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A novel ventricular restraint device (ASD) repetitively deliver *Salvia miltiorrhiza* to epicardium have good curative effects in heart failure management

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ABSTRACT

A novel ventricular restraint is the non-transplant surgical option for the management of an end-stage dilated heart failure (HF). To expand the therapeutic techniques we design a novel ventricular restraint device (ASD) which has the ability to deliver a therapeutic drug directly to the heart. We deliver a Traditional Chinese Medicine (TCM) *Salvia miltiorrhiza* (Danshen Zhusheye) through active hydraulic ventricular support drug delivery system (ASD) and we hypothesize that it will show better results in HF management than the restraint device and drug alone. SD rats were selected and divided into five groups (n = 6), Normal, HF, HF + SM (IV), HF + ASD, HF + ASD + SM groups respectively. Post myocardial infarction (MI), electrocardiography (ECG) showed abnormal heart function in all groups and HF + ASD + SM group showed a significant therapeutic improvement with respect to other treatment HF, HF + ASD, and HF + SM (IV) groups on day 30. The mechanical functions of the heart such as heart rate, LVEDP, and LVSP were brought to normal when treated with ASD + SM and show significant (P value < 0.01) compared to other groups. BNP significantly declines in HF + ASD + SM group animals compared with other treatment groups. Masson's Trichrome staining was used to study histopathology of cardiac myocytes and quantification of fibrosis was assessed. The large blue fibrotic area was observed in HF, HF + ASD, and HF + SM (IV) groups while HF + ASD + SM showed negligible fibrotic myocyte at the end of study period (30 days). This study proves that novel ASD device augments the therapeutic effect of the drug and delivers *Salvia miltiorrhiza* to the cardiomyocytes significantly as well as provides additional support to the dilated ventricle by the heart failure.

1. Introduction

Heart failure (HF) is a multifaceted pathophysiological syndrome. It arises from the debilitated function of the heart to pump the blood sufficiently. The clinical manifestations of HF are

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associated with myocardial insult, including coronary artery disease, genetic factors or hypertension, and their attendant sequela. It is estimated that HF is the primary cause of over 55,000 deaths each year, and the incidence of symptomatic HF rises with the increasing age [1–3]. Chronic HF (CHF) generally occurs due to continuous left ventricular (LV) remodeling and the progressive loss of heart function, leading to abnormalities in diastolic or systolic function [4]. After Myocardial infarction (MI), different physiological as well as molecular changes take place like changes in the cardiomyocytes structure, changes in gene and protein expression and a series of complex remodeling responses [5]. Mechanism by which the heart reduces stress on the ventricular wall by enlarging individual myocyte size to augment cardiac pump function and decrease ventricular wall tension in Hypertrophic growth [6,7] for HF, use of therapeutic agents as a treatment is very effective in reducing hypertrophy and negative remodeling of the myocardium such as Angiotensin-converting enzyme inhibitors (ACE), angiotensin receptor antagonists, calcium channel blockers, and beta-blockers [6,8]. Additionally, the rate of hospitalizations is reduced by biventricular pacing, Left ventricular assist device (LVAD), coronary bypass surgery and other intervention, in term to minimize mortality and improving the functional status of the heart [9–11], Despite optimal treatment with existing approaches can treat the heart failure symptomatically but do not cure the heart except heart transplantation which still remain challenging due to donor pool limitation and socio-economic factors [12]. The conventional application of drugs is limited by several pharmacological challenges, such as weak effectiveness, low solubility and poor bioavailability [13–15]. Therefore, novel therapeutic strategies are urgently necessary to reduce the high mortality rate, Acorn CorCap in ventricle reconstruction therapy (VRT) serves the purpose, mechanically constrain the heart at end-diastole by wrapping the dilated failing heart with prosthetic material and prevent further remodeling, which finally improves ventricular function, patient heart failure symptoms, and survival [16]. Up till now 4 premature ventricular restraint devices i.e. Cardiomyoplasty (multicenter FDA phase 2 trail, nonrandomized trial) [17,18], Acorn CorCap (randomized trial) also called Cardiac Support Device (CSD) [19,20], Paracor Heart Net device (randomized trail) [21,22] and Quantitative Ventricular Restraint QVR (Animal studies) [23,24] studies extensively by scientists [1]. *Salvia miltiorrhiza* is known as red sage or Danshen. It contains Tanshinone IIA (Tan IIA) that has cardiovascular activities like vasorelaxation and cardioprotective effects [25–31]. It also regulates many survival pathways of the myocytes [32] and has been reported to preserve cardiac function and prevent cardiac injury [33]. Moreover, in a mouse model of post-infarct myocardial remodeling, Tanshinone IIA has shown anti-fibrotic effects by up-regulating the expression of microRNA-29b, which is mediated via T GFβ-Smad3 signaling pathway, Tanshinone IIA has shown beneficial effects on the cardio-vascular system with minimal side effects [34–36]. Tanshinone IIA sulfonate injection (commercially available) as a traditional Chinese medicine in the form of injections have strong anti-inflammatory, anti-platelet activity, reduces coagulation and inflammatory lesions, which serves to prevent damage to a certain extent. It can reduce the occurrence of platelet-associated thromboembolic disease as well. Salvia ketone IIA has an anti-oxidant effect and is also an anti-oxygen free base which helps in controlling myocardial deficiency against perfusion injury. It also protects the function of the heart and can prevent

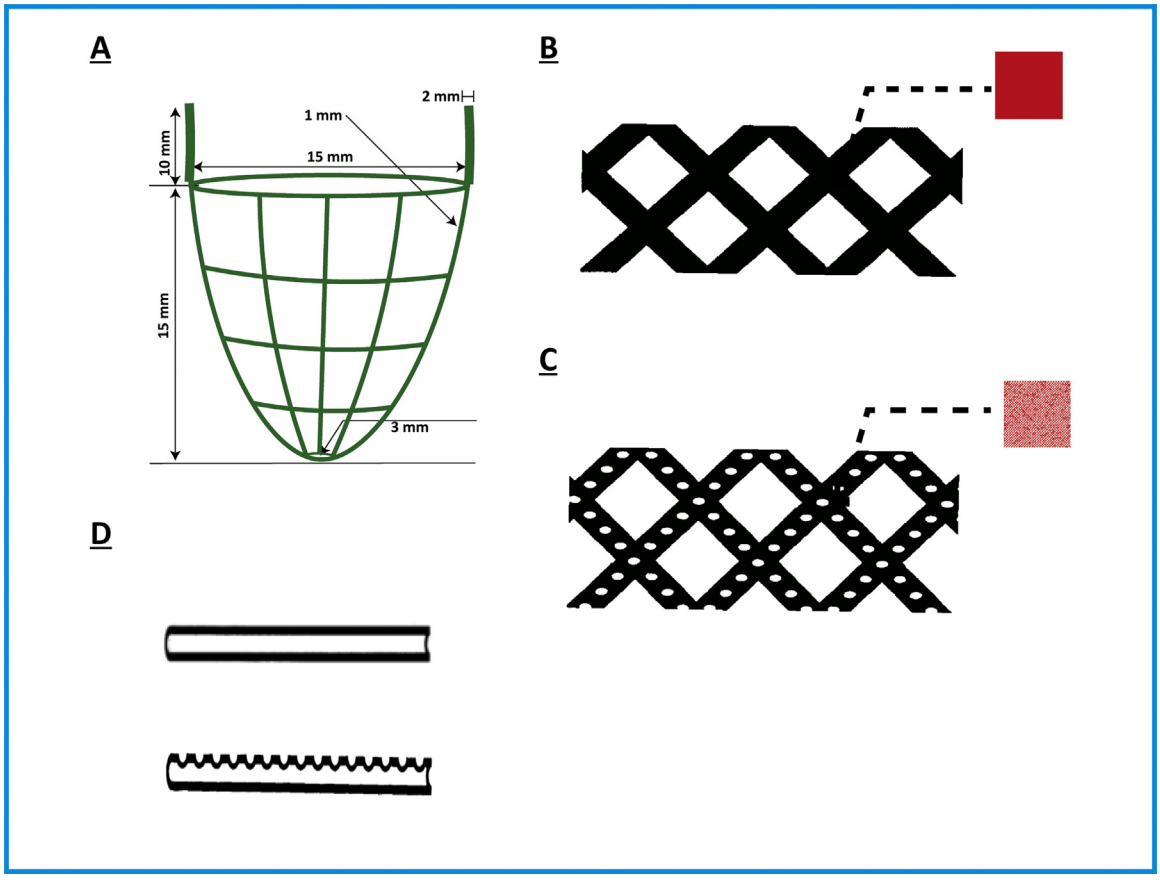

Fig. 1. Different view angles of ASD. **A**. dimensions of ASD**, B**. outer and inner lining of tubules, **C**. inner lining of tubules, **D**. cross section area of tubules.

