A less-invasive left atrial assist device concept for diastolic heart failure: First in vitro and in vivo assessment

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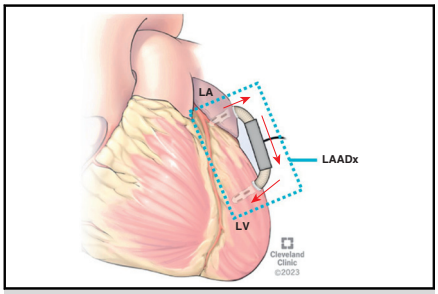
ABSTRACT

Objective: A less-invasive left atrial assist device (LAADx) is a novel and implantable, extracardiac blood pump concept, intended for the treatment of diastolic heart failure, represented by heart failure with preserved ejection fraction.

Methods: A mixed-flow pump was used as the working LAADx model. Its performance was evaluated at 3 speeds, using an in vitro pulsatile mock circulatory loop, with a pneumatic pump that can simulate diastolic heart failure conditions by adjusting the diastolic drive pressure. The LAADx model was implanted in 4 healthy calves. The pump's inflow and outflow cannulas were inserted into the left atrium (LA) and left ventricle (LV), respectively, without cardiopulmonary bypass. The LAADx was operated at 3 speeds, and diastolic heart failure-like conditions were induced by inflating a balloon, inserted into the LV.

Results: With the in vitro study, diastolic heart failure-like conditions were successfully induced, exhibiting decreased cardiac output and aortic pressure as well as increased mean LA pressure both mitigated with the LAADx support. With regard to the in vivo study, simulated diastolic heart failure conditions showed a decrease in aortic pressure and an increase in LA pressure and LV end-diastolic pressure, which were again mitigated by the LAADx. Echocardiography showed good positioning of the outflow cannula and neither cardiac dysfunction nor mitral interference was observed.

Conclusions: Initial in vitro and in vivo results confirmed that the LAADx model, a device concept driven by creating an extracardiac route from the LA to LV, has the potential to mitigate high LA pressure and improve LV filling of heart failure with preserved ejection fraction pathology. (JTCVS Open 2024;21:180-90)



Schematic drawing of the extracardiac left atrial assist device.

CENTRAL MESSAGE

In vitro and in vivo results of the less-invasive LAAD demonstrated potential effects to mitigate high left atrial pressure of heart failure with preserved ejection fraction.

PERSPECTIVE

Device-based therapies for diastolic heart failure are limited, but the concept of a less-invasive left atrial assist device was created as an option. It can create an extracardiac route between the left atria and the ventricle to improve ventricular filling. Initial in vitro and in vivo studies showed its potential effects in improving parameters of diastolic heart failure.

The incidence of heart failure (HF) is increasing, especially when considering relative global population ageing. HF with preserved ejection fraction (HFpEF) has now progressed to comprise more than half of all HF hospital admissions.[1] Unlike HF with reduced ejection fraction (HFrEF), most HFpEF cases are characterized by multimorbidity, with approximately half of all these patients exhibiting 5 or more major comorbidities,[2] as well as commonly

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Abbreviations and Acronyms

AoP = arterial pressure
CO = cardiac output
CPB = cardiopulmonary bypass
CVP = central venous pressure
DHF = diastolic heart failure
HF = heart failure
HFpEF = heart failure with preserved ejection fraction
HFrEF = heart failure with reduced ejection fraction
LA = left atrium
LAAD = left atrial assist device
LAADx = extracardiac left atrial assist device
LAP = left atrial pressure
LV = left ventricle
LVAD = left ventricular assist device
LVEDP = left ventricular end-diastolic pressure
P_{in} = inlet pressure port
P_{out} = outlet pressure port

showing diastolic dysfunction, defined as the impaired filling of the left ventricle (LV), causing high left atrial (LA) pressure (LAP) rise, and pulmonary edema.[2,3]

Although pharmacological therapies targeting HFpEF have demonstrated comparative efficacy on reducing the risk of cardiovascular mortality and HF hospitalization,[4,5] device-based therapies have yet to be included amongst standard strategies in HFpEF treatment, in contrast to left ventricular assist devices (LVADs) in HFrEF populations. For those with end-stage HFrEF, LVADs largely contribute toward improving patient quality of life and rates of mortality as the recommended, standard therapy. In the HFpEF population, the relative cavity stiffness and narrowness of the LV are usually not suitable for LVAD implantation. In addition, there are limited options for end-stage HFpEF with the outcomes remaining very poor.

Recently, device-based therapies featuring innovative concepts tailored to HFpEF pathology are receiving more attention.[6,7] Out of this context, our team has developed a left atrial assist device (LAAD) that can be implanted at the mitral plane, and will help LA decompression and LV filling.[8,9] So far, its performance—in a mock circulatory loop and in calves—has been reported with simulated levels of diastolic HF (DHF) conditions.[10,11] The primary advantage of the LAAD is its ability to create physiological flow (from the LA to LV) and improve LV filling. However, this must be prefaced with its 2 disadvantages: the implantation procedure includes approaching the mitral valve, similar to a regular mitral valve replacement that requires cardiopulmonary bypass (CPB) use and cardiac arrest, and if pump failure occurs, both mitral valve stenosis and regurgitation through the LAAD would occur, which could be critical to the heart when it is already at end-stage HF. To address these disadvantages, we sought to develop a less-invasive, miniature version of the LAAD (ie, LAADx) that is implanted outside of a beating heart, without using CPB, and that can create similar hemodynamics to the LAAD. Herein, we report the in vitro and in vivo evaluations of proposed the LAADx pump concept with simulated DHF conditions.

METHODS

LAADx Pump Model

The LAADx device concept (Figure 1, *A*) has evolved and has been developed as an extracardiac version of the LAAD pump (Figure 1, *B*). The LAADx pump's underlying principle was axiomatically guided by the following: pump blood from the LA and thereby properly fill the LV.

