Cardioprotective effect of silicone built restraint device (ASD), for left ventricle remodeling in rat heart failure models

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Abstract

Purpose: This study was to assess the feasibility and cardio-protective effects of biocompatible silicon built restraint device (ASD) in rat's heart failure (HF) model. Background: Ventricle restraint therapy (VRT) is a well-established and promising approach for management of advanced-stage dilated HF. Previous VRT devices offer a subjective level of restraint to the dilated heart muscles. However, the impact of the restraint nature, mesh tubular design and biocompatibility of VRT devices is not well investigated. Method: The performance and compliance of ASD were determined in vitro by adopting a pneumatic drive and ball burst test. SD rats were grouped into four (n=24); control, HF, ASD+HF and CSD+HF groups, respectively. HF was induced by left anterior descending artery ligation in all groups except the control group. ASD and CSD devices were implanted in the heart of ASD+HF and CSD+HF groups respectively. Results: The functional and expansion ability of ASD was observed to be safer and suitable to attenuate ventricular remodeling. ASD treated rats showed normal heart rhythm which was validated by a smooth -ST and asymmetrical T-wave. Hemodynamic parameters, and systolic and diastolic functions improved in the ASD+HF group and reduction in ventricular wall stress indicated reverse remodeling. Furthermore BNP values were reduced in ASD+HF group which confirmed ASD feasibility and reverse remodeling at a molecular level. ASD+HF group also showed no fibrosis thus proposing that ASD has its significant curative effects on the heart muscles. Conclusion: ASD was found to be a promising restraint therapy than the previously standard restraint therapies.

Introduction

Heart failure (HF) is a devastating disorder which brings about insufficient supply of blood to tissues and organs. A variety of factors may contribute to its pathogenesis like myocardial infarction (MI), valvular heart disease (VHD), cardiomyopathy and hypertension; these are marked by loss of myocytes, hypertrophy, and an increment in interstitial fibrosis[1]. HF is a global health problem and worsens as population ages[2,3]. During the last three decades, HF management by devices intervention significantly improved the survival rate[4] and mean life expectancy in HF patients[5]. However, despite the advancement in therapies, the mortality rate (five years) of HF is nearly 50% worse than any type of cancers[6].

Ventricle restraint therapy (VRT) is a well-established and promising therapy in managing advanced stage dilated HF. VRT devices are made up of biocompatible materials that offer a supportive role to the heart muscles without directly being in contact with blood[7,8] They have been extensively investigated and also studied at different clinical phases[9–11]. However, despite the long investigation history, they haven't been used in clinical practice yet[12,13]. Recent research now focuses more on how to improve the nature of the restraint and biocompatibility of VRT to ensure reverse left ventricular (LV) remolding in the dilated heart[8,14,15] LV remodeling occurs when neurohormonal, mechanical and most likely genetic factors modify ventricular shape, function and size[1]. Previous VRT devices offer a subjective level of restraint to the dilated heart

muscles. However, the impact of the restraint nature, mesh tubular design and biocompatibility of VRT devices is not well investigated. Here, we modified VRT into exo-organoplasty intervention[16], by designing a highly biocompatible silicon material ventricular attaching device; ASD[17,18]. The objective was to fill the ASD device tubules with a characteristic fluid and observe its restraint property. Furthermore, through this system pharmacological and biological agents can be delivered to the heart locally[19,20] In this study, we have addressed the following important questions. Firstly, whether silicon built restraint device is feasible to attenuate ventricle remodeling in rats model of HF or not? Secondly, whether, hydraulic restraint is more promising therapy than former standard CSD restraint therapy or not?

