Left Atrial Circulatory Assistance in Simulated Diastolic Heart Failure Model: First in Vitro and in Vivo

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ABSTRACT

Background: We are developing a left atrial assist device (LAAD) that is implanted at the mitral position to treat diastolic heart failure (DHF) represented by heart failure with preserved ejection fraction.

Methods: The LAAD was tested at 3 pump speeds on a pulsatile mock loop with a pneumatic pump that simulated DHF conditions by adjusting the diastolic drive. The LAAD was implanted in 6 calves, and the hemodynamics were assessed. In 3 cases, DHF conditions were induced by using a balloon inserted into the left ventricle, and in 2 cases, mitral valve replacement was also performed after the second aortic cross-clamp.

Results: DHF conditions were successfully induced in the in vitro study. With LAAD support, cardiac output, aortic pressure and left atrial pressure recovered to normal values, whereas pulsatility was maintained for both in vivo and in vitro studies. Echocardiography showed no left ventricular outflow tract obstruction, and the LAAD was successfully replaced by a mechanical prosthetic valve.

Conclusions: These initial in vitro and in vivo results support our hypothesis that use of the LAAD increases cardiac output and aortic pressure and decreases left atrial pressure, while maintaining arterial pulsatility. (*J Cardiac Fail 2022;28:789–798*)

Key Words: Mechanical circulatory support, left ventricular assist device, diastolic dysfunction, animal model, heart failure with preserved ejection fraction.

Heart failure (HF) is an epidemic; it affects more than 20 million people worldwide.[1] In the United States alone, 6.2 million Americans > 20 years old experienced HF between 2013 and 2016,[2,3] and by 2030, > 8 million people are projected to have HF.[4] In this population, more than half appear to have preserved systolic function[5,6]; this qualifies their disease-decompensation profile as HF with preserved ejection fraction (HFpEF), which has become an increasingly predominant form of the disease.[7] The prevalence of this condition is also increasing compared to HF with reduced ejection fraction (HFrEF).[8] HFpEF is a systemic syndrome that is highly heterogeneous, and it goes far beyond just a single type of diastolic dysfunction.[8,9] Generally, it has the phenotype of an increase in left ventricular (LV) diastolic pressures, followed by left atrial (LA) pressure (LAP) rise and pulmonary edema, which would lead to the noticeable and common symptoms of HF. More specifically, lack of LV compliance limits the Frank-Starling mechanism, which dramatically reduces cardiac output (CO) and leads to hemodynamic morbidity.

Traditionally available therapies for HFrEF have failed to improve the mortality rates or the morbidity of the patients with HFpEF. Also, the prognosis of HFpEF is as poor as it is for HFrEF, sharing similar high mortality and readmission rates.[10] The survival rates of patients with HFrEF have improved over the past decade,[11] but those of patients with HFpEF have not changed.

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Device-based therapies that have innovative concepts and are tailored to patients with HFpEF are receiving more attention.[12] Herein, we report our initial in vitro and in vivo studies aiming to (1) evaluate the left atrial assist device (LAAD) performance in a mock circulatory loop and, in calves, to simulate differing levels of diastolic HF (DHF) conditions, and (2) to confirm the operational performance and biocompatibility in calves.

Methods

LAAD Pump

The LAAD has been developed with the unique idea of implantation at the mitral position to pump blood from the LA to properly fill the LV (Fig. 1A,B). It can mitigate high LAP by draining blood directly from the LA, and it can also offer an immediate increase in CO by providing additional volume to the LV. We have developed the first working prototype of the LAAD and revised its design after several in vivo experimental efforts.

The latest prototype of the LAAD is shown in Fig. 2A,B,C, and the schematic illustrations are displayed in Fig. 2D,E,F, respectively. The dimensions are: diameter, 33.5 mm, height, 33.5 mm and weight, 39.7 g. This is a mixed-flow pump, and it utilizes a hydrodynamic bearing for radial support of the rotating assembly and a passive magnetic bearing to fix its axial position. The pump is driven by a custom, 3-phase, brushless, sensorless DC motor that was designed and built in-house. It is able to pump over a wide operating range (up to 10 L/min and up to 180 mmHg of pressure rise) to maintain optimal flow in support of CO.

Surgically, the LAAD is intended for intracardiac positioning in proximity to the atrioventricular groove, either replacing or on top of the mitral valve.[13] The pump housing design underwent minor changes during in vivo experiments to prevent suction events and improve its biocompatibility. The revised pump (Fig. 2) has a wider inlet portion and was tested in the last 2 in vivo experiments, as well as the in vitro experiments.

In Vitro Study

Mock Circulatory Loop. The in vitro mock circulatory loop setup (Fig. IA, Supplementary Data) was composed of a pneumatic mock ventricle (AB5000; ABIOMED, Danvers, MA) that simulated the native LV, an adjustable arterial afterload and compliance, LA chamber, and the LAAD (Fig. IB, Supplementary Data) that is placed between the LA chamber and the mock ventricle. A mixture of water and glycerin (specific gravity of 1.060) was used as the working fluid to simulate blood. Whenever the LAAD was on, the inflow valve of the AB5000 (working as the mitral valve of the mock ventricle) was secured by a plastic tube (Fig. IC, Supplementary Data) that was large enough to keep the inlet valve open (regurgitant) to simulate LAAD implantation at the mitral position (simulating mitral valve resection).

