Short Report

Severe hypoxaemia with a left ventricular assist device in a minipig model with an undiagnosed congenital cardiac disease

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Abstract

We describe the placement of a left ventricular assist device (LVAD) in a pig with spontaneously occurring atrial septal defect (ASD) (incidental finding) that created a right–left cardiac shunt, with subsequent severe hypoxaemia. Early diagnosis was critical in order to prevent end-organ damage due to hypoxaemia. Adequate monitoring alerted us to the deterioration in oxygenation, haemodynamics and cerebral oxygen metabolism. This forced us to change the level of assistance provided by the pump, and thus dramatically correct this impairment. Necropsy revealed an ostium secundum ASD. In conclusion, if hypoxaemia presents after implementation of an LVAD, the presence of a right–left shunt must be ruled out. The first step must be a judicious reduction in assist device flow to minimize intracardiac shunting. Subsequently, atrial septal closure of the defect should be considered. We report an experimental model of severe hypoxaemia after placement of an LVAD as part of a larger research project.

Keywords: Heart-congenital defects, heart-ventricles, hypoxaemia, surgery-cardiovascular

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Ventricular assist devices (VADs) are increasingly used in routine clinical practice as a bridge to recovery of the native ventricle, to transplantation, as well as for destination therapy.[1] We describe the placement of a left ventricular assist device (LVAD) in a pig with an atrial septal defect (ASD) (incidental finding) that created a right–left cardiac shunt. Adequate monitoring alerted us to the deterioration in oxygenation, haemodynamics and cerebral oxygen metabolism. As a right–left cardiac shunt was suspected, the VAD flow was lowered, thus correcting the impairment.

The study subject was a male minipig aged 49 days and weighing 20 kg. The animal line was developed by Sachs at the National Institutes of Health in Bethesda (MD, USA). The animal used in our experiment came from the farm of the Technological Institute of Agrarian Development (EX 013-C), which is licensed to breed and supply animals for research and other scientific purposes in the Community of Madrid, Spain. In this centre, animals are housed in facilities built specifically for pigs. The pigs were moved from this farm to the Experimental Medicine and Surgery Unit of the Hospital Gregorio Marañón (EX/017U) 24 h before surgery and housed in individual cages, where they remained under a controlled environment (20–22°C and relative humidity of 55%) until the intervention.

The study was performed in accordance with the European Union guidelines for the protection of animals used for experimental and other scientific purposes (Guideline 86/609/EEC and Spanish Royal Decree 1201/2005 BOE). Our institutional Animal Care and Ethics Committee approved the protocol. We studied the haemodynamic behaviour of a VAD, the Biomedicus centrifugal pump (Biomedicus 540, Medthonic, Minneapolis, MN, USA) as part of a larger research project analysing the haemodynamic behaviour of several VADs.

The animal was simultaneously premedicated with ketamine 20 mg/kg (Ketolar, Parke-Davis, Madrid, Spain) and atropine 0.04 mg/kg (Atropine, Braun, Serra-Pamies, Tarragona, Spain) intramuscularly. After premedication, a 22-gauge intravenous catheter was inserted into the marginal ear vein. Throughout the procedure, an electrocardiogram (ECG) was recorded and regional cerebral oxygen saturation (rSO_2, 5100 INVOS System, Somanetics