Active hydraulic ventricular attaching support system (ASD) is a silicon built netlike device configured in a heart shape composed of flexible interconnected hollow tubes and covers both heart ventricles. It further contains two tubes at the top which are channeled outside the body after surgery; these link the ASD with a desired medical equipment[16]. The ASD system is an integrated treatment platform that integrates diagnosis, monitoring and therapeutic precision treatment in one system. It was designed to deliver ventricular restraint, pharmacological and biological therapeutic agents locally to heart muscles[20]. ASD tubes are filled with a fluid thereby exerting continues pressures on the dilated ventricles (**Fig.I**)[16,21]

The Laplace law provides a basis for understanding ventricle remodeling. It suggests that ventricular wall stress can be reduced by three factors individually or in combination; that is, reduction in transmural pressure (Ptm), cardiac chamber radius reduction, or increasing ventricular wall thickness[22]. The objective of ASD is to reduce ventricular wall stress through counter-pressure mechanism**Fig. 1** by exerting repetitive elastic force on the heart during the entire cardiac cycle, not just at end-diastole. Furthermore, the current study investigated the compliance and functional characteristics of ASD in-vitro. Here, the feasibility, biocompatibility and, nature of restraint of ASD device was studied in rat's HF model. We observed that ASD is feasible and highly biocompatible, thereby provided an adjustable and measurable ventricular hydraulic restraint (AMVR), thus it could be a promising therapy to treat dilated HF.

Results

In vitro experiments

Functional characteristics of ASD

Flow characteristics and pressure results of the ASD showed that afterload varied and the drive pressure regulated to obtain 6.6 L/min flow rate **(Fig. 2a).** Drive pressure was changed and the afterload maintained as a constant in order to establish the flow rate generated by the device (**Fig. 2b).** These in vitro assessments represent ASD's performance for a completely failed ventricle.

Compliance characteristics of the ASD

The compliance experiments showed that ASD experiences multiaxial expansion under load. Low loading resistance is indicated by the initial shallow part of the curve which is then accompanied by transition to a higher load resistance until ASD failure. There's a shallow slope initially until 5lbs and 0.8cm in deformation but as the load increased beyond 5lbs the curve steepened. At 46lbs ASD reached its load capacity and failed. **(Figure 2c).**

Fig. 2d Plot representing the uniaxial compliance curve for ASD model directed towards the longitudinal and circumferential paths and multiaxial compliance curve for collation. The multiaxial compliance curve is 4 times larger than the uniaxial curves between 25% and 45% strain. However, the projected compliance curve is only 1.4 to 1.5 times greater than uniaxial compliance curves between 77% and 100% strain

In vivo studies experiments

Electrocardiography

All groups showed normal T-wave, no pathological Q-wave, isoelectric ST-segment and upright T-wave prior to any surgery fig 3(a1,b1,c1,d1). ST-segment got elevated early after 25 minutes of ligation in HF, CSD+HF

and ASD+HF groups fig 3(b2,c2,d2). HF group showed broad T-wave and smaller R-waves on 7^{th} and 15^{th} day fig 3(b3,b4), followed by pathological Q-waves and elevated ST-segment on the 30^{th} day fig 3(b5). In the CSD+HF group T-wave started out smaller with a broader R-wave on the $7^{th}$and 15^{th} day fig 3(c3,c4), but pathological Q-wave and elevated ST-segment emerged on the 30^{th} day fig 3(c5). However, in ASD+HF group T-wave was asymmetrical (upright) and R-wave deflected upward on 7^{th} and 15^{th} day fig 3(d3,d4), while on the 30^{th} day a smooth ST-segment (concave upward) and no pathological Q-wave was observed fig 3(d5).

Histopathology

Masson's trichrome staining revealed the infarcted region of the collagen fibers and myocardial fibrosis regions were stained blue, while normal muscle fibers were stained red. The control group displayed no blue fibrotic area, HF group revealed a blue fibrotic area whereas the CSD+HF showed less blue fibrotic area at the border zone. The ASD+HF displayed a fibrotic free blue area (Fig. 4a). Furthermore, the quantification of fibrosis by ImageJ software also revealed similar observations (Fig. 4b)

Hemodynamic parameters

Figure 5 illustrates the nature of restraint level on LVSP, LVEDP and ventricle contractility assessment ±dP/dtmax. As expected LVSP decreased significantly in HF group (89.74mmHg), but had no significant difference in ASD treated groups (106.97mmHg) as compared with control group. LVEDP level decreased in ASD+HF group (-1.92mmHg) and showed a significant difference when compared to the control group (1.88mmHg), while in HF group it increased significantly (14.71mmHg). dP/dtmax decreased in HF group ($p<0.001$), and increased in ASD treated group as compared with the control. Whereas -dP/dtmax showed a high significant value in HF and CSD+HF group ($p<0.001$) and no significant value in ASD+HF treated rats was observed as compared with control group. The heart rate of ASD+HF group was also normalized as compared to the other treatment groups (Fig. 6b).

