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The Occlutech Atrial Flow Regulator™ to Treat Right Ventricular Failure in Severe Pulmonary Hypertension

Special Cases and Considerations, and the PROPHET-Trial

By Ingram Schulze-Neick, MD; Anja Lehner, MD; André Jakob, MD; Lina Armbrust, MD; Robert Dalla Pozza, MD; Nikolaus A. Haas, MD

Abstract

The Balloon Atrial Septostomy (BAS) procedure is performed to relieve severe symptoms of right heart failure caused by end-stage pulmonary hypertension or other causes. We present a novel device, the Occlutech Atrial Flow Regulator (AFR), a purpose designed interventional device to stabilize the result of the BAS, controlling the shunt flow, and keeping the created atrial defect patent.

Here we show, as an example, the results in three patients who have been treated with the BAS/AFR combination intervention on a compassionate basis. All AFR devices remained in situ and patent over the observation times of > 1 year. On one occasion, complete endothelialisation of the AFR device was confirmed when the patient received a heart transplantation.

These results are encouraging and might support the notion to offer the BAS, supported with the AFR device, more often and perhaps at an earlier time point within the algorithm for treatment of pulmonary hypertension.

Introduction

Pulmonary hypertension remains a devastating disease despite the advent of multiple new medications in inhaled, oral, and intravenous form. Clinically, most patients eventually suffer chronically from the sequelae of decompensated right heart failure, which also is the leading final cause of death[1]. In some patients, however, who have very reactive Pulmonary Vascular Disease, acute pulmonary hypertensive crisis following certain triggers such as aspiration, lung infection, or serious exercise, may lead to acute right heart failure and present as syncope with possible premature death, despite apparent otherwise, and at rest, good right heart function[2]. The pathophysiology of both forms - acute and chronic decompensated - include venous congestion and a lack of systemic forward flow due to impaired forward flow through the pulmonary capillaries[3]. Echocardiographically, this causes enlargement of the right ventricle, eventually also with the right atrial enlargement and with a bulging of the right atrial septum into the left atrium, while on the left, postcapillary side, an underfilled, and almost collapsed, left atrium and similarly underfilled and, therefore, banana-shaped left ventricle[4] cannot be missed.

In this situation, it has been observed that patients with an Atrial Septal Defect (ASD) show longer survival despite comparable disease severity[5,6]. The ASD offers several circulatory advantages for the patient who suffers from the pathophysiology of right heart failure:

1. As the ASD allows for right-to-left shunt on the atrial level, it offloads the large venous system from high pressure, thus alleviating organs (i.e. liver, kidney, gastrointestinal system) and reducing the clinical symptoms of right heart failure (ascites, edema, etc.).
2. The ASD offloads the failing right ventricle from high preload, thus allowing this ventricle to return to the more

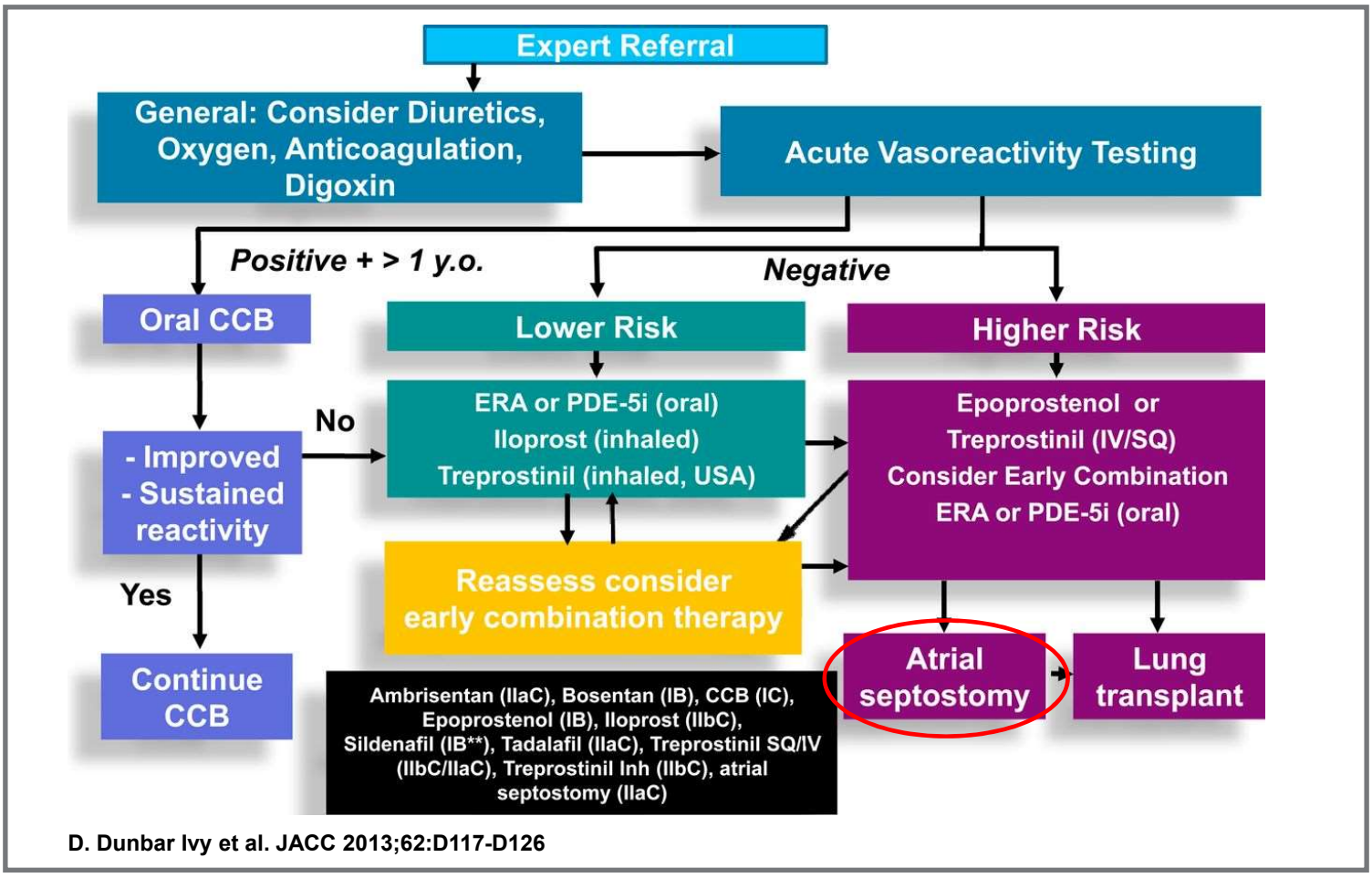

Figure 1. Algorithm for the treatment of different forms of Precapillary Pulmonary Hypertension, according to severity upon presentation. Figure cited from[4]. Note the place of the ballon atrial septostomy as a last resort mechanical intervention.

favourable part of the Frank Starling curve with recovery of myocardial contractility.

3. The right-to-left shunt delivers more blood to the left ventricle and the systemic vasculature. Cardiac output increases so that systemic hypotension is avoided, and despite a decrease of oxygen saturation from the right-to-left shunt, systemic oxygen and nutrient delivery are improved.

Based on this observation, creating an ASD by balloon atrioseptostomy (ie. BAS) has been used as a treatment in this patient group (Figure 1)[7]. So, a graded and patient approach evolved using static balloon dilatation to avoid uncontrolled rupture of the atrial septum with uncontrolled right-to-left blood flow, with acute and detrimental hypoxemia from cardiac desaturation[2]. However, the results were disappointing in about 25% of the cases due to early closure of the created ASD[8]. Regrettably, this caused the balloon septostomy to fall into disregard, although survival in patients with pulmonary hypertension was improved with it.

In an attempt to address this problem, interventionalists have combined devices to create a makeshift solution for this problem, such as poking a hole into an available ASD occluding device, or to provide a vent with the help of inserting a coronary stent into it[9]. The re-occlusion rate was high when fenestrations were handmade, or used with a diameter of 5 mm or less, or when there was a high amount of surrounding material in place. The results were mechanically not very

Patient Initials	Age in Years	Sex	Abridged Diagnosis	AFR Size (mm)	Months Post Implantation	Device in Situ	Device Patent	Shunt Direction	Benefit to Patient
TM	35	M	s/p VSD	10	17	Yes	Yes	LR	+++
MK	8	F	iPAH	8	16	Yes	Yes	LR	+++
SS	56	M	Non Com	8	10	Yes	Yes	RL	++

Table summarising patients with AFR-implantation. s/pVSD, post operation of Ventricular Septal Defect; iPAH, idiopathic pulmonary arterial hypertension; Fontan, decompensation chronically failing Fontan-type Circulation (see text); Non Com, non-compaction, sponge-like myocardiopathy.