calcium ion overload within the cell which poses an increased risk of cell injury. This compound also inhibit inflammatory cellular responses and factors responsible for heart failure [26]. Most commonly used drug carriers for heart failure include liposome's, hydrogels and polymeric microparticles, osmotic pumps [37,38]. The convention administration of drugs is limited by several disadvantages, such as a weak effect of the drug moiety, poor biodistribution, and poor bioavailability at target site [13–15]. All of these drawbacks drive researchers for further development and optimization of new drug strategies to overcome HF more effectively to enhance release patterns and improving overall efficacy. In the present study, we designed a novel ventricular restraint device (ASD) made-up with biocompatible such as silicon [39], which not only provide cardiac support to a heart failure candidate but also have the potential to deliver drug locally to the heart simultaneously. In this study, we hypothesize that effect of this combined therapy (SM + ASD) is a safe and effective therapeutic option for heart failure management despite the use of cardiac support device (ASD) and SM drug individually.

2. Materials and methods

SD rats (250–300 g) were purchased from College of Veterinary Medicine Yangzhou University (License no: SCXK (Su) 2015-2005, Yangzhou, China. The animals received care in compliance with the Principles of Laboratory Animal Care and the Guide for the Care and Use of Laboratory Animals. Experiments followed a protocol approved by the China Pharmaceutical University Institutional Animal Care and Use Committee.

Danshen Zhusheye injection 10 g/10 ml (*Salvia miltiorrhiza*) of 95% purity was purchased from Chiatai Qingchunbao Pharmaceutical Co. LTD, Nanjing, Jiangsu, China. Ventilator (HX-300S) and ECG were obtained from Chengdu technology & market Co. LTD, Chengdu, China. 6.0 polypropylene sutures and silk suture were purchased from Shanghai Jinhuan Chemical Co.,Ltd, Shanghai, China. Implantable catheter and polyethylene catheter were purchased from Jiangxi Hongda Medical Equipment Group Co. LTD. Nanchang, Jiangxi, China. Phosphate buffered saline (PBS) (1:100) were purchased from Keygen Biotech, Nanjing, China. Trichrome's staining kit and Biebrich scarlet–acid fuchsin kits were purchased from Beyotime Institute of Biotechnology. Haimen, China. Rat BNP ELISA kit was purchased from Shanghai Jinma Biological Co. LTD, Shanghai, China.

2.1. Designing of ASD

The present invention relates to a device for treating various kinds of heart diseases, more particularly for treating heart failure or various kinds of cardiomyopathies. Active hydraulic ventricular Support Drug delivery system (ASD) [40] device can provide 1) Physical support 2) Biological and pharmacological agents delivery 3) Real time heart monitoring. The ASD is a mesh-like device consisting of several hollow tubules, which surrounds both ventricles of the heart as shown in Fig. 1. All the hollow tubes are completely interconnected to form a plurality of independent areas and the interior of each independent area is intercommunicating, while the independent areas are not communicating. No matter with or without the apertures, each of the independent areas forming the net cover has two or more ends connected to the exterior of body and diameter of the apertures is not larger than a half of the diameter of the hollow tubes. The hollow ASD tubules can be filled with various kinds of liquid of different physical

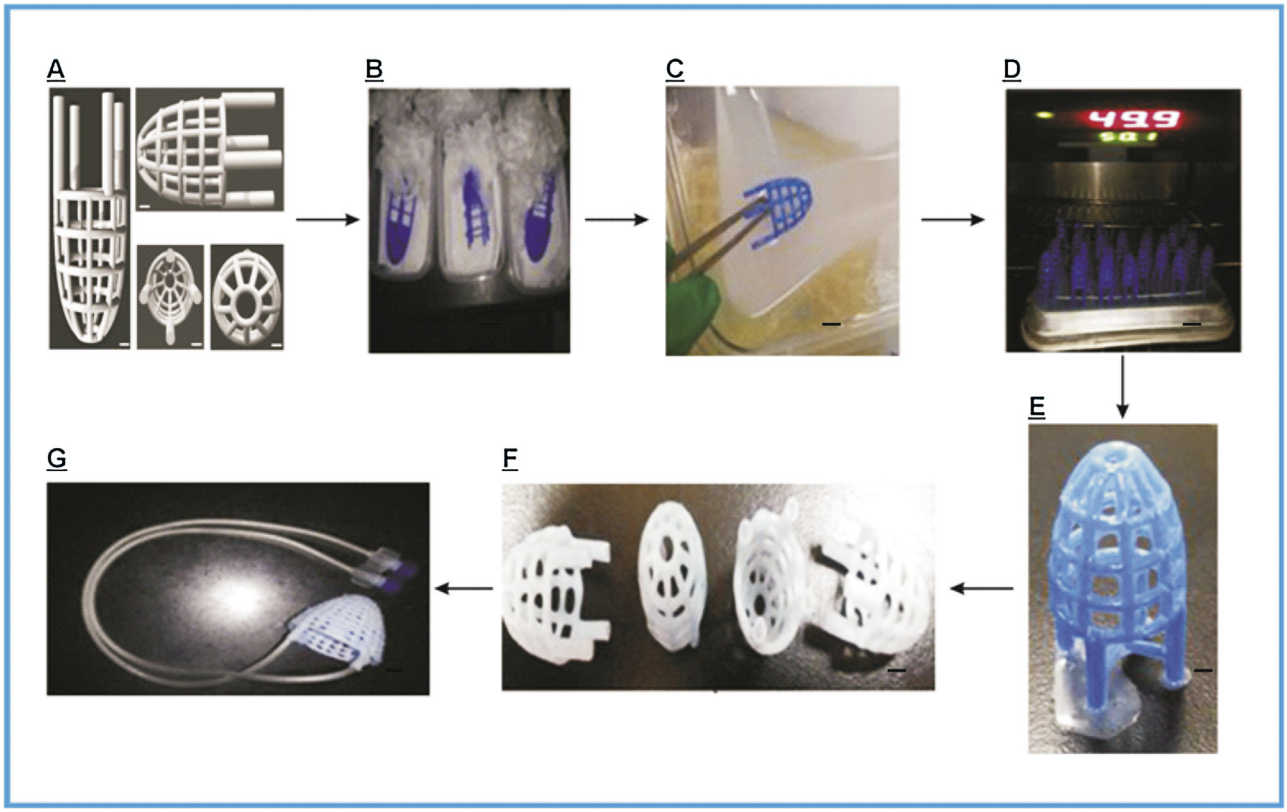

Fig. 2. ASD fabrication **A**. 3-D model of ASD, **B**. 3-D blue wax model, **C**. Wax model of ASD was plunge into liquid silicon, **D.** Model put into oven for 1 h at 50 °C, **E**. Blue wax start melting from the ASD model at 100 °C for 30 min, **F**. ASD from pure silicon, **G**. ASD connected with implantable catheter, scale bar 100 μm.

characteristics, and then the corresponding reaction pressure generated can be applied to the ventricle and the surfaces of the heart as shown in Fig. 1**B**. A pneumatic pump can be attached externally with ASD tubules, which can deliver an adjustable and measurable optimized restraint at the beginning of therapy as well as the heart shrinks during active reverse remodeling. We hypothesize that ASD will attenuate LV remodeling and improve heart performance. The system also can be incorporated with local administration of biological and therapeutic agents. A semi-permeable membrane can be attached with the apertures of ASD tubules for selective delivery in order to control the size, structure and permeation flow rate of the drug molecules applying on the heart epicardium as shown in Fig. 1**C**. We believe that ASD has potential to deliver drugs to the heart with more control and in a precise manner. Similarly, ASD has ability to deliver drugs like SM locally to the epicardium of the heart. The gold standard building material of ASD is silicon [41], very common, highly biocompatible and immunogenic material [42] and the wall from other materials of macromolecule and flexible physical characters, selected from nanophase materials capable of loading and releasing the medicine. The safety of biomaterial is important for successful drug delivery without any complications. Leak testing (Cincinnati Test Systems Shanghai) was performed to ensure any leakage and blockade in ASD tubules. First of all 3D model of ASD was designed by Using Rhinoceros 5.0 software (Robert and Mc Neel, USA) then a blue wax model was designed by Nanjing Shining 3D Tech Co. LTD, Nanjing, China. A prepared silicon solution was filled in wax model, which was then cured by heating at 50 °C for 1 h. Next, the assembly was subjected to a temperature of 100 °C for 30 min to let the wax melt and get pure silicone ASD device as shown in Fig. 2. In present study, the ASD tubules were punched to make apertures for the delivery of SM by using laser beam DNUVM8 (Nanjing DiNai laser sci. &Tech, Co. LTD, Nanjing, China) as shown in Fig. 1**C**. ASD has four tubules like appendages among of these four tubules two were extended for *Salvia miltiorrhiza* delivery in SD rats as shown in Fig. 2**G**. Dimensions of ASD device are different for different experimental animals. In this study, the dimensions of ASD for SD rats are described in Fig. 1**A**.