Plasma BNP level

Coronary artery ligation resulted from the increase in plasma BNP level in all groups. BNP level was evaluated at different stages during the treatment period. After placing the restraint device, plasma BNP levels gradually decreased in ASD (51.983 μg/L) and CSD (59.462 μg/L) treated rats, but didn't show any significant difference till the end of treatment period as compared with HF (70.125 μg/L) group. However, by the end of the one-month treatment period, plasma BNP level significantly reduced in ASD+HF group ($p<0.001$) as compared to the HF group (Fig. 6a).

Discussion

Ventricular restraint therapeutic approach has shown promise in treatment and management of HF. Previous animals and human studies showed that CSD (Acorn CorCap) and Paracor HeartNet devices reverse the pathologic LV remodeling[10,11]. However, to recommence interest and further optimization of restraint therapy, it requires exhaustive understanding of the proper relationship of its restraint nature by optimizing its design and biocompatibility with the host heart. Previous studies of CSD and HeartNet used polypropylene and nitinol mesh to deliver standard restraint and reverse pathologic LV remodeling[11,14].

In vitro studies by the use of a pneumatic drive showed the functional ability of ASD (Fig. 2). The unique characteristics of ASD device are; amplification volume, here the hydraulic stroke volume required to actuate the device is less than the consequent blood stroke volume. Due to energy conservation, the amplification volume is obtained by the necessity for greater drive pressure. The entire physiological afterload pressure and the stroke volume is equal to or less than that of the hydraulic drive pressure and the hydraulic stroke volume[23]. Considering the normal flow rate and afterload pressure, the functional ability of the ASD is in the normal range which is vital for normal heart function (Fig. 2).

Compliance and device related fibrosis can also be affected by the heart shape and the nature in which ASD is fitted on the heart[24]. During mechanical loading, a comparative amount of intertwined movement within

the ASD device can be observed. Exposure of ASD to multiaxial stress-strain study revealed expansion of the material between 12% and 22% as the material was exposed to a load up to about 5lbs per inch. The compliance value below the first loading allows the ASD device to fit closely to the surface of the heart during implantation and prohibits unnecessary load growth at end-diastole[25]. The external force applied by the heart during the time of diastole filling is somewhat less than 5lbs of the equivalent burst load[26]. Thus in actual application, the multiaxial extension of the ASD remains within the shallow part of the multiaxial stress-strain curve. Comformity in the longitudinal direction is fairly higher than in the circumferential direction (Fig.2c, d), hence the hypothesis that it promotes a chronic shape modification to the heart from a spherical to a more ellipsoid shape[24,27]. Multiaxial compliance values were observed to be lower than individual uniaxial compliance values signifying that confining stiffness of ASD in multiaxial or uniaxial loading is identical. However, strain to achieve that restraint is reliant on the loading direction.

Electrocardiography results in HF showed numerous anomalies (Fig.3). The most widely observed electrocardiographic anomalies are broad T-waves, small R-waves, deep Q-waves and ST-elevation which denote MI and dilated ventricles[28]. These were seen in HF group at days 7, 15 and 30 fig.3(b3-b5) and it was similarly noted in CSD treated rats at day 30 fig.3 (c5). ASD results reported progression in managing the dilated ventricles, ventricular relaxation and relieving HF symptoms. This is depicted by a smooth ST-segment, upright T-wave and normal Q-wave fig.3 (d4,d5) [29,30]. Therefore ASD device was postulated to be a safer and viable; furthermore, it mended cardiac performance without tampering with the myocardial structure and function.

Masson's trichrome staining is a widely used staining technique to distinguish collagen fibers from tissues and muscles. Myocardial tissue was stained with an acidic dye due to the presence of acidophilic cytoplasm. Collagen is easily penetrable by most dye because of its comparatively loose texture. However, the dye easily diffuses out allowing aniline blue to stain the collagen giving blue stained collagen fiber[31]. After LAD coronary artery ligation cardiac cell death takes place[32] and this was noticeable in HF group on day 30th. Left ventricle remodeling after LAD coronary artery ligation is categorized by hypertrophy and fibrotic changes to the heart[33]. Cardiac cell death leads to decrease in contractile force[34]. The CSD treated rats showed a blue stained border zone, which may be as a result to the reaction of the device placement to the heart. Whereas, SD rats treated with ASD device showed no blue stained areas (Fig. 4).