Static Condition

The in vitro testing of the LAAD was performed on the static mock loop with the pneumatic ventricle off to obtain pressure-flow curves at various pump speeds (3000 rpm, 3600 rpm, 4400 rpm, 5200 rpm, and 6000 rpm). The pressure was measured just before the LAAD (P_{in}) and just after the LAAD (P_{out}). The arterial resistance was changed in 5 or 6 steps to produce a range of LAAD delta pressure (P_{out}/P_{in}) conditions.

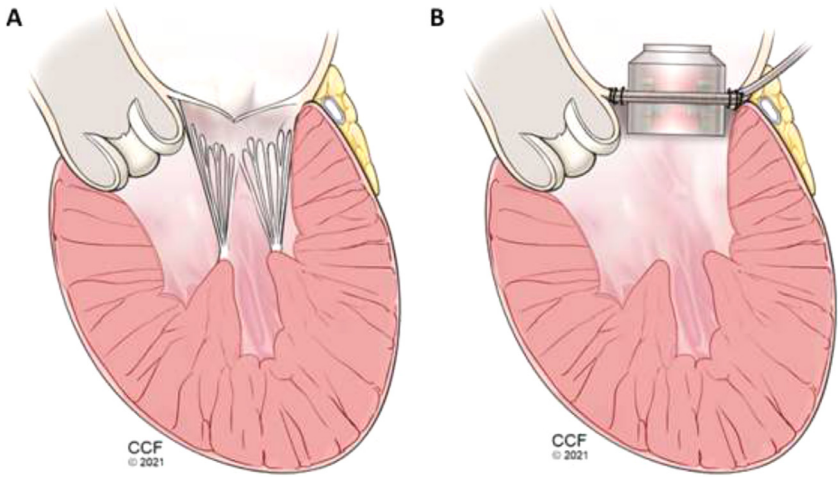

Fig. 1. Schematic drawing of the left atrial assist device (LAAD) concept. A, a dilated left atrium (LA), thick left ventricular (LV) wall and small LV cavity in heart failure with preserved ejection fraction (HFpEF). B, the LAAD is implanted in the mitral position to replace the mitral valve.

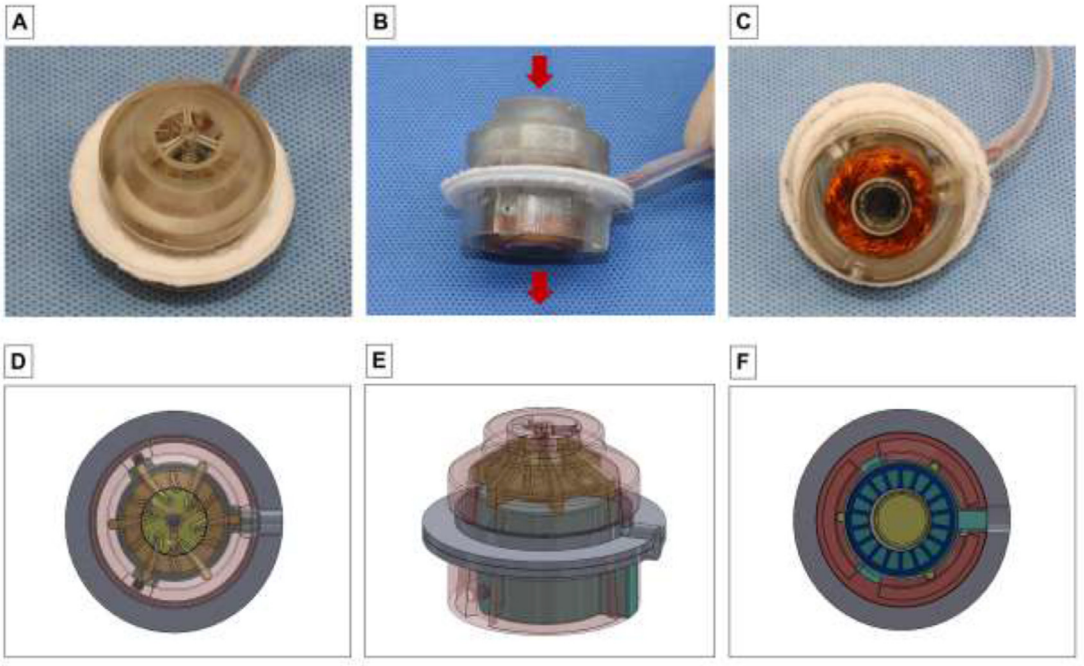

Fig. 2. Photos and illustrations of the LAAD. A, the prototype of the LAAD seen from inlet portion (LA side). B, the side view of the LAAD. Red arrows show the direction of the blood flow created by the LAAD. C, the prototype of the LAAD seen from outlet portion (LV side). D, a schematic illustration of the LAAD seen from the LA side; E, translucent schematic illustration of the LAAD seen from the front; F, schematic illustration of the LAAD seen from the LV side.

