Alternative approach for right ventricular failure after left ventricular assist device placement in animal model†

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Abstract

OBJECTIVES: Right ventricular failure after left ventricular assist device (LVAD) implantation is associated with high mortality. This study was designed to evaluate the effectiveness of an atrial septostomy with a membrane oxygenator incorporated in an LVAD as a novel approach for right ventricular failure after LVAD implantation.

METHODS: The outflow and inflow cannulae were placed in the carotid artery and left ventricular apex, respectively. A centrifugal pump and an oxygenator were sequentially placed between the inflow and outflow cannulae in seven anesthetized goats. While right ventricular failure was induced by pulmonary artery banding, a balloon atrial septostomy was performed using a 19-mm balloon catheter under echocardiographic guidance. We investigated the effects of the interatrial shunt on LVAD flow and haemodynamics.

RESULTS: Development of right ventricular failure decreased LVAD flow (2.7 ± 0.6–0.9 ± 0.6 l/min), causing a state of shock [mean arterial pressure (MAP) of 41 ± 12 mmHg]. Following a balloon atrial septostomy, LVAD flow and MAP were significantly improved to 2.7 ± 0.4 l/min (P < 0.001) and 53 ± 18 mmHg (P = 0.006), respectively, while right atrial pressure decreased from 18 ± 5 to 15 ± 5 mmHg (P = 0.001). Furthermore, arterial blood oxygenation was maintained by the membrane oxygenator incorporated in the LVAD.

CONCLUSIONS: In the present model of right ventricular failure after LVAD implantation, LVAD flow was significantly increased and haemodynamics improved without compromising systemic oxygenation by the use of an interatrial shunt and a membrane oxygenator incorporated in the LVAD. Our results indicate that this novel approach may be less invasive for a right ventricular failure after LVAD implantation.

Keywords: Circulatory assist device • Animal model • Heart failure • extracorporeal membrane oxygenation

INTRODUCTION

Right ventricular failure is a critical complication after implantation of a left ventricular assist device (LVAD) and causes a significant increase in mortality [1, 2]. Although the use of a right ventricular assist device (RVAD) declined after the introduction of the implantable continuous flow pump, along with the use of inhaled nitric oxide and phosphodiesterase inhibitors to lower pulmonary vascular resistance and restore right ventricular function in patients with LVAD [3, 4], 13% of patients still required an RVAD in addition to LVAD implantation [5]. Since additional implantation of an RVAD involves further surgical stress, the prognosis of LVAD patients who require an RVAD is poor [6]. Management of two different assist devices creates additional complications, including a two-fold increase in infections, a three-fold increase in neurological problems and a four-fold increase in bleeding complications [5]. In order to improve the outcome of the patients who required RVAD after LVAD implantation, less invasive right ventricular supports including a pulsatile catheter pump [7] and a percutaneous RVAD with CentriMag [8] were tested clinically. However, implantation of the pulsatile catheter pump required a thoracotomy and percutaneous RVAD required placement of a relatively long cannula from the internal jugular vein to the pulmonary artery and from the femoral vein to the right atrium, which may facilitate thrombus formation around cannulae [9].

Balloon atrial septostomy is a time-tested less invasive procedure that can be performed in a percutaneous manner and has been successfully utilized for congenital cardiac anomalies for mixing deoxygenated blood in the atrium [10]. This procedure has also been used for right ventricular failure in patients with primary pulmonary hypertension [11–13]. The concept aims at creating a ‘safety valve’ by unloading the right ventricle and increasing left ventricular preload and output. Its validity was demonstrated in a clinical setting [11–13] as well as an animal study [14]. However, this concept has never been applied in case of right ventricular

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failure after LVAD implantation. The aim of the present study was to elucidate the effectiveness of an atrial septostomy with a membrane oxygenator incorporated in LVAD as a novel approach for right ventricular failure after LVAD implantation in an acute animal model.

