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Transapical mitral valve implantation: the Lutter valve

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ABSTRACT

The development of transcatheter techniques for treatment of severe mitral valve regurgitation in the beating heart is focus of recent research. An off-pump treatment technique poses great benefits, particularly for multi-morbid patients, often being non-compliant to the gold standard treatment, being open heart surgery with use of a cardiopulmonary bypass. Thereto, two approaches are being followed: transcatheter valve repair and transcatheterimplantation of a valved stent into the native mitral valve annulus. A valved stent has to provide safe and secure fixation within the high pressure system of the left heart. One of the main challenges in the development of such a valved stent is the complex anatomy of the mitral valve, with no clearly defined structures for device anchorage. Our group has developed a self-expanding nitinolvalved stent for transapical implantation in the beating heart. During the development process of thevalved stent, different design iterations were conducted to decrease the risk of paravalvular leakages, to enhance the reproducibility and to improve the overall stent performance. This article reviews the major milestones passedin the development process of our mitral valved stent and advances achieved withinthe last years. Multiple design iterations lead to a prototype providing secure stent deployment, hig h reproducibility, low paravalvular leakages and only mild stent deformation in the beating heart. In future, further long-term in vivo trials have to be conducted before attempting the step towards clinical application of this novel device.

Keywords: *mitral, valved stent, transcatheter, beating heart, off-pump.*

Transcatheter procedures for treatment of diseased heart valves in selected patients are of increasing importance, with promising results following transcatheter aortic valve implantation (TAVI). The performance of TAVI procedures has rapidly increased in the past years. The number of catheter-based isolated aortic valve surgeries in Germany tripled from around 2,500 procedures in 2009 to around 7,500 procedures in 2011 (1, 2); 58.6% of these have been performed in patients with an advanced age of 80 to 89 years (2). Without the necessity for open surgery and cardio-pulmonary bypass, these percutaneous procedures are of particular benefit to multi-morbid patients. The demand for alternative, less invasive treatment options, which avoid the use of a cardio-pulmonary bypass, is rapidly growing as the number of patients of advanced age is further increasing due to demographic changes. In 2010, the cohort of seniors aged 65 and over was 13.1% of the total population in the USA (3) and this number is projected to increase to 21.6% in 2025 (4).

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Next to TAVI, the catheter based treatment of the atrio-ventricular valves in the beating heart is focus of recent research. The main challenge is that, unlike in the aortic or pulmonary position, no conveniently defined adjacent structures there are no convenient adjacent defined structures for device anchoring.

The first experimental off-pump transcatheter stent implantation into the mitral valve via the left atrium implantation via the left atrium into the mitral valve has been reported by Ma et al. in 2005 (5). Seven years later, the first-in-human transfemoral transcatheter mitral valved stent implantation was performed by Søndergaard and colleagues in Copenhagen in June 2012 (6). An 86-year-old male suffering from severe MR was treated and survived for 2.5 days. Further details have not yet been published. Simultaneously, our group has reported multiple studies, showing the feasibility of successful mitral valved stent implantation via transapical approach with follow up times of up to two months (7-12), in which a self-expanding valved stent was implanted in the native mitral position under transesophageal echocardiographic (TEE) guidance in the beating heart. The nitinol stent frame (Euroflex GmbH, Pforzheim, Germany), comprised of a ventricular stent body and an atrial element connected at a preset angle, was covered with a polytetrafluoroethylene (PTFE) membrane (Zeus Inc., Orangeburg, SC, USA) to minimize paravalvular leakage (PVL). A tri-leaflet bovine pericardial or native porcine aortic heart valve was sewn into the ventricular body and a ventricular fixation system, consisting of four individual neo-chordae, was attached to the ventricular rim of the stent (*Figure 1*).

In the in vivo trials mitral valved stents were successfully implanted in healthy pigs. This was achieved by an adequate valved stent design, a well functioning delivery system and deployment strategy, and a professional interdisciplinary team. First prototypic designs included a star-shaped atrial element to prevent stent migration into the left ventricle *(Figure 2A*) (7, 10-12). Iterative changes of this design result-