Pulsatile Condition

The pneumatic ventricle was activated with a pneumatic driving pressure of 200 mmHg for systole and −35 mmHg for diastole (negative value indicates a vacuum). The systolic duration was set to 250 msec to simulate a normal heart condition, which generated a CO of approximately 4.0 L/min without the LAAD (which was replaced by a plain straight tube). The arterial compliance and resistance were adjusted to set an aortic pressure (AoP) of 120/80 mmHg under normal heart conditions and were not changed throughout the entire study.

To simulate 3 different levels of DHF, the diastolic filling of the pneumatic ventricle was restricted by increasing the diastolic drive pressures of the pneumatic driver from −35 mmHg at the normal heart condition to 0 mmHg (mild DHF), +20 mmHg (moderate DHF) and +40 mmHg (severe DHF). The systolic drive pressures of the pneumatic driver and the heart rate were kept constant throughout the entire study at 200 mmHg and 80 bpm, respectively. The AB5000 pneumatic driving pressures were not the same as the actual pressures generated by the system in the flow path.

The LAAD was operated at 3 different speeds at each DHF condition: 3,600 rpm, 4400 rpm and 5200 rpm. For the basic data without the LAAD, we used a normal competent inflow valve of the AB5000 and a circuit to bypass the LAAD to avoid resistance by the inactive pump.

For each condition, we recorded CO by a flow probe clipped to the outside of the tube (ME20PXL and TS410 Tubing Module; Transonic Systems, Ithaca, NY). AoP and LAP (which is P_{in}) were monitored with fluid-filled lines, pressure transducers (13-6615-50; Gould Electronics, Chandler, AZ) and amplifiers (M21018; Honeywell, Charlotte, NC).

In Vivo Study

The study was approved by the Cleveland Clinic's Institutional Animal Care and Use Committee (#2018-2004). A total of 6 acute in vivo studies were performed using male Jersey calves (mean body weight: 84.1 ± 11.8 kg). Under general anesthesia with a right lateral position, a central venous pressure (CVP) monitoring line was placed in the left jugular vein. A left thoracotomy was performed in the 4th intercostal space, and an AoP monitoring line was placed in the left internal thoracic artery. A 28 mm flow probe (28PAU113, 28PAX307; Transonic Systems, Ithaca, NY) was placed around the main pulmonary artery to measure CO, and a fluid-filled LAP line was inserted in the LA.

After full heparinization (5 mg/kg), cardiopulmonary bypass (CPB) was started with an arterial cannula in the left carotid artery and a venous cannula in the

right ventricle through the main pulmonary artery. The LA was opened after aortic cross-clamping with cardioplegia (modified Buckberg cardioplegia[14]). A patent foramen ovale was observed in 1 case, and it was closed with a single stitch. The mitral leaflets were resected, and the LAAD was implanted at the mitral annulus with interrupted pledgeted sutures (Fig. 3A). The driveline of the LAAD was placed out from the LA incision (Fig. 3B) at its closure.

A fluid-filled (n = 1) or a micro-manometer Millar catheter (n = 5) was inserted into the LV from the LV free wall near the apex. After declamping the aorta, the LAAD was started, and CPB was gradually weaned and then stopped as the LAAD speed was increased. Due to the post-CPB low output and low blood pressure, dobutamine (2.0 μg/min/kg) was used in 1 case, and norepinephrine (4−8 mg bolus) was infused in another case before taking data.

After confirming stable conditions, 5−10 minutes from the point of each setting change, the hemodynamic and pump-related data were taken at the pump speeds of 3600, 4400 and 5200 rpm. Epicardial echocardiography was performed to evaluate anatomical fit and to look for any regurgitation through the LAAD.

After the fourth study, we revised the housing design of the pump, especially the inlet section, for prevention of suction events. Additionally, 2 new procedures were added during the in vivo studies (after collecting the basic LAAD data described above): (1) hemodynamic data measurements during DHF conditions using a balloon catheter inserted from the LV apex and inflated with 50−70 cc saline (Fig. 3C) inside the LV cavity (performed in 3 of 6 calves); and (2) evaluation of the replacement of the LAAD with a mechanical valve replacement, using a 29 mm mechanical bi-leaflet mitral prosthetic valve (500DM29; Medtronic ATS Medical, Minneapolis, MN) (Fig. 3D) after collecting the pump-related data with a second aortic cross-clamping (performed in 2 of 6 calves).

