A Short-Term In Vivo Evaluation of the Istanbul Heart Left Ventricular Assist Device in a Pig Model

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Abstract

Objectives: **A continuous-flow centrifugal blood pump system has been recently developed as an implantable left ventricular assist device for patients with end-stage heart failure. The objective of this study was to evaluate the initial in vivo performance of a newly developed left ventricular assist device (iHeart or Istanbul heart; Manufacturing and Automation Research Center, Koc University, Istanbul, Turkey) in an acute setting using a pig model.**

Materials and Methods: **Three pigs (77, 83, 92 kg) received implants via a median sternotomy, with animals supported for up to 6 hours. An outflow cannula was anastomosed to the ascending aorta. Anticoagulation was applied by intravenous heparin administration. During the support period, pump performance was evaluated under several flow and operating conditions. All pigs were humanely sacrificied after the experiments, and organs were examined macroscopically and histopathologically.**

Results: **Flow rate ranged between 1.5 and 3.6 L/min with pump speeds of 1500 to 2800 revolutions/min and motor current of 0.6 to 1.3 A. Initial findings confirmed that the iHeart ventricular assist device had sufficient hydraulic performance to support the circulation. During the experimental period, plasma free hemoglobin levels were found to be within normal ranges. Thrombus formation was not observed inside the pump in all experiments.**

Conclusions: **The iHeart ventricular assist device demonstrated encouraging hemodynamic performance and good biocompatibility in the pig model for use as an implantable left ventricular assist device. Further acute in vivo studies will evaluate the short-term pump performance prior to chronic studies for long-term evaluation.**

Key words: *Animal experiment, Centrifugal blood pump, Heart failure, Mechanical circulatory support*

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Introduction

Heart failure is a global life-threatening condition that affects more than 35 million people worldwide.[1,2] In Turkey, more than 2 million people have heart failure according to data from the Turkish Cardiology Association.[3] Although heart transplant is the best solution for treatment of end-stage heart failure, it is only available for a limited number of patients (< 100 patients) per year in Turkey.[3] Ventricular assist devices (VADs) have become an alternative therapy for patients with end-stage heart failure as a bridge to transplant, recovery, or destination treatment.[4-8] The demand for implantable VADs with a hydrodynamic impeller or magnetic suspension systems has been increasing worldwide because these devices show great potential for long-term survival and have extreme mechanical durability.[9-11] In 2001, Kucukaksu and associates performed the first application of an implantable left ventricular assist device (MicroMed DeBakey LVAD; MicroMed Technology, Houston, TX, USA) in Turkey.[12] However, the number of LVAD implantations remains restricted due to high operational costs. Cost-effective devices are thus needed to increase the clinical use of LVADs in Turkey.[13] Given these facts, a new centrifugal flow-type LVAD, named iHeart VAD (or Istanbul heart; Manufacturing and Automation Research Center,

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Koc University, Istanbul, Turkey), has been recently designed and manufactured for long-term support of patients in Turkey. In this initial study, our objective was to evaluate the feasibility of the iHeart VAD in an acute animal model and to determine pump flow performance, short-term hemocompatibility, and anatomic fitting.

Materials and Methods

Device description

The iHeart VAD is a centrifugal-flow, rotary VAD that utilizes conventional ceramic bearings to support the impeller. The newly developed pump consists of an inlet with 3 guide blades and the impeller structured by 5 blades and splitters. The external motor is embedded inside the casing to drive the impeller through a magnetic coupling. The pump-and-motor unit is 51 mm in diameter and 69 mm in total height, has a 25-mm inflow cannula height, and weighs 283.75 g. Figure 1A shows the main components of the iHeart VAD. All blood-contacting components are made of Ti6Al4V alloy. The percutaneous driveline, which is connected to the external controller, is 171 × 121 × 55 mm. The controller acquires data from the pump and adjusts the power according to the desired operating conditions. Two lithium-ion batteries are connected to the controller for redundancy. As shown in Figure 1B, the iHeart VAD is designed to operate in a wide range of flow rates, from 1.5 to 7 L/min, with pump speeds of 1500 to 3200 revolutions/min (rpm).

Animal model

Three female White Yorkshire pigs were used for this study (92, 83, and 77 kg). Large pigs were chosen to avoid possible surgical-, fitting-, or anesthesia-related complications. This study was approved by the Acıbadem University Ethical Committee (ACU-HADYEK 2017/37, No: HDK-2017/43), and all animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" and institutional guidelines. Identical surgical procedures were used for all 3 animals.