In the present study on day 30, the hemodynamic parameters were assessed and revealed that LVSP and -dp/dtmax were decreased while LVEDP and +dp/dtmax rose significantly in HF group as compared with the control. This indicated that both systolic and diastolic function in HF rats were impaired[35]. However, after treatment with ventricular restraint therapy, these pathological changes were restored. The result showed that hydraulic restraint (ASD+HF) led to superior and faster reduction in LVEDP as compared to standard restraint (CSD+HF). LVEDP reflects the compliance of the LV and its ability to receive blood from the left atrium during diastole[36]. Moreover, as the LV compliance decreases, the LVEDP rises, thereby initiating MI, ventricular dilatation and other cascade of HF[37,38]. Furthermore, LVSP and -dp/dtmax positively correlated with systolic function showing no significant difference as compared with the control after treatment with hydraulic restraint (Fig. 5)[38,39]. In summary, there was both systolic and diastolic dysfunction in HF group. Hydraulic restraint (ASD+HF) had significant reduction in LV trans-myocardial pressure and ventricular wall stress which lead to superior reverse remodeling in comparison to standard restraint. Furthermore, ASD is feasible, biocompatible and didn't impair the hemodynamic parameters. It delivers hydraulic pressure to the ventricle throughout the cardiac cycle, not only at systolic but also at diastolic phase.

To further validate the functional and morphological changes, evaluation of the molecular markers of HF at different time intervals during the study was done (Figure 6). BNP levels were elevated with the progression of HF after coronary artery ligation. This is due to response to myocardial stretch and ventricle dilatation due to pressure or volume overload[40]. Till the middle of the treatment period, rats treated with ASD showed a slight decline in BNP level but not significantly different. However, at the end of treatment period, ASD+HF group was significantly different from HF group. While CSD+HF group showed little significance as compared to HF group (Fig. 4). Nonetheless, our study demonstrated that hydraulic restraint provided

by ASD device could lead to decreased BNP associated remolding. It might be one possible mechanism by which restraint applied through ASD prompts reverse remolding at a molecular level.

Materials and Methods

Sprague-Dawley (SD) male rats weighing 240–260g were acquired from College of Veterinary Medicine Yangzhou University (License # SCXK (Su) 2015-2005, Yangzhou, China. Silk and polypropylene 6.0 sutures from Shanghai Jinhuan Chemical Co., Ltd, Shanghai, China. ECG and HX-300S ventilator from Chengdu technology & market Co. LTD, Chengdu, China. The implantable and polyethylene catheters from Jiangxi Hongda Medical Equipment Group Co. LTD. Nanchang, Jiangxi, China. Biebrich scarlet-acid fuchsin and trichrome's staining kits from Beyotime Institute of Biotechnology, Haimen, China. Rat BNP ELISA kits from Shanghai Jinma Biological Co. LTD, Shanghai, China and finally CSD from Ethicon, Inc, Somerville, NJ USA. All procedures performed in studies involving animals were in accordance with the ethical standards of China Pharmaceutical University under the guidelines published by research council by the school of pharmacy, China pharmaceutical university and conforms to the guidelines for the care and use of laboratory animals published by US national institutes of Health (NIH, 1996).

ASD fabrication

A three-dimensional computer model of ASD (design as discussed in the introduction) was developed by using Rhinoceros 5.0 software. A blue wax model of ASD was then printed using 3D printing technology. The wax model was immersed in liquid silicon and dried in an oven at 50@C for 3 hours. The wax was then melted from the ASD and silicon built ASD model was obtained[1920]. Leak testing using Cincinnati Test Systems Shanghai was finally performed to ensure no leakage or blockage in the ASD tubes.

