The Effect of Intermittent Low Speed Mode Upon Aortic Valve Opening in Calves Supported With a Jarvik 2000 Axial Flow Device

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We assessed the effects of an axial flow left ventricular assist device (LVAD) upon aortic valve opening, pump outflow, and biologic and hematologic parameters when operated in intermittent low speed (ILS) mode. An ILS controller equipped Jarvik 2000 LVAD was implanted in six calves. Pump speed was maintained at 10,000 rpm, and pump outflow was measured throughout the study period (71 ± 6 days [mean ± SD]). Hematologic and biochemical parameters were analyzed daily for the first 10 days, weekly for the first month, and biweekly thereafter to monitor for kidney or liver dysfunction, hemolysis, bleeding, or infection. Before study termination, esmolol hydrochloride was infused to induce low cardiac output and totally impair aortic valve opening. Radiopaque cineaortography was performed over 30 second intervals (10 seconds before, 10 seconds during, and 10 seconds immediately after ILS controller activation) to assess the effect of ILS mode upon aortic valve opening. After study termination, major end organs and the major vascular tree were removed and examined macroscopically and histologically for thrombus formation and infarction; the aortic valve was examined for thickening and fusion. All pumps were explanted and examined for thrombus formation. All six calves recovered without surgical or mechanical complications. Hematologic and biochemical parameters did not change significantly between baseline and study termination. The aortic valve successfully opened when ILS mode was activated, even under low cardiac output conditions. No thrombus was detected in the major end organs and vascular tree, except for some small renal infarcts in three calves that did not affect renal function. These results indicate that operating an axial flow LVAD in ILS mode allows aortic valve opening and aortic root washout. *ASAIO Journal* 2005; 51: 139–143.

The left ventricular assist device (LVAD) is currently used as a bridge to transplantation,[1] a bridge to recovery,[2] or destination therapy[3] in patients with end-stage heart failure refractory to conventional medical and surgical treatments. Despite technologic advances, prolonged use of LVADs has raised concerns about their long-term effects upon flow properties and end-organ physiology, such as disturbances in aortic valve motion and related complications.[4–6]

The Jarvik 2000 (Jarvik Heart, Inc., New York, NY), designed for temporary or permanent circulatory support in severe heart failure, is an axial flow LVAD that provides continuous flow from the left ventricle to the aorta.[7] Axial flow devices operating at higher speeds may cause extensive left ventricular (LV) unloading, resulting in reduced wall stresses, myocardial contractility, and cardiac output (CO).[8,9] The resulting reduction of forward ejection across the aortic valve and increase of aortic diastolic pressure because of increased pump outflow into the aorta may impair aortic valve opening and cause aortic flow stagnation, which may in turn cause thrombosis or fusion of the aortic valve during long-term support.[7] To prevent hemostagnation in the aortic valve, the pump speed may be lowered so as to reduce unloading and allow for some degree of valve opening to wash out the aortic root.[7,10] However, in some cases of severe heart failure, decreased native heart function results in diminished or totally impaired aortic valve ejection, even at lower pump speeds, and makes such adjustment impossible.[11]

To alleviate this problem, an intermittent low speed (ILS) controller for the Jarvik 2000 has been designed and tested in a calf model. In the present study, we assessed the effects of the controller upon aortic valve opening, pump outflow, biochemical and hematologic parameters, and end-organ physiology in six calves supported with Jarvik 2000 pumps.

Materials and Methods

Device

The Jarvik 2000, a 90 g, 20 cc, intraventricular axial flow pump, is capable of augmenting the flow of the natural heart by up to 6 L/min. Total cardiac output measured in the pulmonary artery reaches 8–10 L/min in some cases. When the pump is equipped with a regular controller (as opposed to the ILS controller used in the present study), the pump speed is set manually in the range of 8,000–12,000 rpm. With the natural heart contracting, the device typically produces pulsatile flow instantaneously; this flow varies by as much as 5–8 L/min over the cardiac cycle. Typically, the pulsatile pressure is approximately 15–25 mm Hg but may be lower in patients with very poor natural ventricular function or in patients whose pumps operate at speeds high enough to capture the full cardiac

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output and prevent ejection through the aortic valve. The ILS controller, which is also set manually in the range of 8,000–12,000 rpm, is identical to the regular controller with the exception of the ILS function.