2.2. Animal model

30 adult (250–300 g) male SD rats (Sprague-Dawley) were divided into 5 groups (n = 6) namely, Normal, HF, HF + SM (IV), HF + ASD, HF + ASD + SM as shown in Fig. 3. Heart failure was induced by ligation of the left anterior descending (LAD) coronary artery as previously described method with few modifications [43]. All the rats were weighed, shaved, scrubbed and disinfected with 75% ethanol from neck and chest area and anesthetized by injecting 3% pentobarbital sodium (30 mg/kg). Anesthetized rats were placed in a supine position and endotracheal intubation was performed. Ventilation was acquired by connecting the endotracheal tube to HX-300S ventilator at a breathing rate of 80/min and tidal volume of 10 ml. After achieving steady breath, the chest was opened between the 3rd and 4th intercostal space and a chest retractor was placed to expose the left ventricle. Left coronary artery (LCA) was identified and ligated with 6.0 polypropylene

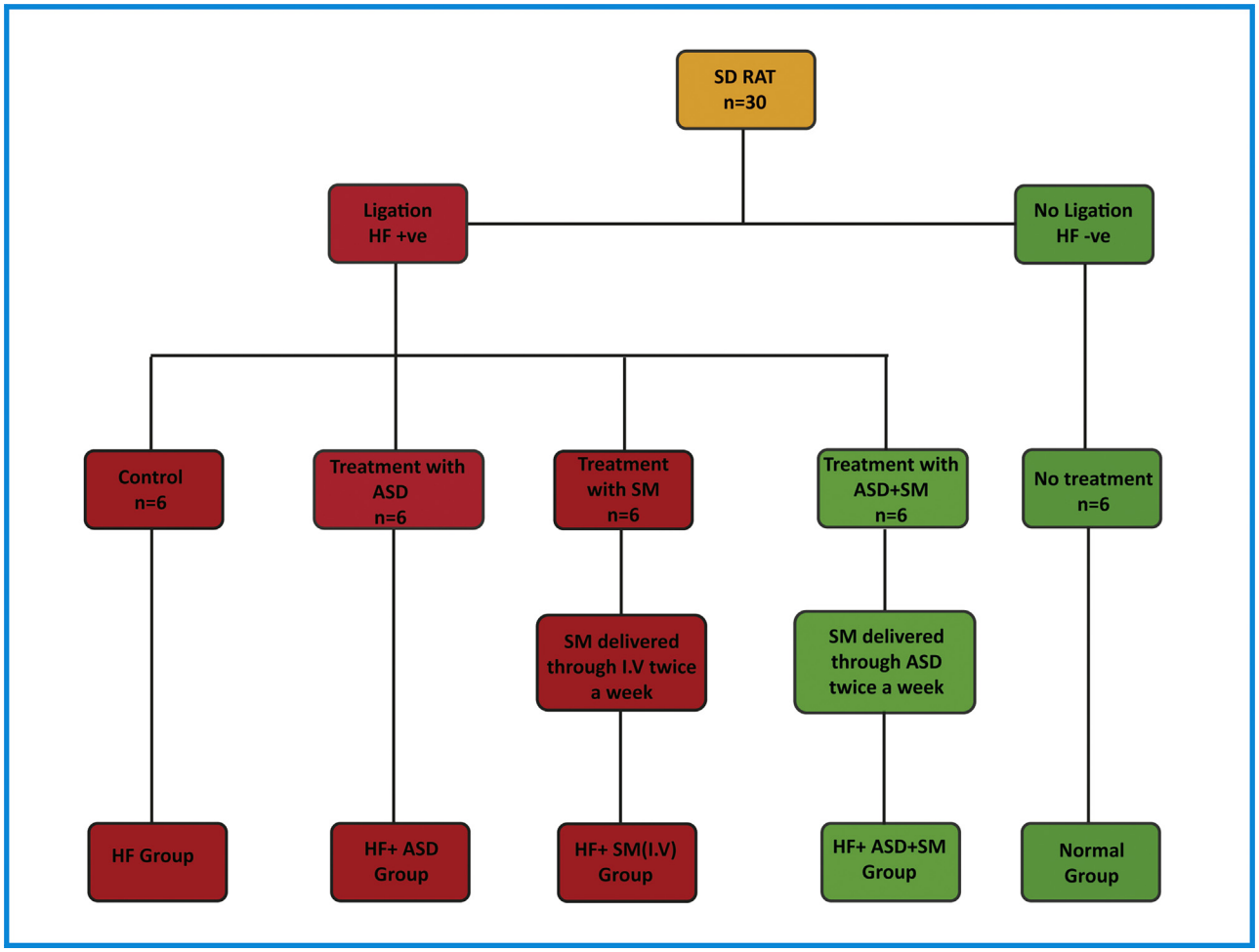

Fig. 3. Flow chart design of experiments.

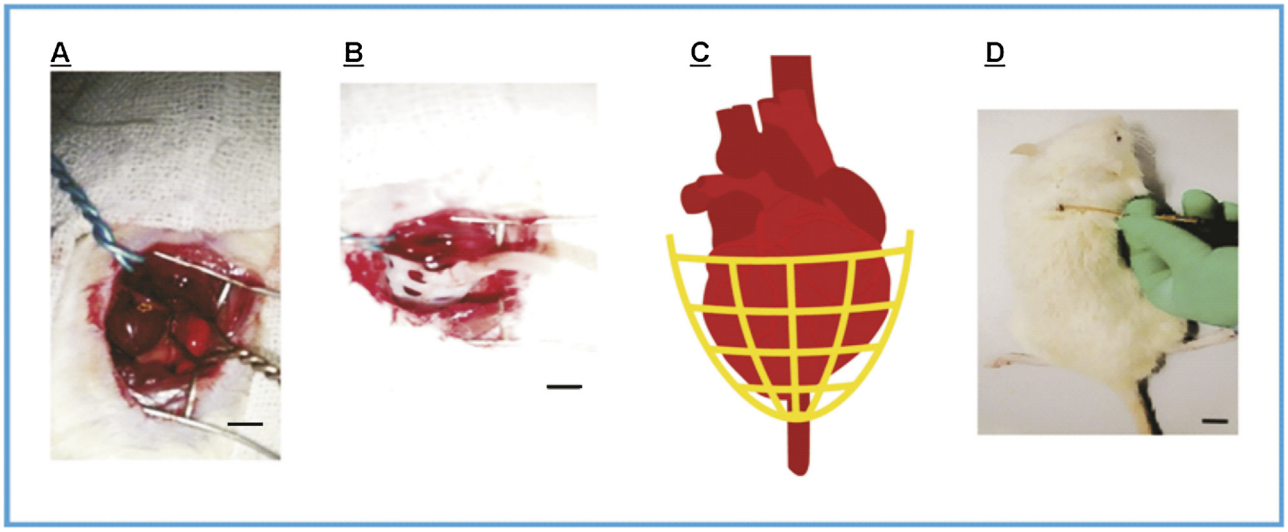

Fig. 4. A. HF model, arrow indicates the ligation of coronary artery, **B**. ASD implanted in SD rat, **C**. ASD attached to atrioventricular junction, **D**. Catheter opening in skin for SM injection, scale bar 100 μm.

sutures to induce heart failure as shown in Fig. 4**A**. The heart failure was confirmed by ECG and BNP level.