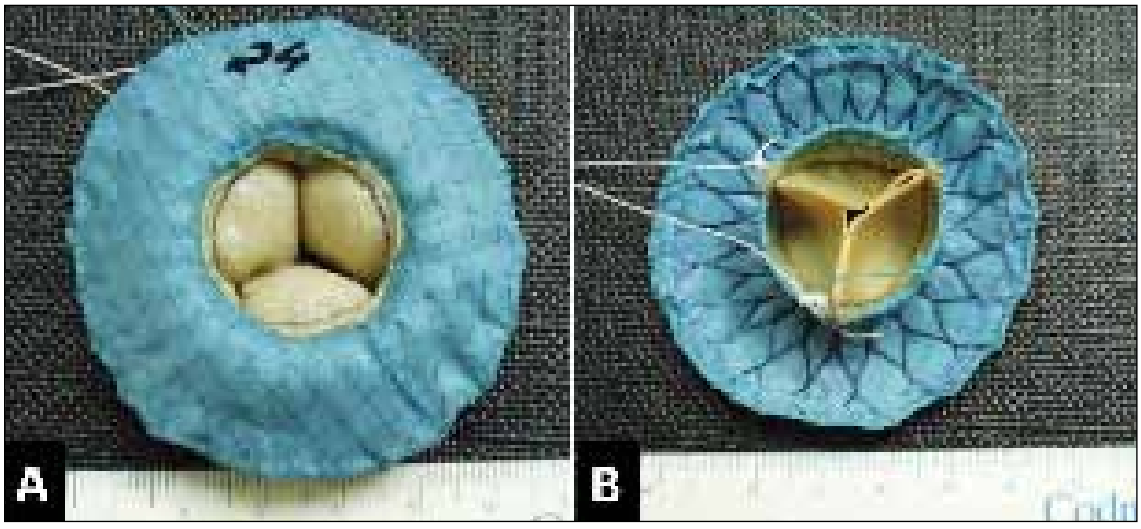

Figure 1 - *Mitral valved stent for transapical implantation into the beating heart. A: atrial view; B: ventricular view showing the ventricular fixation system consisting of four neo chordae attached to the ventricular rim of the valved stent.*

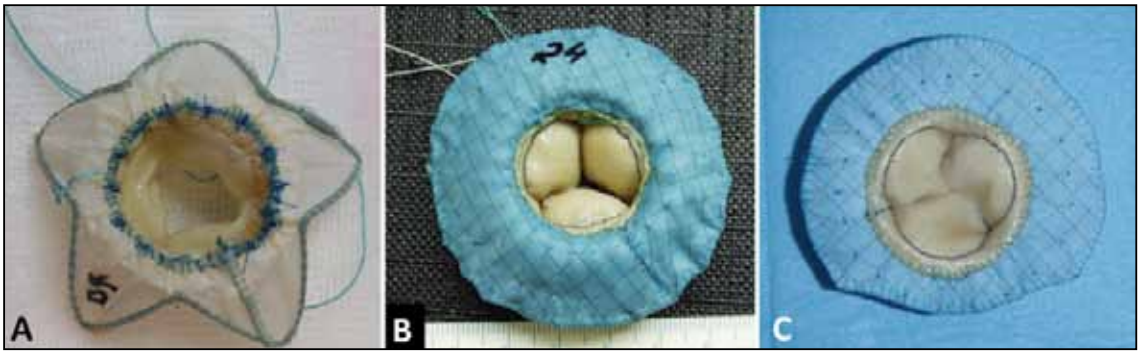

Figure 2 - *Different prototype designs resulting from iterative development of the mitral valved stent. A: valved stent with star shaped atrial element; B: valved stent with crown shaped atrial element attached at 45° to the ventricular element, C: valved stent with a D-shaped atrial element for better alignment in the antero-medial area.*

ed in a crown shaped atrial element connected to the ventricular body at a preset angle of 45° (*Figure 2B*) (8). In first studies 30 pigs underwent off-pump mitral valved stent implantation with follow up times of 60 min (n = 17) and 7 days (n = 13) (7). Transesophageal echocardiography and computed tomography were used to evaluate stent function and positioning following a standardized protocol. After valved stent deployment, accurate adjustment of the intra-annular position reduced PVL in all animals. Accurate positioning was established in all but five animals. No valved stent migration, embolization, systolic anterior movement or left ventricular outflow tract obstruction was observed. These studies proved the feasibility of reproducible deployment of the mitral valved stent that achieved low gradients across the left ven-