Corporation, Troy, MI, USA) was monitored. General anaesthesia was induced with fentanyl 2.5 μg/kg (Fentanest, Kern Pharma, Barcelona, Spain) and propofol 2 mg/kg (Diprivan 1%, Astra Zeneca, Madrid, Spain) intravenously. Anaesthesia was maintained with fentanyl (2.5 μg/kg/every 30 min) and propofol (11–12 mg/kg/h) intravenously. The lungs were mechanically ventilated using an SA1 Dräger respirator (Dräger Medical AG, Lübeck, Germany) with an FIO_2 of 1, a tidal volume of 12–15 mL/kg and the respiratory rate adjusted to maintain normocapnia. A 9 F arterial catheter was inserted in the right femoral artery for continuous mean systemic arterial pressure measurement (AP_m) and a pulmonary artery catheter (7.5 F Swan-Ganz CCOmbo catheter, Edwards Lifesciences, Irvine, CA, USA) connected to an oximetry monitor (Vigilance, Edwards Critical-Care Division, Irvine, CA, USA) was inserted into the right internal jugular vein to measure continuous cardiac output (CO), mean pulmonary artery pressure (PAP_m) and mixed venous oxygen saturation (SvO_2). After median sternotomy, the output cannula of the device was anastomosed to the ascending aorta and the animal received heparin at a dose of 4 mg/kg (intravenous). The input cannula was placed through the apex of the left ventricle and both cannulae were connected to the device. VAD was initiated with a continuous flow of 2.6 L/min. Cyanosis was observed immediately and was accompanied by a decrease in AP_m (50 mmHg), CO (2 L/min), SvO_2 (40%), right rSO_2 (40%) and left rSO_2 (37%) (Table 1), and an increase in PAP_m (57 mmHg). Arterial blood gases showed severe hypoxaemia (PaO_2 40 mmHg, with a previous PaO_2 of 490 mmHg). As a right–left cardiac shunt was suspected, the VAD flow was lowered from 2.6 to 1.6 L/min. At this point, there was a significant improvement in arterial blood gases, haemodynamics and regional cerebral oxygen saturation. Thirty minutes after the start of total assistance, these parameters were as follows: PaO_2 165 mmHg, AP_m 65 mmHg, PAP_m 15 mmHg, CO 2.3 L/min, SvO_2 44%, right rSO_2 60% and left rSO_2 52%. This improvement was even more dramatic when VAD flow was lowered to 0.8 L/min. After 30 min of partial assistance, respiratory, haemodynamic and regional cerebral oxygen saturation values were as follows: PaO_2 475 mmHg, AP_m 74 mmHg, PAP_m 20 mmHg, CO 3 L/min, SvO_2 63%, right rSO_2 61% and left rSO_2 53%. After the experiment, the animal was sacrificed with potassium chloride, and necropsy revealed the existence of an ostium secundum ASD of approximately 0.5×1 cm.

ASD accounts for 30% of congenital lesions in adults, and the prevalence of patent foramen ovale (PFO) is 26%.[2] The various subtypes of ASD are classified according to the location of the defect. Ostium secundum is due to the absence of tissue in the fossa ovalis and is the most common defect (75%). Ostium primum (15%) is due to a deficiency in the lowest or inlet portion of the septum and is a form of partial endocardial cushion defect. Sinus venosus defect (5–10%) is the result of an error in the incorporation of the sinus venosus chamber into the right atrium.[3,4] Coronary sinus defect (1%) is rare and is associated with 'unroofing' or absence of the coronary sinus, with a direct connection of the left superior vena cava to the left atrium.[3] PFO is a flap-like communication in which the septum primum covering the fossa ovalis overlaps the superior limbic band of the septum secundum.[5] In most patients, flow is predominantly left to right, and the degree of the shunt depends on the size of the defect, compliance of the right ventricle and left ventricle, and the relationship of pulmonary vascular resistance to systemic vascular resistance. Under normal conditions, the right ventricle is more compliant than the left ventricle. Therefore, when all four cardiac chambers are in free communication during diastole, blood from the left atrium is shunted to the right atrium, causing increased blood flow and gradual dilation of the right atrium, right ventricle and pulmonary arteries. Over time, the augmented pulmonary blood flow can result in medial hypertrophy of the pulmonary arteries, which can cause increased pulmonary vascular resistance and increased pulmonary arterial pressure.[3] The fact that our study subject (49 days of age) was asymptomatic is not unusual, since the onset of symptoms usually occurs with ageing. In patients with no obvious right heart lesions (tetralogy of Fallot, pulmonary stenosis, right heart tumours, tricuspid atresia, tricuspid stenosis), shunt reversal (right-to-left shunt) may develop due to the following: instantaneous changes in the difference between right

Table 1 Laboratory values of arterial blood gases, haemodynamic data and regional cerebral oxygen saturation values before the start of assistance, at the start of the assistance, 30 min after the start of total assistance and 30 min after the start of partial assistance

	Before assistance	Start assistance	30 min total assistance	30 min partial assistance
pH (mmol/L)	7.41	7.46	7.42	7.34
PaO_2 (mmHg)	490	40	165	475
$PaCO_2$ (mmHg)	41	35	37	42
BE (mmol/L)	1.4	1.1	−0.5	−3.1
HCO_3 (mmol/L)	26	24.9	24	22.7
SpO_2 (%)	100	78	100	100
AP_m (mmHg)	68	50	65	74
PAP_m (mmHg)	14	57	15	20
SvO_2 (%)	63	40	44	63
CO (L/min)	2.7	2	2.3	3
Assistance flow (L/min)	–	2.6	1.6	0.8
Right rSO_2 (%)	58	40	60	61
Left rSO_2 (%)	51	37	52	53