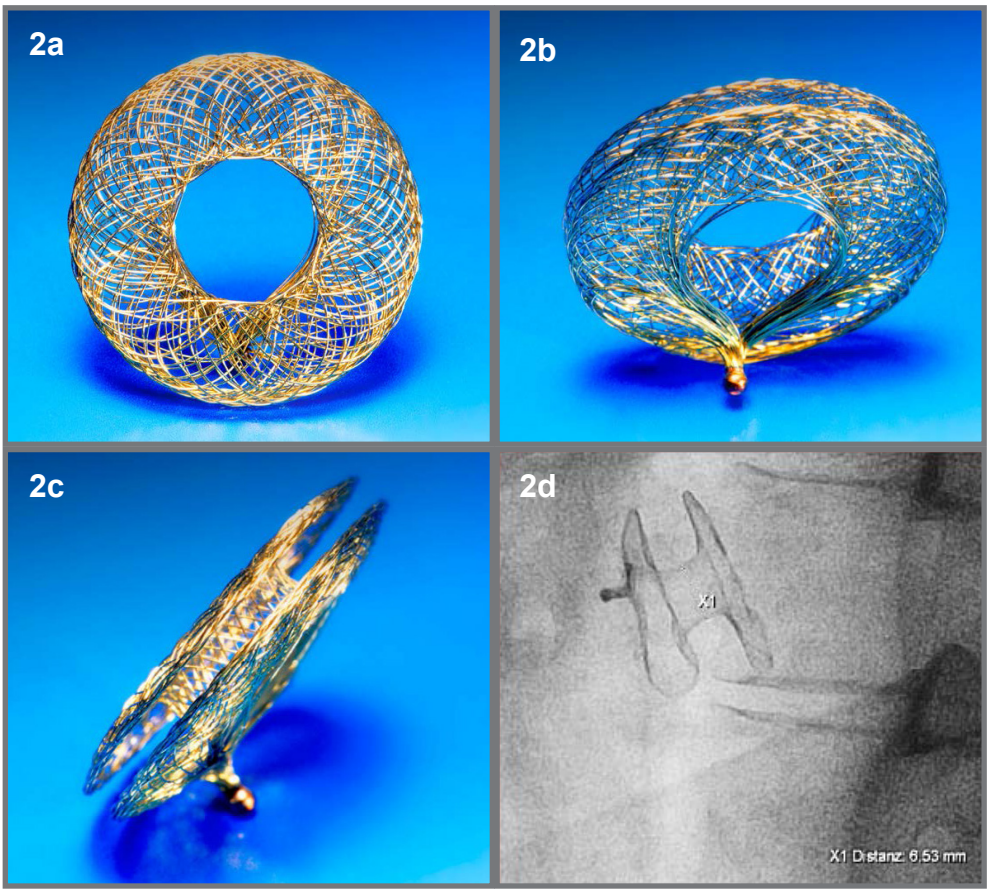

Figure 2. Details of the AFR device.
2a. The frontal view from the left atrial side shows the circular shape with the central fenestration of the device.
2b. The oblique view from the right-atrial side shows the connection hub to the delivery cable which is identical to the delivery set of the Occlutech Flex II® device family. Compare this view with Figure 8, see further below.
2c. The lateral view delineates the flat profile of the device, here a device with 2 mm thickness.
2d. After implantation into a standard atrial septum the fluoroscopy sows the flat profile of a device with a 5 mm thickness (marked "X1") between the disks and 6 mm fenestration width.

convincing, and demonstrated the need for a proper solution.

Recently, Occlutech (Sweden) has developed a purpose built and industrially made device which consists of the basic structure of their ASD occluder, but contains - in contrary to the ASD closure devices - only a fenestration of varying diameters (6-10 mm) secured by two discs (Figure 1). Here, we will present three different patients who have been provided with this device on a compassionate use basis for severe right heart failure. The device is currently off-label, but studies to obtain European CE-marking are underway since 2017 under the guidance of our department at the University Hospital of Ludwig Maximilians University, Munich, Germany.

Patients, Methods and Results

Ethical advice was sought beforehand with the local ethical committee, and all patients received the AFR device as acute ultima ratio compassionate treatment, with informed and signed consent obtained beforehand. All patients had multiple drug treatments for severe symptoms without any further treatment options available or individually tolerable or appropriate, except heart and lung transplantation, as described in the guidelines for treatment of pulmonary arterial hypertension according to the WHO-supported *World Conference in Pulmonary Hypertension 2013* in Nice, France[10]. There were no further systematic criteria which were used for selection of the individual patient except those directly required for hemodynamic success of the device. In summary, the criteria were as follows:

1. The increase of pulmonary vascular resistance fulfilled the internationally accepted definition contained in a most recent version of guidelines of pulmonary arterial hypertension[8].
2. The treatment of pulmonary vascular resistance had been advanced to the farthest level as possible, tolerable or appropriate for the patient in accordance with those guidelines, with the last remaining option being that of lung transplantation, with the patient either actually listed, or not listed because of a too decompensated clinical condition.
3. Right heart failure, in its acute, intermittent or chronic form, or its hemodynamic analogue in the Fontan circulation, was present or deducible from the patient's history, defined as increased venous or right atrial pressure, so that venous pressure was > 15 mmHg and the right atrial septum bulged into the left atrium.
4. A defect in the atrial (or conduit) wall had been created by a preceding static BAS but had closed again, or the ASD had been there congenitally but had been too small, or the ASD would be created only with high risk, so that any strategy to avoid repetition of the BAS procedure would be very beneficial to the patient.
5. The created defect in the atrial (or conduit) wall showed a strong right-to-left shunt. An exception to this rule was possible when there was clear evidence from the patient's history of acute or intermittent episodes of right heart failure, in which case a left-to-right shunt was acceptable and allowed.

The following patients are reported in timely consecutive order and represent the spectrum and age of patients with Pulmonary Vascular Disease treated in our division. All AFR devices had been donated by Occlutech company, Helsingborg, Sweden.

Case 1

A 35-year-old man presented in end-stage right heart failure due to late postoperative pulmonary hypertension. He had a Ventricular Septal Defect surgically closed at age nine. He was in NYHA functional class IV+, short of breath at rest, with pronounced venous congestion in his legs, massive ascites, and renal failure requiring daily dialysis. Pulmonary vasodilating therapy included four different agents using subcutaneous, inhaled and oral administration.

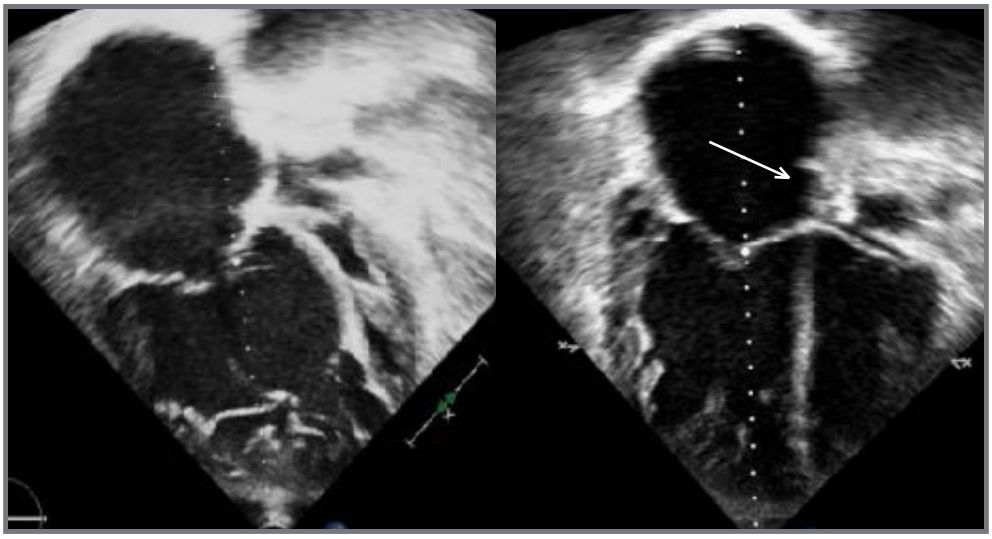

Figure 3. Patient with severe decompensated right heart failure due to an operated ventricular septal defect in childhood. Left side, situation before BAS and AFR implantation (see text) with huge right atrium and ventricle, and squashed left atrium and ventricle. Right side, situation post intervention with the AFR device in place (white arrow), and better filling of the left sided heart structures.

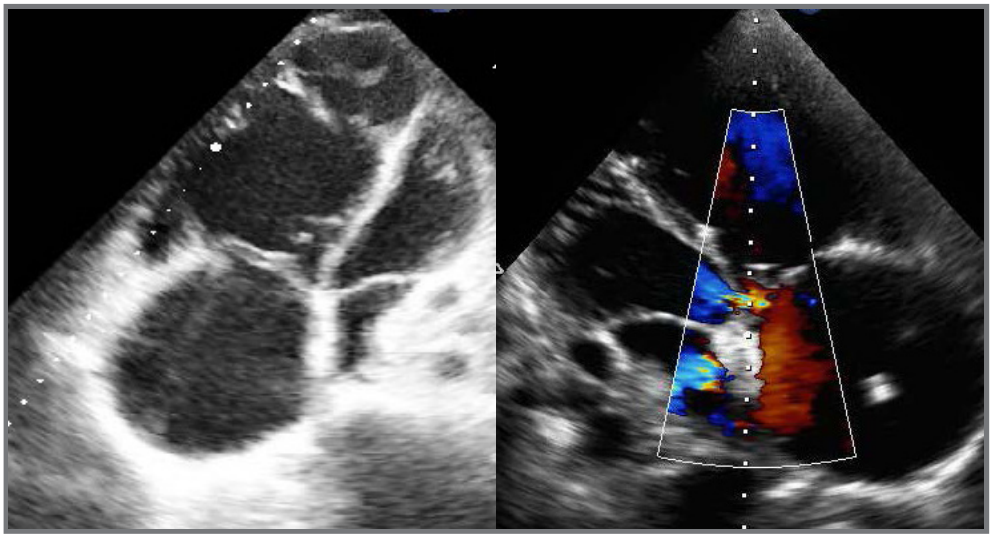

Figure 4. Same patient as in Figure 3, demonstrating situation before and after intervention, with the shunt through the AFR device apparent in color Doppler imaging (right image) in the long axis image. Note aortic regurgitation in the middle of the picture, the AFR device directly underneath it with the right-to-left shunt occurring through the device into the small left atrium.