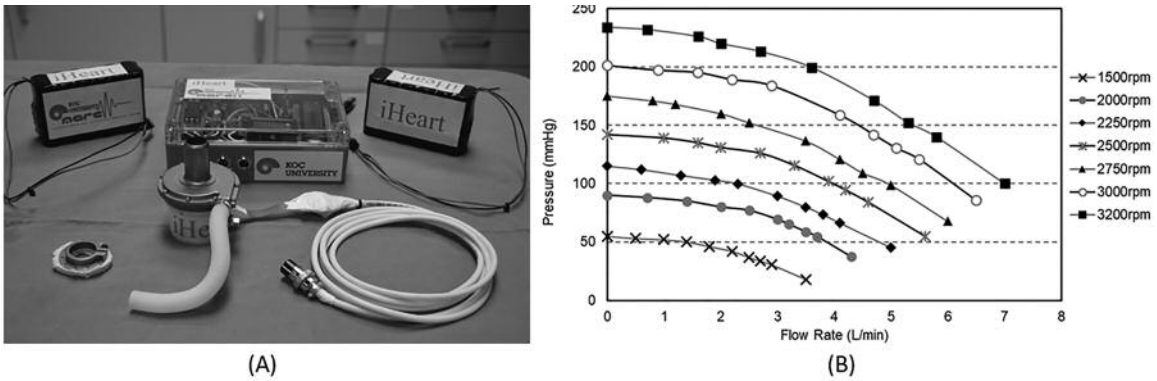
Surgical procedure

Animals were premedicated with intramuscular administration of ketamine (10 mg/kg), xylazine (2 mg/kg), and atropine (0.02 mg/kg); anesthesia was induced with fentanyl (10 mg/kg) and midazolam (0.2 mg/kg) and maintained with isoflurane. The chest was opened via median sternotomy. Heparin (100-300 IU/kg) was administered intravenously for systemic anticoagulation. Activated clotting time was between 450 and 500 seconds.

For the pump implant procedure, a cardiopulmonary bypass was used (Sarns 9000 heart-lung machine; Terumo Medical Corporation, Somerset, NJ, USA). The iHeart VAD was primed with a heparin/saline solution and tested for 5 minutes to ensure normal working conditions. The left ventricular (LV) apex was elevated by placing lap sponges underneath the heart. Figure 2A shows a circular incision that was made on the beating heart. The sewing ring was attached to the LV apex with 10 to 12 interrupted 2-0 Ethibond pledgeted sutures (Ethicon, Johnson & Johnson, New Brunswick, NJ, USA) with polytetrafluoroethylene felt, as shown in Figure 2B. The pump was inserted into the LV cavity and secured with the screw on the sewing ring (Figure 2C).

An echocardiograph was performed to verify the position of the pump in the LV cavity (Figure 2D). A

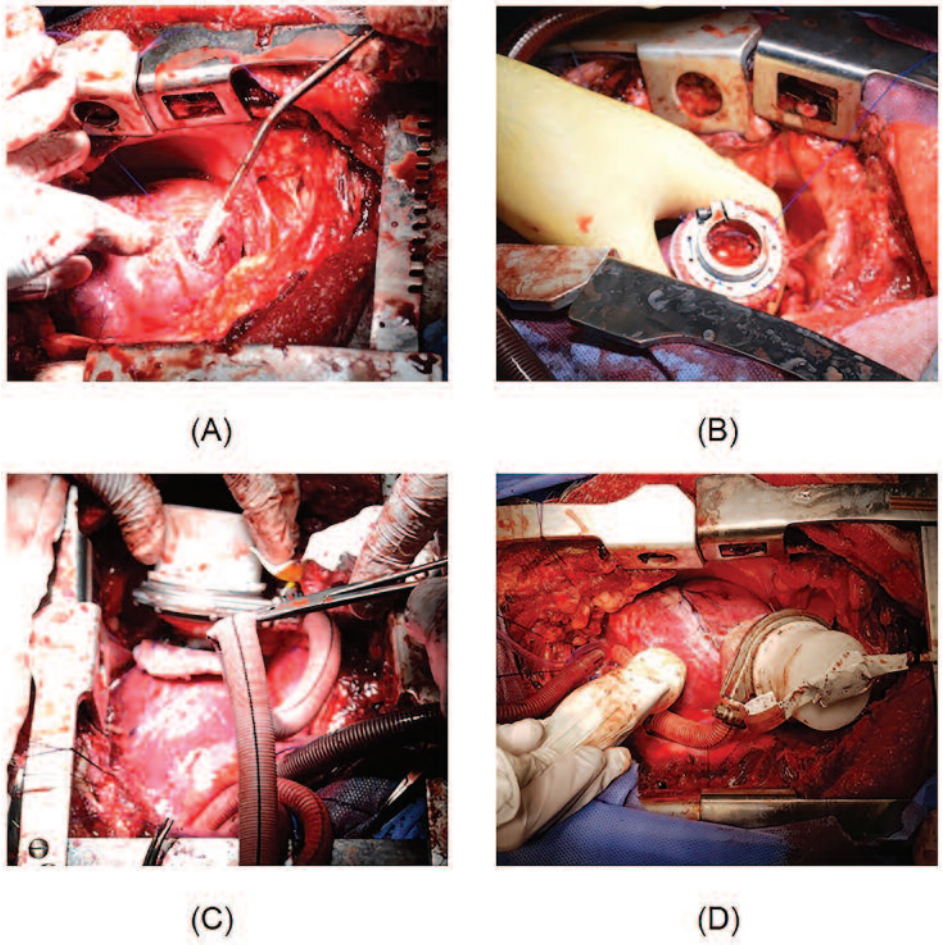
Figure 1. iHeart Ventricular Assist Device System



