see whether the surgery has any impact on cardiac function, LVES, LVED and LVEF were measured before surgery, after atrial septa puncture, after implantation of syringe and one month after surgery. The results were shown in Table I. Comparisons of LVES, LVED and LVEF at various time points did not show any significant difference ($p > 0.05$), indicating atrial septal puncture did not affect cardiac function, even after the implantation of myocardial syringe.

Discussion

There are advantages and disadvantages for the current commonly used means of stem cell transplantation [14-16]. There has no report of implanting cardiac syringe under endocardium in left ventricle through the venous system. The advantages of this route of stem cell transplantation are: 1. Suitable for multiple stem cell transplantation, especially before scar tissue formation in the infarcted area in acute myocardial infarction; 2. Reducing complications of stem cell transplantation through the femoral artery, such as bleeding, hematoma, arteriovenous fistula, and also reducing the cost of surgery as well as the pain of prolonged bed rest after surgery.

Table I. Comparison of various echocardiography indexes at different time points.

Time point	n	LVES (mm)	LVED (mm)	LVEF (mm)
Before surgery	6	20.13±1.523	6.51±1.61	59±3%
After atrial septa puncture	6	20.93±1.553	5.53±1.57	57±2%
After syringe implantation	6	21.23±1.243	7.53±1.68	57±3%
One month after surgery	6	20.88±1.003	6.52±1.48	59±2%

Note: Comparisons of LVES, LVED and LVEF at various time points did not show any significant difference ($p > 0.05$).

In the present study, we demonstrated that via the venous system, the myocardial syringe can reach all parts of the left ventricle through the atrial septum, which means that in actual stem cell transplantation, myocardial syringe can transplant stem cells to endocardium of any part of the left ventricle.

Atrial septal puncture has been widely used in clinical work, especially for atrial radiofrequency ablation. Because the myocardial syringe needs to pass the atrial septa, and it also needs to constantly change the piercing angles in order to reach all parts of the left ventricle through the mitral valve, whether there exists a large tear in the atrial septa puncture site and whether it affects myocardial function is the focus of our concern. In this study, the diameters of atrial septal puncture before and after myocardial syringe passed through were 4.1 ± 0.5 mm and 8.4 ± 0.7 mm, respectively. The difference is statistically significant ($p < 0.01$), indicating that the passing of myocardial syringe through atrial septa may indeed lead to atrial septal tear. But echocardiographic data showed that there was no significant change in cardiac function either immediately after myocardial syringe implantation or one month later, indicating that the atrial septal tear did not affect cardiac function and the damage may be ignorable.

Conclusions

Our experiments demonstrated that it is feasible to transplant stem cells through the femoral vein, but the surgical procedures and techniques need to be further improved, in particular, the length of the soft part at the end of the myocardial syringe needs to be increased, and a different material is needed to make the outer part of the syringe softer, thus to reduce the probability of atrial septal tear. In general, this surgical procedure has been proved to be safe by both clinical outcomes and echocardiography analysis. Actually, we have designed this new device and got Chinese patents.

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Conflict of Interest

The authors declare no conflict of interest.

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