Schematic illustrations of the DHF condition with a balloon and after the mitral valve replacement are illustrated in Fig.4A and B, respectively. These

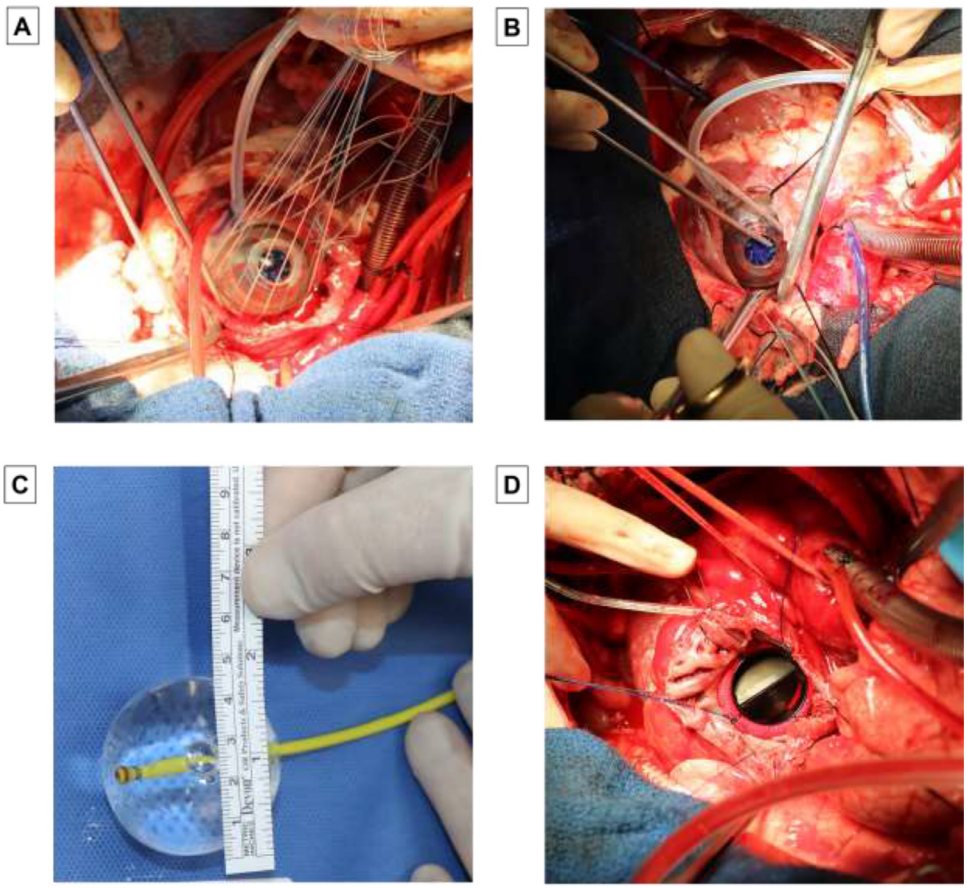

Fig. 3. Intraoperative images. A, the surgical view of the implantation of the LAAD at the mitral position with interrupted pledgeted sutures. A venous return cannula was inserted from the pulmonary artery into the right ventricle. B, the surgical view of the LAAD after implantation at the mitral position. The driveline will be fixed in the place of LA closure anastomosis. C, a balloon catheter, which will be inserted from the LV apex. The balloon diameter was approximately 45 mm, inflated with 70 cc of saline. D, The mechanical prosthetic mitral valve of 29 mm was implanted after the LAAD had been removed in the second aortic cross clamp.

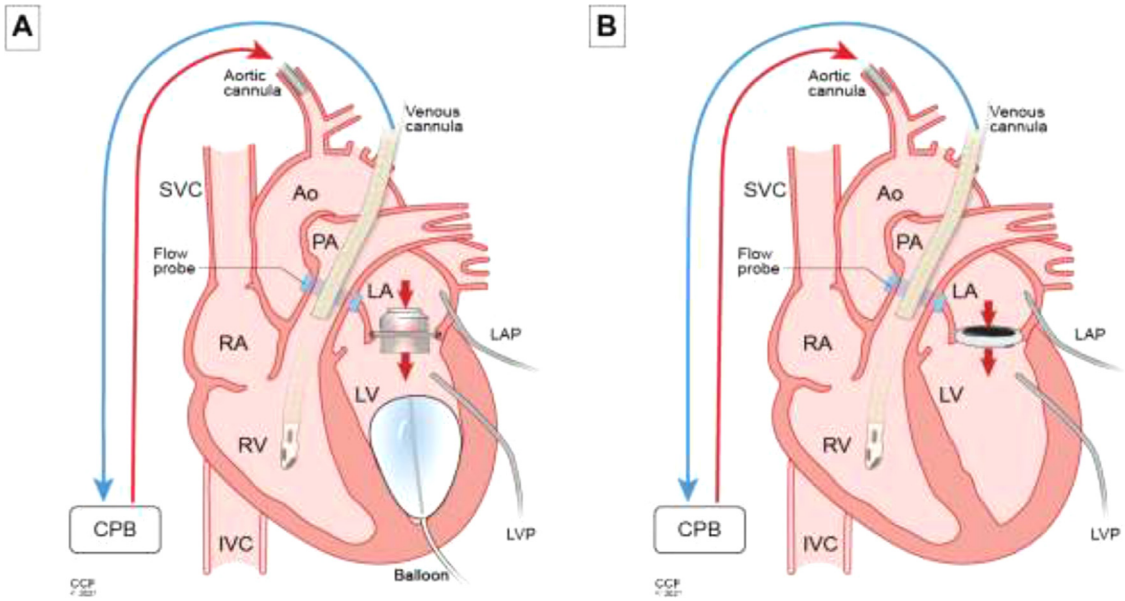

Fig. 4. Schematic illustrations of in vivo experimental setting. A, schematic illustration of in vivo DHF setting. A balloon was inserted from the LV and inflated to 70 cc at most. Red arrows show the blood flow created by the LAAD. An arterial cannula was inserted in the right carotid artery and a venous cannula tip was placed at the RV through the pulmonary artery. B, schematic illustration after the mitral valve replacement.