(A) (B)

(A) iHeart ventricular assist device (VAD) system. **(B)** Pressure-volumetric flow rate curve of the iHeart VAD.

Figure 2. Pump Implant Process



(A) Circular incision. **(B)** Sewing ring placement. **(C)** Pump insertion. **(D)** Pump operation.

10-mm-diameter woven Dacron outflow graft (Intergard, Maquet, Germany) was anastomosed to the ascending aorta with 6-0 polypropylene sutures in an end-to-side fashion. The air was removed from the system, and pump flow was initiated at 1250 rpm prior to the removal of the occlusion clamp from the outflow graft. Protamine was administrated to neutralize heparin (1:1). As the pump flow was gradually increased, the cardiopulmonary bypass was reduced in steps and eventually removed from the blood flow circulation. The pump speed was adjusted to between 1500 and 3000 rpm to achieve the target set point of 2 to 3 L/min against the physiologic blood pressure (mean of 80 mm Hg). The rotation speed of the iHeart VAD was adjusted to achieve maximum heart unloading during the tests, and the animals were supported for up to 6 hours. The status of the heart was continuously monitored with an electrocardiogram using the surface probe.

Echocardiographic examination

Transthoracic echocardiography. All echocardiographic assessments were done after the pigs had appropriate sedation and anesthesia and were made with pigs in left lateral semi-decubitus position. All echocardiographic imaging scans were performed with a custom-built scanner (Vivid S6, General Electric Healthcare, Wauwatosa, WI, USA) with a cardiac probe (2.4-8.0 MHz) (GE 6S-D, KPI Healthcare Inc., Yorba Linda, CA, USA). The baseline transthoracic echocardiography was assessed by parasternal long-axis, short-axis, and apical view in the left lateral decubitus position. A baseline echocardiography was used to assess myocardial function, dimension of heart chambers, and valvular performance before the experimental procedure.

Epicardial echocardiography. Epicardial echocardiography was performed by placing the same

ultrasonographic transducer on the epicardial surface of the heart to acquire 2-dimensional and color flow and spectral Doppler images in multiple planes. The probe was placed into a sterile cover along with sterile acoustic gel or saline to optimize acoustic transmission.

Biocompatibility measurements

To assess the hemodynamic performance of the iHeart VAD, aortic pressure, heart rate, mean arterial pressure, pulmonary artery pressure, pump flow, and rotational speed were recorded during the in vivo experiments. Blood samples were collected from the outlet graft at 1-hour intervals to analyze blood-gas levels (including oxygen and carbon dioxide partial pressures and oxygen saturation) and to measure hematocrit and hemoglobin levels. Hematologic and biochemical data were analyzed in a hemodynamics laboratory.

Animal necropsy and histopathologic evaluation

At the end of the experiment, animals underwent intravenous administration of pentobarbital (50 mg/kg) and potassium chloride (120 mEq/L) until death in compliance with the Panel on Euthanasia of the American Veterinary Medical Association. After the termination of each experiment, the iHeart VAD was removed, disassembled, and photographed for postimplant evaluation. Any evidence of thrombus inside the pump or scratches on the surface components were inspected during the assessment. Tissues from animals underwent pathologic assessment.