Animal model and ASD implantation

24 SD male rats were obtained and randomly divided into four groups (n=6) Control group, HF group, CSD+HF group and ASD+HF group respectively. HF model was then induced in all groups except the control group by left anterior descending (LAD) coronary artery ligation[41]. The method and process of ligation was performed as described by Sufia et.al and Naveed et.al with minor modifications[19,20] After confirmation of HF in the rats, ASD was then implanted in the ASD+HF group. After steady-state baseline measurement, the ASD device was placed around the heart and sutured to the atrioventricular (AV) groove using prolene sutures (4–0) to cover both ventricles. The ASD device consists of two access lines connected with implantable catheters. The ASD portacath was channeled subcutaneously through the second intercostal space into the left anterior chest wall and extended outside the body through a 1cm opening made in the skin at spinotrapezius. The sternum and portacath incision was then closed in layers[19,20] Saline was instilled in 20 ml increments into ASD tubules and electrocardiogram was monitored. AMVR was observed as the maximum pressure applied by the ASD to the epicardium through a constant volume of saline inside the ASD tubules. Maximum ASD pressure occurred at end diastole (the time point when the heart volume is large).

CSD device implantation

CSD was made of a polypropylene mesh and used as a positive control. CSD is a previously used restraint device to deliver standard restraint and has extensively been investigated in animal models as well as clinical trials. After the establishment of HF model, CSD device was implanted to the heart of CSD+HF group rats by wrapping it around the heart and secured to the AV groove. The electrocardiogram was monitored in accordance with guidelines used for placement of the Acorn CorCap cardiac support device (Acorn Cardiovascular, Inc, St Paul, Minn) such that LVEDP decreased by 5% [10,42]

Functional and compliance characteristics of the ASD

The performance of ASD was determined by using a pneumatic drive and a hydraulic drive was used for the implantable system. ASD was attached to a cylindrical flexible blood pump with a diastolic diameter of 6 cm and length of 5 cm. This in-vitro study was performed by adopting the standard protocol of the previous

study by Robert T. V. Kung et.al[43]. Compliance characteristics of the ASD were studied by adopting ball burst test (TMI Trading Shanghai Co., Ltd). The test was performed according to manufacturer instructions. Briefly, the pressure was applied by pressing a ball against the ASD tubules within a circular fixture. The ASD was determinedly held around the edge of this circular fixture through a pneumatic clamping device. The ASD distorts in multiaxial behavior when the pressure was applied. The load at which ASD fails to withstand the pressure was recorded by the transducer. Furthermore, uniaxial compliance curve for ASD model was plotted in the longitudinal and circumferential directions and multiaxial compliance curve was plotted for comparison.

In-vivo experiments

Electrocardiography

Animals were given 10% chloral hydrate as a sedative and were placed in supine posture on a surgical table. A BL-420 electrocardiogram was used to analyze ECG and signals were recorded on a personal computer. This electrocardiogram consists of four electrodes; red, black, yellow and green which were subcutaneously inserted into the animal's right upper limb, right lower limb, left upper limb and left lower limb respectively(according to manufacturer instruction). ECG was then recorded in series in all animals; before ligation and after ligation on days 7, 15 and 30.

Hemodynamic parameters

For terminal studies (At day 30), all hemodynamic parameters like left ventricular systolic pressure (LVSP), left ventricular end diastolic pressure (LVEDP), dp/dtmax and -dp/dtmax were taken digitally at steady hemodynamic state and mean data was recorded at the end of the study. The heart rate was also measured using a BL-420 multi-channel physiological signal system on preoperative, postoperative and on days 7, 15 and 30. The mean data was then calculated at the end of the entire study period.

Histopathology

At the end of the observation period (30days), animals were subjected to euthanasia and extraction of the skin and muscle tissue till the neck region from the metasternum was carried out and the chest plate removed thereby exposing the heart. To avoid bleeding the aorta was laced with a silk suture and the heart was harvested. It was then filled with PBS (1:100) in order to remove any blood traces, fixed in 10% formalin and then incised into 5μm coronal sections. It was dehydrated with series of ascending ethanol before embedding it in paraffin. Collagen and muscle fibers were distinguished using Masson's trichrome staining. Weigert iron hematoxylin and Biebrich scarlet-acid fuchsin (plasma stain), phosphomolybdic-phosphotungstic acid and aniline blue (fiber stain) was used on the 5μm sliced section of the heart to achieve trichrome staining[44]. The slides were finally observed under the photonic microscope with DFC420 camera fitted for histopathological changes. Images from the sections were digitally captured using image manager software and the level of fibrosis quantified by ImageJ software 4.7.0.