additional procedures were performed after repeating the same basic data collection as the previous 4 in vivo experiments with the revised pump. As for the DHF configuration made by the balloon, the baseline data, without LAAD with 0 cc, 50 cc and 70 cc of inflated balloon, had been taken before CPB was started.

After recording all the data points, the animal was sacrificed by an intravenous bolus injection of Beuthanasia (75 mg/kg). The heart was extracted, and the pump position and any findings inside the LA or LV were evaluated. Although these working prototype of the LAADs were created by 3D printed parts, the LAAD was disassembled and potential depositions or damages were evaluated.

Data Analysis

All data were recorded at 100 or 200 Hz using a PowerLab data acquisition system (ADInstruments, Colorado Springs, CO), analyzed using LabChart (ADInstruments), and then downloaded into Microsoft Excel (Microsoft, Redmond, WA) to summarize and chart the test results.

Results

In Vitro Study

Static Condition. The pressure-flow curves at various pump speeds are shown in Supplementary Data, Fig. II. They showed almost straight lines with relatively steep slopes. At 5200 rpm, the LAAD produced 6 L/min of pump flow at 90 mmHg of delta pressure.

Pulsatile Condition

Supplementary Data, Table I, summarizes the mean CO, mean AoP, mean LAP, and aortic pulse pressure. With the LAAD out of the loop and the mitral valve functioning normally, CO decreased from 4.6 L/min under normal heart conditions to 3.4, 2.2, and 1.1 L/min under mild, moderate and severe DHF conditions, respectively (Fig. 5A). With LAAD support at 4400 rpm, CO recovered to the normal heart condition. Interestingly, at 5200 rpm, the CO recovered to the same level as normal heart condition, regardless of the severity of the 3 DHF conditions.

Similar to the results with CO, the mean AoP decreased dramatically from 103 mmHg under normal heart condition to 69, 46 and 30 mmHg with mild, moderate and severe DHF conditions, respectively (Fig. 5B). With LAAD support, the AoP recovered to a level of the normal heart condition at 5200 rpm.

The mean LAP increased dramatically from 4.7 mmHg for the normal heart condition to 13.5, 18.8 and 20.7 mmHg for mild, moderate and severe DHF conditions, respectively (Fig. 5C). With LAAD support, the LAP decreased gradually with increasing pump speed and reached a level similar to that of the normal heart condition at 5200 rpm.

The aortic pulse pressure decreased from 61 mmHg for the normal heart condition to 57, 44 and 25 mmHg for mild, moderate and severe DHF