MATERIALS AND METHODS

Surgical preparation

All animals received humane care in compliance with the ‘Principles of Laboratory Animal Care’ formulated by the National Society for Medical Research, and the ‘Guide for the Care and Use of Laboratory Animals,’ prepared by the National Academy of Science and published by the National Institute of Health (NIH Publication 86–23, revised 1985). In addition, all experiments were approved by the Animal Experiment Ethics Committee of the National Cerebral and Cardiovascular Center Research Institute and performed within the guidelines prepared with the guidance of veterinarians.

Seven adult goats with a mean weight of 59 ± 8 kg (range, 54–70 kg) were used. The animals were anesthetized with an intramuscular injection of ketamine (Daiichi Sankyo Co. Ltd, Tokyo, Japan) (10 mg/kg) and inhaled isoflurane (Air Water, Inc., Osaka, Japan). After a tracheotomy, the animals were ventilated with breathing frequency set between 10 and 20/min and a maximum airway pressure not greater than 30 mmHg. In a right decubitus position, 1 mg/kg of atracurium (Astellas Pharma, Inc., Tokyo, Japan) was intravenously administered prior to the skin incision and general anesthesia was maintained by inhaled isoflurane. After a general anesthetic condition mimicking right ventricular failure.

Following systemic heparinization (300 U/kg), an apical sewing ring was sutured with eight buttressed sutures. Inflow (Nipro inflow cannula 24 F; Nipro, Osaka, Japan) and outflow (Bio-Medicus Femoral cannula 21 F; Medtronic, Minneapolis, MN, USA) cannulae were placed in the left ventricular apex and left carotid artery, respectively, and connected to a centrifugal pump (Jostra RotaFlow; Maquet Cardiopulmonary AG, Hirrlingen, Germany), in which an extracorporeal membrane oxygenator (Biocube 6000; Nipro, Osaka, Japan) was incorporated between the centrifugal pump and outflow cannula, as shown in Fig.1. LVAD flow was measured using an ultrasonic flow meter (TS420; Transonic Systems, Inc., Ithaca, NY, USA) placed on the outflow cannula. The rotational speed of the pump was increased to between 2200 and 3300 rpm until maximum effective flow was obtained, and then maintained at nearly constant speed during the experiment. An 80% fraction of inspiratory oxygen with a 1:1 gas-to-blood flow ratio was continuously delivered to the membrane oxygenator during the experiment.

After the LVAD was placed, the proximal pulmonary trunk was encircled by a 1-cm wide Teflon felt for pulmonary artery banding. By tightening the Teflon felt under flow monitoring, pulmonary artery flow was regulated at approximately 1–2 l/min. A marking stitch was made on the Teflon felt to provide a constant experimental condition mimicking right ventricular failure.

Subsequently, a purse-string suture with tourniquet was placed at the left atrial wall to control bleeding. Then, the atrial septum was identified by direct echocardiography (Vivid 7 Pro; GE Medical Systems, Inc., Raleigh, NC, USA). Under echocardiographic guidance, the atrial septum was punctured using an 8-F introducer via the left atrial wall. A 5-F Miller balloon atrial septostomy catheter (Edwards Lifesciences Japan, Tokyo, Japan) was advanced into the right atrium cavity through the introducer using the

![Figure 1: Schematic drawing of an experimental model. Inflow and outflow cannulae are placed in the left ventricular apex and left carotid artery, respectively and the centrifugal pump and membrane oxygenator are sequentially placed between the inflow and outflow cannulae. After left ventricular support is initiated, right ventricular failure is induced by pulmonary artery banding (A). After the interatrial shunt is opened, deoxygenated blood is drained from the right atrium to the left atrium and ventricle and oxygenated by a membrane oxygenator in the circuit (B).](https://academic.oup.com/ejcts/article-abstract/48/1/98/415973)
Seldinger technique. After the balloon was inflated to 19 mm in size with a 4-ml infusion of saline, the catheter was sharply withdrawn into the left atrium (Video 1). Successful creation of the shunt by balloon atrial septostomy was confirmed by echocardiographic findings.

