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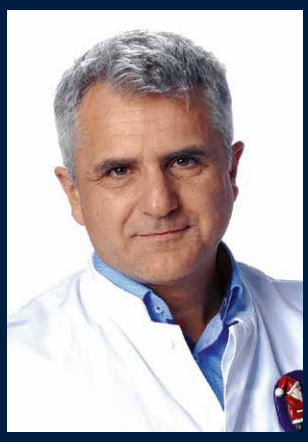

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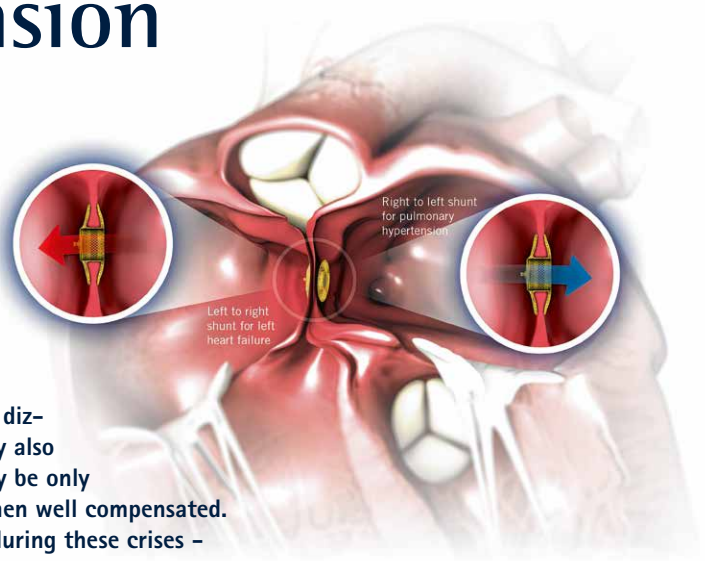
A new interventional management strategy for patients with pulmonary hypertension



The atrial flow regulator (AFR device)

Despite modern medical and pharmaceutical therapeutics, elevated pulmonary vascular resistance (i.e. pulmonary hypertension) is still a disease with high morbidity and mortality. The majority of patients with chronically elevated pulmonary artery pressure do suffer from the clinical signs of chronic and/or acute right heart failure, which finally is the leading cause of death in most cases. If patients suffer from a form of pulmonary hypertension with a very variable reactivity of the pulmonary artery pressure, they usually present with syncope, acute fainting and/or dizzyness; nevertheless these acute onset pulmonary hypertensive crises may also lead to acute death. In these patients, the pulmonary artery pressure may be only moderately elevated during routine examination and the right heart is then well compensated. These patients however show suprasystemic pulmonary artery pressures during these crises – and the right ventricular function may be impaired for several days or weeks thereafter. For all these patients – i.e. those with severe permanent pulmonary hypertension as well as those with intermittent severe pulmonary hypertension and syncope a new and potentially life-saving treatment modality has been developped – the AFR device

Pathophysiology

Pulmonary hypertension is defined as a mean pressure in the pulmonary artery of more than 25 mmHg, whereas the normal value is about 15 mmHg. In Germany there are about 4 out of 1 million patients with a new onset pulmonary hypertension, i.e. about 350 new patients per year in 2014. Unfortunately, there are no reliable data for children.

Pulmonary hypertension is caused by an impaired transpulmonary blood flow due to vasoconstriction of the smallest pulmonary blood vessels, the capillaries. In addition to the constriction there is an obstruction of these blood vessels. This leads to an eleveated work load of the right heart, that can be managed by the heart initially. Over time and with further elevation of the blood pressure in the lungs, right heart decompensation will follow. This leads to a congestion of the venous system and secondary to an inadequate perfusion of the left, i.e. arterial side.

In general the patients show very untypical signs such as shortness of breath, tiredness, chest pain and impaired exercise capacity and sometimes blue lips. These clinical signs are also used to classify the severity of the disease – the more the daily activity of a patient is impaired, the higher will be the functional class (see table 1)

class 1

Patients with pulmonary hypertension without limitation of exercise capacity. Normal daily exercise or activity will not result in dyspnoe and tiredness, thoracic pain or syncope

class 2

Patients with pulmonary hypertension and moderate impairment of exercise capacity. No problerms at rest. Normal daily exercise or activity will lead to tiredness and dyspnoea, thoracic pain or syncope

class 3

Patients with pulmonary hypertension and severe impairment of exercise capacity. No problems at rest. Very mild normal daily exercise or activity will lead to tiredness and dyspnoea, thoracic pain or syncope

class 4

Patients with pulmonary hypertension who cannot perform normal daily exercise or activity without symptoms. Clinical signs of right heart failure. Tiredness and dyspnoea at rest. Minimal activity will worsen symptoms.

Table 1. Classification of the severity of pulmonary hypertension based on clinical exercise tolerance.

Clinical presentation

The Patients show distended jugular veins, an enlargement of the liver, peripheral and pulmonary edema, aszites (fluid accumulation in the abdomen with distended abdomen), cool and bluish extremities as signs of right heart failure and impaired systemic perfusion.