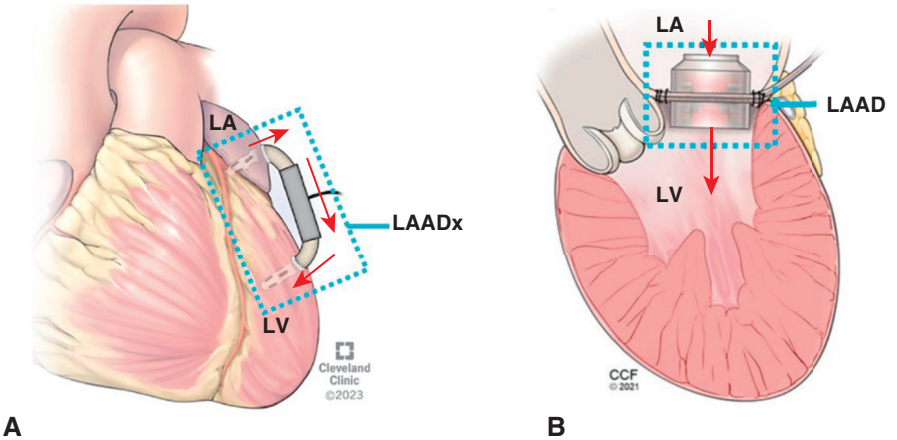

FIGURE 1. Schematic drawing of the extracardiac left atrial assist device (*LAADx*), and the original left atrial assist device (*LAAD*) concept, in a heart with heart failure with preserved ejection fraction. A, The LAADx is implanted outside of the heart, with cannulas inserted into the left atrium (*LA*) and left ventricular (*LV*) free wall. B, The LAAD is implanted in the mitral position.

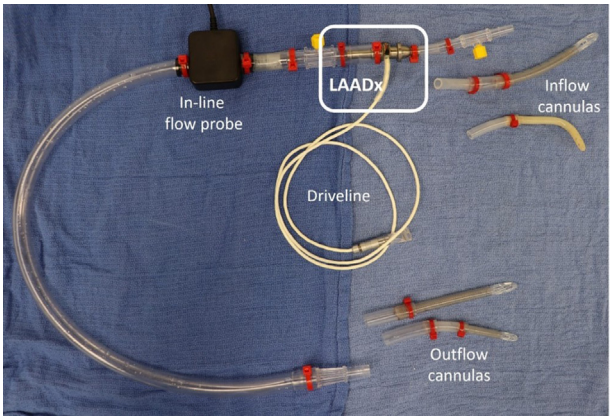

FIGURE 2. A photo of the extracardiac left atrial assist device (*LAADx*) model complex, used for in vitro and in vivo studies.

The difference is that the LAADx creates additional flow outside of the heart as a parallel pathway to the natural flow. High LAP can be mitigated by draining blood directly from the LA and an immediate increase in cardiac output (CO) is expected because the pump provides additional blood volume to the LV.

Because the actual working prototype of the LAADx is currently under development, the hemodynamic concept was tested with PediPump,[12-15] as a preliminary LAADx model. PediPump is a passive, magnetic-bearing, mixed-flow, rotary dynamic pump designed to support pediatric patients, including neonates. The pump measures approximately 11 mm at its maximum diameter, with its total length of 70 mm. Comprising a pump rotor and a stator, PediPump can produce up to 3.5 L/minute. The LAADx model complex is shown in Figure 2.

In Vitro Study

Similar to our group's previous in vitro study with the LAAD,[10] the in vitro mock circulatory loop setup for the LAADx (Figure 3, *A*) was composed of a pneumatic mock ventricle (AB5000; Abiomed Inc) that works as a mock native LV, an adjustable arterial afterload and compliance, a reservoir as a mock LA chamber, and the LAADx. A mixture of water and glycerin (specific gravity of 1.060) was used as the working fluid to simulate blood. The LAADx is placed in a parallel route to the main mock circuit, branched between the LA chamber and mock ventricle, and merged into the mock ventricle (Figure 3, *A*). The parallel route contains the inlet and outlet pressure port (P_{in} and P_{out}). At the main route, CO, LAP, LV pressure (LVP), and arterial pressure (AoP) are measured, as indicated in Figure 3, *B*.

For simulating a normal heart condition, the pneumatic ventricle was driven with a pneumatic driving pressure of 200 mm Hg for systole, and −35 mm Hg for diastole (negative value indicates a vacuum). The heart rate and systolic duration were set to 80 bpm and (250 milliseconds, respectively. The arterial compliance and resistance were adjusted to obtain a CO of approximately 4.0 L/minute, and an AoP of 120/80 mm Hg, without the LAADx (measured when branched route is clamped). The compliance and resistance were not changed throughout the entire study.

Three different degrees of DHF were simulated on this setting via restricting the diastolic filling of the pneumatic ventricle by increasing the diastolic drive pressures of the pneumatic driver: from −35 mm Hg at the normal heart condition to 0 mm Hg (ie, mild DHF), +20 mm Hg (ie, moderate DHF), and +40 mm Hg (ie, severe DHF). The systolic drive pressures of the pneumatic driver were maintained throughout the entire study at 200 mm Hg. Preset driving pressures of the AB5000 indicate the pressures of pushing/drawing the membrane of the pneumatic ventricle, to empty/draw fluid in the ventricular space of the AB5000. Therefore, they are not the same as the actual fluid pressures in the flow circuit created by the system. The same setting was used and validated in our previous studies for the LAAD.[10,16]

During the study, the LAADx was operated at 3 different speeds (16 000, 18 000, and 20 000 rpm), at each DHF condition (ie, mild, moderate, severe, and normal). For each condition, CO was recorded, using a flow probe clipped to the outside of the tube (ME20PXL; Transonic Systems Inc). For measuring the LAADx flow, an in-line flow probe (ME13PXN; Transonic Systems Inc) was utilized. AoP, LAP, P_{in}, and P_{out}, were monitored with fluid-filled lines and pressure transducers (13-6615-50; Gould Electronics), and amplifiers (M21018; Honeywell). For the pump speeds, they were set by the head curves of the PediPump from previous studies[13] to create at least 2.0 L/minute of flow toward the delta pressure of 100 mm Hg.