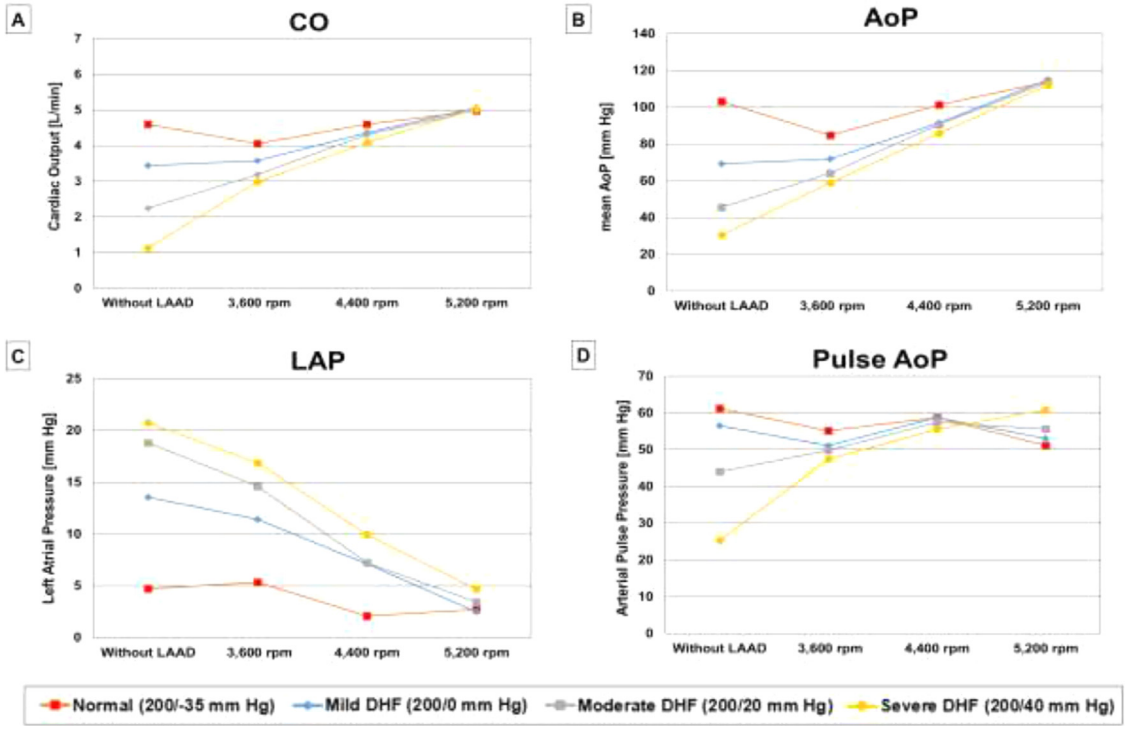

Fig. 5. The in vitro changes of each parameter by the pump speed with comparisons among normal heart condition and mild, moderate, and severe DHF conditions. A, mean cardiac output (CO); B, mean arterial pressure (AoP); C, mean left atrial pressure (LAP); D, arterial pulse pressure (pulse AoP).

conditions, respectively (Fig. 5D). With the LAAD support, the aortic pulse pressure was maintained even at high pump speed.

In Vivo Study

The hemodynamic status during data collection was stable in all animals, and the LAAD responded to all control inputs exactly as expected during the experiment. Table II in the Supplementary Data summarizes the mean CO, heart rate and stroke volume calculated by CO and heart rate. The basic hemodynamic data with the LAAD collected before introducing the DHF conditions were as follows:

- CO increased from 5.4 to 6.1 L/min by increasing the pump speed from 3600 to 4400 rpm, but it stayed nearly the same when the pump flow was increased from 4400 to 5200 rpm (Fig. 6A).
- A similar trend was observed in mean AoP (from 65 to 72 mmHg, at 3600 to 4400 rpm) (Fig. 6B).
- LAP decreased by increasing the pump speed from 3600 to 5200 rpm (Fig. 6C); however, the LAP values at 5200 rpm showed a large variation between the experiments, including a negative value (Supplementary Data, Fig. III), because pump inlet suctions were observed in some of the studies, although any major hemodynamic influences related to the negative value were not observed.
- The CVP (Fig. 6D) and heart rate remained the same for all the pump speed conditions.
- The aortic pulse pressure was essentially maintained throughout the pump speed changes (Fig. 6E).
- The LV end-diastolic pressure (LVEDP) increased slightly from 3600 to 4400 rpm but stayed the same at high pump speed (Fig. 6F).
- The typical waveforms are displayed in Supplementary Data, Fig. IV.

Epicardial echocardiography showed that the LAAD was in the correct position, with no evidence of obstruction or acceleration of blood flow at the LV outflow tract (Fig. VA,B in the Supplementary Data). There was no obvious leakage around the LAAD detected by epicardial echocardiography, and no regurgitant flow through the LAAD was observed.

Mitral valve replacement was performed after the second aorta cross-clamp and explant of the LAAD, without any surgical difficulties. Epicardial echocardiography was conducted again and showed good positioning of the mechanical valve (Fig. VC, Supplementary Data).

As for the DHF conditions, Fig. VD in the Supplementary Data shows the balloon view (50 cc) obtained by the intraoperative epicardial echocardiography. Each parameter change with balloon (0 cc,