On auscultation there is a loud second heart sound, the auscultation of the lungs is otherwise normal.

The ECG shows a dilatation of the right atrial chambers and right ventricular hypertrophy. When arrhythmias occur they will lead to an acute deterioration or right heart failure. The chest X-ray typically shows enlarged central pulmonary markings and reduced peripheral perfusion.

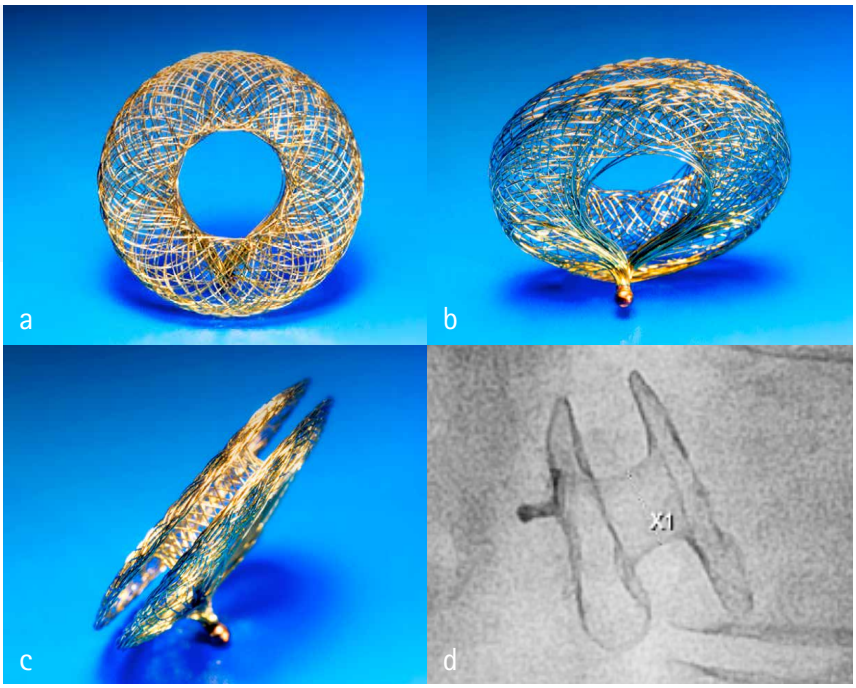


Figure 1: details of the AFR device
Figure 1a: the round central fenestration
1b: the connection to the delivery cable
1c: lateral view, flat profile of the device
1d: fluoroscopy, lateral view, 5 mm thick device, 6 mm fenestration, marked with X1

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Echocardiography is the main diagnostic tool – based on the regurgitation jet across the tricuspid valve the right ventricular pressure can be calculated. In addition there is a large right ventricle and dilated right atrium as well as a small left ventricle and left atrium caused by the impaired transpulmonary blood flow. The left ventricle has a typical banana shape appearance.

Therapeutic options

In Germany there are now 7 different medications available for the treatment of pulmonary hypertension. These include PDE 5 inhibitors (Sildenafil, Tadalafil), Endothelin-receptor antagonists (Bosentan, Macitentan) and prostacyclin derivatives (Prostacyclin, Iloprost, Trepostinil). The mortality of the patients could be reduced by 43% when these medication is used. Nevertheless pulmonary hypertension remains a severe and not curable disease.

It is well known from the early years before medical therapy was available that patients who have an atrial septal defect (ASD) did show a lower mortality and better quality of life. An ASD offers some major advantages in these patients especially if right heart failure occurs.

1. An ASD does allow a righ-to-left shunt across the atrial septum and thereby may decompress the venous system from its high and unphysiological pressure. This is of special importance for all the abdominal organs such as kidneys, liver and gut that are impaired by this venous congestion caused by right heart failure. The clinical symptoms of right heart failure such as ascites and edema are reduced. In addition the right ventricle does not have an extensive dilatation that will result in an improved performance over a longer time.

2. The most important effect is however on the systemic perfusion. With the help of the right-to-left shunt there is an improved filling of the left side, especially the left ventricle. This leads to an improved perfusion of the systemic circulation and better oxygen as well as energy delivery. The downside is a minor desaturation (80-85%), this is however well tolerated and in summary the imporoved perfusion will prevent weight loss and cachexia. This is of special importance for those patients who suffer from PHT crises and syncope. Ideally the size of the (small) ASD and the needs for a right to left shunt are balanced.

Balloon-Atrio-Septostomy (BAS)

Based on these clinical observations physicians used the creation of an atrial septal defect in patients with right heart decompensation and pulmonary hypertension and performed a balloon septostomy (BAS). In a BAS a septal defect is created by rupturing the atrial septum with the help of a balloon catheter. The initial results were however not encouraging – and this was caused by the (crude) technique of rupturing an unbalanced hole – in some patients the hole was too big – resulting in acute and severe desaturation and even death; the other possibility was that the hole was too small and closed off very soon.