2.3. ASD device implantation

After the confirmation of post-infarction heart failure, pericardium was exposed and the ASD device is placed below the heart around the ventricles (Right and Left Ventricle), which were achieved by sliding the device over the epicardium, up to the level of the atrioventricular junction as shown in Fig. 4**B**. After acquiring the correct position on heart it was then stitched with atrioventricular junction using Prolene sutures (4–0) [44] as shown in Fig. 4**C**. ASD is connected to implantable catheter and the ASD portacath was tunneled subcutaneously through the second intercostal space into the left anterior chest wall and was extended outside the body through 1 cm opening in skin at Spinotrapezius as shown in Fig. 4**D**. Chest retractors were withdrawn and the ribs were rejoined together by discontinued stitching. After placement of the ASD device, the rats were divided into two experimental groups namely HF + ASD group (n = 6) and HF + ASD + SM group (n = 6). Postoperatively, animals received penicillin sodium (5 wU/100 g intramuscularly every 24 h for 5 days) for antibiotic prophylaxis.

2.4. Salvia miltiorrhiza *(SM) injection*

After successful implantation of ASD system in the rats, *Salvia miltiorrhiza* (Danshen Zhusheye 10 g/10 ml) 0.5 ml/kg.day was injected into HF + ASD + SM group twice a week through the exterior opening as shown in Fig. 4**C**. In second group HF + SM (IV), Danshen Zhusheye (*Salvia miltiorrhiza*) 0.5 ml/kg day was injected through IV route after heart failure twice a week.

2.5. Electrocardiography

Rats were sedated with 10% chloral hydrate, and then held in supine position on table and the electrocardiogram machine having four electrodes was inserted in the rat limbs subcutaneously. Briefly, Red electrode was inserted into the right upper limb, Black electrode into the right lower limb, Yellow electrode into the left upper limb and the Green electrode into the left leg respectively. A Series of ECG was established in all rats at pre-infarction, post-infarction, day 7, 15 and 30 days after the infarction.

2.6. Assessment of B-type natriuretic peptide (BNP) biomarker level

B-type natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP) are the gold standard biomarkers in determining the diagnosis and prognosis of HF. B-type natriuretic peptide serum level was measured by using RAT BNP ELISA kit (Shanghai Jingma, Shanghai China) according to the manufacturer instructions.

2.7. Investigation of hemodynamic parameters

At the end of study period rats were shaved, scrubbed and disinfected with 75% ethanol from neck area and anesthetized by injecting 3% pentobarbital sodium (30 mg/kg). Anesthetized rats were placed in a supine position and endotracheal intubation was performed. Ventilation was acquired by connecting the endotracheal tube to HX-300S ventilator at a breathing rate of 80/min and tidal volume of 10 ml. After achieving steady breath, right carotid artery was distally ligated through a longitudinal incision in the right side of the neck and tied to prevent excessive bleeding. The one end of polyethylene catheter was introduced into left ventricle through right carotid artery and the other end was connected with BL- 420 multi-channel physiological signal system. At steady state of hemodynamic all parameters were measured namely, mean left ventricular systolic pressure (mLVSP), mean left ventricular end-diastolic pressure (mLVEDP), dp/dtmax and −dp/dtmax. The readings were taken digitally through BL-420 multi-channel physiological signal system (Chengdu Instruments, Chengdu, China) and mean data was recorded at the end of study. Heart rate was also taken digitally through BL-420 multi-channel physiological signal system on preoperative, postoperative day 7, 15 and 30 days and mean data was recorded at the end of study.

2.8. Histological analysis

All the rats were euthanized at the end of study period (30 days) then the skin and muscle tissues were excised up to neck region from the xiphoid, and heart was exposed by completely removing

the chest and ribs along the surrounding muscles. The aorta was tied with silk suture to avoid bleeding and then heart was harvested. Before fixation of heart in 10% formalin the heart was flush several times in Phosphate buffered saline (PBS) (1:100) to remove the remaining blood. The heart was then sliced into 5 μm in coronal sections, dehydrated with 70, 80, 90, 95 and 100% series of ethanol in ascending order, and embedded in paraffin. For differentiation between collagen and muscle fibers Masson's Trichrome staining was performed. The histological sections were analyzed and imaged using Digital Pathology (NanoZoomer 2.0 RS, UK) and extent of fibrosis was quantified by using ImageJ software 4.7 (USA).

2.9. Statistical analysis

SPSS 19.0 was used for statistical data analysis. Data are expressed as the mean ± standard deviation, and difference was considered statistically significant as a $P^* < 0.05$, $P^{**} < 0.01$, $P^{***} < 0.001$.

3. Results

3.1. Electrocardiography

Prior to start any experiment all the rats were subjected to electrocardiography. All rats displayed a normal electrocardiographic waveform, with distinct P waves, QRS complexes, and T waves as seen in pre-operative group all treatment groups Fig. 5(a, f, k, p). The ECG show noticeable abnormalities immediately after 25 min of HF induction including, QRS, widening, ST elevation, PR interval prolongation and a peak known as 'hyper acute T' wave [45] in HF group Fig. 5(b), on day 7 and 15 "T" wave become abnormal and show obvious pathological symptoms. "Q wave" was demonstrated on day 30 evident from Fig. 5(c–e). The elevated "ST" at 25 min was reported in Fig. 5(l) and it was declined on day 7 and 15 in HF + ASD group, and ECG was obtained normal on day 30 Fig. 5(m–o). In HF + SM (IV) group ST elevation at 25 min Fig. 5(g) and pathological Q wave on day 7 and 30 were observed, and arrhythmia on day 15 was reported Fig. 5(h, i, j). While, after initial elevation of ST segment at 25 min on day 7 and 15 "ST" segment declined Fig. 5(q) and a normal ECG was reported in HF + ASD + SM group on day 30 Fig. 5(r–t) in comparison to other treatment groups. Which proves that HF + ASD + SM group significantly normalizes the cardiac function (rhythm) in HF-induced animal model at the end of study period (30days).

3.2. Measurement of B-type natriuretic peptide biomarker level

The BNP level was measured in Preoperative, Postoperative, 7, 15 and 30 days (after ligation) and result showed that HF + ASD + SM group revealed significantly low BNP level as compared to HF, and other treatment groups. Interestingly, the BNP value of HF + ASD + SM on day 30 is significantly lower than BNP level in preoperative, postoperative, 7 and 15 days as shown in Fig. 6**B**.