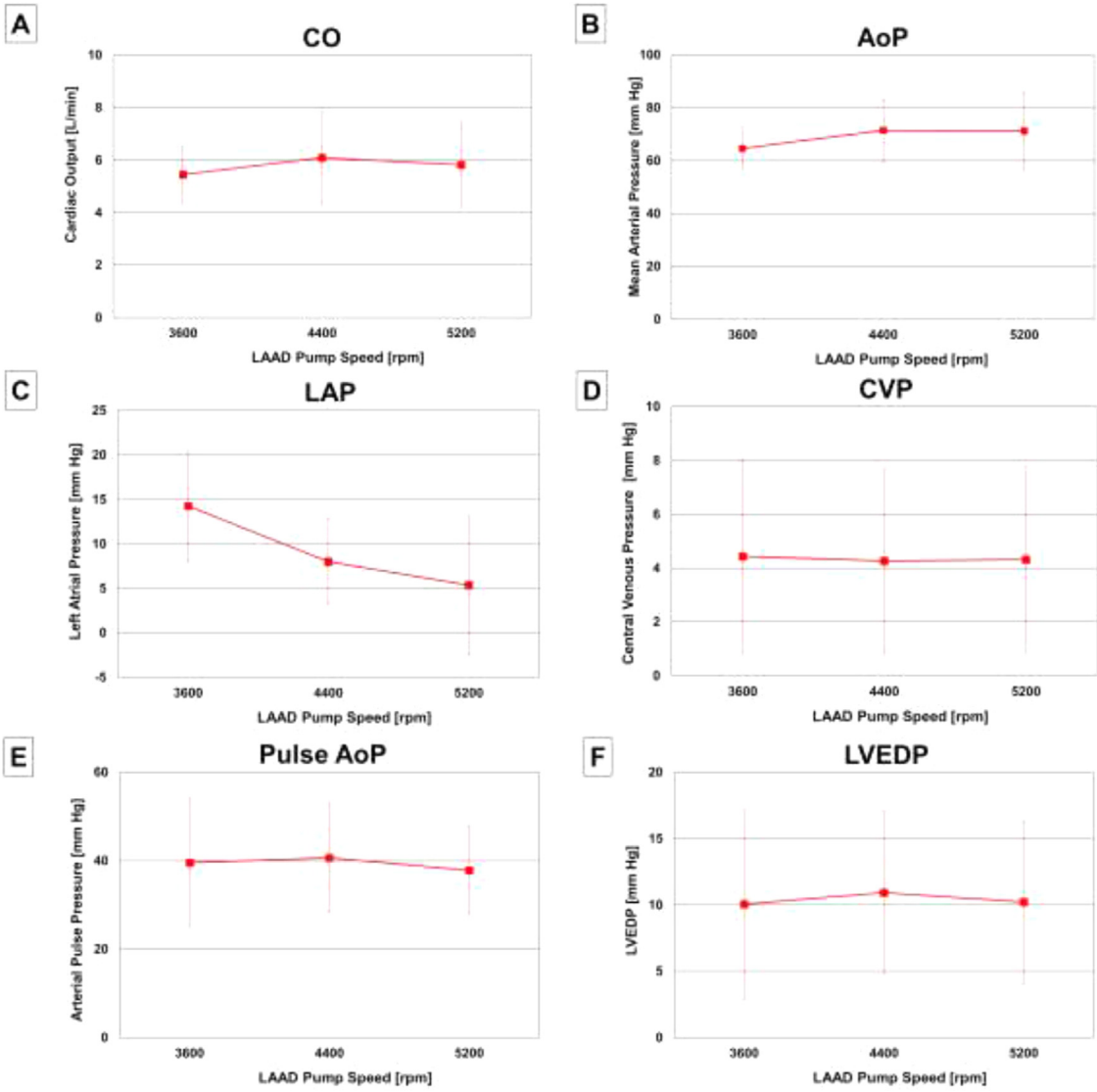

Fig. 6. The in vivo changes of each parameter by the pump speed. A, mean cardiac output (CO); B, mean arterial pressure (AoP); C, mean left atrial pressure (LAP); D, mean central venous pressure (CVP); E, mean arterial pulse pressure (pulse AoP); F, mean left ventricular end-diastolic pressure (LVEDP).

50 cc and 70 cc) with/without the LAAD, obtained from 3 in vivo experiments, are shown in Supplementary Data, Fig. VI.

Without the LAAD, the balloon inflation caused a decrease in the CO and AoP (Supplementary Data, Fig. VIA, B). The LAP and LVEDP increase (Supplementary Data, Fig. VIC, D), which could be considered as a configuration similar to DHF, was successfully replicated by balloon inflation inside the LV.

With LAAD support, the differences between each balloon size were reduced in CO, AoP, and LAP (Supplementary Data, Fig. VIA,B,C). The LVEDP did not increase with balloon inflation, even at high LAAD speed (Supplementary Data, Fig. VID). The balloon size seemed to not affect the CVP (Fig. VIE). There was a large difference in the absolute values with and without the LAAD, but this might have been caused by the effect of CPB.

At necropsy, the correct pump position was confirmed from the LA side (Fig. VIIA) and the LV side (Fig. VIIB, C). There were no thrombi in the LA or LV. In some of the first 4 cases, some suction marks were observed, but in the most recent 2 cases (with the revised pump), no suction mark was found in the LA or LV. The positional relation of the balloon and the LAAD is shown in Fig. VIID.

The explanted pumps were disassembled and inspected thoroughly by the engineering team. In the first prototype (RD-01) of the LAAD, some thrombi and tissues were found between the impellers or on the strut ends (Fig. VIIIA, B, C, D), which could possibly attributed to minor suction events caused by the housing design of the pump. With the

subsequent design change of the LAAD (RD-02), little to no thrombotic deposition or tissue adhesion was observed (Fig. VIIIE, F).

Discussion

The results of our initial in vitro and in vivo studies demonstrated that the LAAD increased CO and AoP and decreased LAP under DHF conditions while maintaining arterial pulsatility and full functioning of the aortic valve. We previously reported very similar in vitro results using an investigational, continuous-flow blood pump that is not designed to be implanted at the mitral position, to prove the concept.[15] We have now successfully developed an actual working prototype that is implantable at the mitral position and functions as expected. In patients with HFpEF, the LA is typically dilated, LAP is elevated, and it increases with exercise. We believe a patient with HFpEF would be a potential subject for treatment with the LAAD.