Echocardiography demonstrated the typical features of decompensated right heart architecture with very low right ventricular and low left ventricular contractility, a huge and very trabeculated right ventricle which squashed the left ventricle to a banana shape, with the ventricular septum in massive curvature into the left ventricle, and a huge, 8cm measuring right atrium, and a left atrium where the atrial septum touched the left atrial free wall. There was severe tricuspid and pulmonary valve regurgitation.

Cardiac catheterization confirmed low cardiac output, and a BAS was performed. Unfortunately, over the course of the next seven days, the created atrial defect gradually closed down to merely a 1 mm opening. After repeat BAS, an AFR device with 8 mm fenestration was deployed and anchored without problems. Post-interventionally, a strong right-to-left shunt could be demonstrated through the fenestration (see Figures 3 and 4).

Over the course of the next days and weeks, the patient experienced a gradual stabilization and even slight recovery. Creatine levels fell, indicating improved renal function, and renal dialysis could be reduced and was eventually was withheld entirely (see Figure 5). The ascites also improved, and overall clinical status improved to NYHA II-III.

Two months following these interventions, he had a successful lung transplant. During the operation, while he was receiving a lung transplant, there was intraoperative shunt reversal through the device's fenestration to be observed, and the shunt device showed a left to right shunt when the transplantation operation had been finished successfully.

When checked last time, now more than 24 months after AFR device implantation, he was very well indeed, in functional class NYHA II, with his entire intracardiac architecture having recovered almost to normal.

Case 2

An 8-year-old school girl presented with recurrent syncope of increasing frequency and severity, with mild-to-moderate pulmonary hypertension in intervals. She was in good physical condition, without the signs of heart failure. However, her exercise tolerance was reduced with stopping to take a short rest after one flight of stairs. She was on a triple combination of pulmonary vasodilators, including the frequent inhalations with iloprost. As she was very needle phobic and already silently depressed, any more invasive therapy was out of the question for her. Echocardiography showed moderate pulmonary hypertension which was confirmed at cardiac catheterization, without overt signs of right heart function.

The BAS procedure and AFR implantation were performed in combined fashion at the same cardiac catheterization session and proved to be unproblematic and without complications. She was discharged after three days in accordance with our protocol for uncomplicated interventions. During further follow-up, i.e. more than 18 months, she had not experienced a single further syncope. The inhaled iloprost was discontinued which had been a great burden to her. However, she also experienced an increase in exercise performance, and gained psychological robustness and happiness which the parents continued to praise us for and attribute to us. She was able to run upstairs four flights, with almost no desaturation.

Case 3

A middle-aged male adult of 56 years presented with symptoms of severe left

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- **DO NOT implant in the aortic or mitral position. Pre-clinical bench testing of the Melody valve suggests that valve function and durability will be extremely limited when used in these locations.**
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- DO NOT use if there are clinical or biological signs of infection including active endocarditis. Standard medical and surgical care should be strongly considered in these circumstances.
- Assessment of the coronary artery anatomy for the risk of coronary artery compression should be performed in all patients prior to deployment of the TPV.
- To minimize the risk of conduit rupture, do not use a balloon with a diameter greater than 110% of the nominal diameter (original implant size) of the conduit for pre-dilation of the intended site of deployment, or for deployment of the TPV.
- The potential for stent fracture should be considered in all patients who undergo TPV placement. Radiographic assessment of the stent with chest radiography or fluoroscopy should be included in the routine postoperative evaluation of patients who receive a TPV.
- If a stent fracture is detected, continued monitoring of the stent should be performed in conjunction with clinically appropriate hemodynamic assessment. In patients with stent fracture and significant associated RVOT obstruction or regurgitation, reintervention should be considered in accordance with usual clinical practice.

Potential procedural complications that may result from implantation of the Melody device include the following: rupture of the RVOT conduit, compression of a coronary artery, perforation of a major blood vessel, embolization or migration of the device, perforation of a heart chamber, arrhythmias, allergic reaction to contrast media, cerebrovascular events (TIA, CVA), infection/sepsis, fever, hematoma, radiation-induced erythema, blistering, or peeling of skin, pain, swelling, or bruising at the catheterization site. Potential device-related adverse events that may occur following device implantation include the following: stent fracture,* stent fracture resulting in recurrent obstruction, endocarditis, embolization or migration of the device, valvular dysfunction (stenosis or regurgitation), paravalvular leak, valvular thrombosis, pulmonary thromboembolism, hemolysis.

*The term "stent fracture" refers to the fracturing of the Melody TPV. However, in subjects with multiple stents in the RVOT it is difficult to definitively attribute stent fractures to the Melody frame versus another stent.

For additional information, please refer to the Instructions for Use provided with the product or available on http://manuals.medtronic.com.

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- Patients with stenotic prosthetic RVOT conduits or bioprostheses where the risk of worsening regurgitation is a relative contraindication to balloon dilatation or stenting

Contraindications

- Venous anatomy unable to accommodate a 22 Fr size introducer sheath
- Implantation of the TPV in the left heart
- RVOT unfavorable for good stent anchorage
- Severe RVOT obstruction, which cannot be dilated by balloon
- Obstruction of the central veins
- Clinical or biological signs of infection
- Active endocarditis
- Known allergy to aspirin or heparin
- Pregnancy

Potential Complications/Adverse Events: Potential procedural complications that may result from implantation of the Melody device include the following: rupture of the RVOT conduit, compression of a coronary artery, perforation of a major blood vessel, embolization or migration of the device, perforation of a heart chamber, arrhythmias, allergic reaction to contrast media, cerebrovascular events (TIA, CVA), infection/sepsis, fever, hematoma, radiation-induced erythema, pain, swelling or bruising at the catheterization site. Potential device-related adverse events that may occur following device implantation include the following: stent fracture.* stent fracture resulting in recurrent obstruction, endocarditis, embolization or migration of the device, valvular dysfunction (stenosis or regurgitation), paravalvular leak, valvular thrombosis, pulmonary thromboembolism, hemolysis.

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heart failure (FS < 10%) combined with recurrent episodes of decompensated right heart failure with severe recurrent ascites and pleural effusion, which required drainage of 4 to 8 litres of effusion fluid every 3 to 5 weeks. His diagnosis was a non-compaction cardiomyopathy of the left ventricle and impairment of both right and left ventricular function. He was in functional class NYHA IV. He was admitted to be listed for heart transplantation.

Echocardiography demonstrated the features of non-compacted left ventricular myocardium, with a fraction of shortening less than 10%, and an ejection fraction of less than 20%. Cardiac catheterization measured both pulmonary wedge, left and right atrial pressures to be 15 to 20 mmHg with mild pulmonary hypertension of 52/18, mean 29 mmHg.

Clinical state did not allow to list for cardiac transplantation. Over the following months, a number of agents and different treatment strategies failed to control his symptoms. Thus, it was eventually decided that he would have a BAS performed, followed by a 10 mm AFR device to be implanted. Both interventional procedures were straight forward and without complications. The necessity to drain ascites and pleural effusions ceased for about half a year following this procedure (see Figure 6). Clinically he improved to functional class NYHA II-III. As a result of his clinical improvement, he was accepted on the transplant list and successfully transplanted 10 months later. The AFR device was fully endothelialised as shown in Figure 7.

Discussion

These three patients are unified by having one clinical feature in common – i.e. severe imbalance of pre- and postcapillary pulmonary blood flow, either chronically as evidenced by right ventricular dysfunction and atrial congestion, or acutely, at times or during exercise, but with almost normal heart function at rest. Performance of a static BAS, with subsequent implantation of the AFR device, led to sustained clinical improvement, while the created atrial communication provided controlled shunt flow and while the device remained in situ and patent.