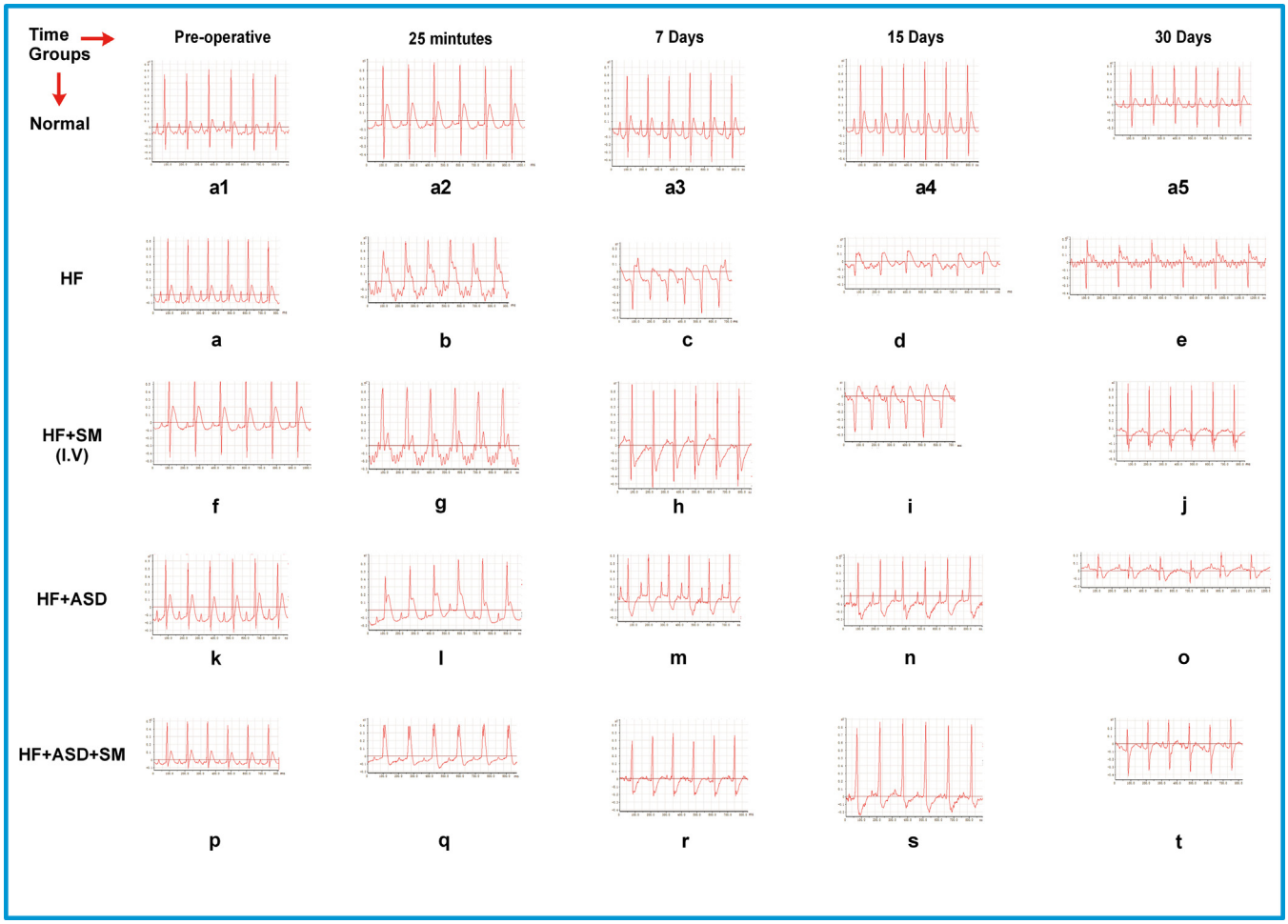

Fig. 5. Electrocardiogram (ECG) observations for preoperative, 25 min, 7, 15 and 30 days after ligation of different treatment groups, normal, HF, HF + SM (I.V), HF + ASD, HF + ASD + SM, n = 3.

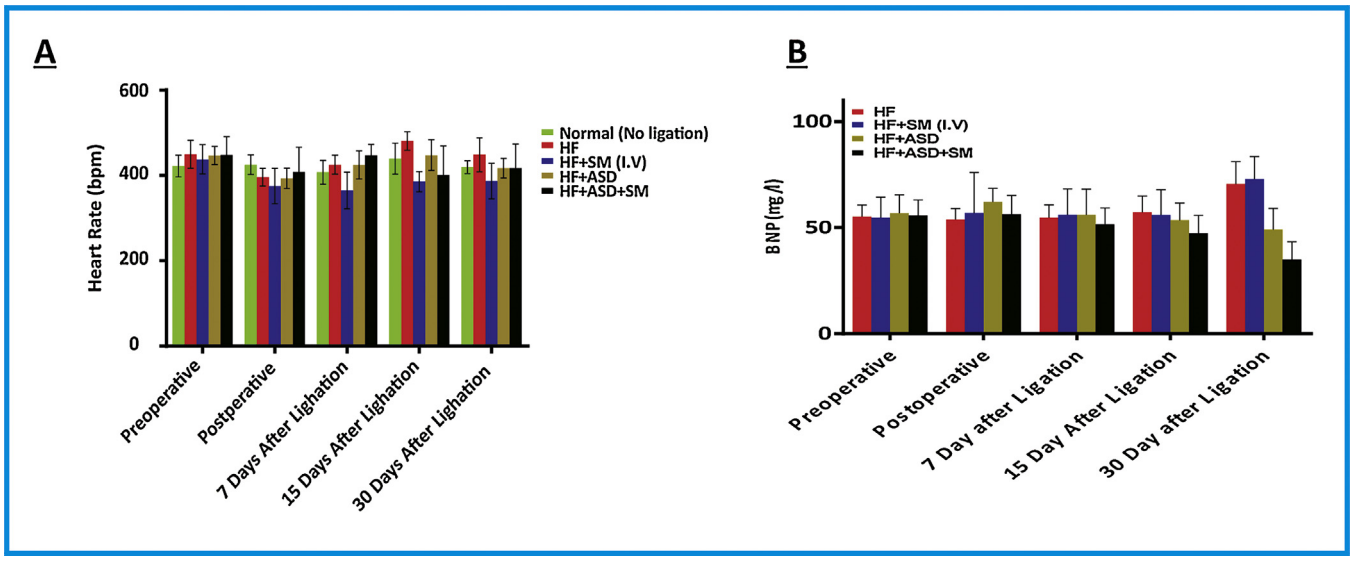

Fig. 6. Heart rate **A**. and BNP level **B**. for preoperative, postoperative, 7, 15 and 30 days after ligation of different treatment groups, normal, HF, HF + SM (I.V), HF + ASD, HF + ASD + SM, n = 3.

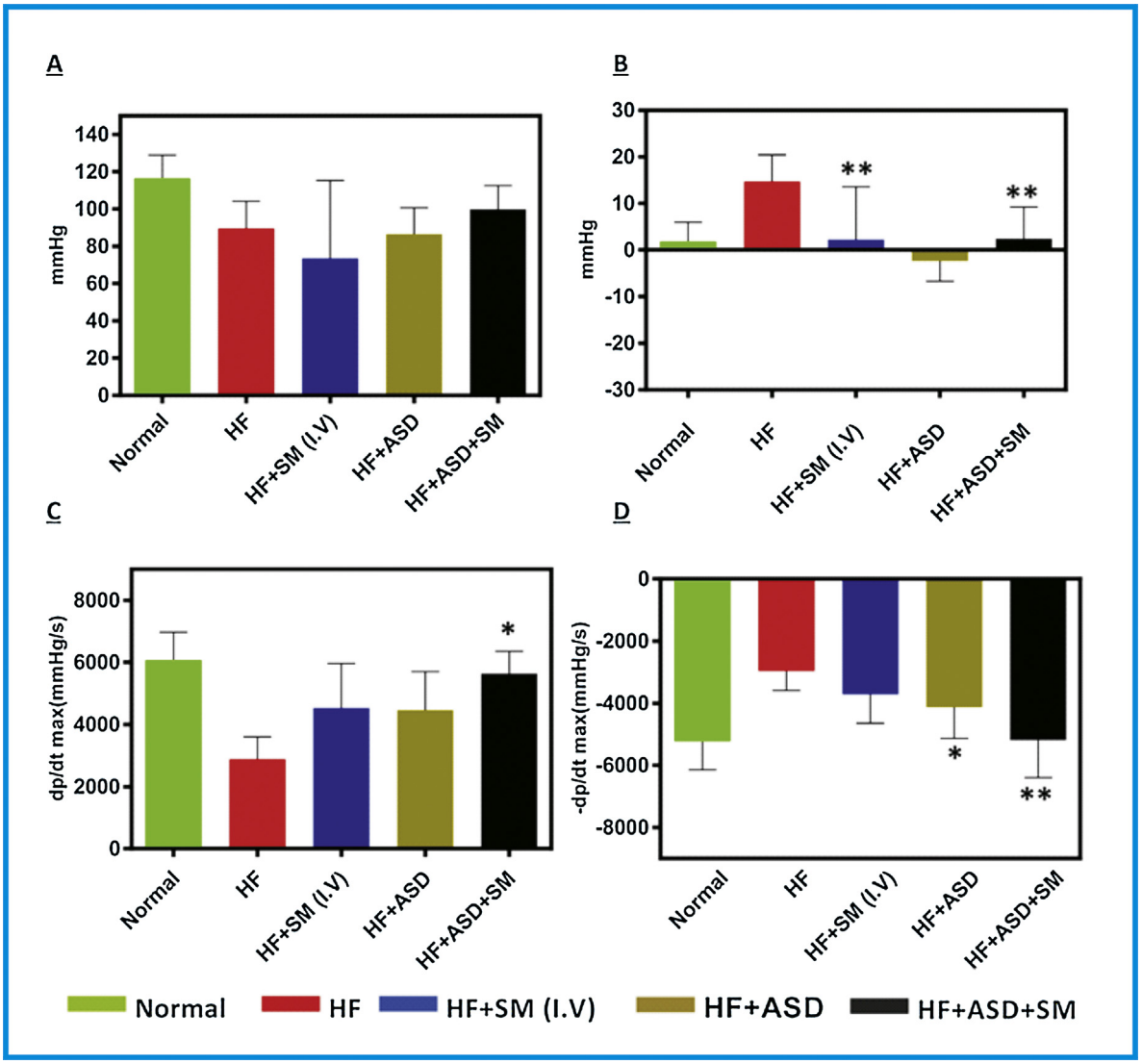

Fig. 7. Hemodynamic parameters **A**. LVSP, **B**. LVEDP, **C**. dp/dt max, **D**. −dp/dt max of different treatment groups, normal, HF, HF + SM (I.V), HF + ASD, HF + ASD + SM, n = 3, $^{*}P < 0.05$ and $^{**}P < 0.01$.