Experimental protocol and data measurements

Following shunt creation, the shunt was obstructed with an inflated occlusion balloon (Nipro occlusion balloon catheter; Nipro, Osaka, Japan) (Video 2). After confirming that the shunt was totally occluded by the balloon catheter from echocardiographic findings, LVAD pump flow, pulmonary artery flow, arterial pressure, pulmonary artery pressure and both left and right atrial pressures (RAPs) were measured for 30 s using Lab Chart (AD Instruments Pty Ltd, Bella Vista, Australia) as ‘baseline’ parameters. After right ventricular failure was induced by tightening the felt strip to a fixed length around the pulmonary artery, the animal was allowed to stabilize for 3 min, then all haemodynamic parameters were measured for 30 s as ‘right ventricular failure with no shunt’ (Fig. 1A). After those measurements, the shunt was opened by deflation of the occlusion balloon, the animal was allowed to stabilize for 3 min, then all haemodynamic parameters were measured again for 30 s as ‘right ventricular failure with a shunt’ (Fig. 1B).

After completion of the haemodynamic measurements, the animals were euthanized by increased anaesthetics, then, after confirming cardiac arrest, the hearts were extirpated for macroscopic observations.

Statistical analysis

Continuous variables are expressed as the mean ± standard deviation and were compared using a paired t-test for paired data. The strength of the association between the two continuous variables was estimated using Pearson’s correlation coefficient. Data were analysed using StatView 5.0 (SAS Institute, Cary, NC, USA) and a probability value of less than 0.05 was considered to be statistically significant.

RESULTS

Haemodynamic effects of pulmonary artery banding are shown in Table 1. Mean pulmonary artery pressure, pulmonary vascular resistance and RAP were significantly increased, while pulmonary artery flow, LVAD flow, mean arterial pressure (MAP) and left atrial pressure were significantly decreased after pulmonary artery banding. Under the condition of right ventricular failure induced by pulmonary artery banding, interatrial shunt was opened and the impacts of interatrial shunting on LVAD flow and haemodynamics were investigated. The interatrial shunt significantly increased LVAD flow and MAP, while RAP was significantly reduced after the interatrial shunt was opened (Fig. 2). There was no significant change in pulmonary artery flow (0.9 ± 0.5 vs 0.7 ± 0.2 l/min, P = 0.309) and pulmonary artery pressure (25 ± 6 vs 24 ± 6 mmHg, P = 0.749) between before and after shunt was opened, while left atrial pressure was significantly increased after the shunt was opened (7 ± 3 vs 12 ± 4 mmHg, P = 0.009).

Blood flow through the shunt was estimated from differences between LVAD flow and pulmonary artery flow when the interatrial shunt was opened, because echocardiography confirmed that the aortic valve was not opened during LVAD support. Therefore, LVAD flow was thought to equal the sum of pulmonary artery flow and shunt flow. Shunt flow was estimated to be 1.9 ± 0.4 l/min, which was 73 ± 8% of LVAD flow and there was significant correlation between the shunt flow and the increase in LVAD flow after the shunt was opened (Fig. 3). However, there was no significant correlation between the shunt flow and the size of the interatrial shunt (correlation coefficient: -0.007, P = 0.9890, Fig. 4).

Because deoxygenated blood coming through the shunt was mixed in the left ventricle and then oxygenated by the membrane oxygenator in the circuit, neither arterial hypoxia, nor acid–base
Table 1: Comparison of haemodynamic parameters between before and after pulmonary artery banding in animals with left ventricular assist device

<table>
<thead>
<tr>
<th>Haemodynamic parameters</th>
<th>Before PAB (n = 7)</th>
<th>After PAB (n = 7)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>67 ± 9</td>
<td>41 ± 12</td>
<td>0.004</td>
</tr>
<tr>
<td>Left atrial pressure (mmHg)</td>
<td>10 ± 2</td>
<td>6 ± 3</td>
<td>0.016</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure (mmHg)</td>
<td>23 ± 2</td>
<td>28 ± 4</td>
<td>0.01</td>
</tr>
<tr>
<td>Right atrial pressure (mmHg)</td>
<td>7 ± 3</td>
<td>14 ± 7</td>
<td>0.022</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (Wood units)</td>
<td>2.7 ± 0.6</td>
<td>9.7 ± 2.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Pulmonary artery flow (l/min)</td>
<td>4.2 ± 1.7</td>
<td>1.5 ± 1.1</td>
<td>0.007</td>
</tr>
<tr>
<td>LVAD flow (l/min)</td>
<td>2.7 ± 0.6</td>
<td>0.9 ± 0.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Pulmonary vascular resistance = (mean pulmonary artery pressure – mean left atrial pressure)/pulmonary artery flow.
LVAD: left ventricular assist device; PAB: pulmonary artery banding.