Case 1 demonstrates the potential of the BAS/AFR device implantation as a to bridge to transplantation by stabilizing the hemodynamically compromised patient and allowing even for some limited recovery, making them better candidates for transplantation. The newly designed AFR device presented here does have a similar mechanism and functions like the formerly

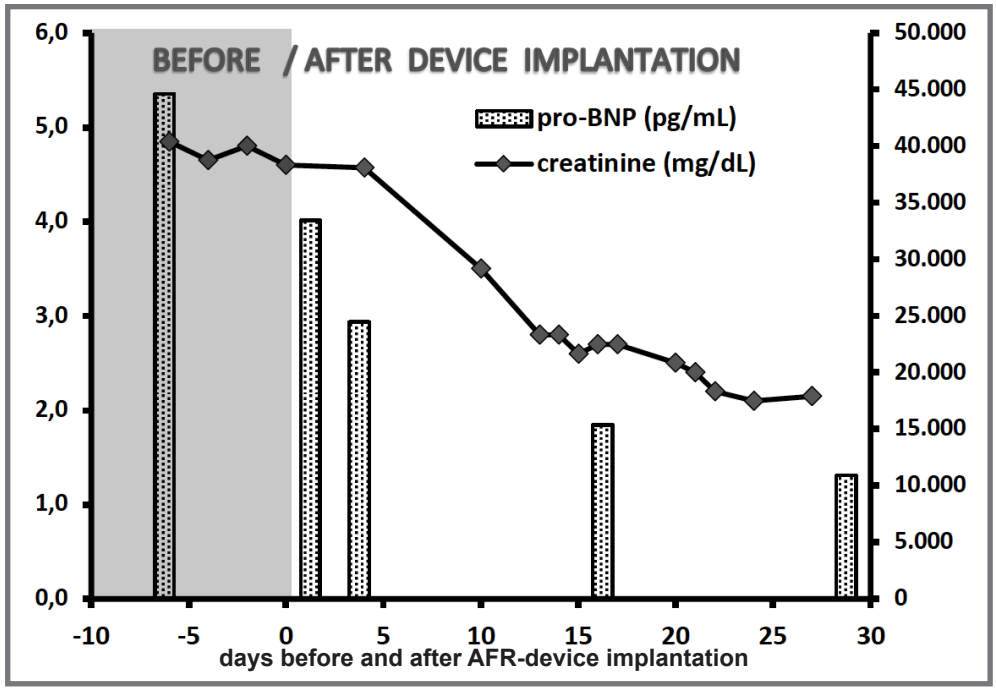

Figure 5. Same patient as in Figure 3. Serum creatinine and serum pro-brain natriuretic peptide (pro-BNP) before (gray background of graph) and following (white background of graph) AFR device implantation; both BNP and creatinine respond with a trend towards normalization.

available Amplatzer-Fenestrated ASD device that was used in patients to relieve atrial congestion in failing ventricles[11] and in children with pulmonary hypertension[12] but, unfortunately, had an unfavourable device/hole relation with relatively small holes (4 mm) compared to the large discs. The new AFR device used here shows a relatively large hole and less remaining left and right-sided discs and no thrombogenic patch material inside the discs; this may prevent an early re-occlusion and potentially decrease the risk of rapid and excessive endothelialisation[13].

Case 2 points out the other indications for the BAS (followed by AFR device implantation), which probably will evolve to be:

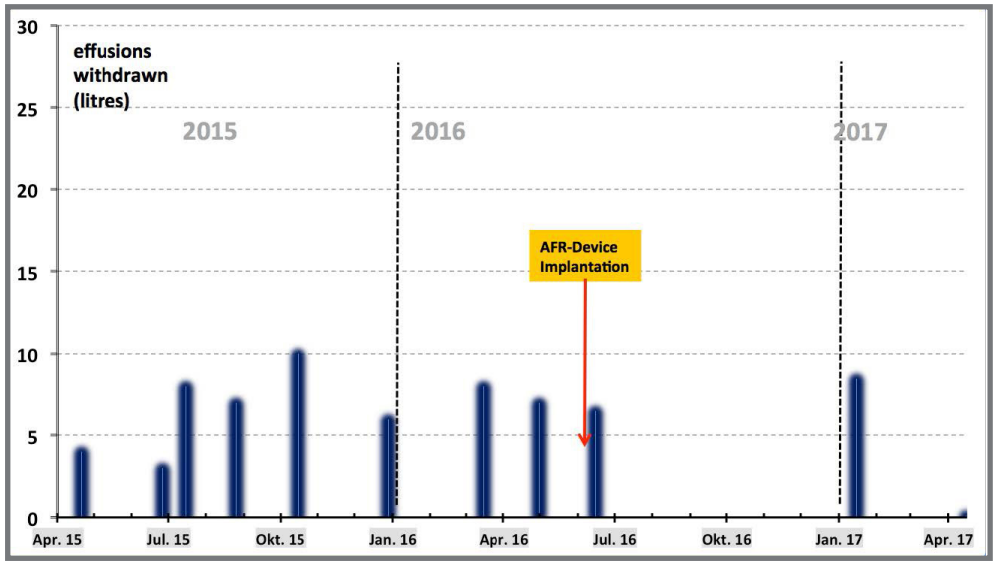

Figure 6. Result after implantation of the AFR device for episodic right heart decompensation with biventricular heart dysfunction (Case 3, see text). After implantation the episodes of heart decompensation with symptoms of right heart failure leading decreased and the necessary taps of pleural and abdominal effusions decreased in number and volume over time.

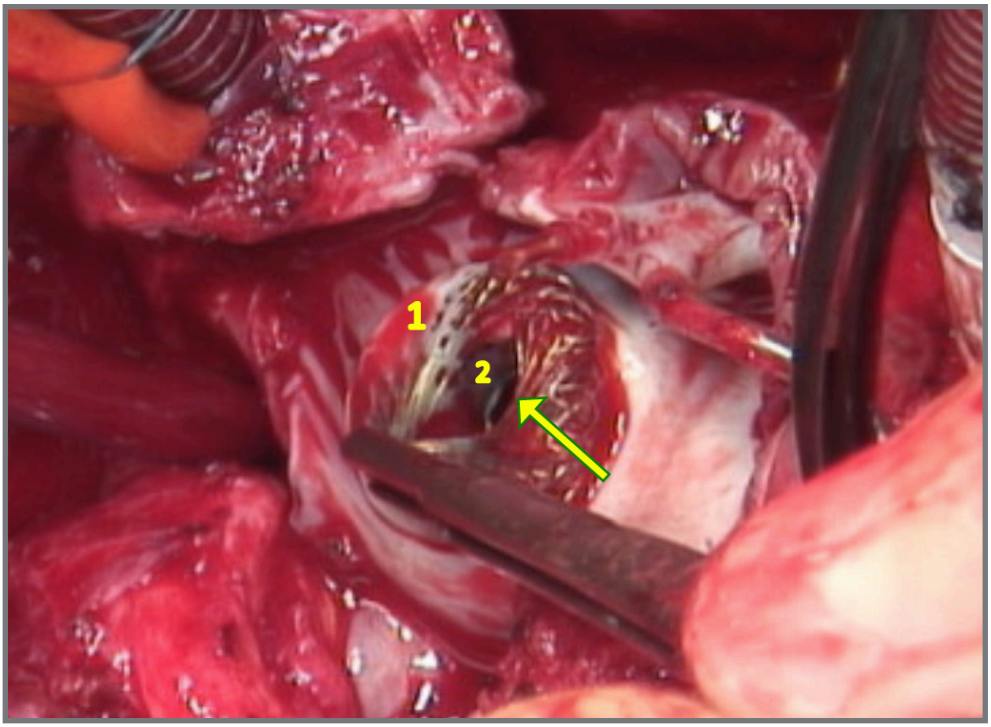

Figure 7. Result after implantation of the AFR device (Case 3, see text) and during cardiac operation immediately before heart transplantation. The patient's heart is seen from the right atrium towards the atrial septum. The AFR device is in situ and displayed with its right-sided sided disk[1]. The tweezer holds the device's connection hub. The wire meshwork of both the disk and the fenestration[2] shows endothelisation. The left atrium is visible through the fenestration (arrow) which is patent and free of thrombi. Time from AFR device implantation to heart transplantation had been 10 months.

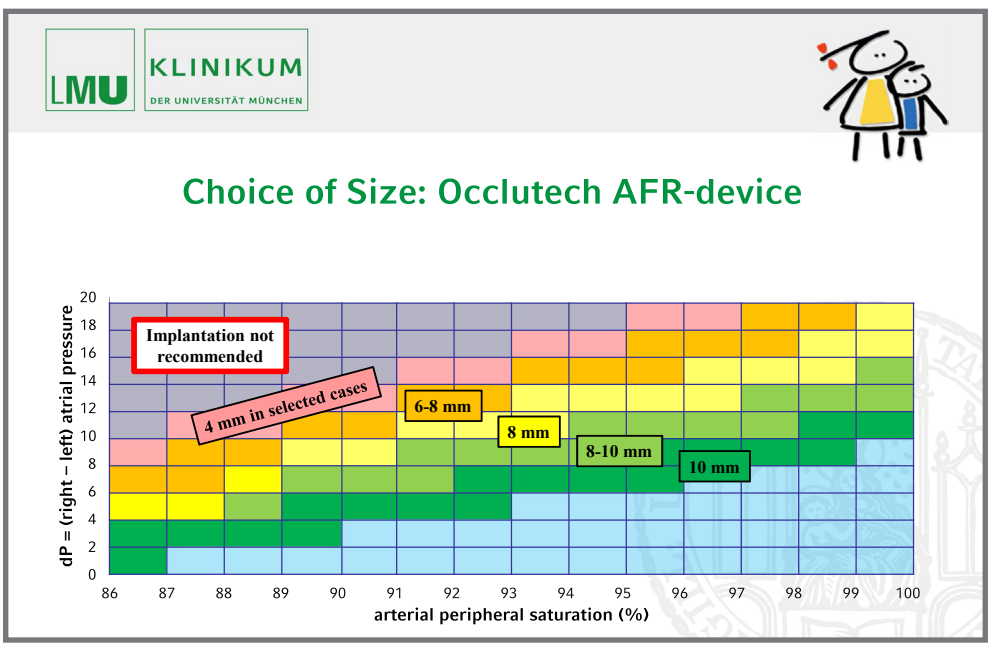

Figure 8. Recommendation for choice of size of the Occlutech AFR device implantation in an individual patient, on the basis of the systemic arterial saturation (x-Achsis) pre-implantaton and supported by oxygen, as individually necessary, and the difference of the atrial pressures (y-achsis). Important Disclaimer: This recommendation is based on clinical experience with use of the device in compassionate cases, and is only a guideline for the Occlutech AFR device implantation. A 4 mm device is available in very selected cases and circumstances.