Animal Model

Experiments were conducted on six Corriente crossbred calves, each weighing between 108 and 135 kg. All animals received humane care in compliance with the *Principles of Laboratory Animal Care* (National Society of Medical Research) and the *Guide for the Care and Use of Laboratory Animals* (National Institutes of Health publication no. 85–23, revised 1996). Our institution's Animal Care and Use Committee approved all protocols used in the present study. All animals were given intravenous warfarin (5 mg/day) beginning 3 days before surgery.

Anesthesia and Surgical Preparation

A standard anesthesia protocol was followed. Food was withheld from each calf 12 hours before induction of anesthesia. A 12 Fr, triple lumen, venous catheter was inserted percutaneously into the right external jugular vein. Anesthesia was induced with intravenous diazepam (0.1 mg/kg) and ketamine (5–10 mg/kg). A cuffed endotracheal tube and an orogastric decompression tube were inserted. General anesthesia was maintained with isoflurane (1.0–3.0%) in oxygen (40–100%). The anesthetized calf was then placed on the operating table in the right lateral decubitus position in preparation for a left thoracotomy and left neck cutdown.

Operative Technique

A detailed description of the surgical implantation procedure has been published elsewhere.[9] Briefly, a left thoracotomy was performed in the fifth intercostal space, and the fifth rib was removed. An arterial pressure catheter was placed into the left internal thoracic artery (LIMA). The left carotid artery and left jugular vein were exposed for cardiopulmonary bypass (CPB) cannulation. After heparinization (300 units/kg), a 16 mm Dacron outflow graft was anastomosed to the descending thoracic aorta in end to side fashion with a 5–0 propylene suture using a partially occluding vascular clamp. After partial CPB was initiated, a silicone/polyester sewing cuff was sewn to the LV apex with pledgeted, coated, braided, 2–0 polyester mattress sutures. The LV apex of the beating heart was cored with a circular knife. The Jarvik was inserted into the LV apex and secured with cotton tape and band(s) tied around the cuff. After the pump was secured, the outflow graft was connected to the pump outflow and was secured with two pieces of cotton tape. The pump and graft were deaired using an 18 gauge needle, and the resulting needle hole was repaired with 5–0 propylene sutures. A 16 mm ultrasonic flow probe (Transonics Inc., Ithaca, NY) was placed on the outflow graft and tunneled out from the eighth intercostal space. After removal of the CPB cannulae, the arterial pressure catheter was removed from the LIMA and transferred to the left carotid artery for postoperative follow up. A #40 chest tube was placed into the left pleural space, and the incisions were closed in standard fashion.

Postoperative Care and Follow Up

Postoperatively, each calf was transported to the recovery room and weaned from the ventilator as soon as it regained the chewing reflex. Aortic pressure (AoP), heart rate, temperature, respiration rate, appetite, and pump flow were monitored hourly. All animals received a low dose heparin infusion (8–10 U/kg/hour) for 48 hours. After removal of the chest tube and AoP line 1–3 days after surgery, the calves were examined daily by veterinarians. Intravenous antibiotic therapy (cefazolin, 3 g/day) was continued until all intravenous catheters were removed 7–10 days after surgery. Warfarin was administered orally to all calves until study termination to maintain an international normalized ratio (INR) between 2.0 and 4.0. The pump speed was maintained at 10,000 rpm throughout the study.

Hematologic and biochemical parameters were analyzed daily for the first 10 days, weekly for the first month, and biweekly thereafter to monitor for signs of kidney or liver dysfunction, hemolysis, bleeding, or infection.