There are several reports of other devices for patients with HFpEF. For instance, Burkhoff et al.[16] proposed Synergy System (Medtronic, Minneapolis, MN), a device to draw blood from the LA and pump it directly into the aorta. In this configuration, the risk of thromboembolism due to blood stagnation in the LV is a concern. And aortic pulsatility would be remarkably reduced, as we previously reported.[15]

There are limited reports using left ventricular assist devices (LVADs) for the HFpEF phenotype.[17] Although they have been used for patients with HFrEF,[18] the patients with hypertrophic cardiomyopathy or restrictive cardiomyopathy are generally excluded because of the reduced LV end-diastolic dimensions[19] and the perceived risk of suction. The LVAD use with an LA cannulation[20] can prevent an LVAD suction event, but stagnation of blood in the LV and reduced pulsatility would be the same concerns as those with the Synergy System.

Another treatment option to reduce the LAP is to place a shunt between the left and right atria, as represented by the InterAtrial Shunt Device reported by Kaye et al.[21] Clinical trials with interatrial shunts are ongoing, but the reduction in the LA pressure reported is very modest.

The LAAD has some advantages in providing a pulsatile flow, directly reducing LAP, filling the LV, and the potential of inducing LV remodeling, and there is less risk of suction due to the high LAP of HFpEF characteristics. Most important, all flow paths created by the LAAD follow natural (anatomical and physiological) patterns. Therefore, the LAAD can maintain arterial pulsatility, which may prevent complications such as gastrointestinal bleeding and aortic insufficiency.

One major concern with the pump concept is that the LVEDP could elevate unacceptably through forced filling of the LV. This would cause endocardial ischemia, but in vitro experiments could not evaluate it. Subsequently, we observed the change in LVEDP during the in vivo studies, which did not show much elevation even under the DHF conditions, at least not in these short periods of time. Even with the in vivo data conditions, the influence of post-CPB status might have affected the LVEDP strongly.

As for DHF conditions, we attempted the balloon method for the first time to reduce the LV volume by 50mL−70 mL. This method showed hemodynamics similar to those of in vitro DHF conditions, and the aspect of the reduced LV volume was considered reproduced. Although the LAAD showed reasonable efficacy under these configurations, the simulated conditions did not completely mimic all the features of HFpEF hemodynamics. Especially under the DHF conditions, an increase in pump speed seemed to have limited influence on LVEDP or CO. The fidelity of the DHF conditions after LAAD implantation seemed to be much more limited than the in vitro results, mainly because of the systolic dysfunction, the influence of anesthesia or right ventricular dysfunction in post-CPB status. We need to evaluate these parameters with chronic studies after at least 1 week of recovery from the surgical stress and/or the effects of anesthesia, and this would be an important future step.

Nevertheless, because there is no established animal model of DHF or HFpEF that has high fidelity, even partial simulation of the hemodynamics is valuable for better understanding of pump performance.

Study Limitations

The major limitation of our in vivo study is that the data were obtained from healthy calves, even though we attempted to introduce DHF conditions. Our new acute DHF model achieved by inflating a balloon inside the LV reduces, not only the LV filling, but also the LV compliance because the LV cavity is enclosed by a part of the LV wall and a part of a very stiffly inflated balloon. This model, however, has not been extensively evaluated to simulate DHF. The entire range of potential effects of the LAAD on hemodynamic parameters in the DHF conditions has not been fully addressed. Moreover, we did not aim to evaluate right heart failure in this series of experiments. The balloon model may also have induced systolic dysfunction; however, we did not aim to differentiate between diastolic and systolic dysfunction by echocardiography at this early stage. To evaluate the accurate capability and incapability of this attempt, evaluations under chronic circumstances

that are free from the effects of CPB, anesthesia and surgery itself are required.

The second limitation is that pump inlet suctions were observed at high pump speeds in some of the in vivo studies using the first prototype (RD-01). Patients with HFpEF typically have enlarged LAs with high LAP, so the suction risk seems to be very low. Also, our second prototype (RD-02) has successfully prevented the suction event so far. However, there is potentially some risk of suction events during the recovery phase once the LAAD is implanted in a human. With this concern, replacement of the LAAD with the prosthetic mitral valve was confirmed.

The final limitation is that the biocompatibility evaluation is limited in acute studies, so we will need to perform future chronic studies to confirm the biocompatibility and the requirements for anticoagulation in detail. Also, we will consider how to exteriorize the driveline from LA to a controller outside the body.

Conclusions

The in vitro data have demonstrated the LAAD's capability to increase CO and AoP while decreasing LAP when the systolic function is preserved. The LAAD effectively improved each parameter of DHF models in the in vitro experimental setup. The in vivo study showed the feasibility of the pump implantation; further long-term studies will be necessary to evaluate the stability of LAAD-assisted hemodynamics under DHF conditions and to elucidate the design's viability in long-term biocompatibility models.

Lay Summary

- The left atrial assist device (LAAD) is a novel pump that aims to be a treatment option for heart failure with preserved ejection fraction. Initial in vitro and acute in vivo experiments have been performed, and diastolic heart failure conditions were evaluated.
- The LAAD showed improvements in cardiac output and mean aortic pressure with reducing left atrial pressure under normal and diastolic heart failure conditions while maintaining arterial pulsatility and full function of the aortic valve.
- The implantation did not cause left ventricular outflow tract obstruction, and the replacement of the LAAD with a mitral prosthesis was confirmed.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2021.11.024.

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