1. Acute (within seconds or minutes) right heart failure, presenting clinically as syncope, which may typically occur in the beginning of Pulmonary Hypertensive Disease and when there is high response to triggers, pulmonary vasodilators and especially calcium antagonists. There still may be moderate pulmonary hypertension in the interval between the syncopal events.
2. Combined global myocardial depression with episodic right heart failure decompensating over the course of days or weeks, controllable only with more and more pharmacologic support as the heart disease progresses.

It is important to note that the BAS/AFR intervention not only takes away the effect of sudden increase in venous pressure by right heart decompensation from the venous system. In addition, it will prevent the recurring sudden increase in pulmonary vascular resistance that causes repetitive damage of right heart function. Thus, both systemic venous system recovery, and right ventricular function recovery take place and are the results of the BAS/AFR interventions. As a result, the patient not only experiences a relief of syncope or heart decompensation, but also has a somewhat unexpected added benefit of protected right heart function, resulting in increased exercise tolerance and improved clinical status.

Case 3 is a case of left heart failure due to non-compaction-myocardiopathy, as well as right heart failure. Cardiac catheterisation excluded left-ventricular failure induced inappropriate pulmonary hypertension as the cause for right heart failure. The assumption of an especially sensitive right heart due to the underlying diagnosis, worsening episodically due to small fluctuations of changes of ventricular-ventricular interactions together with pulmonary vascular resistance changes, with the BAS/AFR treatment directed against it, and resulted in clinical success.

In general, these patients demonstrate the benefits of a BAS in different settings, which are well known and have been performed often. However, we here wish to stress the impact of a protected BAS, as shown by a device which is easy to use, repositionable and virtually without risk to implant. It remains to be formally shown that the device continues to fulfil the other parts of its promise, that is, reliable anchoring in the atrial septum, and most importantly, persistent patency. However, results so far in our institution, and worldwide (> 57 devices implanted at the time of writing) are quite encouraging.

For this discussion here and the proper functioning of the AFR device, we must assume that the preceding BAS was correctly done, in terms of both the indication and the technique. The technical side can be notoriously very tricky and risky, as illustrated again in our cases, and must remain in experienced hands. If the indication is wrong, the BAS will not help. At best, it will also do no major harm, but the risk of the interventional BAS procedure is then not met with a benefit for the patient, and is done in vain. Only when there have been a past or will be future episodes where right heart decompensation and right atrial congestion were or will be very likely, then a left-to-right shunt directly after the BAS procedure does not contradict future success of it and hence positive clinical value and impact.

However, in all situations where the BAS is correctly indicated and done, the AFR device will be very beneficial as derived from theoretical considerations and current experience. The main advantages and arguments for implantation are the similarity with the technique of the ASD device by Occlutech company, with which many worldwide have worked previously[17]. Those doctors will need minimal training and will be able to properly implant the device almost instantly. The AFR device is easy to use after standard transseptal puncture has been done. Prior balloon dilatation using high pressure balloons to a diameter of the created ASD of 4-6 mm larger than the desired diameter of the AFR device fenestration is recommended. The final shape of the device shows a flat profile and allows an easy passage up the hole with potential of subsequent transatrial interventions or placement of catheter electrodes. Thus, the ease and low risk to implant the device is one crucial argument for its use. The remaining advantages in the long term are especially important for children and women, with endothelialisation occurring within three months after which the time for anticoagulation becomes unnecessary.

While the BAS – intervention carries a concrete risk and can be very difficult in individual cases, the AFR device implantation is very straight forward, due to the just created defect in the atrial septum and the guide wire, which remains in position and allows swift positioning of the AFR implantation gear. This is important to mention as the additional risk burden by the AFR intervention to the entire combination of (the two) interventions is minimal, once the BAS has been performed successfully, but adds – and this is the important part – significantly to the overall success of this intervention, while adding only minimal risk to the patient.

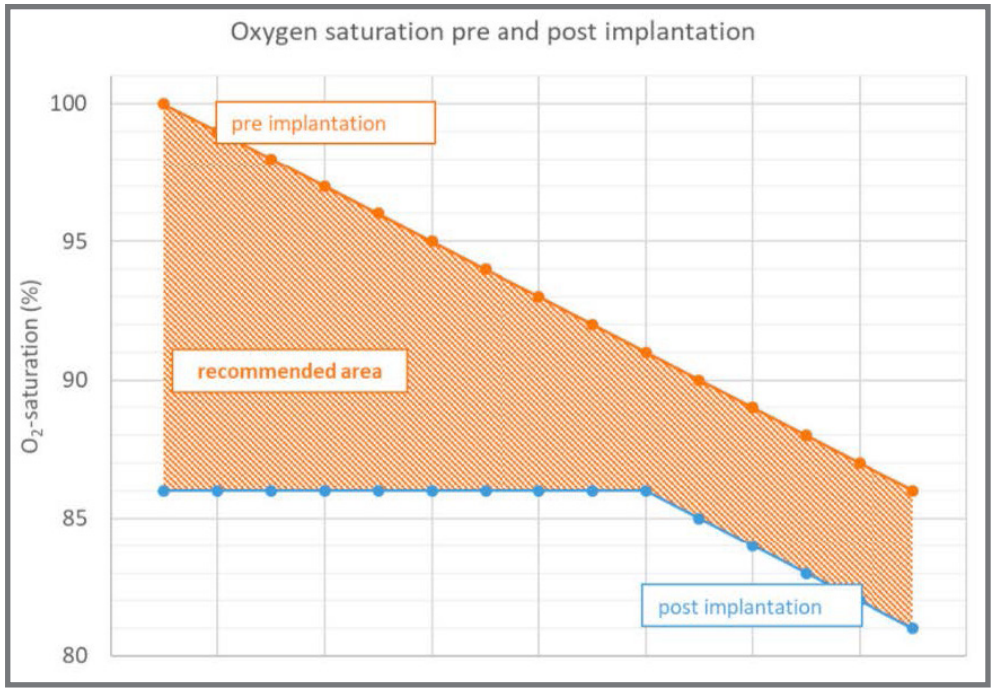

Figure 9. Recommendation for the situation after the chosen AFR device has been implanted (see Figure 8). With the AFR device implanted and functioning and providing a RL-shunt, the patient's saturation should remain in the pink field, after a waiting time of some 15-25 min had been given. If saturations remain below the field and/or patient feels unwell, a smaller device should be implanted after removing the previous one. Important disclaimer: This recommendation is based on clinical experience with use of the device in compassionate cases, and is only a guideline for the Occlutech AFR device implantation.

Figure 10. Diagram of the PROPHET Trial with shared responsibilities of investigators regarding structural requirements and clinical recruitment.

The overall success is not only the securing of the mechanical intervention, but also the consequential benefit of not needing to do a repeat catheterization and intervention, and being able to avoid plasmatic anticoagulation. The AFR device thus supports the BAS to produce the crucial change in hemodynamics in severely compromised patients, who, when selected properly, will profit significantly from it.

Limitations

- In general, patient selection must be done almost on a case-by-case basis. This is despite general guidelines and inclusion criteria for performing a BAS and for implanting an AFR device with a specific fenestration diameter. Considerations also must include the experience of handling a case with severe pulmonary hypertension by the interventionalist, the cardiac anaesthetist's or intensivist's experience for the immediate care during and shortly after the procedure, and the team's experience with the long-term PHT care. Indeed, these considerations are by far not trivial: both the interventional and PHT teams must work very closely and honestly and, ideally, consist of several individuals who have dual experience.
- More specifically, the choice of the device size to be implanted is also a complex decision. Recoil of the right atrium when smaller, compliance of the left atrium and, as the right-to-left shunt volume is directly flowing into it, the compliance of the left ventricle, which in turn is determined by septum reposition due to the offloading, myocardial compliance, which in turn again, is determined by age and aggressiveness of the PHT disease – a number of factors that feed back into each other in a complex loop and can only be "guesstimated" by some guidelines derived from experience (see Figures 8 and 9).

The PROPHET Trial

This study (www.clinicaltrials.gov; Identifier: NCT03022851) started in 2017 in our institution and continues to run Europe-wide, aims to show the safety and reliability of the Occlutech AFR device. Also, its benefits for patients with precapillary pulmonary hypertension and acute or chronic right ventricular failure as discussed above will be assessed. We hope to show that the AFR device serves as a reliable and easy-to-use device. The ultimate aim would be, as it will be used increasingly, that the treatment potential of the well-known BAS in a still incurable disease despite all medications, and in view of too small a number of available donor lungs for transplantation – will, hopefully, become appreciated and used more and more, as the procedure is supported by the Occlutech AFR device.

Conclusion

Protecting the result of a correctly indicated and performed BAS intervention by using the new AFR device is a safe procedure that is very easy to perform. The AFR device provides a relatively flat fenestration anatomy without protrusion into the circulation which reduces potential thrombus formation and untoward closure of the fenestration while providing a reliable and defined fenestration diameter. The use of this device may ensure a permanent clinical improvement of these patients. We believe that this device is not only a very helpful addition in the armamentarium of interventional cardiologists treating these complex patients, but specifically, may allow the BAS to re-emerge as the useful and worthwhile intervention it originally was conceived to be[18].

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Crossing the Health Care Digital Divide with Remote Monitoring

By Stuart Long and Colin Movsowitz, MD

In 2019, where you live shouldn't dictate your access to medical treatment.