Histologic examination was performed on heart, lung, liver, kidney, and brain tissues. For histopathologic examination, representative tissue samples were fixed in 10% buffered formalin for a minimum of 24 hours, processed through an automatic tissue processor, and embedded in paraffin. Sections (4 μm thick) were obtained in a microtome, and the slides were stained with hematoxylin and eosin for microscopic examination.

Results

Physiological parameters and pump assessment

Three animals underwent successful iHeart VAD implantation and survived the surgery. The pump speed was adjusted to approximately 2100 rpm on startup to achieve an initial average target pump flow of 2 L/min. The actual pump flow ranged between 1.5 and 3.6 L/min by adjusting the pump speed in response to changes in systemic vascular resistance. As expected, the motor current consumption was observed in parallel with the flow rate and motor speed, which ranged between 0.6 and 1.3 A (mean of 0.79 ± 0.03 A). Aortic pressure varied between 60 and 110 mm Hg throughout the testing. All VADs were implanted successfully without surgical complications. The 3 animals remained hemodynamically stable throughout the acute evaluation of the device. All experiments are summarized in Table 1.

Table 1. Summary of the 3 Animal Experiments

Number	Body weight, kg	Test Duration, h	Mean Rotational Speed, rpm	Mean Aortic Pressure, mm Hg	Outcome
Pig 1	92	3	2192 ± 338	101 ± 21	Electively terminated
Pig 2	83	4	2085 ± 287	93 ± 12	Electively terminated
Pig 3	77	6	2382 ± 283	85 ± 21	Electively terminated

Abbreviations: rpm, revolutions per minute

During the hemodynamic measurements, the mean heart rate, mean arterial pressure, pulmonary artery pressure, and aortic pressure were within normal ranges. A minimum pump flow of 1.5 L/min was obtained, with rotational speed of 1500 rpm corresponding to aortic pressure of 60 mm Hg. Maximum pump flow of 3.6 L/min was obtained at 2800 rpm when aortic pressure was 110 mm Hg. For the 3 animal experiments, the average pump flow was 2.5 ± 0.6 L/min.

Hematology and biocompatibility

Table 2 summarizes the hematologic and biochemical data collected in our study. As expected, decreases in red blood cells and hematocrit levels were observed in all pigs after implantation. The hematocrit level was within a normal range for cardiopulmonary bypass conditions.[14] The plasma free hemoglobin levels were lower than 100 mg/dL for all 3 animals, with average plasma free hemoglobin of 67.9 ± 31.2 mg/dL, which is within an adequate range of hemolysis.

Echocardiographic assessment

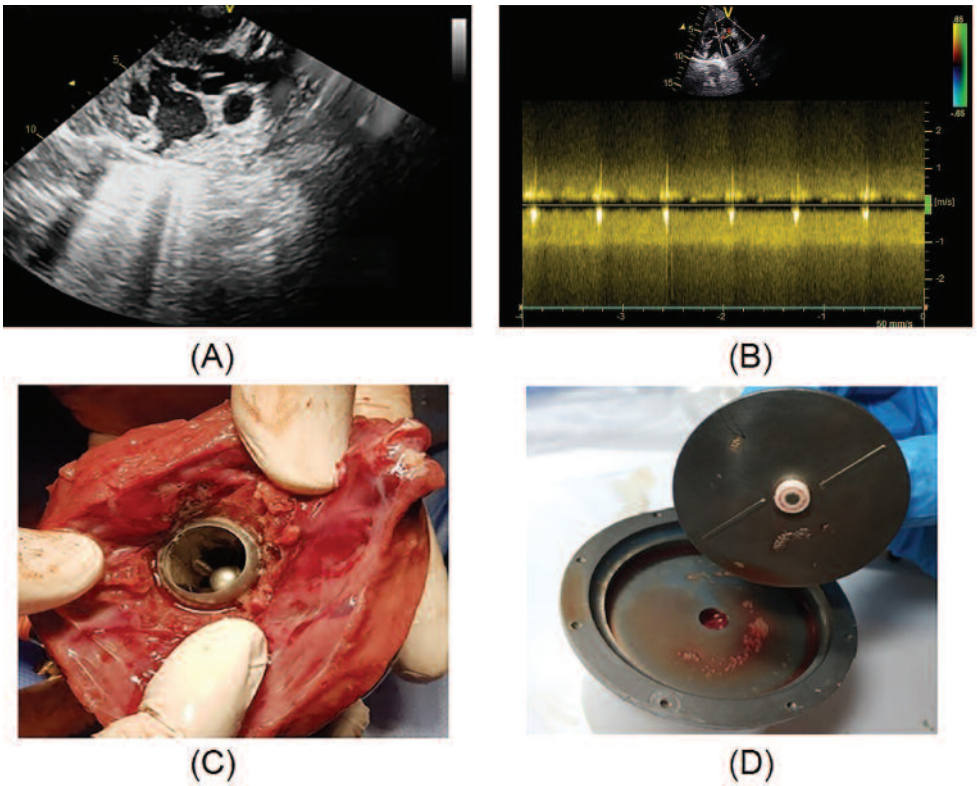
Atrioventricular opening, relative LV and right ventricle sizes, ventricular septal position, inflow cannula position, and flow velocities were assessed after full LVAD support (Figure 3A). Preoperative assessment showed no mitral regurgitation. All