3.3. Hemodynamic parameters

Left ventricular (LV) hemodynamic parameters were measured in all groups for assessment of ventricular performance in term of ventricular pressure and heart rate. The LVSP in HF + ASD + SM group significantly improves the systolic pressure as compared to adjacent HF + SM (IV), HF + ASD, HF treatment groups. The LVEDP in HF group was higher as compared to HF + ASD, HF + SM (IV) and HF + ASD + SM groups. The result reflected that LVEDP value in HF + ASD + SM group was very low and no significant difference was observed as compared to normal group. The cardiac contractility parameters dp/dt_{max} of HF + ASD + SM group is significantly increased as compared to HF group and other experimental groups and $-dp/dt_{max}$ significantly decreased in HF + ASD + SM group as compared to HF and other treatment groups as in shown Fig. 7. Heart rate was brought to normal in HF + ASD + SM group as compared to other treatment groups as shown in Fig. 6**A**.

3.4. Histological analysis

Image developed from the Masson's Trichrome stained tissue specimens was highlighting the collagen fibers and fibrosis with blue coloration as shown in Fig. 8**A** and **B**. It is obvious from the results that the normal group show healthy myocardium stained red in picture, while HF group contain a large quantity of blue fibrotic tissues. The HF + ASD and HF + SM (IV) groups they also showed less blue fibrotic tissue than HF group. Interestingly, the fibrotic tissue in HF + ASD + SM group was completely replaced by healthy myocardium cells which confirm that HF + ASD + SM significantly improved myocardium compared to HF + SM (IV), HF + ASD, and HF groups. Furthermore, the quantification of fibrosis data also showed similar observations as shown in Fig. 8**C**.

4. Discussion

Despite the use of existing drugs for optimal treatment in end-stage heart failure, overall effectiveness of these therapeutic

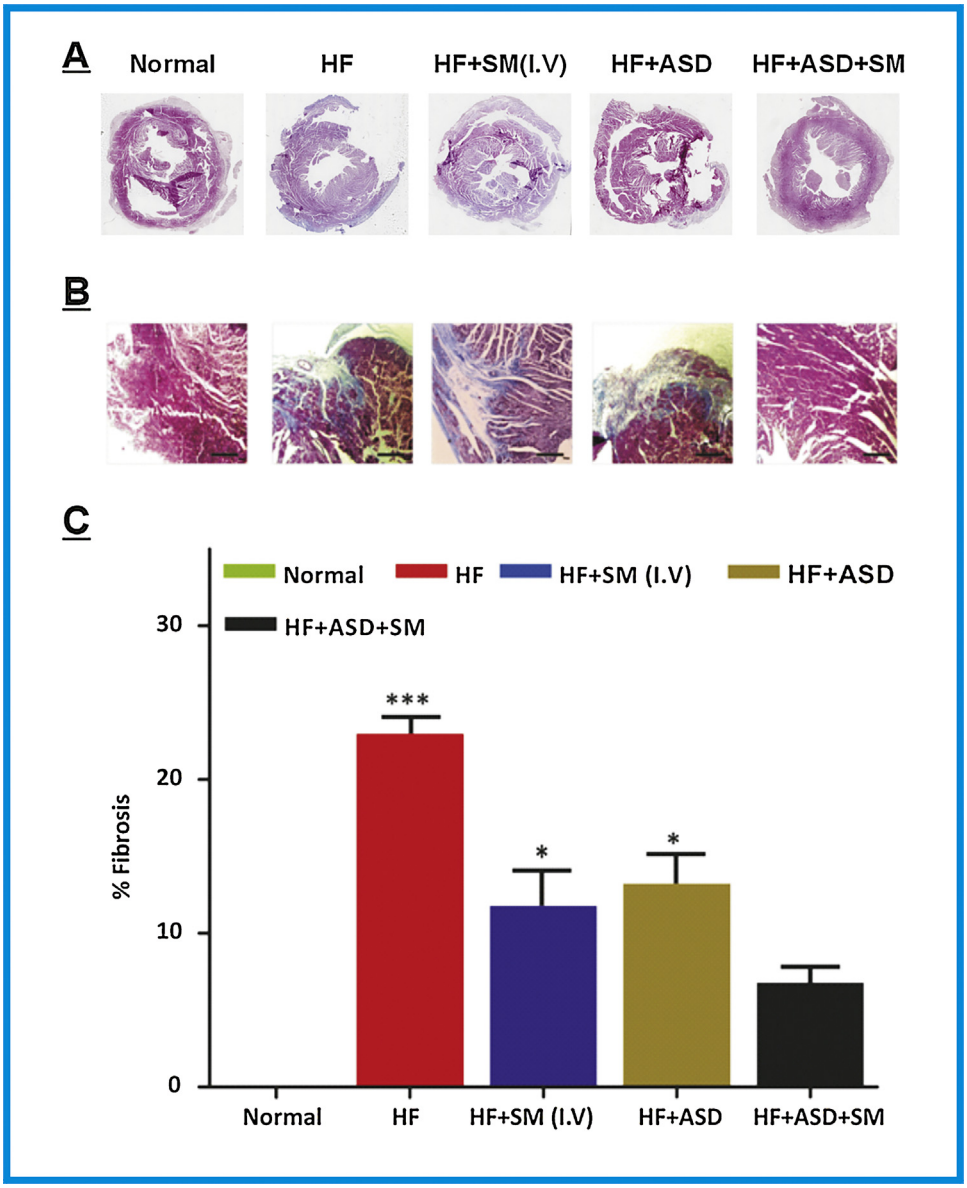

Fig. 8. Histopathology of heart tissue **A**. Image using Digital pathology (NanoZoomer 2.0 RS), n = 3, **B**. Fibrosis mark-up on digitized slides (photomicroscope, original magnification ×4), **C**. Quantification of fibrosis of heart tissues obtained from different treatment groups, scale bar 100 μm, n = 3, $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$.

approaches is limited as well as possible lethal side effects must be considered to attain desired therapeutic effects. Therefore, novel therapeutic strategies are exigent [6,46], which have potential to combat with multiples etiology. Not only the successful delivery of therapeutic drugs at the target site (with minimal or no side effects) but also the biosafety of these therapeutics must be consider [47]. In present study, ASD was used which is made from silicon, a highly biocompatible material and is the best option for safe delivery of many therapeutic drugs to the heart muscle [47] without causing any significant side effects. The mesothelium cells in the heart, which forms the epicardium, actively transport cells, fluids and they have ability to synthesize and secrete different inflammatory mediators and these mediators respond to an external stimulus that plays important roles in the regulation of different responses like inflammatory, immune and tissue repair [48,49]. ASD is an innovative therapeutic device which not only successfully delivers *Salvia Miltiorrhiza* to the pericardium of the heart to treat heart failure but also has a supportive action, which helps in further preventing dilatation and attenuation of LV remodeling. Furthermore, ASD has ability to deliver drug in a temporal manner and maintain a therapeutic level of drug to the heart. Interestingly, ASD also has a permeable membrane with the small pores which help in selected drug delivery to the heart muscles.

It was demonstrated that during heart failure both systolic and diastolic functions of the heart were impaired, which were presented by decreased LVSP and dp/dtmax, increased LVEDP, and prolonged dp/dtmax [50]. There are several mechanisms involve in the pathogenesis of heart failure such as cardiomyopathy, hypertension, coronary artery disease etc. SM was delivered by ASD within an optimized therapeutic level was identified to restore physiology and maximize reductions in mLVEDP throughout the cardiac cycle, decrease the area of infarction damage, improving mechanical efficiency and minimizing the effects on systemic hemodynamic [51]. Optimized ventricular restraint also reversed pathological LV dilation and *Salvia miltiorrhiza* further improve LV functions significantly [52]. The LVSP in the HF + ASD + SM group was high then the HF + SM (IV) and HF + ASD groups. The LVEDP was noted to decline in HF + ASD + SM group as compared to HF + SM (IV) and HF + ASD groups respectively. This further supports the fact that cardiac mechanical functioning ability is improved by using ASD system with therapeutic drugs such as SM. Similarly, the cardiac relaxation parameter was also improved when we gave SM locally rather than an intravenous route.