At the end of the 10^{th} week, the calves were fully heparinized (300 units/kg), and a Swan-Ganz catheter was placed to measure cardiac output. Esmolol hydrochloride infusion was initiated to induce severe biventricular heart failure. Pump speed was then increased to 12,000 rpm to test aortic valve opening under conditions of low cardiac output and maximal continuous flow retrograde through the aortic valve. An 8 Fr introducer was inserted into the left carotid artery, and a 6 Fr pig tail catheter was advanced into the aortic root. Radiopaque cineaortography was performed with an OEC 9800 Plus Cardiac C-arm fluoroscope (General Electric) over 30 second intervals (10 seconds before, 10 seconds during, and 10 seconds after ILS controller activation) to assess the effect of ILS upon aortic valve opening. Then, all calves were euthanized. Complete autopsies were performed and documented photographically. The heart, brain, lungs, kidneys, liver, spleen, and major vascular tree were removed and examined macroscopically and histologically for signs of thrombus formation and infarction; the aortic valve was examined for signs of thickening and fusion. All pumps were explanted and grossly examined for thrombus formation.

Results

The Jarvik 2000 axial flow LVAD was successfully implanted in all six calves, and all calves recovered from the implantation procedure without surgical or mechanical (device) complications. The early postoperative and follow up period (71 ± 6 days [mean ± SD]) was uneventful. All calves were killed at study termination according to the approved protocol. The mean pump flow throughout the study was 4.1 ± 0.2 L/min.

Hematologic and biochemical parameters are shown in **Tables 1 and 2**. There was no significant change in hematologic parameters from baseline to study termination, except for an elevation in prothrombin time (PT) and INR in the first postoperative week that may have been related to the preoperative intravenous administration of warfarin. Levels of serum glutamic oxaloacetic transaminase (SGOT), lactate dehydrogenase (LDH), and creatine kinase (CK) increased after surgery but returned to normal limits within 3–7 days after surgery.

Table 1. Preoperative (Baseline) and Postoperative Hematologic Parameters[a]

		Postoperative Day			
	Baseline	1	7	28	60
WBC ($\times$ 1,000/mm^3)	11.4 ± 2.1	13.6 ± 2	9.6 ± 2.4	9.3 ± 2.5	9.8 ± 3.1
RBC ($\times$ 1,000,000/mm^3)	9.6 ± 1.2	8.5 ± 0.7	6.5 ± 0.9	7.6 ± 1	7.2 ± 1.1
Hemoglobin (gm/dl)	11.5 ± 1.1	10.7 ± 0.9	8.4 ± 1.3	10.8 ± 1.1	10.8 ± 1.4
Hematocrit (%)	33 ± 2	28 ± 2	23 ± 3	30 ± 3	31 ± 4
Platelets ($\times$ 1,000/mm^3)	413 ± 150	231 ± 70	672 ± 167	223 ± 86	249 ± 184
Neutrophils (%)	18 ± 4	55 ± 8	31 ± 12	43 ± 11	37 ± 15
Lymphocytes (%)	73 ± 13	44 ± 11	65 ± 13	53 ± 16	60 ± 17
PT (sec)	14 ± 1	24 ± 2	21 ± 2	16 ± 1	16 ± 2
INR	1.7 ± 0.3	4.9 ± 0.4	4.1 ± 0.3	2 ± 0.2	1.9 ± 0.3
PTT (sec)	32 ± 3	40 ± 4	49 ± 4	37 ± 3	44 ± 6
Fibrinogen (mg/dl)	516 ± 120	456 ± 98	672 ± 116	443 ± 99	506 ± 106
Plasma free Hgb (mg/dl)	5 ± 0.6	2.8 ± 0.1	2 ± 0.2	2.1 ± 0.3	2.1 ± 0.2

WBC, white blood cells; RBC, red blood cells; PT, prothrombin time; INR, international normalized ratio; PTT, partial thromboplastin time; Plasma free Hgb, plasma free hemoglobin.
[a] Values are mean ± SD.