Figure 2: Haemodynamic effect of interatrial shunt on right ventricular failure (RVF) induced by pulmonary banding. Opening of interatrial shunt significantly increased left ventricular assist device (LVAD) flow (A) and mean arterial pressure (MAP) (B), and decreased right atrial pressure (RAP) (C).

Figure 3: Correlation between interatrial shunt flow and increase in left ventricular assist device (LVAD) flow after balloon atrial septostomy.

Figure 4: There was no significant correlation between interatrial shunt flow and shunt size.
imbalance, nor anaemia due to haemolysis through the shunt was observed during the experiment \( \text{pH} = 7.44 \pm 0.09 \) (7.34–7.54), \( \text{PaO}_2 = 394 \pm 93 \) (310–501) mmHg, \( \text{PaCO}_2 = 30 \pm 7 \) (22–37) mmHg, haemoglobin = 7.4 ± 1.6 (5.8–9.2).

**Macroscopic findings**

We excised the hearts from all animals at the end of the experiment. Macroscopic findings confirmed that each shunt was created in the centre of the fossa ovalis. It was also observed that the mean diameter of the shunts created by the 19-mm balloon septostomy catheter was 9 ± 1 mm (range, 8–12 mm), which was 47% of the balloon size.

**DISCUSSION**

Right ventricular failure has been the leading cause of perioperative mortality after LVAD implantation, and patients who required an RVAD in addition to LVAD implantation had poorer prognosis [15]. Delayed introduction of an RVAD is associated with multiple organ failure resulting in high mortality [16, 17]. Additional RVAD placement requires a re-thoracotomy and increases the risk of bleeding in critically ill patients [5]. In our less invasive approach for right ventricular failure after LVAD placement, we proved that LVAD flow was significantly increased and haemodynamics improved by the use of an interatrial shunt created by balloon atrial septostomy in an animal model of acute right ventricular failure. In clinical settings, our approach can be established by a percutaneous transcatheter procedure without a thoracotomy, and thus right heart support can be introduced without delay either during or after LVAD implantation when signs of right ventricular failure appear.

Since preoperative cardiogenic shock is recognized as a significant risk factor for severe right ventricular failure after LVAD implantation and the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) registry has documented that implantable LVAD use in shock patients has been considerably reduced [5, 6], our approach may be feasible for patients in cardiogenic shock who require right ventricular support after placement of short-term extracorporeal LVAD as a bridge to decision. Long-term support with our system is difficult due to the presence of an oxygenator and a weaning concept is important. In a patient whose pulmonary vascular resistance decreases and right ventricular function recovers during support, interatrial shunt can be temporarily occluded by transcatheter occlusion balloon as reported [18] and the possibility of weaning can be evaluated less invasively. When haemodynamics and pulmonary function are stable during an occlusion test, the shunt can be closed in a percutaneous manner using an atrial septal occluder device and the patient can be shifted to a single LVAD support without a thoracotomy [19].