In this study, it was revealed that ASD + SM can significantly decrease the severity of heart failure and no cardiac dysfunction was noticed in rats. BNP which is an important biomarker secreted in the response to heart failure [49], was successfully brought back to normal range when treated with ASD + SM group as compared with SM given by IV route. The level of BNP in HF + ASD + SM group was found significantly lower from that of HF and HF + SM (IV) group, revealing the effective delivery of SM by ASD which, proves our hypothesis that the potential of ASD with SM have a greater beneficial effect in heart failure in single action then the restraining device alone. The histological examination in this study by staining showed a clear picture of all the groups, the heart failure group showed a high blue fibrotic area which confirms the successful induction of HF [46–49,53], but after the treatment with ASD + SM showed an obvious improvement when compared with ASD, HF and SM(IV) group.

The results of this study guarantee that the drug delivery with novel ventricular restraint therapeutic device (ASD) could be a promising strategy for the treatment of heart failure. Delivering the drug though ASD as a combination therapy is a smart therapeutic option. Present work could prove that combination therapy is a useful strategy to treat major diseases like heart failure than single drug administration.

5. Conclusion

In concluding remarks ASD is a novel ventricular restraint device, sets up a novel therapeutic platform for the management of end-stage heart failure. It showed excellent therapeutic outcomes in combination over the conventional delivery of therapeutic and diagnostic agents. In this respect, different potent drugs can be delivered to the heart through novel ASD device more safely and effectively. Future exploration is needed to determine the effect of long-term drug delivery and increase therapeutic benefits through ASD device. Therefore, the future aim of our research is to deliver biological therapeutic agents and hydraulic pressure to heart though ASD and this initial feasibility study will provide a push to move forward. However, further studies will be needed to report that whether pathologic remodeling persists after termination of restraint therapy or not? What is the effect of ASD implantation on ventricle shape, size, and myocardial structure, as well as load independent indices of ventricle function over a longer treatment period? The advent of the ASD represents a promising start in the quest for transcatheter, device-based ventricular restoration.

Conflict of interest

The Authors declare no conflict of interest.

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References

[1] D.M. Kaye, H. Krum, Drug discovery for heart failure: a new era or the end of the pipeline? Nat. Rev. Drug Discov. 6 (2) (2007) 127–139.
[2] F.J. Haddy, Heart failure-incidence and survival, N. Engl. J. Med. 348 (2003) 660.
[3] D. Levy, S. Kenchaiah, M.G. Larson, E.J. Benjamin, M.J. Kupka, K.K. Ho, J.M. Murabito, R.S. Vasan, Long-term trends in the incidence of and survival with heart failure, N. Engl. J. Med. 347 (18) (2002) 1397–1402.
[4] A. Siryk-Bathgate, S. Dabul, A. Lymperopoulos, Current and future G protein-coupled receptor signaling targets for heart failure therapy, Drug Des. Dev. Ther. 7 (2013) 1209–1222.
[5] C.X. Santos, N. Anilkumar, M. Zhang, A.C. Brewer, A.M. Shah, Redox signaling in cardiac myocytes, Free Radic. Biol. Med. 50 (7) (2011) 777–793.
[6] J.H. van Berlo, M. Maillet, J.D. Molkentin, Signaling effectors underlying pathologic growth and remodeling of the heart, J. Clin. Invest. 123 (1) (2013) 37–45.
[7] J.A. Hill, E.N. Olson, Cardiac plasticity, N. Engl. J. Med. 358 (13) (2008) 1370–1380.
[8] M.R. Zile, C.F. Baicu, W.H. Gaasch, Diastolic heart failure—abnormalities in active relaxation and passive stiffness of the left ventricle, N. Engl. J. Med. 350 (19) (2004) 1953–1959.
[9] J. Plessis, K.W. Fresse, Z. Cahouch, V. Letocart, T. Manigold, M. Lamer, L. Le Gloan, P. Guerin, TCT-279 the value of image fusion in coronary angiography for the detection of coronary artery bypass grafts, J. Am. Coll. Cardiol. 66 (15_S) (2015).
[10] U. Kervan, E. Unal, D. Sert, M. Pac, Heart Ware left ventricular assist device implantation combined with surgical ventricular reconstruction, Exp. Clin. Transplant. (2016), doi:http://dx.doi.org/10.6002/ect.2016.0056.
[11] J. Steffel, N. Varma, M. Robertson, J. Singh, J. Bax, J. Borer, K. Dickstein, I. Ford, J. Gorcsan 3rd, D. Gras, Effect of gender on outcomes after cardiac resynchronization therapy in patients with a narrow QRS complex: a subgroup analysis of the EchoCRT trial, Circ. Arrhythmia Electrophysiol. 9 (6) (2016).