Table 2. Hematologic and Biochemical Data Collected During the In Vivo Experiments

	Mean Collection Time ± Standard Deviation						
	Preoperative	60 min	120 min	180 min	240 min	300 min	360 min
			Hematologic analysis				
WBC, 106/μL	12.2 ± 6.7	7.4 ± 3.4	6.1 ± 2.4	5.5 ± 0.4	6.6 ± 0.2	5.4	6.4
RBC, 106/μL	5.4 ± 1.2	5.7 ± 1.3	5.8 ± 2.2	4.9 ± 1.1	4.4 ± 1.4	5.3	5.1
HGB, g/dL	11.2 ± 2.8	11.7 ± 2.3	11.7 ± 4.0	10.9 ± 2.0	9.7 ± 2.5	10.4	10.2
HCT, %	42.1 ± 4.8	37.5 ± 6.4	35.1 ± 12.9	33.3 ± 5.9	34.1 ± 8.1	33.8	32.4
MCV, fL	64.2 ± 1.5	66.4 ± 3.8	65.9 ± 3.5	67.7 ± 4.8	64.4 ± 1.5	63.3	65.7
MCH, pg	20.1 ± 0.8	20.7 ± 0.6	20.2 ± 0.9	20.1 ± 0.8	19.9 ± 0.5	19.5	19.7
MCHC, g/dL	31.2 ± 0.6	31.2 ± 0.8	30.6 ± 0.3	29.7 ± 0.9	30.8 ± 0.1	30.8	29.9
PLT, 103/μL	151.7 ± 64.8	96.5 ± 9.2	92.3 ± 4.5	86 ± 3.6	88.5 ± 3.5	89	81
RDW-SD, fL	38.1 ± 2.7	40.7 ± 0.1	40.3 ± 2.7	40.3 ± 2.4	37.8 ± 1.1	37	37.8
RDW-CV, %	24.1 ± 1.4	21.8 ± 1.8	20.9 ± 2.5	18.6 ± 0.5	17.5 ± 0.3	16.3	16.1
			Biochemical analysis				
AST, U/L	25.5 ± 6.2	216 ± 5.9	318 ± 41.6	278 ± 19.7	206	133.8	-
ALP, U/L	29 ± 8.5	41 ± 10.2	50 ± 21.2	40 ± 18.2	74.5 ± 25.9	114	29
ALT, U/L	26.7 ± 6	30 ± 1.7	37.7 ± 15.1	23 ± 14.7	17.5 ± 10.6	10	10
BUN, mg/dL	6.7 ± 2.5	5 ± 2.5	7.3 ± 3.2	8.3 ± 3.1	18.5 ± 1.9	34	17
CREA, mg/dL	1 ± 0.2	0.8 ± 0.2	1 ± 0.2	2.6 ± 0.8	6.1 ± 0.8	11.6	5.9
GGT, U/L	40.7 ± 12.1	29 ± 8.3	28 ± 8.9	19 ± 6.6	16 ± 1.7	4	0
TBIL, mg/dL	0.3 ± 0.1	0.6 ± 0.2	0.7 ± 0.3	1 ± 0.3	1.3 ± 0.8	1.9	0.1

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CREA, creatinine; GGT, gamma-glutamyltransferase; HCT, hematocrit; HGB, hemoglobin; LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; PLT, platelet count; RBC, red blood cell; RDW-CV, red cell distribution width-complete volume; RDW-SD, red cell distribution width standard deviation; TBIL, total bilirubin level; WBC, white blood cell

Figure 3. Echocardiographic Assessment and Macroscopic Postexplant Analyses



(A) Epicardial atrioventricular long-axis view shows mitral valve, left ventricular outflow tract, aortic valve opening, and aortic outflow cannula. **(B)** Continuous wave-Doppler flow pattern obtained on aortic graft flow. **(C)** Position of pump inside the left ventricle apex. **(D)** Postoperative pump inspection after the first experiment.

pumps were well positioned inside the LV apex as verified by epicardial echocardiography. Pumps were not touching the septum or free wall of the LV.