The Atrial Flow Regulator-Device (AFR-DEVICE)

Since the end of 2016 a dedicated device was presented for these patients by the Occlutech company. The device is engineered like an ASD occluder device, there is however a centrally located fenestration of a defined diameter (it comes in 4, 6, 8 and 10 mm, see picture1). By using this device it is now possible to create a fenestration in a defined and precise diameter and secure a permanent shunt. The clinical studies for CE registration are currently under way, leading clinical center is our department at the LMU university in Munich, Germany.

Clinical examples

We would like to present two patients who were treated on the basis of compassionate care with this device. One patient presented with severe right heart failure, the other patient presented clinically with multiple syncopes caused by PHT crises. In both patients, all other medical therapies were used and both patients had no other treatment options according to the current guidelines.

Case 1

The 35 year old man had severe pulmonary hypertension caused by late closure of a VSD. He was referred for lung transplantation but had massive right heart failure. He required daily dialysis and showed liver failure. Despite 4 medications for PHT, he was to sick to be accepted for the transplant list. Echo revealed a massively dilated right heart and a banana-shaped and underfilled left ventricle. After implantation of the 10 mm AFR device, the right ventricle was decompressed and the left ventricle refilled again (see figure 2).

This led to improved systemic perfusion and the liver and kidney function recovered rapidly over the following days, ascites disappeared and kidney function normalized. 6 weeks later the patient was discharged home in clinically improved condition. He was accepted on the lung transplant list and successfully transplanted 2 months later.

Case 2

This 8 year old girl presented with primary pulmonary hypertension and with recurrent syncope despite triple therapy. The episodes with syncope worsened over time, she was unable to climb more than one floor of stairs, her exercise capacity was dramatically reduced. She reported many episodes of dizzyness which she managed by spontaneous hyperventilation – even during night time and sleep. The ECHO in unremarkable intervals however showed nearly normal right heart function.

After the implantation of a 6 mm AFR device she did not show any other episodes of syncope or dizzyness any more over a follow-up time of now 12 months. She is now able to climb 4 floors of stairs without stopping, clinically she only has mild cyanosis after exercise. In general the parents report of a completely changed „new" child.

Discussion

The new AFR device presented here is designed to create a restrictive ASD of defined size. The various sizes available can be used according to the patients disease and severity of disease. After implantation there is a very flat and natural profile and this may result in a very low thrombogenicity. Endothelialization will occur in about three months, this results in an anticoagulation with Aspirin necessary for 3-6 months only.

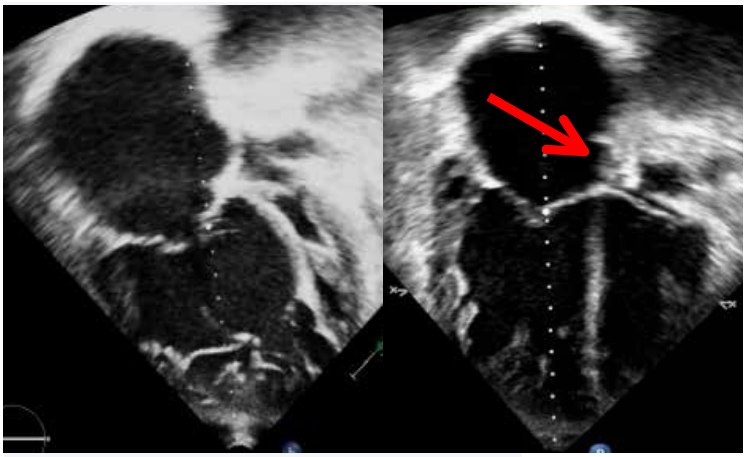

Figure 2. severe decompensated right heart failure in patient 1 with late corrected ventricular septal defect. Left: ECHO before BAS and AFR device implantation. There is a gigantic right atrium and dilated right ventricle. The left ventricle is underfilled and shows typical banana-shape configuration. The left atrium is small and underfilled. Right: After intervention with AFR device in position (red arrow), improved filling of the left ventricle. The left atrium directs the blood flow directly to the LV.

The cases presented may highlight the possibilities of the clinical use of this AFR device. In general, the BAS/AFR implantation may serve as bridge-to-transplantation in patients with right heart failure. Another indication is the preservation of cardiac output in patients with syncope caused by PHT crises. This is generally reversible and usually presents in the early stages of pulmonary hypertension.

In addition to the reduction of right atrial pressures, the AFR device may protect the right ventricle from overdistension and excessive dilatation. This will lead to a reduction of syncope or pre-syncope as well as an improved right ventricular recovery and improved exercise capacity. This is clinically best documented by the dramatical improvement of the functional class in the patients presented.

Summary

The combination of a balloon septostomy together with the implantation of an AFR device is an important interventional management element in patients with pulmonary hypertension. The AFR device will not only play a role in patients with pulmonary hypertension, but also be clinically used in patients with left sided heart failure. This combination will increase the safety profile of the BAS in patients with PHT. Currently clinical studies are under way and are coordinated by our department. If you require additional information, please do not hesitate to contact our team at the LMU Munich.

Informationen

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At the university hospital Munich, Campus Grosshadern, the department of pediatric cardiology and intensive care offers a dedicated outpatient service for patients with pulmonary hypertension (children and adults with congenital heart defects). We do offer this specific and new therapy for these patients.

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