[12] J.F.B. Chick, S.N. Reddy, G.J. Nadolski, Y. Dori, M. Itkin, Single-session endolymphatic glue embolization of lymphocele after heart transplantation, J. Vasc. Interv. Radiol. 27 (6) (2016) 929–930.
[13] D. Nevozhay, U. Kańska, R. Budzyńska, J. Boratyński, Current status of research on conjugates and related drug delivery systems in the treatment of cancer and other diseases, Postepy higieny i medycyny doswiadczalnej (Online) 61 (2006) 350–360.
[14] J. Cao, S. Zhai, C. Li, B. He, Y. Lai, Y. Chen, X. Luo, Z. Gu, Novel pH-sensitive micelles generated by star-shape copolymers containing zwitterionic sulfobetaine for efficient cellular internalization, J. Biomed. Nanotechnol. 9 (11) (2013) 1847–1861.
[15] P. Ojer, L. Neutsch, F. Gabor, J.M. Irache, A.L. de Cerain, Cytotoxicity and cell interaction studies of bioadhesive poly (anhydride) nanoparticles for oral antigen/drug delivery, J. Biomed. Nanotechnol. 9 (11) (2013) 1891–1903.
[16] K.J. Koomalsingh, W.R. Witschey, J.R. McGarvey, T. Shuto, N. Kondo, C. Xu, B.M. Jackson, J.H. Gorman, R.C. Gorman, J.J. Pilla, Optimized local infarct restraint improves left ventricular function and limits remodeling, Ann. Thorac. Surg. 95 (1) (2013) 155–162.
[17] L.F.P. Moreira, N.A. Stolf, E.A. Bocchi, F. Bacal, P.M. Pêgo-Fernandes, H. Absensur, J.C. Meneghetti, A.D. Jatene, Clinical and left ventricular function outcomes up to five years after dynamic cardiomyoplasty, J. Thorac. Cardiovasc. Surg. 109 (2) (1995) 353–363.
[18] A.P. Furnary, M. Jessup, L.F.P. Moreira, Multicenter trial of dynamic cardiomyoplasty for chronic heart failure, J. Am. Coll. Cardiol. 28 (5) (1996) 1175–1180.
[19] J.F. Wenk, L. Ge, Z. Zhang, D. Mojsejenko, D.D. Potter, E.E. Tseng, J.M. Guccione, M.B. Ratcliffe, Biventricular finite element modeling of the Acorn CorCap Cardiac Support Device on a failing heart, Ann. Thorac. Surg. 95 (6) (2013) 2022–2027.
[20] Y. Kubota, S. Miyagawa, S. Fukushima, A. Saito, H. Watabe, T. Daimon, Y. Sakai, T. Akita, Y. Sawa, Impact of cardiac support device combined with slow-release prostacyclin agonist in a canine ischemic cardiomyopathy model, J. Thorac. Cardiovasc. Surg. 147 (3) (2014) 1081–1087.
[21] G.H. Oliveira, S.G. Al-Kindi, H.G. Bezerra, M.A. Costa, Left ventricular restoration devices, J. Cardiovasc. Transl. Res. 7 (3) (2014) 282–291.
[22] P. Atluri, M.A. Acker, Diastolic ventricular support with cardiac support devices: an alternative approach to prevent adverse ventricular remodeling, Heart Fail. Rev. 18 (1) (2013) 55–63.
[23] R.K. Ghanta, A. Rangaraj, R. Umakanthan, L. Lee, R.G. Laurence, J.A. Fox, R.M. Bolman, L.H. Cohn, F.Y. Chen, Adjustable, physiological ventricular restraint improves left ventricular mechanics and reduces dilatation in an ovine model of chronic heart failure, Circulation 115 (10) (2007) 1201–1210.
[24] J.A. Magovern, Experimental and clinical studies with the Paracor cardiac restraint device, Seminars in Thoracic and Cardiovascular Surgery, Elsevier, 2006, pp. 364–368.
[25] L. Zhou, Z. Zuo, M.S.S. Chow, Danshen: an overview of its chemistry, pharmacology, pharmacokinetics, and clinical use, J. Clin. Pharmacol. 45 (12) (2005) 1345–1359.
[26] C. Shao-Jun, Drug-target networks for Tanshinone IIA identified by data mining, Chin. J. Nat. Med. 13 (10) (2015) 751–759.
[27] S. Chun-Yan, M. Qian-Liang, K. Rahman, H. Ting, Q. Lu-Ping, Salvia miltiorrhiza: traditional medicinal uses, chemistry, and pharmacology, Chin. J. Nat. Med. 13 (3) (2015) 163–182.
[28] A.N.A. Abad, M.H.K. Nouri, F. Tavakkoli, Effect of Salvia officinalis hydroalcoholic extract on vincristine-induced neuropathy in mice, Chin. J. Nat. Med. 9 (5) (2011) 354–358.
[29] D.-D. Sun, H.-C. Wang, X.-B. Wang, Y. Luo, Z.-X. Jin, Z.-C. Li, G.-R. Li, M.-Q. Dong, Tanshinone IIA: a new activator of human cardiac KCNQ1/KCNE1 (I Ks) potassium channels, Eur. J. Pharmacol. 590 (1) (2008) 317–321.
[30] J. Gao, G. Yang, R. Pi, R. Li, P. Wang, H. Zhang, K. Le, S. Chen, P. Liu, Tanshinone IIA protects neonatal rat cardiomyocytes from adriamycin-induced apoptosis, Transl. Res. 151 (2) (2008) 79–87.
[31] W. Xu, J. Yang, L.-M. Wu, Cardioprotective effects of tanshinone IIA on myocardial ischemia injury in rats, Die Pharm.–Int. J. Pharm. Sci. 64 (5) (2009) 332–336.
[32] I. Shiraishi, J. Melendez, Y. Ahn, M. Skavdahl, E. Murphy, E. Schaefer, K. Walsh, A. Rosenzweig, D. Torella, D. Nurzynska, Nuclear targeting of Akt enhances kinase activity and survival of cardiomyocytes, Circulation Res. 94 (7) (2004) 884–891.
[33] T. Matsui, J. Tao, F. del Monte, K.-H. Lee, L. Li, M. Picard, T.L. Force, T.F. Franke, R.J. Hajjar, A. Rosenzweig, Akt activation preserves cardiac function and prevents injury after transient cardiac ischemia in vivo, Circulation 104 (3) (2001) 330–335.
[34] T.-W. Wu, L.-H. Zeng, K.-P. Fung, J. Wu, H. Pang, A.A. Grey, R.D. Weisel, J.Y. Wang, Effect of sodium tanshinone IIA sulfonate in the rabbit myocardium and on human cardiomyocytes and vascular endothelial cells, Biochem. Pharmacol. 46 (12) (1993) 2327–2332.
[35] R. Lin, W.-R. Wang, J.-T. Liu, G.-D. Yang, C.-J. Han, Protective effect of tanshinone IIA on human umbilical vein endothelial cell injured by hydrogen peroxide and its mechanism, J. Ethnopharmacol. 108 (2) (2006) 217–222.
[36] H. Yong-Sheng, L. Zhang, D. Peng, C. Wan-Sheng, Cloning and induction of phenylalanine ammonia-lyase gene from Salvia miltiorrhiza and its effect on hydrophilic phenolic acids levels, Chin. J. Nat. Med. 7 (6) (2009) 449–457.
[37] A.S. Hoffman, Hydrogels for biomedical applications, Adv. Drug Deliv. Rev. 64 (2012) 18–23.
[38] W.T. Al-Jamal, K. Kostarelos, Liposomes: from a clinically established drug delivery system to a nanoparticle platform for theranostic nanomedicine, Acc. Chem. Res. 44 (10) (2011) 1094–1104.
[39] X. Zhou, X. Chen, T.-c. Mao, X. Li, X.-h. Shi, D.-l. Fan, Y.-m. Zhang, Carbon ion implantation: a good method to enhance the biocompatibility of silicone rubber, Plast. Reconstr. Surg. 137 (4) (2016) 690e–699e.
[40] X. Zhou, Active hydraulic ventricular attaching support system, Google Patents, 2010.
[41] D.L. Bernik, Silicon based materials for drug delivery devices and implants, Recent Patents Nanotechnol. 1 (3) (2007) 186–192.
[42] M.A. Tölli, M.P. Ferreira, S.M. Kinnunen, J. Rysä, E.M. Mäkilä, Z. Szabó, R.E. Serpi, P.J. Ohukainen, M.J. Välimäki, A.M. Correia, In vivo biocompatibility of porous silicon biomaterials for drug delivery to the heart, Biomaterials 35 (29) (2014) 8394–8405.
[43] Q. Qiu, C. Li, Y. Wang, C. Xiao, Y. Li, Y. Lin, W. Wang, Plasma metabonomics study on Chinese medicine syndrome evolution of heart failure rats caused by LAD ligation, BMC Complement. Altern. Med. 14 (1) (2014) 1.
[44] R.C. Starling, M. Jessup, Worldwide clinical experience with the CorCap™ cardiac support device, J. Card. Fail. 10 (6) (2004) S225–S233.
[45] N.K. Khan, K.M. Goode, J.G. Cleland, A.S. Rigby, N. Freemantle, J. Eastaugh, A.L. Clark, R. Silva, M.J. Calvert, K. Swedberg, Prevalence of ECG abnormalities in an international survey of patients with suspected or confirmed heart failure at death or discharge, Eur. J. Heart Fail. 9 (5) (2007) 491–501.
[46] L.M. Rademakers, L.X. Van Nunen, Ventricular septal defect after acute myocardial infarction, N. Engl. J. Med. 374 (23) (2016) e28.
[47] S.P. Hudson, R.F. Padera, R. Langer, D.S. Kohane, The biocompatibility of mesoporous silicates, Biomaterials 29 (30) (2008) 4045–4055.
[48] S.E. Mutsaers, S. Wilkosz, Structure and function of mesothelial cells, Peritoneal Carcinomatosis, Springer, 2007, pp. 1–19.
[49] P. Karlström, P. Johansson, U. Dahlström, K. Boman, U. Alehagen, Can BNP-guided therapy improve health-related quality of life, and do responders to BNP-guided heart failure treatment have improved health-related quality of life? Results from the UPSTEP study, BMC Cardiovasc. Disord. 16 (1) (2016) 1.
[50] S.M. Eleawa, M. Alkhateeb, S. Ghosh, F. Al-Hashem, A.S. Shatoor, A. Alhejaily, M. A. Khalil, Coenzyme Q10 protects against acute consequences of experimental myocardial infarction in rats, Int. J. Physiol. Pathophysiol. Pharmacol. 7 (1) (2015) 1.
[51] K.J. Lavine, M. Sintek, E. Novak, G. Ewald, E. Geltman, S. Joseph, J. Pfeifer, D. Mann, Coronary collaterals predict improved survival and allograft function in patients with coronary allograft vasculopathy, Circ.: Heart Fail. 6 (4) (2013) 773–784, doi:http://dx.doi.org/10.1161/CIRCHEARTFAILURE.113.000277.
[52] A.M. De Jong, I.C. Van Gelder, I. Vreeswijk-Baudoin, M.V. Cannon, W.H. Van Gilst, A.H. Maass, Atrial remodeling is directly related to end-diastolic left ventricular pressure in a mouse model of ventricular pressure overload, PLoS One 8 (9) (2013) e72651.
[53] J. Li, S. Umar, M. Amjedi, A. Iorga, S. Sharma, R.D. Nadadur, V. Regitz-Zagrosek, M. Eghbali, New frontiers in heart hypertrophy during pregnancy, Am. J. Cardiovasc. Dis. 2 (3) (2012) 192–207.