We also compared the preoperative versus postoperative LV end-diastolic dimensions at different pump speeds as a clinical measurement of the degree

of LVAD-mediated LV unloading. The reduction of dimensions corresponded well with the increased pump speed, indicating effective unloading of the LV. We observed no acute severe right ventricle dysfunction or tricuspid regurgitation induced by an excessive LVAD pump speed.

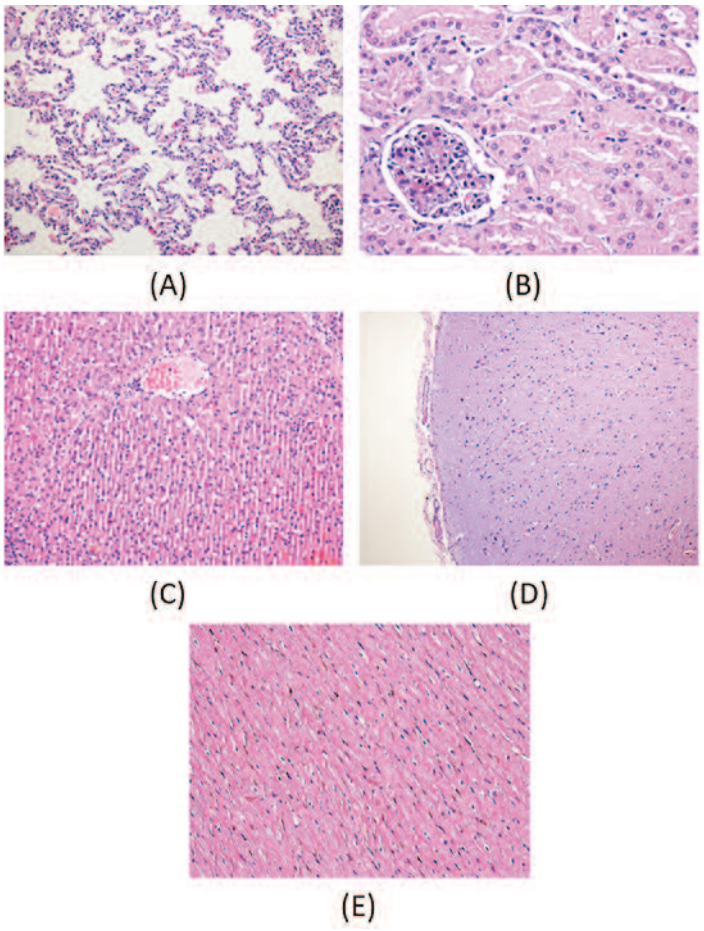
Macroscopic postexplant analyses

After each pig experiment, the iHeart VAD was explanted, disassembled, and visually inspected. The position of the pump inside the LV apex, the pump inlet, outflow grafts, and the aorta were also inspected (Figure 3C). The pump housing and impeller were carefully checked for thrombus formation. The disassembled iHeart VAD indicated no sign of thrombus formation on the blood contacting surface including the bearing zone (Figure 3D). Moreover, no residual tissue was observed inside the pump geometry and outflow graft.

Histopathologic evaluation

Hematoxylin and eosin-stained sections of heart, lung, kidney, liver, and brain tissues were examined, and representative microphotographs were obtained (Figure 4). Overall, there were no significant changes with regard to early or late ischemia in the form of ballooning degeneration, cellular swelling, or vacuolar change of the cytoplasms in most of the tissues. Some of the renal tubular cells showed mild cytoplasmic surface blebbing, but no eosinophilia or marked swelling of the cells was observed. Sections of the myocardium showed no significant necrosis, but slight eosinophilia of scattered myocardial cells was noted. Other organ samples, including brain, lung, and liver, showed no histologically discernible changes attributable to ischemia. No tissue samples showed microvascular or macrovascular thrombi. The tissues were free of inflammatory infiltration. Tissue results were similar for all 3 experimental animals.

Figure 4. Histologic Sections of Representative Tissues From Pig 2



(A) Lung (×200). **(B)** Kidney (×400). **(C)** Liver (×200). **(D)** Brain (×200). **(E)** Heart (×200). Hematoxylin and eosin stain was used.