BE: base excess; AP_m: mean systemic arterial pressure; PAP_m: mean pulmonary arterial pressure; SvO_2: mixed venous oxygen saturation; CO: continuous cardiac output; rSO_2: regional cerebral oxygen saturation

atrial and left atrial pressure during each cardiac cycle, respiration-induced transient positive right atrial–left atrial pressure gradient and preferential flow from the inferior vena cava towards the PFO. Shunt reversal can occur during the perioperative period as a result of the effect of mechanical ventilation, pulmonary embolism, right ventricular failure, pericardial tamponade, right pneumonectomy or an increase in intra-abdominal pressure.[6] Hypoxaemia caused by a right–left atrial shunt, with normal pressures in the pulmonary artery, is exceptional. Under normal circumstances, left atrial pressure exceeds right atrial pressure; however, placement of an LVAD can reverse this relationship and cause hypoxaemia in a patient with ASD.[7] This occurred in our study, and pulmonary pressure increased. The increase in pulmonary arterial pressure depends on the size of the defect and the size of the shunt.

Patients in their fourth and fifth decades of life may begin to develop symptoms associated with ASD. The initial presentation in adults includes dyspnoea and palpitations, atrial flutter/fibrillation and a paradoxical embolic event. The diagnostic work-up for a patient with suspected ASD is directed at defining the presence, size and location of the defect, as well as the functional effect of the shunt on the right and left ventricles and pulmonary circulation. Clinical findings include precordial lift, systolic pulmonary murmur and fixed splitting of the second heart sound. ECG shows right-axis deviation, right atrial enlargement, incomplete right bundle-branch block (secundum ASD), superior left axis deviation (primum ASD) and an abnormal P-wave axis (superiorly located sinus venosus ASD). The chest X-ray may show enlargement of the right ventricle and right atrium, a prominent pulmonary artery segment and increased pulmonary vascularity. Transesophageal echocardiography (TEE) is considered the 'gold standard' in the diagnosis of ASD. Contrast echocardiography with intravenous agitated saline injection is used to confirm the presence of a right-to-left atrial shunt if imaging and colour Doppler are not conclusive. Cardiac catheterization is rarely needed to confirm the diagnosis.[5]

A search of the literature revealed some cases in humans in which placement of a VAD was accompanied by the incidental finding of an ASD. In one of these cases, undiagnosed ASD led to death, and in another continuous mixed venous oxygen saturation revealed the ASD.[7] Patients with a VAD must be closely monitored during the perioperative period to obtain an early diagnosis of any associated complications (haemodynamic, ventilatory, neurological) and to act promptly in order to reduce morbidity and mortality.[7,8] In the case we present, the decrease in rSO_2 and SvO_2 alerted us to the severe clinical deterioration of the animal when the VAD began to function. As a complement to arterial oxygen saturation measured by pulse oximetry, cerebral tissue oxygen saturation reflects regional cerebral metabolism and the balance of local cerebral oxygen supply/demand.[9] In our case, pulse oximetry proved to be unreliable, as the device was a continuous flow VAD.[10] rSO_2 monitoring in cardiac surgery prevents deep cerebral desaturation, making it possible to take corrective action and is associated with a lower incidence of organ dysfunction.[11] No studies have examined the effectiveness of monitoring rSO_2 in VADs. In our case, severe decline in SvO_2 and rSO_2 forced us to change our therapeutic approach in order to improve the severe clinical deterioration caused by the shunt resulting from cardiac ventricular assistance in the presence of an ASD. As a result of this action, the improvement in ventilatory, haemodynamic and cerebral oxygen metabolism was evident. However, this type of situation is much less likely to occur in clinical practice, because an ASD is detected by intraoperative echocardiography.[12] Preoperative diagnosis of septal defects is very important in minipigs, because they have a higher incidence of congenital abnormalities.[13] Similar scenarios might arise in patients with undiagnosed PFO, patients who have undergone mitral valve surgery with access through the atrial septum that could cause a residual surgical ASD, and patients with acute myocardial infarction and ischaemic rupture of the interventricular septum. In these cases, the decrease in pressure in the left cavities determined by the functioning of the VAD will cause a right–left shunt similar to that observed in our experimental model. When a right–left shunt is suspected, ventricular assistance flow should be decreased to diminish the pressure gradient between the right and left atria. TEE is considered the 'gold standard' in the diagnosis of ASD, and can help decide when to perform closure of the ASD.[14]

In conclusion, our report suggests that, if hypoxaemia presents after implementation of a VAD in an animal model, the presence of a right–left shunt must be ruled out. The first step must be a judicious reduction in assist device flow to minimize intracardiac shunting. Subsequently, atrial septal closure of the defect should be considered. Early diagnosis is critical in order to prevent end-organ damage due to hypoxaemia. Continuous monitoring is necessary for suspected diagnosis (rSO_2 monitoring could be included as standard). This case shows an experimental model of severe hypoxaemia after placement of an LVAD.

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