BNP measurement

ELISA kit was used to determine the B-type natriuretic peptide serum concentration using rats BNP kit following the manufacturer guidelines. Briefly, the animal's blood was obtained, centrifuged at 2000rpm/min for a couple of minutes at 4°C and the supernatant (blood plasma) obtained. The supernatant was then diluted 1:4 with a sample solution followed by addition of a stop solution and then the BNP was evaluated.

Data Analysis

Hemodynamic data is displayed as mean ±SEM (n=3), one-way ANOVA followed by Dunnett's Multiple Comparison Test was used for statistical significance of other groups compared with control group. While BNP results are expressed as mean ±SD, Two-way ANOVA followed by Bonferroni test was used for statistical analysis compared with HF group. Where, *p =0.05, **p<0.01, ***p<0.001.

Conclusions

ASD device is structurally composed of silicon a non-immunogenic and biocompatible material and provides promising restraint therapy as compared with previous standard restraint therapies. It improves cardiac function and reverses ventricular remodeling. Therefore, the future aim of our research is to deliver biological therapeutic agents to the heart though ASD and this initial feasibility study will provide a push to move forward. However more research is needed to assess whether pathologic remodeling persists after termination of restraint therapy or not and also assess the effect of ASD implantation on ventricular shape, size, and myocardial structure, as well as load-independent indices of ventricular functions over a longer treatment period.

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Author Contributions:

Conceptualization, Kiganda Raymond and Xiaohui Zhou; Methodology and software, Gang Wang; Validation, Kiganda Raymond, Muhammad Naveed and Gang Wang; Formal Analysis, Sufia Yasmeen; Data Curation, Ziwei Liu; Writing – Original Draft Preparation, Muhammad Naveed; Writing – Review & Editing, Kiganda Raymond; Supervision, Project Administration and Funding Acquisition, Xiaohui Zhou.

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Figure Legend

Fig. 1 Laplace law explains the dilated ventricles mechanism and provides a framework for ventricle remodeling. (T) is the dilated heart which is directly proportional to left ventricular end diastolic pressure (LVEDP) (P) and radius chamber (R), inversely by wall thickness. Laplace law explains the concept of ASD effect on ventricle remodeling. The relationship between transmural pressure (Ptm) and LVEDP is explained by an equation as shown above. (a) Cross-sectional view of ASD covering both ventricles from base to apex. (b) ASD overview off the epicardium. The two extended tubes are subcutaneously channeled outside of the body and connected to a medical device to load and release fluid (c) View of ASD tubes interconnected with each other.

Fig.2 Functional characteristics of ASD device. (a) Pressure and (b) flow generated by ASD as a function of drive pressure respectively for a flow of 6.6 L/min and an after-load of 120mmHg. Calculations are shown as a solid curve. (c) Ball burst test of ASD, a pressure is given by pressing the ball at the center of ASD fixed in a circular fixture. ASD undergo multiaxial expansion by the pressure of the ball. (d) Uniaxial circumferential and longitudinal curve. A multiaxial curve compliance curves are plotted for comparison

Fig.3 Electrocardiographic exploration of all rats' groups at various time periods. ECG contains a P-wave, followed by the QRS-complex and the T-wave. All parameters were recorded in a milliseconds

Fig.4 (a) Masson's trichrome-stained section of rats' heart in various groups by a photonic microscope (Original magnifications x4) revealing a segment of the heart fibers enclosed in collagen (blue) and overlying the myocardium (red). (b) Evaluation of fibrosis of heart tissues acquired from different treatment groups, n = 3, Where, *p<0.05, **p<0.01, ***p<0.001, scale bar 100μm.

Fig.5 Hemodynamic parameters represented as mean ±SEM (n=6) (a) LVSP (b) LVEDP (c) dp/dtmax (d) -dp/dtmax, nsp=no significance;**p<0.01; ***p<0.001 vs. Control

Fig.6 (a) The BNP results formulated as mean ±SD, (b) The heart rates of the control and treatment groups; HF, CSD+HF, ASD+HF groups. n=3