But a discrepancy still exists between access to healthcare in urban and rural areas. Digital health technologies are the tools to shrink that gap.

In the era of innovation that we live in, there is no reason that anyone should lack proper access to healthcare. More than 46 million Americans—or 15% of the population—live in rural areas. This translates into a need for more than 4,000 additional doctors[1].

Those same communities are in need of hospitals too. Over the last decade, we have seen 100 hospitals in 30 states close their doors, with Texas (20) Tennessee (12) and Georgia and Oklahoma (seven each) having the highest number of closures[2].

In addition to the lack of facilities and physicians, residents in rural areas statistically have unhealthier habits than other populations. Rural residents pursue less physical activity and smoke more than urban dwellers[3].

Rural areas also have a higher concentration of adults aged 65 years and older than urban or suburban counties. This adds another layer of complexity to the issue. According to the *National Council on Aging*, about 80% of older adults have at least one chronic disease, and 68% have at least two. Those chronic diseases place a significant burden on individuals, often requiring constant medical monitoring and hospital visits. For city-dwellers, this could be 10-20 minutes away. For rural patients, this could mean a drive of 30 minutes at the minimum.

With the aging Baby Boomer generation in need of sufficient healthcare options, the lack of doctors and the loss of these facilities is taking a toll.

According to the Centers for Disease Control, rural Americans are more likely to die from heart disease, cancer, unintentional injury, chronic lower respiratory disease and stroke than their urban counterparts[4]. In general, residents of rural areas in the United States tend to be older and sicker than their urban counterparts. These statistics, although startling, are not beyond repair[5].

What Does All This Mean?

It means that most rural populations are woefully under-served when it comes to healthcare. All patients deserve access to the best medical solutions, regardless of their location. It's vital for healthcare providers to incorporate remote monitoring and telemedicine procedures into their longitudinal patient care plans to serve this segment of the country.

The Solution

Telehealth is—and will continue to—play a major role in serving rural communities and their healthcare needs. Simple apps and consumer wearable devices can help patients track their fitness activity, eating habits, sleep patterns and heart rates to facilitate a better quality of life. These are a good start for those in rural areas looking to improve their general health overall. Sometimes these products even lead patients to more advanced medical monitoring devices, like mobile cardiac monitors.

Remote Patient Monitoring (RPM) can help doctors and other healthcare professionals monitor a patient's chronic health conditions without the patient needing to visit an out-of-the-way hospital or bear the cost of an office visit.

Colin Movsowitz, MD, is a user of remote cardiac patient monitoring in his practice and knows firsthand the benefits of this technology are unprecedented.

"Monitoring plays a key role in electrophysiology and even in general cardiology. For example, a patient may feel dizzy or symptomatic, but when they come to the office, their heart may be well be in a normal rhythm. That does not an exclude an arrhythmia as the cause of their problem. What you need to do is correlate the patients symptoms with the arrhythmia—which are commonly episodic. They may occur daily. Sometimes weekly. But, on occasion, patients will present with symptoms which only occur monthly or sometimes every six months. And so, to make a diagnosis, you need to be able to provide the patient with the means to record the heart rhythm while they have symptoms," said Dr. Movsowitz.

In the context of all patients, this is a vital technology that properly assesses a patient's needs and enables the development of an effective treatment plan. In the context of rural patients, this is especially pivotal, as they often cannot make frequent appointments due to their distance.

But not all monitors are made the same. There are currently a few types of mobile cardiac telemetry monitors on the market:

- **Holter:** Provides 24-48 hours of continuous heart monitoring. The data isn't available to the physician until the patient returns the monitor.
- **Event:** The next monitor is a variation on the Holter monitor. It's called a loop recorder. A loop recorder is not as user-friendly because the patient has to attach the monitor to themselves, so they have to be prepared to have stickers placed on their chest. They can put it under their clothes. They can take it off in their shower, but they must keep putting it on. It can give patients rashes as well.
- **Mobile:** Mobile cardiac outpatient telemetry is intended to simulate what a patient would have if they were in a hospital.

These remote cardiac monitoring devices and other telehealth technologies are a huge part of the solution for the large rural areas of our country. They give people the freedom to live in areas where the healthcare workforce and hospital shortages exist, while still remaining securely connected to a healthcare professional in real time.

In laymen's terms, it's safe to say that remote patient monitoring is a pretty big deal. As a doctor, they've aided Dr. Movsowitz—and others like him—immensely in monitoring and treating patients. And for patients—they have the peace of mind to live freely while their doctor monitors their activity from miles away.

InfoBionic's MoMe Kardia device and other telehealth services are just one fraction of the complex puzzle required to solve the rural healthcare challenge. There is still

a need for healthcare industry leaders to develop and implement programs to support remote networks in order to support patients and work with manufacturers to ensure the remote monitoring technology requirements can meet the healthcare demands of rural patient populations.

With RPM technology, rural patients don't have to live without the standard of healthcare they deserve. While the broadband infrastructure in rural areas still lags behind their urban and suburban counterparts, the opportunities exist to bring stakeholders together–from patients, doctors, software developers and even telecommunications providers–to extend the reach of these lifesaving monitoring technologies.

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Medical News, Products & Information

Compiled and Reviewed by Kate Baldwin and Tony Carlson

New Cardiac Pump Clinically Superior, Safer for Patients

Final results from MOMENTUM 3 show reduction in strokes, bleeding and near elimination of pump thrombosis

Brigham and Women's Hospital

The final results are in for MOMENTUM 3, the largest Left-Ventricular Assist Device (LVAD) trial ever conducted. The study of more than 1,000 patients with severe heart failure not only confirms that the HeartMate 3™, a next-generation LVAD device, markedly reduced the need for re-operations due to pump malfunctions, but also found that it lowered risk of bleeding events and strokes, compared to the HeartMate II™. Results were presented in a Late-Breaking Clinical Trial at the *American College of Cardiology's 68th Annual Scientific Session* by Mandeep R. Mehra, MD, Executive Director of the Center for Advanced Heart Disease and Medical Director of the Heart & Vascular Center at Brigham and Women's Hospital, and published simultaneously online in the *New England Journal of Medicine*.

"We are thrilled to have completed the largest LVAD trial in the world, to see that all of the early benefits we observed in interim analyses were sustained, and to report reductions in pump-related thrombosis, strokes and mucosal bleeding -- three measures of hemocompatibility -- compared to the previous generation of cardiac pump," said Mehra. "Our results should spur confidence that we now have a much more forgiving pump and should provide reassurance to clinicians that we do not need to wait until a patient is 'near death' to consider this option for our patients."

MOMENTUM 3, sponsored by Abbott Inc., compared Abbott's HeartMate 3™ left-ventricular assist system, a magnetically-levitated, continuous centrifugal-flow circulatory pump, to the HeartMate II™, a commercial axial flow pump. The trial evaluated how many participants, two years after receiving their device, had not suffered a disabling stroke or had an operation to replace or remove a malfunctioning device.

A total of 1,028 patients were randomized to receive either the centrifugal flow pump or the axial flow pump. The team found that 397 patients (76.9%) in the centrifugal-flow pump group did not experience a disabling stroke or need a re-operation compared to 332 (64.8%) in the axial-flow pump group. Only 12 people who received the centrifugal-flow pump needed a re-operation compared to 57 patients who received the axial pump. The centrifugal-flow pump reduced risk of stroke by 58%, major bleeding by 36% and gastrointestinal hemorrhage by 36%. Infection rates and rates of right heart failure were no different between the two groups.

MOMENTUM 3 launched in 2014 and was designed to dramatically reduce the overall timeline for clinical trials. All patients with refractory heart failure who needed a cardiac pump were eligible for the trial, regardless of whether the pump was intended as a bridge to transplantation or destination therapy. Based on the study's first interim analysis at six months, the HeartMate 3™ was approved in 2017 by the FDA for use as a short-term device, such as for a bridge to transplantation. Last fall, supported by the second interim results of MOMENTUM 3, the pump was approved by the FDA as a long-term use device, such as for patients with advanced heart failure who are not eligible for a heart transplant.

The HeartMate 3™ includes several technological adaptations intended to reduce risk of complications. The fully magnetically levitated device runs like a bullet train -- its rotor has no mechanical bearings in it and pushes the blood using only magnetism. It is designed to reduce shear stress and destruction of blood elements as they pass through the pump, which is thought to cause blood clots to form in pumps.

Reductions in bleeding events, re-operations and strokes could translate to important cost savings. The team calculated that in every 10 patients implanted with the centrifugal-flow pump, compared with the axial-flow pump, 2.2 pump thrombosis events, two strokes and 6.8 bleeding events would be averted over a two-year period.

"Until now, these devices have been considered less cost-effective, which has been a big issue outside of the US," said Mehra. "Our evidence shows a decreased need for hospitalization and re-operations, indicating that the centrifugal-flow pump may be much more cost-friendly in the longer term."

Mehra notes that residual risks remain, including infections, which occur in nearly 50% of patients. Many, but not all, of these infections occur at the entry point of the drive line that powers the device. In addition, low-frequency, right-ventricular heart failure events can occur. Mehra is now chairing a follow-up trial that will specifically examine these challenges and what modifications can be made to address them.

Scientists ID New Metabolic Target to Prevent, Treat Heart Failure at Earliest Stage

Ohio State University Wexner Medical Center

Researchers with The Ohio State University College of Medicine and The Ohio State University Wexner Medical Center have identified a metabolic process in the heart that, if treated, could someday prevent or slow the progression of heart failure. The findings were published in the *Journal of the American Heart Association*.