Esmolol hydrochloride infusion immediately affected several hemodynamic parameters. The heart rate decreased from 75 ± 5 bpm at baseline to 45 ± 6 bpm. Mean AoP decreased from 103 ± 5 mm Hg at baseline to 60 ± 5 mm Hg. Mean systolic pulmonary artery pressure increased from 20 ± 4 mm Hg at baseline to 45 ± 3 mm Hg. Mean cardiac output, as measured by the Swan-Ganz catheter, decreased from 16.6 ± 3 L/min at baseline to 8.2 ± 2.1 L/min. The pump's contribution to native cardiac output increased from 25 ± 5% at baseline to 75 ± 8% in the low cardiac output state. The flow in the vascular bed was totally nonpulsatile, and the aortic valve remained closed in all calves. Radiopaque cineaortography demonstrated that the aortic valve was open during ILS controller activation (10 seconds) (**Figure 1B**) and remained closed until the next activation (50 seconds) in all calves (**Figures 1A and 1C**).

Upon macroscopic examination, two pumps had an organized thrombus on their outer surfaces. In all pumps but one, small, organized, red and white thrombus rings were seen on the inflow and outflow bearings; such rings are frequently seen in both animal and clinical studies and do not negatively affect pump function or increase the risk of thromboembolism. The inner surfaces of the outflow grafts were evenly covered with glistening white neointima and had no organized thrombus formations. Aortic valve leaflet coaptation was normal, and no thrombus, thickening, or signs of regurgitation were detected. Multiple large infarcts were seen in the kidneys of two calves; however, renal function in these two calves remained normal throughout the study, and there was no gross evidence of either acute or chronic infarcts in any other explanted organs. Clinically, there was no evidence of neurologic deficit in any of the calves.

Discussion

Long-term patient outcome after conventional pulsatile LVAD implantation is adversely affected by infection, bleeding, and thromboembolism.[12] These complications may be

Table 2. Preoperative (Baseline) and Postoperative Biologic Parameters[a]

		Postoperative Day			
	Baseline	1	7	28	60
BUN (mg/dl)	11 ± 1.6	5.4 ± 1.1	7.8 ± 3.4	10 ± 2.9	9.3 ± 3.2
Glucose (mg/dl)	105 ± 7.2	107 ± 10.7	105 ± 9.6	98 ± 8.1	94 ± 9.2
Creatinine (mg/dl)	0.8 ± 0.2	0.6 ± 0.2	0.6 ± 0.1	0.6 ± 0.1	0.7 ± 0.2
SGPT (IU/L)	18 ± 2	23 ± 4	7 ± 1	13 ± 3	13 ± 3
SGOT (IU/L)	48 ± 2	184 ± 6	199 ± 7	57 ± 3	46 ± 4
Total protein (g/dl)	6.9 ± 0.4	5.1 ± 0.3	5.9 ± 0.3	6.3 ± 0.4	6.8 ± 0.4
Albumin (g/dl)	3.7 ± 0.3	3 ± 0.2	3.1 ± 0.1	3.5 ± 0.2	3.8 ± 0.2
Direct bilirubin (mg/dl)	0.08 ± 0.01	0.14 ± 0.01	0.18 ± 0.02	0.1 ± 0.01	0.1 ± 0.02
Total bilirubin (mg/dl)	0.1 ± 0.01	0.2 ± 0.02	0.12 ± 0.01	0.1 ± 0.02	0.16 ± 0.02
GGT (IU/L)	19 ± 2	13 ± 4	14 ± 3	17 ± 3	15 ± 3
LDH (IU/L)	520 ± 26	923 ± 42	863 ± 31	740 ± 23	670 ± 19
Cholesterol (mg/dl)	100 ± 16	58 ± 21	68 ± 16	91 ± 33	104 ± 23
ALK (IU/L)	154 ± 31	105 ± 26	117 ± 19	150 ± 25	158 ± 30
CK (IU/L)	268 ± 12	2000 ± 39	156 ± 14	188 ± 31	94 ± 12

BUN, blood urea nitrogen; SGPT, serum glutamic pyruvic transaminase; SGOT, serum glutamic oxaloacetic transaminase; GGT, gamma glutamyl transferase; LDH, lactate dehydrogenase; ALK, alkaline phosphatase; CK, creatine kinase.
[a] Values are mean ± SD.