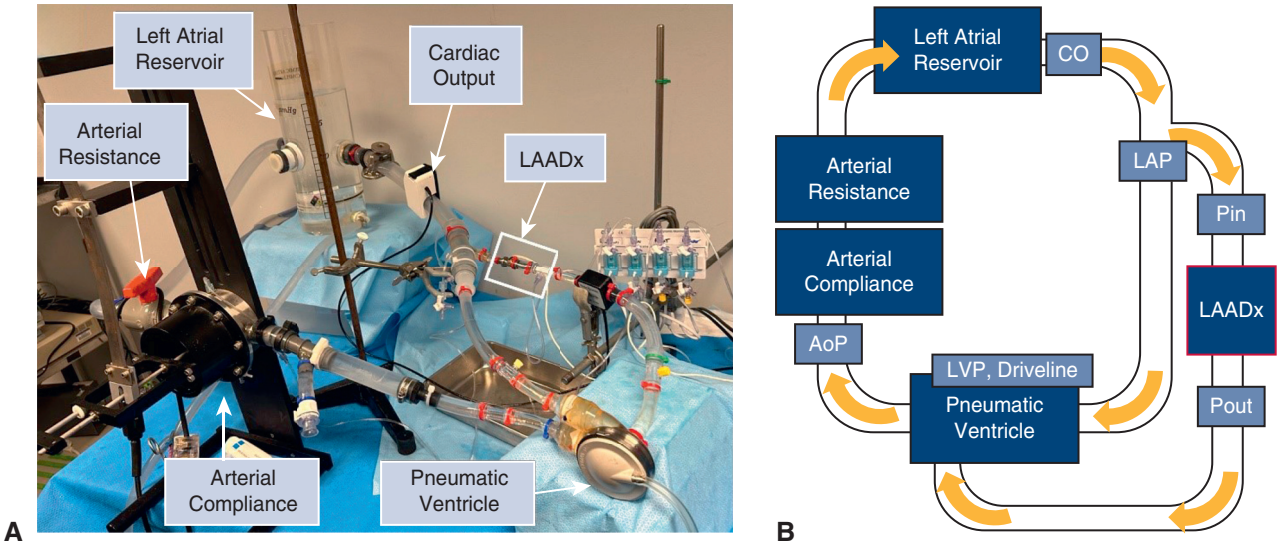

FIGURE 3. A photo and illustration of the extracardiac left atrial assist device (*LAADx*) bench-test setting. A, The mock loop, simulating a systemic circulation with the LAADx pump. B, Schematic diagram of the in vitro mock circuit. *CO*, Cardiac output; *LAP*, left atrial pressure; *LVP*, left ventricular pressure; *AoP*, arterial pressure.

In Vivo Study

After receiving approval from Cleveland Clinic's Institutional Animal Care and Use Committee (#00003117; May 9, 2023), a total of 4 acute in vivo studies were performed using male Jersey calves (mean body weight, 87.8 ± 8 kg). While under general anesthesia with a right lateral position, a central venous pressure monitoring line and AoP line were placed in the left jugular vein and left carotid artery, respectively. A left thoracotomy was performed on the fourth intercostal space and, to measure CO, a 28-mm flow probe (28PAU; Transonic Systems) was placed around the ascending aorta. To achieve systemic heparinization, heparin (300 U/kg) was injected, and a fluid-filled LAP line was inserted in the LA.

An inflow cannula (28 Fr) was inserted into the LA via a purse string suture, and an outflow cannula (28 Fr) was inserted into the LV sidewall via 2 crossing *U*-sutures with a pledget. Pericardial echocardiography was performed to verify the suitable positioning of the outflow cannula. To measure LV end-diastolic pressure (LVEDP), a micromanometer Millar catheter (Sensor: SPC-350 and transducer: TC-510; Millar) was inserted into the LV, from the LV apex. After de-airing of the circuit and the cannulas, the LAADx model circuit was connected to both the inflow and outflow cannulas. The LAADx model circuit was composed of PediPump, inflow/outflow connectors at both ends of the PediPump with inflow/outflow pressure ports to measure P_{in} and P_{out}, an inline flow probe (ME13PXN), and a tube to connect the flow probe and the outflow cannula (Figure 4, *A*). For this study, the LAADx model circuit was made to be much longer than a more-practical design of the circuit so that the pump inflow/outflow pressure and pump flow could be monitored. The eventual prototype design will not include the flow probe or the P_{in} and P_{out} ports. Also, the final design's inflow and outflow cannula will be connected directly to the pump (Figure 4, *B*); therefore, the total length of the circuit (about 30 cm) is within an implantable range.

The LAADx was started at 14 000 rpm. Once stable conditions were achieved, hemodynamic and pump-related data were subsequently taken at pump speeds of 14 000, 16 000, and 18 000 rpm.

Data with simulated DHF conditions were induced with a balloon catheter (Coda Balloon Catheter, G53024; Cook Inc [with in-house modification]), inserted from the LV apex, as shown in Figure E1. These additional procedures were performed after basic data collection was done. Three levels of DHF configurations with 0, 50, and 70 mL of the inflated balloon were induced, and hemodynamic data for each setting were taken. Pericardial echocardiography was performed, looking for any interaction between the outflow cannula, the mitral valve, and the balloon.

After recording all data points, the animal was put to death with an intravenous bolus injection of phenytoin/pentobarbital (100 mg/kg) and the pump was stopped. The heart was then extracted and the LA and LV were observed for any abnormal findings.

Data Analysis

All data were recorded at 200 Hz using a PowerLab data acquisition system (ADInstruments Inc), analyzed with LabChart (ADInstruments Inc), and finally downloaded into Excel (Microsoft Corp) to summarize and chart the test results.

RESULTS

In Vitro Study

As shown in Figure 5, *A*, without LAADx support, CO decreased from 4.2 L/minute under normal heart condition to 3.6 L/minute (ie, mild DHF), then 2.6 L/minute (ie, moderate DHF), and finally to 1.4 L/minute (ie, severe DHF). With LAADx support at 20 000 rpm, CO recovered to normal heart condition levels, regardless of DHF condition severity.

Similar to the results observed with CO without LAADx, the mean AoP decreased dramatically, from 102 mm Hg under the normal heart condition, to 80, 54, and 32 mm Hg, for the mild, moderate, and severe DHF conditions, respectively (Figure 5, *B*). With LAAD support, decreases in AoP, per DHF condition severity, were mitigated more effectively and with higher support. With the LAADx support, even when under the severe DHF condition, AoP recovered to 96 mm Hg.