Before any physical signs or symptoms of heart failure are present, the first maladaptive changes occur in cardiac cell metabolism - how the heart fuels itself to pump blood through the body constantly.

"Our hearts burn fuel, much like combustion engines in cars. Instead of gasoline, our heart cells burn fats and a small amount of glucose," said Doug Lewandowski, Director of Translational Research at Ohio State's Dorothy M. Davis Heart and Lung Research Institute. "When our hearts become chronically stressed, they try to adapt, but some of those changes make things worse."

For their research, Lewandowski's team examined both mouse models of heart failure and human heart tissue obtained from heart failure patients before and after heart-assist devices were surgically implanted. They found that the amount of a reactive

Doug Lewandowski, PhD
Photo Credit: The Ohio State University Wexner Medical Center

fat compound, called acyl-CoA, is nearly 60% lower in failing hearts compared to normal hearts. This disruption in the heart's normal metabolism creates toxic fats that impair the heart's ability to function and pump properly.

Then the team tested mice that overexpressed a gene for a protein called ACSL1, that's known to make acyl-CoA. When exposed to conditions that cause heart failure, the mice kept making normal amounts of acyl-CoA and the extent of heart failure was reduced and delayed.

"By maintaining this fat compound, acyl-CoA, the hearts retained their ability to burn fat and generate energy. Importantly, over-expression of ACSL1 also reduced toxic fats, normalized cell function and reduced the progressive loss of function in the enlarged mouse hearts," said Lewandowski, who is also a Professor of Internal Medicine at Ohio State's College of Medicine.

When the team examined failing human hearts that had the help of a left-ventricular assist device (LVAD), they found similar effects - the levels of acyl-CoA had restored to normal when the sick hearts didn't have to work beyond their capacity.

"This tells us there's an important relationship between fat metabolism in the heart and the inability to pump well, and we need to learn more. We believe targeting the normalization of acyl-CoA through gene or drug therapy or, potentially, dietary protocols, is a new approach to explore," Lewandowski said.

"Heart failure is the only form of heart disease that hasn't dropped in 35 years. As findings like these help identify the metabolic underpinnings of the disease, it gives hope for promising new therapies for patients," said Dr. K. Craig Kent, Dean of the College of Medicine.

Next, Lewandowski's team wants to explore how normalizing acyl-CoA helps reduce toxic fats and increase protective fats inside the heart. Soon, they hope to use advanced imaging to track fat metabolism and function in patients' hearts.

"We need to understand how we're manipulating the chemical reactions and what exactly is leading to the improvement. Then we can look at whether we can supply the heart with fats, supplements or medications that assist with creating acyl-CoA. Ultimately, it's about trying to prevent or slow the progression toward heart failure," Lewandowski said.

Fountain of Youth for Heart Health May Lie in the Gut

Age-related Changes to Microbiome Fuel Vascular Decline, New Study Shows

Why do blood vessels naturally stiffen and degrade as we age, boosting cardiovascular disease risk? New University of Colorado Boulder research has identified a surprising new culprit – and it lives in your gut.

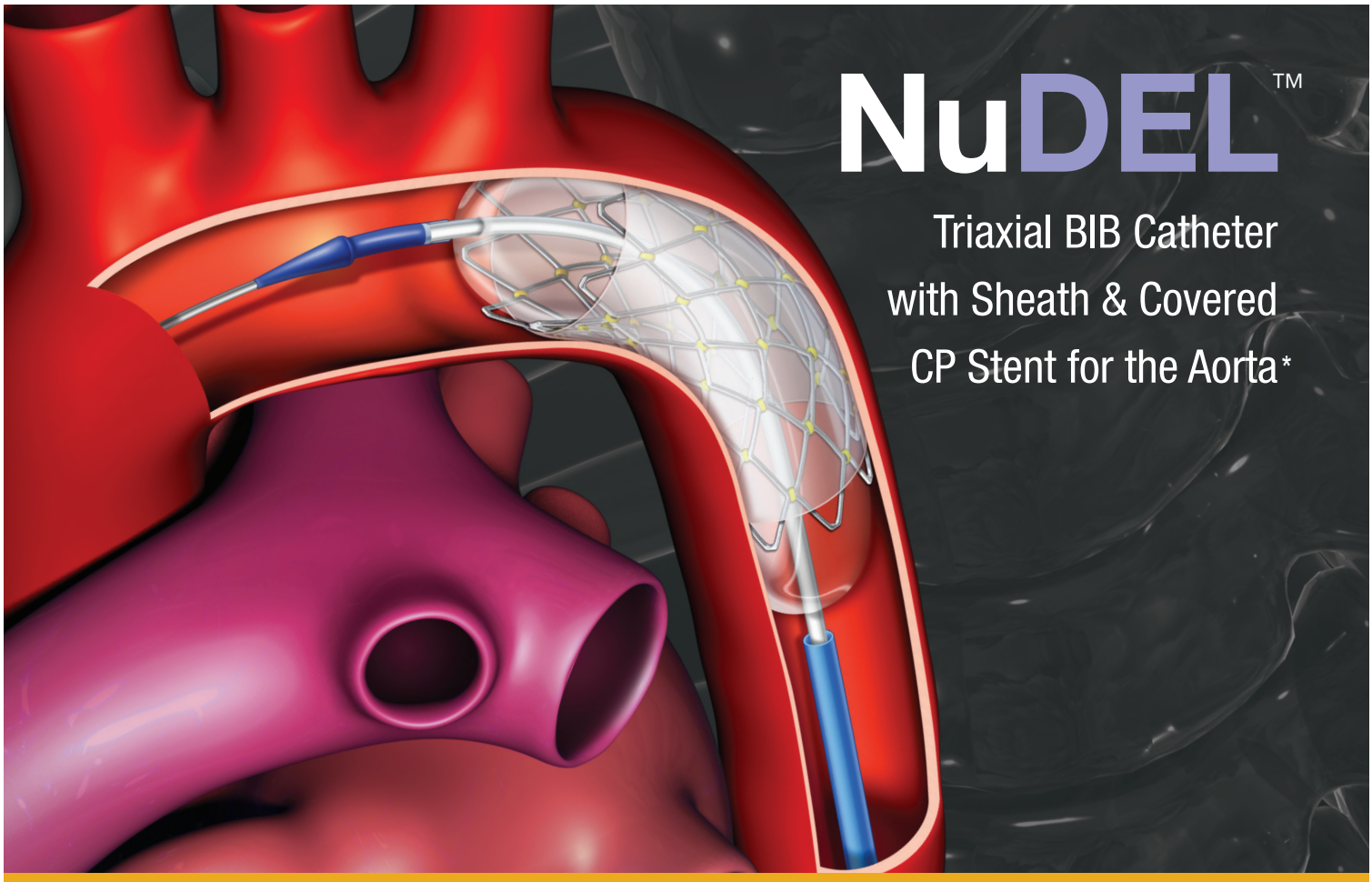
"This is the first study to show that changes in the gut microbiome with aging have an adverse impact on vascular health," said lead author Vienna Brunt, a postdoctoral researcher in the Department of Integrative Physiology. "It opens up a whole new avenue of potential interventions to prevent cardiovascular disease."

For the study, published in the *Journal of Physiology*, researchers gave young mice and old mice broad-spectrum antibiotics to kill off the majority of bacteria living in their gut, aka their gut microbiome. Then they assessed the health of their vascular endothelium (the inner lining of their blood vessels) and the stiffness of their large arteries.

They also measured blood levels of inflammatory compounds, tissue-damaging free-radicals, antioxidants and the blood-vessel-expanding compound nitric oxide in both groups.

After three to four weeks of the treatment, the young mice saw no change in vascular health. The old mice, however, saw vast improvements on all measures.

"When you suppressed the microbiome of the old mice, their vascular health was restored to that of young mice," said senior author and Professor Doug Seals, Director of the Integrative Physiology of Aging Laboratory. "This suggests there is something about those microorganisms that is causing vascular dysfunction."



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Vienna Brunt, Postdoctoral Researcher at University of Colorado at Boulder. Photo Credit: CU Boulder.

To assess what that something may be, the researchers then took fecal samples from another set of mice and had them genetically sequenced, comparing the gut bacteria living in the old mice with that in the young.

"In general, in the old mice, we saw an increased prevalence of microbes that are pro-inflammatory and have been previously associated with diseases," Brunt said.

For instance, the old mice hosted significantly more Proteobacteria, a phyla that includes Salmonella and other pathogens, and pro-inflammatory Desulfovibrio.

To drill down further, the researchers measured blood levels of metabolites – small molecules produced by the gut microorganisms and absorbed into the bloodstream – in old and young mice.

Old mice had three times as much TMAO (trimethylamine N-oxide), a metabolite shown in previous studies to be linked to increased risk of atherosclerosis, heart attack and stroke.

As early as 45, risk of cardiovascular disease begins to creep up, according to the *American Heart Association*. By age 60-79, 70% of people in the United States have it. After age 80, fewer than one in five are free of it.

But just what causes healthy arteries to stiffen and lose function with age has remained somewhat of a medical mystery.

"We have long known that oxidative stress and inflammation are involved in making arteries unhealthy over time, but we didn't know why arteries begin to get inflamed and stressed. Something is triggering this," Seals said. "We now suspect that, with age, the gut microbiota begins producing toxic molecules, including TMAO, which get into the blood stream, cause inflammation and oxidative stress and damage tissue."