Discussion

In recent years, implantable LVADs have been increasingly utilized for patients with end-stage heart failure.[9,15] Although the incidence of end-stage heart failure is rapidly growing in Turkey, the number of donors remains limited. The Ministry of Health of Turkey has provided an insurance reimbursement for implantable LVADs since 2012, but they have had to rely on imported LVADs. Since 2014, the development of a novel LVAD has been pushed forward to achieve a highly durable, hemocompatible, and low-cost clinical device in Turkey. Comprehensive studies, including design optimization, computational analyses, and in vitro performance testing, have been ongoing for the iHeart VAD. After satisfactory in silico and in vitro test results were achieved, an in vivo animal study was performed for the first time in Turkey. In the present study, we investigated the iHeart VAD using 3 pig models and demonstrated promising hemodynamic results of 1.5 to 3.6 L/min flow rate and 60 to 110 mm Hg aortic pressure at rotational speeds of 1500 to 2800 rpm. The pump flow rate was appropriately adjusted by the rotational speed based on the pump characteristic curve. Necropsy results of the pigs revealed that there were no infarcts in the heart, lung, liver, brain, and kidney.

In this acute animal study, we also evaluated hemolysis and thrombosis inside the pump flow as a method to investigate shear stress-induced trauma to erythrocytes and platelets. No thrombus formation was observed inside the pump, graft, or heart. In addition, we observed no evidence of macrovascular or microvascular thrombi in any of the examined tissues. However, pump thrombus results related to chronic complications, such as bleeding, infection, and anticoagulation agents, were not evaluated in this study. It is clear that histologic changes due to tissue hypoxia are difficult to detect at such short durations of perfusion. The determination of histopathologic changes, as well as the use of other methods to recognize hypoxia and thrombus formation, must be performed in the future to detect tissue changes in long-term experiments.

Our biochemical results indicated temporary liver dysfunction after 2 hours, which was determined to be due to hypotension. During surgery, sudden decreases in peripheral resistance can be observed depending on the anesthesia dosing. Moreover, rapid hypovolemia could trigger hypoperfusion, especially if there is an inadequate fluid replacement. These factors can temporarily cause liver dysfunction. However, no histopathologic changes were identified in the liver, which confirmed that the dysfunction was reversible. Our biochemical analyses showed a temporary/reversible kidney dysfunction due to the blood urea nitrogen content. Similarly, the increase in creatinine content declined at the end of our experiment, indicating a reversible kidney dysfunction due to temporary acute damage. Hemoglobin levels were stable during the experiment, and the extent of hemolysis was in the normal range. In summary, the device demonstrated adequate biocompatibility characteristics in the pig model.

Acute animal models have served as an initial in vivo evaluation of blood pumps before long-term experiments are conducted in a chronic setting.[16-18] Our acute experiments investigated in vivo pump performance during the surgical procedure, analyzed the anatomic fitting and inflow cannula configuration, and evaluated cardiac output, short-term biocompatibility, hemodynamic efficiency, and end-organ effects. Our results showed that the iHeart VAD can be reliable and adequate for long-term animal studies. Further long-term experiments (2-week and 30-day experiments) are planned to evaluate chronic problems of long-term VAD therapy that are seen clinically, such as infection, bleeding complications, and device malfunctions.

In general, the use of blood from several species such as calves, sheep, and pigs is appropriate for the purpose of animal testing. However, blood trauma mechanisms differ depending on the species, with differences also shown with regard to blood collection and blood handling methods.[19] Many researchers have utilized sheep to test VADs, but pigs were chosen for our initial in vivo experiments because of their ease of availability for research. Moreover, the properties of porcine blood have been described to be similar to human blood with regard to cardiovascular and hematologic behavior.[19,20] The interpretation of animal data can be also limited due to subject variabilities and species differences.[21] However, our present study can be considered as a useful addition to insight about pigs as a model for testing of VADs. Testing a VAD on a normal heart is a limitation that will be addressed in future experiments by developing a heart failure model on test animals.

Conclusions

The first LVAD developed in Turkey, the iHeart VAD, maintained adequate circulatory support while providing good biocompatibility in a short-term pig model. The objective of this study was to conduct a nonclinical evaluation of the final prototype regarding its biocompatibility, performance, and anatomic fitting in a pig model. In this initial evaluation in 3 pigs, the Istanbul heart VAD (iHeart VAD) demonstrated promising results based on the circulatory support, anatomic fitting, and blood-handling characteristics, including hemolysis / thrombus. Important factors and limitations remain that could have affected the results of the in vivo model. Therefore, further acute studies and chronic vivo studies are still needed.