The mean LAP showed increases from 4.5 mm Hg for the normal heart condition to 10.1, 15.4, and 17.5 mm Hg, for mild, moderate, and severe DHF conditions, respectively (Figure 5, *C*). With LAADx support, the LAP decreased by increasing pump speed, especially for severe DHF conditions; the difference in LAP from normal condition was only 6.2 mm Hg at 20 000 rpm.

The aortic pulse pressure decreased from 48 mm Hg for the normal heart condition to 44, 37, and 19 mm Hg for mild, moderate, and severe DHF conditions, respectively

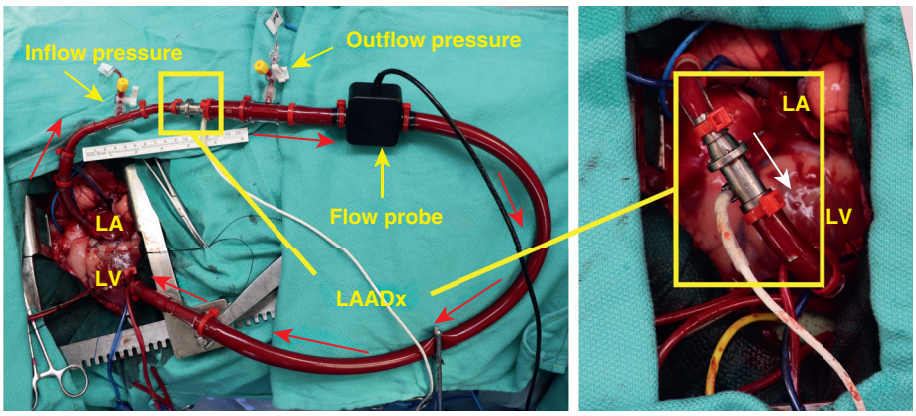

FIGURE 4. Intraoperative images. extracardiac left atrial assist device (*LAADx*) circuit, for implantation surgery in a calf. A, an extended circuit, with inflow/outflow pressure monitors and an inline inflow probe. B, the shortened circuit, composed only of the LAADx pump and inflow/outflow cannulas. *LA*, Left atrium; *LV*, left ventricle.

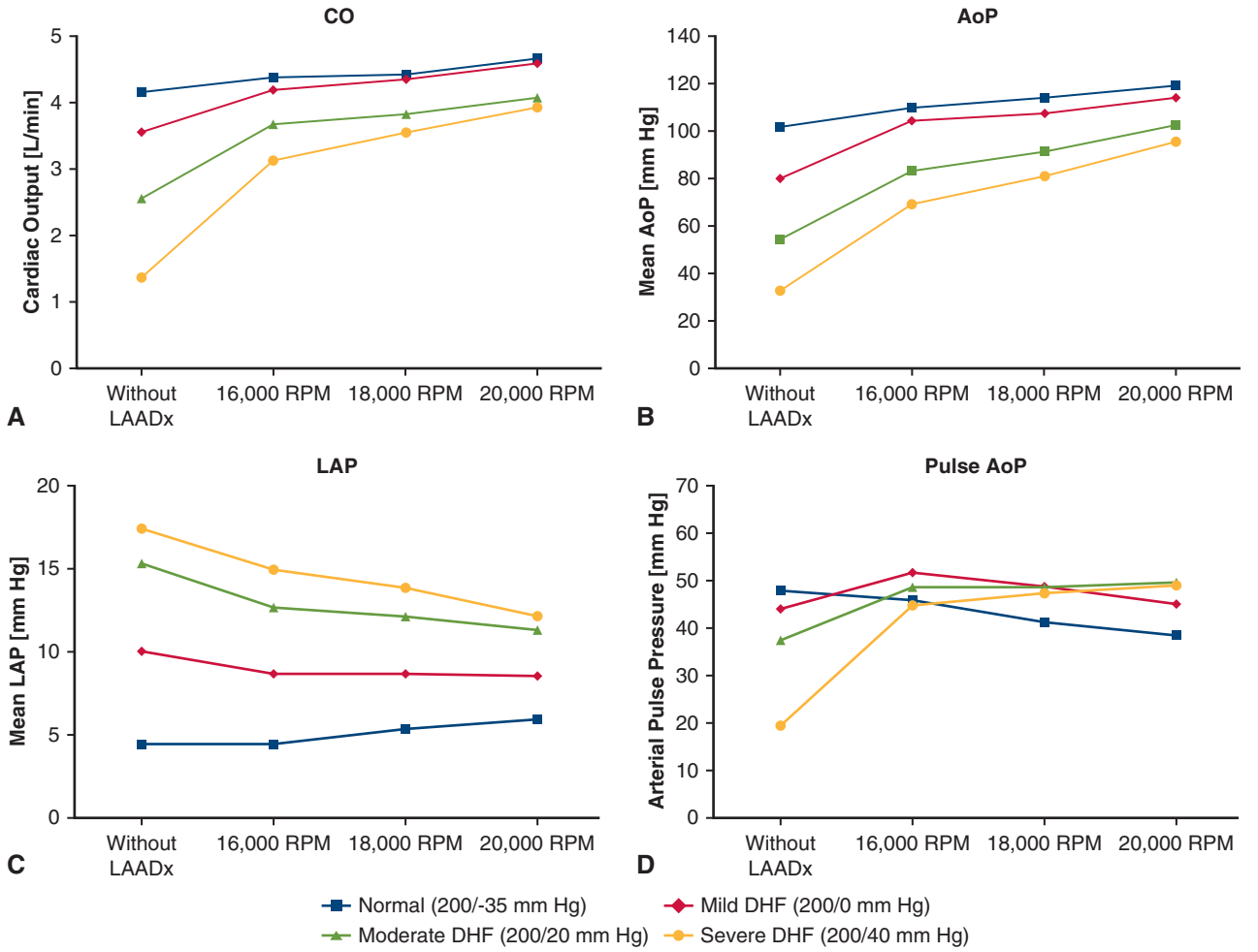

FIGURE 5. The in vitro changes of each parameter by the pump speed, with comparisons among normal heart condition, as well as mild, moderate, and severe diastolic heart failure (*DHF*) conditions. A, Mean cardiac output (*CO*). B, Mean arterial pressure (*AoP*). C, Mean left atrial pressure (*LAP*). D, Atrial pulse pressure (*pulse AoP*).

(Figure 5, *D*). When the LAADx support is set at the pump's highest speed (20 000 rpm), the aortic pulse pressure did not decrease and was maintained.