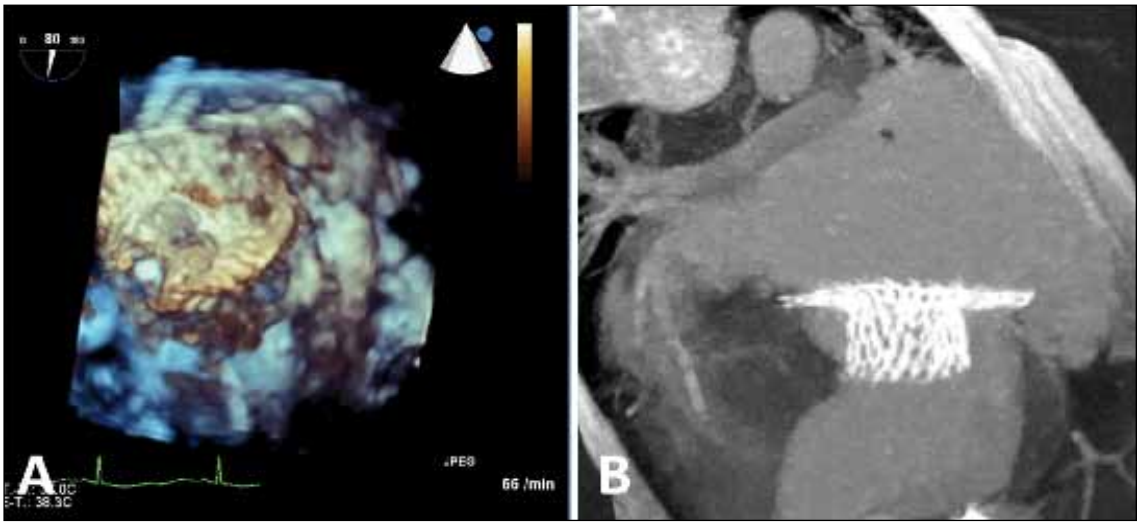

Figure 3 - *A: 3D transesophageal echocardiographic image showing the valved stent after successful deployment in the native mitral annulus during systole. B: 3D reconstruction from cardiac computed tomographic data showing correct position of the valved stent within the native mitral annulus.*

tricular outflow tract, and adequate stent function in acute and short term experimental settings. Stent mal-deployment and stent fracture were two of the main complications seen throughout these studies (7).

A further study focused on the evaluation and comparison of two different designs of a mitral valved stent. In the first case the stent was designed with a circular crown-shaped atrial element connected to a tube shaped ventricular element while in the second case, the same atrial element was D-shaped to achieve better anatomical alignment (*Figure 2C*). The design with D-shaped atrial element depicting the native annulus showed promising results in hydro-static in vitro testing in relation to reduction of PVL and stent alignment. In vivo, a rotation of the stent in the mitral annulus was observed which caused more severe PVL and prevented these advantages to take effect [data not yet published].

Ten days or one month after successful implantation a cardiac computed tomographic (CT) evaluation was performed following a standard protocol. Analysis of the cardiac CT data allowed evaluation of different stent design related and anatomical parameters (*Figure 3*). In the group of design-related parameters, the angle between the ventricular and atrial element (atrioventricular junction) of the valved stent showed to be a critical parameter. In the early prototypes this angle was preset to 45°. In vivo-evaluation showed great deflections of this preset angle of up to 56.4 ± 14.5°. Design iteration of our valved stent included an increase of this angle to 110°. Analysis of the deformation derived from CT data of these optimized stents revealed a lower degree of deflection [data not yet published]. Reduced deformation lowers the mechanical stresses and hence can increase the long-term durability.

Correct alignment within the native anatomy of the left heart and good paravalvular sealing was achieved with the latest prototype in our in vivo experiments. This is crucial, as the occurrence of paravalvular leakage (PVL) is directly linked to the

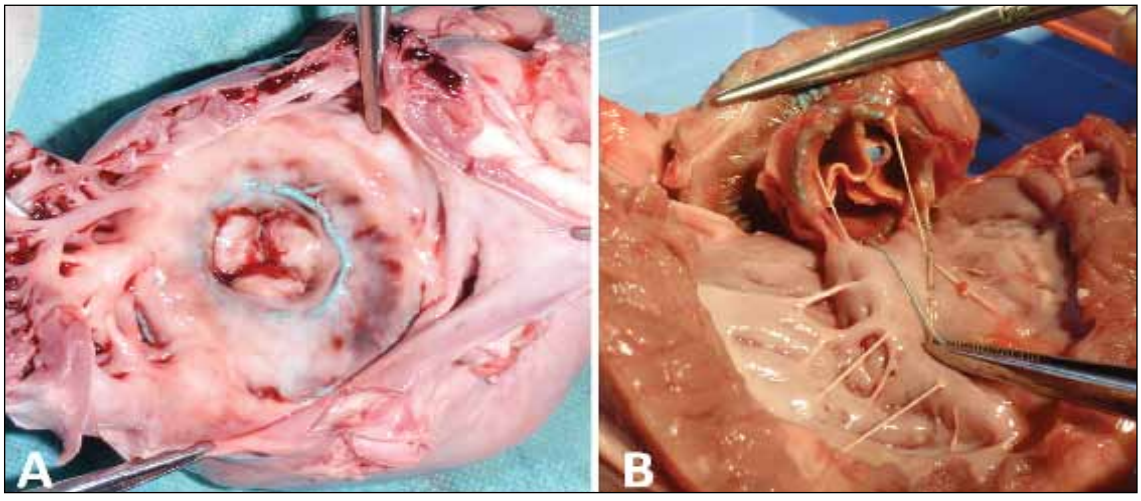

Figure 4 - *Gross evaluation two month after successful implantation showing good ingrowth of the valved stent and adequate stent position. A: atrial view showing the ingrowths of the atrial element; B: ventricular view showing the correct stent position and ingrowth of the ventricular element. Note the attachment inbetween the ventricular edge and the native chordae tendinae. Attachment of the ventricular edge to the native chordae tendinae and papillary muscle.*