Creation of an interatrial shunt for right ventricular failure by a balloon atrial septostomy is not a new concept and has been applied for primary pulmonary hypertension [12–14]. A drawback of this concept is the presence of systemic hypoxia when right to left shunting is excessive. Excessive right to left shunting results in severe hypoxia and death in spite of the doubled cardiac output after balloon atrial septostomy for primary pulmonary hypertension [12]. In contrast, deoxygenated shunt blood is oxygenated by an extracorporeal membrane oxygenator connected to the outflow of the LVAD, which enables a high shunt flow (73 ± 8% of LVAD flow) without compromising oxygen delivery with our approach. At this point, our approach may be more beneficial than biventricular assist devices with extracorporeal membrane oxygenation in patients with a pulmonary haemorrhage due to left ventricular failure, because the presence of an interatrial shunt reduces the amount of blood flow passing through the native lung and may provide an environment to repair alveolar tissue damage or prevent the risk of pulmonary haemorrhage [20]. On the other hand, reduced pulmonary blood flow might have a negative impact on systemic blood pressure, which was relatively low (MAP: 53 ± 18 mmHg) in spite of the significantly increased LVAD flow after creation of an interatrial shunt in this experiment. Pulmonary circulation plays a key role in the metabolism of prostaglandin. In chronic animal models using a veno-arterial extracorporeal membrane oxygenator, we previously demonstrated that a reduction in pulmonary blood flow decreased systemic vascular resistance in association with an increase in plasma prostaglandin E2 concentration [21]. We speculate that organ functions can be maintained by relatively low MAP, while pulmonary blood flow is reduced by the interatrial shunt, because we did not observe liver or renal failure in those chronic animal experiments.

Interatrial shunt flow is determined by the size of the shunt, and the differences in pressure and compliance between the right and left atrium, thus a stepwise increase in diameter of the shunt is important to prevent severe hypoxia due to excessive shunting in balloon atrial septostomy [13]. In our experiment, shunt flow was well correlated with the improvement of LVAD flow, whereas it was not correlated with the size of the interatrial shunt. These findings may indicate that the size of the shunt is less important in our model, employing mechanical circulatory support to enhance the ejecting blood from the ventricle, when it is larger than 8 mm in diameter and might explain why even a small atrial septal defect could cause severe hypoxia after LVAD implantation in clinical settings [22].

Although incorporation of an oxygenator in the LVAD system can prevent systemic hypoxia even with a high right-to-left shunt flow, use of such a device may become a disadvantage with our approach. For patients with an extracorporeal LVAD, oxygenation can be attained by incorporating an oxygenator in the circuit as demonstrated in the present study. However, for those with an implanted LVAD, this approach requires some alterations. Camboni et al. demonstrated that both systemic circulation and arterial oxygenation were well maintained by a 10-mm interatrial shunt in combination with a veno-venous extracorporeal membrane oxygenator in an acute animal model of right ventricular failure due to pulmonary hypertension [23]. On the basis of their results, it is considered that an interatrial shunt is applicable for cases with an implantable LVAD by combined use of a veno-venous extracorporeal membrane oxygenator, which can be separately inserted from peripheral veins. Inflammatory response to a membrane oxygenator may be another concern. However, recent advances in technology, especially development of poly-methylpentene for use as a gas exchange membrane, have improved its biocompatibility and reduced red blood cell and platelet transfusion requirements when compared with previously available oxygenator devices [24] and prolonged support is now possible [25]. We consider that use of an interatrial shunt combined with a new generation oxygenator may be a reasonable therapeutic option for right ventricular failure after LVAD implantation.
LIMITATIONS

In the present study, we created a right ventricular failure model with high pulmonary vascular resistance produced by pulmonary artery banding. However, right ventricular failure after LVAD implantation is not always associated with high pulmonary vascular resistance. Accordingly, it will be necessary to conduct further studies with different models to determine whether an interatrial shunt can effectively improve LVAD flow in patients with low pulmonary arterial pressure and high central venous pressure due to poor right ventricular function. In addition, recovery of right ventricular function was not evaluated in this study. As our approach requiring an oxygenator is feasible for short-term use, recovery of right ventricular functions is crucial. Therefore, prior to clinical application, it is necessary to establish a chronic animal model in which pulmonary vascular resistance can be chemically changed in order to investigate the impact of the present approach on right ventricular recovery.

CONCLUSION

In the present model of right ventricular failure after LVAD implantation, we found that use of an interatrial shunt combined with a membrane oxygenator significantly increased LVAD flow and improved haemodynamics without compromising systemic oxygenation. Since an interatrial shunt can be created and closed in a minimally invasive manner using a transcatheter procedure, we consider that the present approach represents a reasonable less invasive therapeutic strategy for patients with severe right ventricular failure after LVAD implantation.

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