Seals and Brunt stress that they are absolutely not suggesting people use antibiotics as a cardiovascular fountain of youth.

"We purely used antibiotics as an experimental tool. There are far too many side-effects and other problems with using it broadly," Brunt said.

But they do believe that diets high in probiotic-rich cultured food (yogurt, kefir, kimchi) and prebiotic fiber could play a role in preventing heart disease by promoting a healthy gut microbiome.

They're also studying a compound called dimethyl butanol, found in some olive oils, vinegars and red wines, which blocks the bacterial enzyme required to produce TMAO. Ultimately, it could be developed into a dietary supplement.

Bigger picture, the paper – along with studies linking an aging microbiome to gastrointestinal, immune and brain aging – offers one more reason to keep our resident bacteria healthy, notes an editorial accompanying the journal article.

As its authors put it: "The fountain of youth may actually lie in the gut."

New Pediatric Blood Pressure Guidelines Identify More Kids at Higher Risk of Premature Heart Disease

Hypertension Journal Report American Heart Association

New guidelines that classified more children as having elevated blood pressure are better at predicting which kids are likely to develop heart disease when they reach adulthood, according to new research in the *American Heart Association's Journal Hypertension*. The guidelines were issued by the *American Academy of Pediatrics (AAP)* in 2017 and endorsed by the *American Heart Association*.

Compared with the 2004 guidelines from the *AAP*, the 2017 guidelines increased the number of children classified as being in higher blood pressure categories, but it was not clear if the new criteria effectively identified children who were at higher risk of premature heart disease.

"After reviewing years of information from the Bogalusa Heart Study, we concluded that compared with children with normal blood pressure, those reclassified as having elevated or high blood pressure were more likely to develop adult high blood pressure, thickening of the heart muscle wall and the metabolic syndrome - all risk factors for heart disease," said Lydia A. Bazzano, MD, PhD, senior author of the study and Associate Professor of Epidemiology at the Tulane School of Public Health and Tropical Medicine in New Orleans.

The Bogalusa Heart Study enrolled participants in childhood and has followed them for 36 years. Childhood test results on 3,940 children (47% male, ages 3-18 years and 35% African-American) and adult follow-up revealed that:

- 11% of the participants would be identified as having high blood pressure using 2017 guidelines, compared with 7% using 2004 guidelines; and
- 19% of those with high blood pressure under 2017 guidelines developed thickening of the heart muscle during the follow-up period, compared with 12% of those considered to have high blood pressure under 2004 guidelines.
- Not all children identified with high blood pressure under the new guidelines will require medication for the condition.

"For most children with high blood pressure that is not caused by a separate medical condition or a medication, lifestyle changes are the cornerstone of treatment. It's important to maintain a normal weight, avoid excess salt, get regular physical activity and eat a healthy diet that is high in fruit, vegetables, legumes, nuts, whole grains, lean protein and limited in salt, added sugars, saturated- and trans- fats to reduce blood pressure," said Bazzano.

Bazzano stressed that lifestyle changes can improve the health of the entire family as well as the child who has been found to have high blood pressure.

The study is limited by the lack of data on actual heart attacks and strokes during adulthood. That data is currently being collected, according to the researchers. Results on participants in the Bogalusa Heart Study, who are from one community in Louisiana, may not be generalizable to the nation as a whole.

New Study Demonstrates Viral Family Targeted by the Immune Response to Kawasaki Disease

By Preparing Antibodies From Clonally Expanded Peripheral Blood Plasmablasts from Kawasaki Disease Children, Antigens of a Previously Unidentified Virus Targeted by the Antibody Response to the Disease Have Been Identified

A new study identifies antigens targeted by the antibody response of children with Kawasaki Disease (KD). Findings were presented during the *Pediatric Academic Societies (PAS) 2019 Meeting*, that took place in April in Baltimore, MD.

"To identify antigens targeted by the antibody response of children with KD, we identified plasmablasts that were clonally expanded in the peripheral blood of 11 children with KD and made monoclonal antibodies from these plasmablasts," said Anne Rowley, MD, one of the authors of the study. "Monoclonal antibodies from nine of the 11 patients identified intracytoplasmic inclusion bodies in ciliated bronchial epithelium of fatal KD cases. A subset of these antibodies recognizes peptides from a hepacivirus non-structural protein, and an optimized peptide blocked binding of these antibodies to the inclusion bodies, demonstrating the presence of a hepacivirus-like protein in the inclusion bodies. These results strongly suggest that a new human virus, closely related to the hepaciviruses and with a respiratory portal of entry, is etiologically related to KD."

The study isolated peripheral blood (PB) from KD children one to three weeks after fever onset, and characterized the response using single cell RT-PCR. It identified oligoclonal PB sets and highly mutated IgA PB, and generated monoclonal antibodies from these PB. It used the monoclonal antibodies to evaluate reactivity to KD tissues and to a peptide array comprising 29,939 peptides derived from 13,123 B cell epitopes of animal viruses reported in the Immune Epitope Database and Analysis Resource.

The study sequenced 1,156 PB from 11 KD patients, and identified 44 sets of oligoclonal PB in these patients. It prepared 61 monoclonal antibodies (Mab) from oligoclonal PB and from IgA PB that showed high levels of somatic mutation. Ten of these antibodies strongly bind to KD ICI, and 23 weakly bind. Animal virus peptide array revealed that Mab KD4-2H4 (from patient KD4), which strongly binds ICI, recognized multiple similar peptides from a nonstructural protein of hepacivirus C with an identified motif that was highly significant at e-118. Patient KD4 had negative hepatitis C serology. Peptide substitution analysis was performed to identify optimal amino acids for binding of KD4-2H4 at each position. ELISA using an optimized peptide revealed that four other KD Mab from two additional KD patients also recognized this peptide; all three patients had coronary aneurysms. The strong ICI binding of KD Mabs KD4- 2H4 and KD6-2B2 was completely blocked by pre-incubation with the optimized peptide.

Children with KD make antibodies to hepacivirus peptides, and KD ICI contain protein with a hepacivirus-like epitope. These results strongly suggest that a new human virus, closely related to the hepaciviruses and with a respiratory portal of entry, is etiologically related to KD. Identification of the specific etiology of KD could revolutionize KD diagnosis and treatment in the future.

The *PAS 2019 Meeting* brought together thousands of pediatricians and other health care providers to improve the health and well-being of children worldwide. For more information about the *PAS 2020 Meeting*, please visit www.pas-meeting.org.

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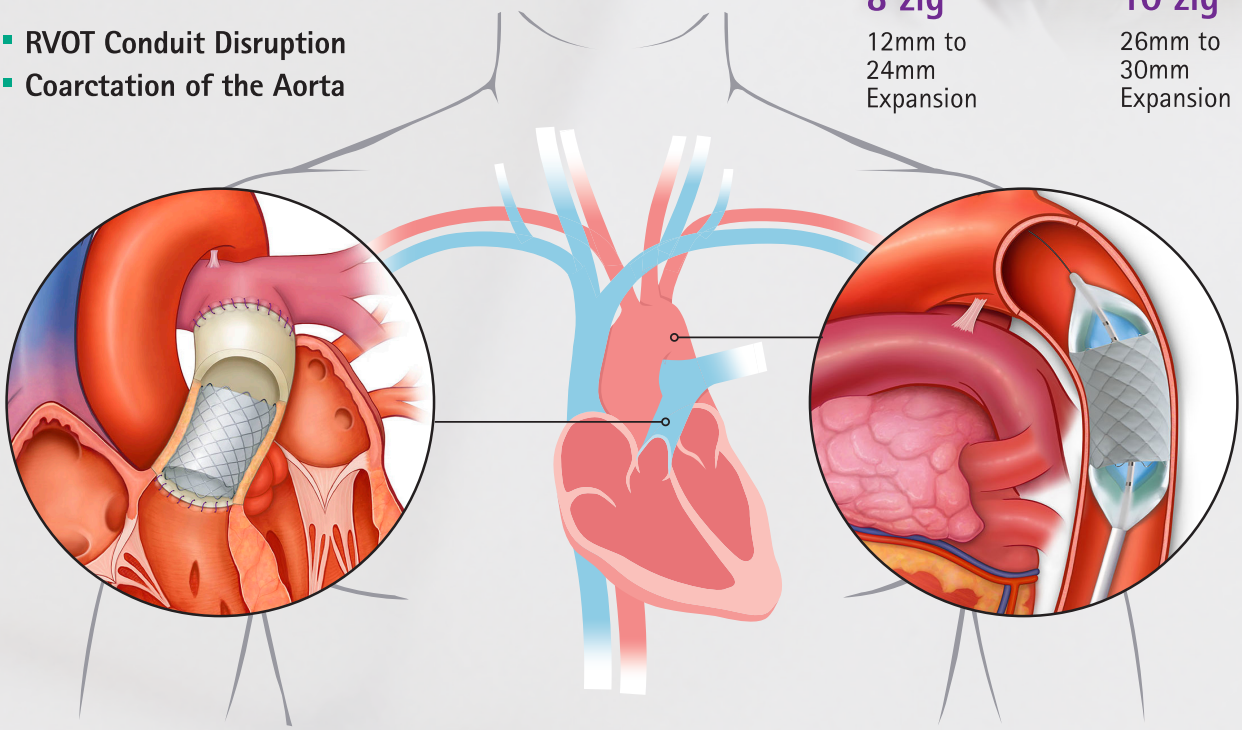

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