In Vivo Study

The LAADx model responded to all control inputs exactly as expected and, during data collection, hemodynamic status was stable in all animals. The primary findings can be summarized as follows:

- The pump flow reasonably increased from 2.3 to 3.3 L/minute, with a pump speed that was increasing from 14 000 to 18 000 rpm ($P < .05$) (Figure 6, *A*). Between pump speeds of 16 000 and 18 000 rpm, a tendency for an increase in the pump flow was observed; but the *P* value was not significant ($P = .054$).
- Throughout the pump speed changes from 14 000 to 18 000 rpm, the mean values in CO and AoP did not change, maintaining similar values as 0 rpm (before starting the pump) (Figure 6, *A* and *B*).
- LAP slightly decreased from 7.7 to 6.6 mm Hg, by increasing the pump speed from 14 000 to 18 000 rpm. The central venous pressure remained the same for all pump speed conditions (Figure 6, *B*).

Subsequent epicardial echocardiography showed that the outflow cannula of the LAADx was positioned correctly in the LV, interfering neither with the mitral valve nor its function (Figure E2, *A*). There was no obvious cardiac dysfunction caused by cannula insertion and no regurgitant flow was observed through the mitral valve.

For the DHF conditions, Figure E2, *B*, shows the balloon view (50 mL), obtained during epicardial echocardiography. The positional relationship between the pump outflow cannula and the balloon is displayed in Figure E2, *C*. Each parameter change, with the intracardiac balloon at 0, 50, and 70 mL, and with/without the LAADx, is shown in Figure 7.

Without the LAADx, mean AoP decreased from 72 to 60 mm Hg via inflating the balloon from 0 to 70 mL,

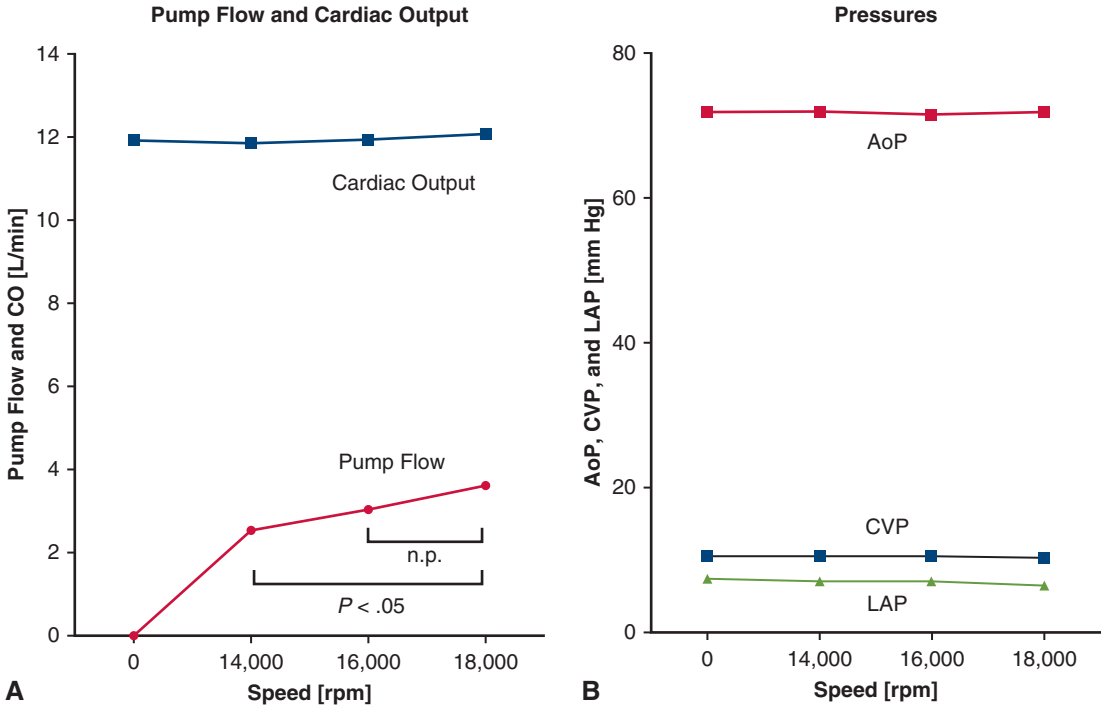

FIGURE 6. The in vivo changes of each parameter by the pump speed. A, Mean cardiac output and Pump flow; B, Mean arterial pressure (*AoP*), Mean left atrial pressure (*LAP*), and Mean central venous pressure (*CVP*).

respectively (Figure 7, *A*). The LAP and LVEDP increased by inflating the balloon to 50 and 70 mL (Figure 7, *B* and *C*). These hemodynamic changes indicated that typical hemodynamics of DHF were successfully replicated with balloon inflation inside the LV.

The hemodynamic changes caused by the balloon (ie, increase in mean LAP and LVEDP and decrease in mean AoP), were mitigated by the LAADx support (Figure 7). There was a significant difference in mean AoP, with 70 mL inflation between 0 and 18 000 rpm ($P = .04$).