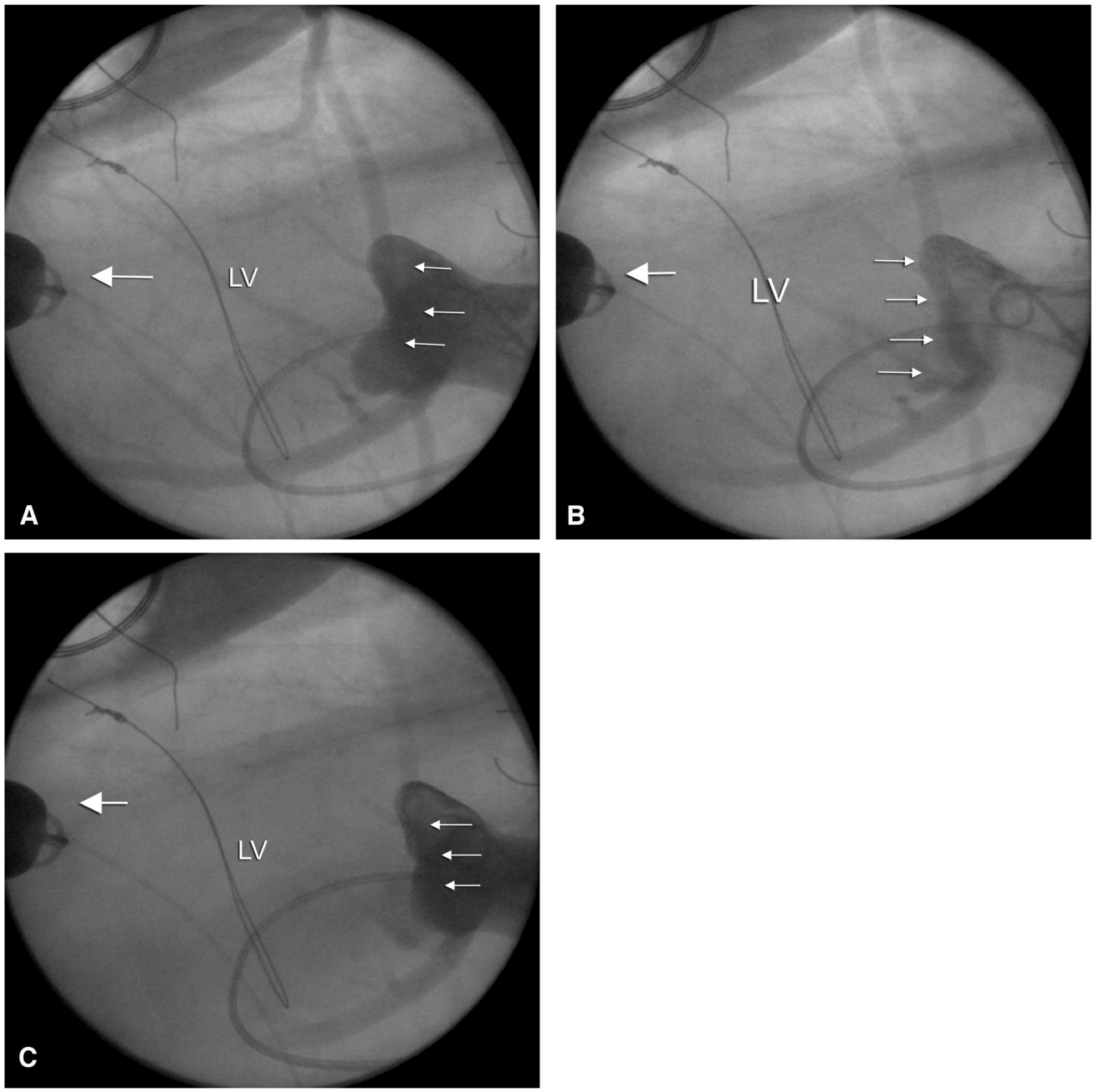

Figure 1. Serial images obtained by radiopaque cineaortography showing aortic valve totally closed when the ILS controller is not activated (A and C) and open when the controller is activated (B). Small arrows indicate aortic valve; large arrows indicate Jarvik 2000 pump. LV, left ventricular cavity; ILS, intermittent low speed.