References

1. Braunwald E. The war against heart failure: the Lancet lecture. *Lancet*. 2015;385(9970):812-824.
2. Kishimoto S, Takewa Y, Tsukiya T, et al. Novel temporary left ventricular assist system with hydrodynamically levitated bearing pump for bridge to decision: initial preclinical assessment in a goat model. *J Artif Organs*. 2018;21(1):23-30.
3. General Directorate of Health Research. *Health Statistic Year Book*. Republic of Turkey: Ministry of Health; 2016.
4. Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med*. 2009;361(23):2241-2251.
5. Khan TI, Sheh Zad H, Lazoglu I, Yalcin O. Development of a novel shrouded impeller pediatric blood pump. *J Artif Organs*. 2018;21(2):142-149.
6. Kervan U, Unal EU, Sert DE, Pac M. HeartWare Left ventricular assist device implantation combined with surgical ventricular reconstruction. *Exp Clin Transplant*. 2019;17(2):278-280.
7. Kemaloglu C, Ozcobanoglu S, Koksel U, et al. Extracorporeal membrane oxygenation therapy-assisted cardiopulmonary resuscitation and successful bridging to cardiac retransplant for cardiac allograft vasculopathy. *Exp Clin Transplant*. Epub 2018 June 28. doi: 10.6002/ect.2017.0336.
8. Brenner P, Wirth TJ, Liebermann A, et al. First biventricular Jarvik 2000 implants (retroauricular version) via a median sternotomy. *Exp Clin Transplant*. 2016;14(2):215-223.
9. Chimanji N, Kilic A, Hasan A, Higgins RS, Whitson BA, Kilic A. Institutional cost comparison between heart transplants and left ventricular assist device implantations. *Exp Clin Transplant*. 2016;14(6):656-659.
10. Rodriguez LE, Suarez EE, Loebe M, Bruckner BA. Ventricular assist devices (VAD) therapy: new technology, new hope? *Methodist Debakey Cardiovasc J*. 2013;9(1):32-37.
11. Xie A, Phan K, Yan TD. Durability of continuous-flow left ventricular assist devices: a systematic review. *Ann Cardiothorac Surg*. 2014;3(6):547-556.
12. Kucukaksu DS, Sener E, Undar A, Noon GP, Tasdemir O. First Turkish experience with the MicroMed DeBakey VAD. *Tex Heart Inst J*. 2003;30(2):114-120.
13. Demir O, Biyikli E, Lazoglu I, Kucukaksu S. Design of a centrifugal blood pump: Heart Turcica Centrifugal. *Artif Organs*. 2011;35(7): 720-725.
14. Tsukiya T, Mizuno T, Takewa Y, Tatsumi E, Taenaka Y. Preclinical study of a novel hydrodynamically levitated centrifugal pump for long-term cardiopulmonary support: In vivo performance during percutaneous cardiopulmonary support. *J Artif Organs*. 2015;18(4): 300-306.
15. Kirklin JK, Pagani FD, Kormos RL, et al. Eighth annual INTERMACS report: Special focus on framing the impact of adverse events. *J Heart Lung Transplant*. 2017;36(10):1080-1086.
16. Fumoto H, Horvath DJ, Rao S, et al. In vivo acute performance of the Cleveland Clinic self-regulating, continuous-flow total artificial heart. *J Heart Lung Transplant*. 2010;29(1):21-26.
17. Ootaki Y, Kamohara K, Akiyama M, et al. Initial in vivo evaluation of the DexAide right ventricular assist device. *ASAIO J*. 2005;51(6): 739-742.
18. Slaughter MS, Giridharan GA, Tamez D, et al. Transapical miniaturized ventricular assist device: design and initial testing. *J Thorac Cardiovasc Surg*. 2011;142(3):668-674.
19. Klaus S, Korfer S, Mottaghy K, Reul H, Glasmacher B. In vitro blood damage by high shear flow: human versus porcine blood. *Int J Artif Organs*. 2002;25(4):306-312.
20. Paul R, Apel J, Klaus S, Schugner F, Schwindke P, Reul H. Shear stress related blood damage in laminar couette flow. *Artif Organs*. 2003;27(6):517-529.
21. Lu Q, Hofferbert BV, Koo G, Malinauskas RA. In vitro shear stress-induced platelet activation: sensitivity of human and bovine blood. *Artif Organs*. 2013;37(10):894-903.