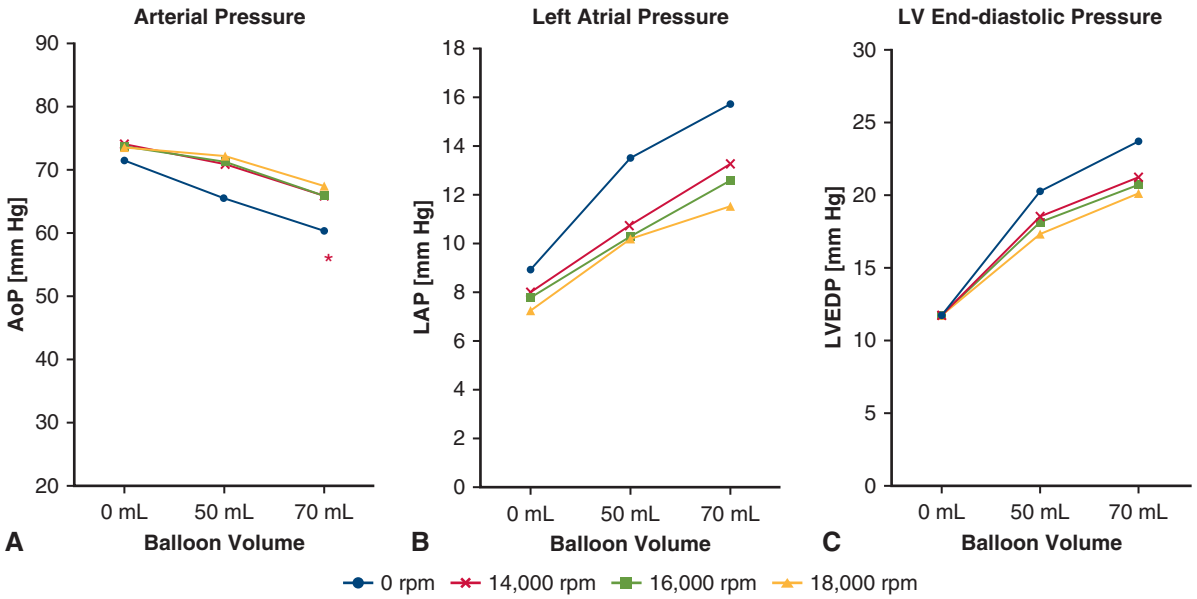

FIGURE 7. The in vivo hemodynamics, under 0, 50, or 70 mL of balloon inflation (inside the left ventricle [*LV*]), by the pump speed. A, Mean arterial pressure (*AoP*). B, Mean left atrial pressure (*LAP*). C, Left ventricular end-diastolic pressure (*LVEDP*). *$P < .05$ between 0 and 18 000 rpm.

At necropsy, pump position was confirmed to be correct from both the LA side (Figure E3, *A*) and the LV side (Figure E3, *B*); thrombi were not found in either the LA or LV. The outside view of the short circuit, in addition to the positional relationship between the balloon and the LAADx (Figure E3, *C* and *D*, respectively). After thoroughly disassembling and inspecting the explanted pump, the engineering team observed neither thrombotic deposition nor tissue adhesion on the heart.

DISCUSSION

Overall, the aforementioned in vitro and in vivo simulation studies utilizing our model concept of the novel LAADx successfully demonstrated significant potential to improve DHF conditions—by decreasing LAP and increasing CO and AoP—while maintaining the arterial pulsatility (Figure 8). Additionally, these studies exhibited that the LAADx model can be less invasively implanted without using CPB and cardiac arrest, and thus it could provide a safer and easier option for patients with HFpEF. This is especially true when compared with the LAAD pump, the other available intracardiac device for HFpEF treatment. Although the actual pump design is still in its developmental stages, the eventual dimensional size and the fundamental pump function will be similar to that of the PediPump.

Considering the present landscape of such devices currently under development for HFpEF, it is significant to note that many share our pump's underlying design concept; namely, drawing blood from the LA (because the LA in HFpEF is usually dilated) and allowing the expanded LA to decrease LAP. Regardless of design, this concept is considered to be the most efficient therapeutic target at this time. Eventually, LVAD use with an LA cannulation[17] could be an option for HFpEF pathology; however, bypassing the LV and returning the blood directly into the aorta