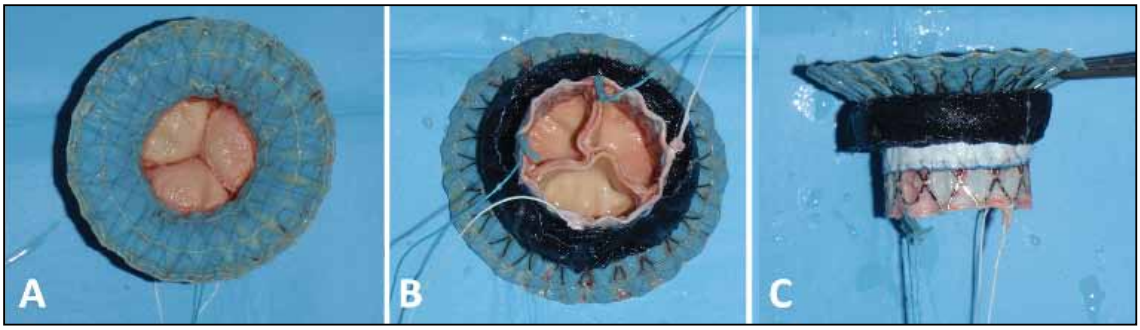

Figure 5 - *Valved stent for transventricular implantation into the native tricuspid valve in the beating heart after short term in vivo evaluation. A: atrial view; B: ventricular view; C: lateral view.*

patients' well-being (13). Of particular importance was that no PVL were found in twelve out of twelve animals directly after implantation in our most recent series of valved stent implantation [data not yet published]. However, an adaptation of the circular stent shape to the oval anatomical shape of the native mitral annulus was detected in this series leading to central MR in some cases.

In-growth of the mitral valved stents into the surrounding tissue was satisfactory after one or more months with similar results in our studies (7-9). We consider the tissue in-growth to be of high importance for the secondary stability and long-term performance of the mitral valved stents. Studies investigating the biological responses of different intracardiac devices showed complete coverage with endothelial cells after three months (14, 15). Therefore we assume that a similar healing process is achievable with our valved stent, since we have also observed good secondary stability up to now (*Figure 4*) (8).

Histological evaluation was carried out in samples taken at defined regions of interest such as the adhesion on the atrial element and the mitral annulus. HE staining was applied to identify tissue structure and cell density. Movat's pentachrome is a standard staining method for cardiac tissue and was used to differentiate between different collagen types, matrix, fibrin structures and muscle cells. Generally, normal myocardial tissue with an endothelial cell layer towards the lumen was detected. In the animals evaluated after 4 weeks or more of follow up no inflammatory signs were found. Instead normal atrial tissue was found in the atrial adhesion with muscle cells and matrix containing mycin and collagen [data not yet published].

However, before attempting the step towards clinical application of the novel device, more long-term *in vivo* data are necessary (no central leakage, maintaining left ventricular function).

Percutaneous implantation of a tricuspid valved stent into the beating heart is investigated in only few studies. These studies either require preliminary TV operations (replacement or conduit implantation) (16) or suggest heterotopic implantation within the Vena cava (17). Boudjemline et al. reported their first steps towards the replacement of the TV using angiographic guidance in 2005 mentioning difficulties of deploying and securing a stent in the tricuspid position (18). In 2012, Pott et al. suggested a novel approach consisting of two tubular anchoring components positioned within the tricuspid annulus and the superior vena cava, which are connected by elastic elements to provide stability (19).

Our group has reported on the feasibility of

off-pump replacement of atrioventricular valves under transesophageal echocardiographic (TEE) guidance and presented first results of an acute study (20). In this study, a nitinol stent was developed composed of a right atrial anchoring element and a right ventricular tubular stent that carried a trileaflet bovine pericardial valve. The self-expanding nitinol stent frame was covered with a PTFE membrane and pouch filled with a super absorband polymer (SAP) was attached to the ventricular stent body. This pouch was specifically designed for sealing between native tricuspid annulus and nitinol stent frame (*Figure 5*). The stent was implanted into the native tricuspid annulus of seven pigs in the beating heart using a transventricular approach and TEE guidance. Short-term evaluation was conducted 1h and 6h after successful implantation following a standard protocol. In six of seven cases the valved stent was correctly deployed and positioned within the native tricuspid annulus and normal hemodynamics were maintained. Mild PVL were observed directly after implantation in two cases, but decreased throughout the observation period. This was related to the full expansion of the SAP sealing pouch in the time between the two evaluation points (20). No right ventricular outflow tract obstruction was detected in this study.

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