reduced by using smaller, more easily implantable LVADs. This led to the development and clinical testing of a new generation of continuous flow (*i.e.*, centrifugal or axial flow) pumps.[13,14] The small, easily implantable, and reliable Jarvik 2000 significantly improves native heart function in patients with end-stage heart failure refractory to conventional medical and surgical treatments[15] and significantly reduces the incidence of postoperative bleeding and infection.[15]

As previously stated, the circulation in patients supported with an axial flow LVAD is partially pulsatile when the pump speed setting allows flow through the native aortic valve.[15] Such partial unloading of the left ventricle may be more effective than total unloading in achieving ventricular recovery during long-term support.[16,17] As the pump speed is increased, the aortic valve remains closed, causing flow stagnation and reducing aortic washout. This, in turn, may trigger a thrombogenic state marked by platelet aggregation, hypercoagulability, and white cell adhesion.[18–20] Blood trauma during axial flow pumping may accelerate this phenomenon by promoting red cell aggregation and reducing cell deformability, which lead to increased blood and plasma viscosity.[21]

If the outflow graft of the axial flow pump is anastomosed to the descending aorta, then there is the potential for retrograde flow, which may encourage stagnation at the aortic

valve.[10,11,15] This phenomenon is not observed when the outflow graft is anastomosed to the ascending aorta, even if the native aortic valve does not open.[15] In patients with severe heart failure, several factors may affect placement of the outflow graft. These factors include previous sternotomy, patient size, LV dimension, presence and extent of coronary artery disease, and aortic calcification or atherosclerosis.[15] In the present study, we preferred to anastomose the outflow graft to the descending aorta to create a worst case scenario in which to assess the long-term effects of ILS upon aortic valve opening.

We proposed alleviating hemostagnation by intermittently minimizing the pump flow to allow opening of the aortic valve. Our rationale was that the systolic ejection time is inversely related to pump speed via decreased LV end-systolic pressure, increased aortic diastolic pressure, and increased retrograde flow, especially when the outflow graft is anastomosed to the descending aorta.[16] In such cases, even if the aortic valve were to continue to open at higher pump speeds, the reduced ejection time and decreased LV contractility might not allow for an ejection powerful enough to wash out the aortic root. This might in turn lead to stasis at the aortic root. In the present study, we demonstrated that aortic valve opening and ejection could be successfully achieved by temporarily reducing the pump speed for 10 seconds each minute (*i.e.*, operating the pump in ILS mode), even in states of low cardiac output associated with total closure of the aortic valve. This allowed the aortic valve to open six times per minute during a 60 bpm cardiac cycle, thus preventing stasis related complications (*e.g.*, thrombosis, emboli, or leaflet fusion) and apparently providing enough flow to wash out the aortic root.

Large animals seem to be able to adapt to nonpulsatile circulation.[22,23] However, over long periods, the blood flow must exceed 90 ml/kg/min for normal organ function to be maintained, and the perfusion pressure must be kept within the normal range.[23] Pulsatile flow seems more likely to maintain normal organ function at reduced flow rates and pressures. The ILS mode increases the degree of pulsatility above and beyond the partial pulsatility generated by contraction of the native heart when the axial flow pump is running at a constant speed. Taking advantage of this observation may help to avoid the need for increased flow requirements, as noted previously, during long-term support.

Conclusion

Our results indicate that operating an axial flow pump at intermittent low speeds allows the aortic valve to open and the aortic root to be washed out even in states of low cardiac output and under continuous flow conditions, thus preventing valvular thrombosis, fusion, or both.

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