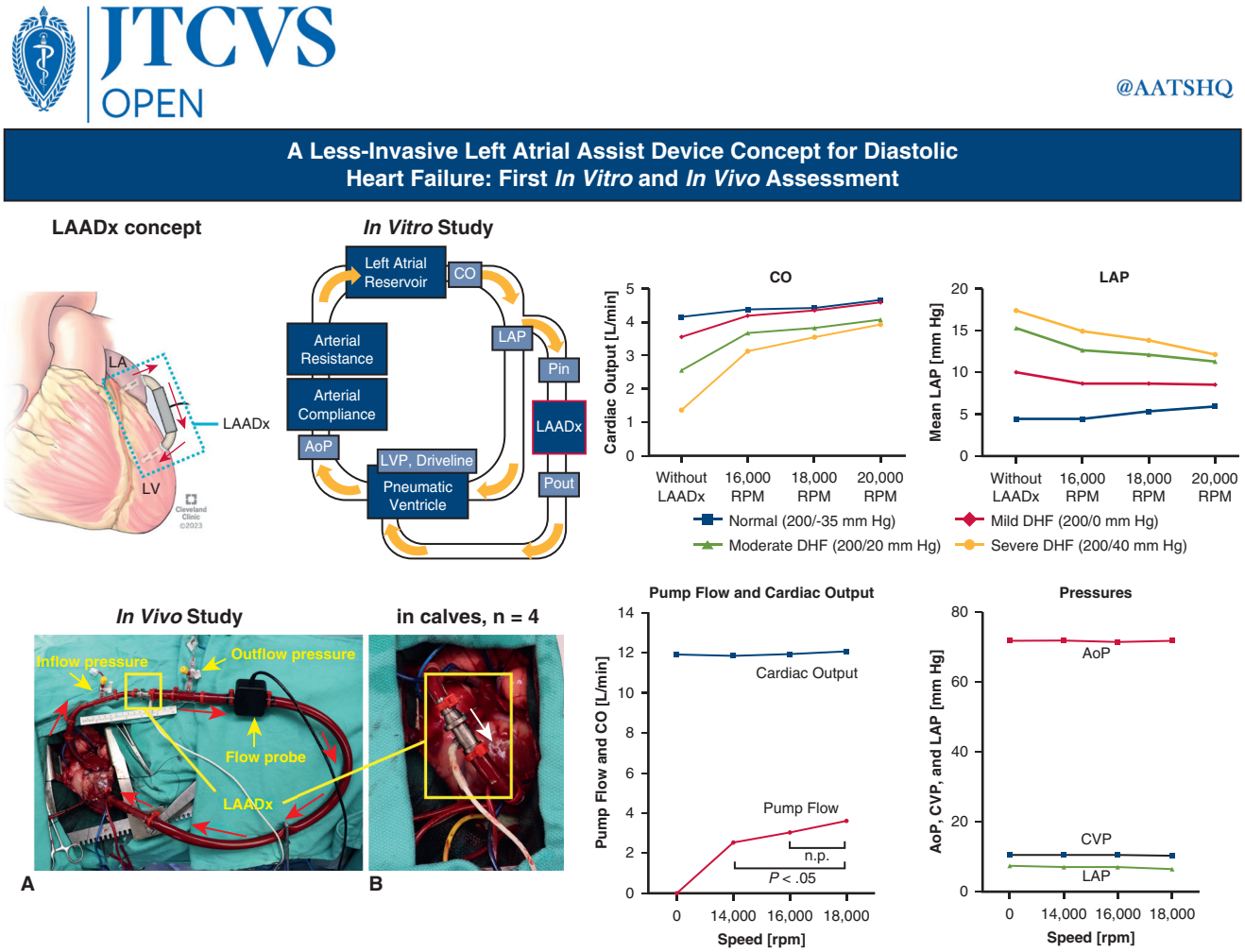

FIGURE 8. Graphical Abstract. Less-invasive left atrial assist device (LAADx) is a novel and implantable, extracardiac pump designed to treat patients with heart failure with preserved ejection fraction. Initial in vitro and in vivo results confirmed the potential of the LAADx concept to mitigate high left atrial pressure and improve left ventricular filling.

could cause blood stagnation inside of the LV. In this configuration, the risk of thromboembolism due to blood stagnation in the LV is a significant concern. In addition, aortic pulsatility could be remarkably reduced, as we previously reported.[18]

The device concepts of the LAADx, as well as the LAAD, have advantages in providing a pulsatile flow, directly reducing LAP, and filling the LV. Both also have the potential of enabling LV remodeling of the thickened LV, a key characteristic of HFpEF. Unlike LAAD, the LAADx pump creates an extra-anatomic flow outside of the heart; thus, the flow path would not be in a natural pattern. Although pumping blood directly to the LV could minimize the risk of stagnation of blood, considering the existence of this extra-anatomic flow and of the inflow cannula in the LA, there might be a need for anticoagulation therapy to prevent the potential thrombotic risk. Another difference between the LAAD and LAADx is that in case of an accidental pump stoppage, the blood regurgitation via the LAADx pump remains much less than if an LAAD was implanted.

One major concern with this pump concept is that the elevation of LVEDP could cause endocardial ischemia via forced filling of the LV. During the in vivo studies we observed the change in LVEDP, which showed some elevation while under the induced DHF conditions. But, at least in these relatively short periods of time, it did not cause any cardiac dysfunction. More specifically, the LAADx could potentially cause higher LVEDP in the diastolic phase, which might later lead to impairment of coronary flow and earlier mitral valve closure. Or if it is favorably influenced, remodeling of the thickened LV could be expected. However, these are not yet demonstrated in our current study setting; therefore, we recognize this scenario should be carefully evaluated in our future chronic animal studies.

For patients with mitral regurgitation, the LAADx cannot be used because recirculation flow during the diastolic phase could occur due to regurgitant flow of the mitral valve. Therefore, this population should be excluded from the candidates for LAADx implantation, or the mitral regurgitation should be repaired before the LAADx application. Instead, if mitral valve function turns out to be insufficient in preimplant evaluation, the LAAD can be used as an alternative option because it can be implanted in the mitral plane replacing the valve. Mitral valve evaluation will be necessary before considering future LAADx implantations. Also, because the LAADx cannot improve the LV stiffness itself, the LAADx instead induces an earlier elevation in LVEDP in the diastolic phase, and thus, the mitral valve will close earlier and endure higher pressure for longer periods of time compared with normal physiology. This could influence long-term mitral valve function and requires long-term observation of it with future chronic animal studies.

Another concern that the LAADx have is that the size of the LA and insertion place of the inflow cannula should be carefully observed and selected to avoid any possible suction or bleeding events. Usually, the LA wall of hearts with HFpEF is thickened and enlarged by experiencing high LAP, and thus possibility of LA suction/bleeding considered low, but in patients whose LA is fragile or not dilated, more careful preoperative planning is required.

For inducing DHF conditions, we attempted the balloon method to reduce the LV volume by 50 to 70 mL, the same settings used in our previous LAAD studies.[10] We chose this method because it can instantly be utilized to evaluate device effects (under DHF-like hemodynamics), where reduced LV volume and stiffened LV wall are reproduced, inherently. Although the LAADx showed reasonable efficacy in this setting, the simulated hemodynamics did not completely mimic all the features of HFpEF conditions. As a future step to create a better HFpEF animal model, we are currently developing an extracardiac constraint device that can limit the volume of the LV from outside. Because there is currently no established large animal model of DHF or HFpEF with high fidelity, this partial reproduction of the hemodynamics remains invaluable to better understand the pump performance and final development.

Study Limitations

One major limitation of our in vivo study is that it is an acute evaluation in healthy animal models, although the intention was to simulate DHF conditions. The entire range of DHF conditions has yet to be replicated in healthy calves; therefore, the LAADx has not completely addressed all DHF conditions. Especially under DHF conditions, an increase in pump speed seemed to have limited influence on LAP, LVEDP, and CO. This could be because the fidelity of the DHF conditions in vivo was more limited than the in vitro evaluations because the influence of anesthesia or postsurgical status, and noncongestive status and limited preload to the LV by using healthy animal models. For the in vitro study as well, the circuit took a shortcut of pulmonary circulation, and the LA chamber and LAP might not be able to represent the actual changes in human/animal hearts. To fully test the capability of the LAADx more accurately, evaluations under chronic circumstances are required. Biocompatibility evaluation is also limited in acute studies, so a detailed confirmation of its biocompatibility and anticoagulation are still necessary.

Another limitation of this study is our selection of using the PediPump instead of an actual, working prototype for the LAADx application. Therefore, the same process should be repeated with a developed prototype of the LAADx, as well as functional evaluations of the pump, such as obtaining pump head curves, performing computational fluid dynamics, confirming possible retrograde flow via the pump, and hemolysis testing. The pump will be designed to have very similar hemodynamic performance to the PediPump, but the design will be updated to make it more biocompatible and to transition to the inlet and outlet

to the cannulas required for the extracardiac location. At this stage of our overall program, our aim was to prove the concept that the LAADx configuration is realistic and achievable and is capable of alleviating HFpEF pathology. We are ready to continue to the next project milestone; the design process of the first LAADx prototype is underway.

CONCLUSIONS

Our novel device, the LAADx, creates an extracardiac route from the LA to LV, to thereby mitigate high LAP and improve LV filling, factors associated with HFpEF pathology. The first in vitro data have already demonstrated that the LAADx is capable of increasing CO and AoP while decreasing LAP, when the systolic function is preserved. Furthermore, the LAADx improved each predetermined parameter of DHF, when using large animal models, during in vivo studies. Further long-term studies will be necessary to evaluate the stability of LAADx-assisted hemodynamics under DHF conditions with a working prototype.

Conflict of Interest Statement

Drs Fukamachi and Karimov, and Mr Kuban are coinventors of the LAADx, an extracardiac left atrial assist device. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handing or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: blood pump, heart failure with preserved ejection fraction, large animal model, mechanical circulatory support, minimally invasive cardiac surgery

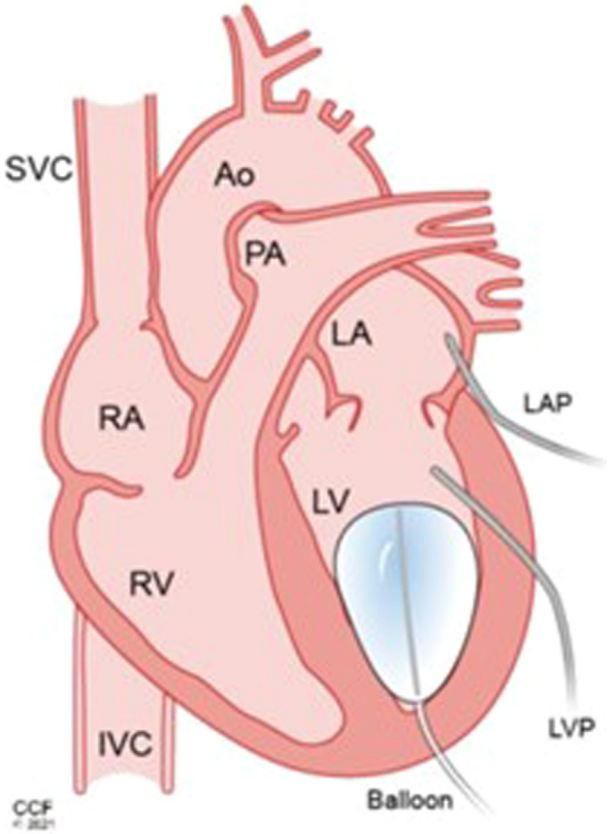

FIGURE E1. Schematic illustrations of in vivo diastolic heart failure setting. A balloon was inserted from the left ventricle (*LV*) and inflated, at most, to 70 mL. *SVC*, Superior vena cava; *Ao*, aorta; *PA*, pulmonary artery; *LA*, left atrium; *LAP*, left atrial pressure; *LVP*, left ventricle pressure; *IVC*, inferior vena cava; *RV*, right ventricle; *RA*, right atrium.

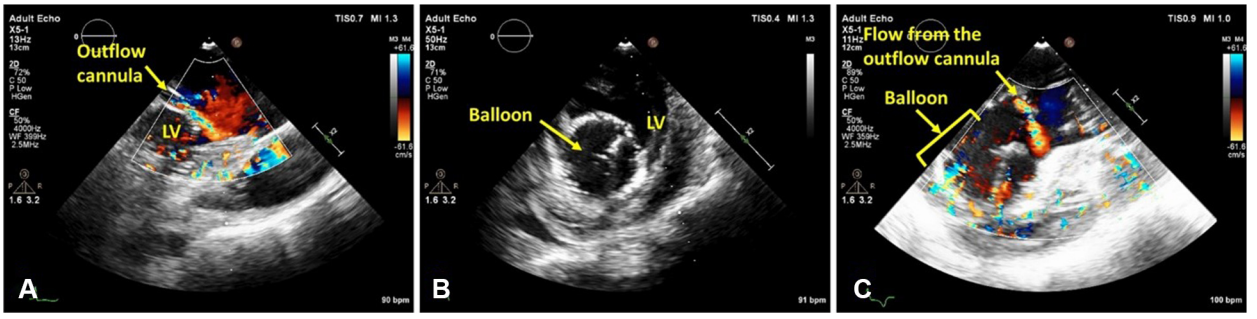

FIGURE E2. A, Epicardial echocardiography, after extracardiac left atrial assist device (*LAADx*) implantation. Notice, the outflow cannula exhibits good positioning, without interfering the mitral valve function. B, The balloon inserted from the left ventricle (*LV*) apex and inflated to reduce the LV volume by 50 to 70 mL. C, View of the inserted balloon and outflow cannula.

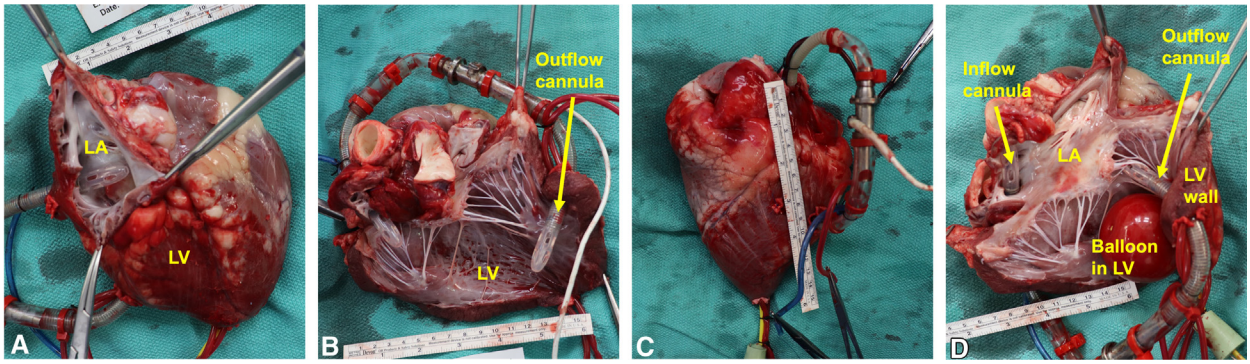

FIGURE E3. The extracted heart, after the extracardiac left atrial assist device (*LAADx*) implantation. A, The view from the left atrium (*LA*) side. B, The view from the left ventricle (*LV*) side. Of note, no laceration or thrombus was observed in the LV. C, The outside view of the short circuit. D, The positional relationship between the balloon (*red*) and the LAADx outflow cannula.