

In vitro haemodynamic testing of Amplatzer plugs for paravalvular leak occlusion after Transcather Aortic Valve Implantation

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ABSTRACT

Objective:

We aimed to in-vitro test Amplatzer devices (Amplatzer Vascular Plug II and Amplatzer Vascular Plug III, SJM St. Paul, MN) in closing PVL generated by transcatheter balloon expandable aortic valve prosthesis in order to quantify the effective treatment of PVL.

Background:

Transcatheter aortic valve replacement (TAVI) procedures represent the treatment of choice for high risk patients. Despite evolving technologies paravalvular leak (PVL) is still a major unaddressed issue. This severe complication significantly impair long-term survival. Percutaneous treatment of this complication is usually performed with the implantation of not specifically designed and not approved vascular devices.

Methods:

A 23mm Sapien XT (Edwards Lifesciences, Irvine, CA) was implanted in a rubber aortic root and a semi-elliptical shape PVL was created. The vascular occluder devices were implanted in the PVL and hemodynamic performance was tested in a pulse duplicator according to international standard ISO 5840-3:2013. Different type of comparison tests together with high speed camera recording allowed us to define the global efficiency of the occluders and their interaction with the transcatheter prosthesis.

Results:

The results revealed that the use of vascular plugs was not per se sufficient to produce an effective or substantial reduction of PVL with a maximum efficiency inferior of 50%. Recorded video showed clearly that the vascular plug always interfered with the leaflet of the prosthetic valve.

Conclusions:

Current used devices do not guarantee effective treatment of PVL and may otherwise compromise the structural integrity of the prosthetic valve implanted. Specific designed devices are required.

Condensed Abstract

Despite evolving technologies, paravalvular leak (PVL) is still a major unaddressed issue after transcatheter aortic valve implantation. Percutaneous treatment of this complication is usually performed with the implantation of Amplatzer devices not specifically designed and not approved for this specific use. We tested in a pulse duplicator Amplatzer devices to occlude PVL generated after implantation of a 26mm SAPIENT XT prosthesis. The results revealed that the use of vascular plugs was not per se sufficient to produce an effective or substantial reduction of PVL. Video showed clearly that the vascular plug always interfered with the leaflet of the prosthetic valve.

Key words: Transcatheter aortic valve implantation, transcatheter aortic valve replacement, paravalvular leak, aortic regurgitation, vascular occluder

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has become the treatment of choice for inoperable patients with severe aortic stenosis [1] and mortality is comparable to surgical aortic valve replacement (SAVR) for patients at high risk [2, 3]. However, TAVI may result in severe complications, the most challenging of which is paravalvular leakage (PVL), due to incomplete sealing occurring between the prosthesis and the native host tissues [3-6]. Despite the evolving technology of transcatheter valves, moderate-severe post-TAVI PVL is not uncommon [1-8] and remains a major predictor of adverse outcome after TAVI even in presence of mild regurgitation. [9-13]. As such, PVL is one of the most important barriers to extend TAVI to lower risk patients [14, 15]. Given that conventional reintervention surgery is not a viable option because the patient is an high-risk/unoperable candidate, several strategies have been used to prevent or treat PVL after TAVI e.g.: heart pacing, balloon overfilling, valve-in-valve, post-dilatation with conflicting results [16, 17]. More recently, percutaneous approaches to PVL closure by mean of different devices (Amplatzer PDA, Amplatzer VSD device, Amplatzer vascular plugs, coils, etc.) have been developed via trans-septal (TS) access, apical left ventricular (LV) access, or retrograde arterial access [18-30] with a reported success rate that range from 55% to 77%. Reasons of procedure failure are various including inability to cross the defect with a wire or delivery catheter, dislodgement/embolization of the device, incomplete closure of the defect, or interference by the device with the prosthetic valve [19-32]. Even if the device is delivered, remains in place, and reduces flow, the treatment might be clinically inadequate.

To this regards, it is notheworthy that most of the devices used are approved for other purposes and not for PVL closure. In clinical practice the most frequently used PVL closure devices after TAVI are the Amplatzer Vascular Plug II and III (*St.Jude Medical, MN*) [31, 32]. The aim of the present study is primarily to test in vitro the hemodynamic efficiency and efficacy of the Ampltazer vascular plugs when used to close PVL after TAVI performed with a balloon expandable valve.

METHODS

In order to verify and quantify the benefit of adapting vascular plugs for reduction of PVL after TAVI, test were performed on two different Amplatzer vascular plugs (*St. Jude Medical Inc, MN*). These are occluding devices, designed to provide embolization of blood vessels by obstructing their lumen. They are self-expandable transcatheter devices, made from a wire mesh tube of superelastic Ni-Ti alloy, thermo-mechanically shaped into different geometries, and then secured at their ends with platinum caps that act as markers. The proximal cap is welded to a stainless steel screw, which engages to a nitinol pusher-wire, used for the delivery, repositioning or removal of the component. In this study, an *Amplatzer Vascular Plug II* of 8 mm diameter (7 mm unconstrained length), and an *Amplatzer Vascular Plug III* of long axis diameter 8 mm (short axis diameter 4 mm, unconstrained length 6.5 mm) were used. The first one is characterized by a multi-layered, multi-segmented cylindrical design, aimed to create six occlusive planes (Fig. 1a). The *Amplatzer Vascular Plug III* has an oblong cross-sectional shape, designed to enhance stability in high-flow vessels (Fig. 1b).

An 26mm diameter *Edwards SAPIEN XT* was used as testing valve (Fig. 1c). This is the most implanted transcatheter valve, and consists of three leaflets of bovine pericardium attached to a balloon-expandable cobalt-chromium frame. A skirt of PET covers about two thirds of the inlet portion of the valve, to reduce paravalvular leakage. The valve was released into a silicone cylindrical holder of 23 mm diameter (the 26mm *SAPIEN XT* is recommended for annular diameters in the range 22-25 mm), using the standard implantation procedure, and delivered in the same angular and axial position for all tests. The holder included a semielliptical shape axial groove (size 5 mm of minor axis 3, mm of major semiaxis and total area of 12 mm²), mimicking a paravalvular leak to be occluded (Fig. 1d).

Tests in several physiological pulsatile-flow operating conditions were performed using a hydro-mechanical pulse duplicator (*ViVitro System, ViVitro Labs Inc.*) in compliance with the international standard ISO 5840-3:2013. In particular, the valves performance was assessed at six simulated cardiac outputs (*CO*) between 2 and 7 l/min, at a normal heart rate (*HR*) of 70 bpm and a normal mean aortic pressure averaged over the cardiac cycle (\bar{p}_{Ao}) of 100 mmHg. Additional tests were run at a normal

simulated CO of 4 l/min, for combinations of three HR of 45, 70 and 120 bpm and three \bar{p}_{Ao} of 80, 120 and 160 mmHg. Phosphate buffered saline solution at 37 °C was used as testing fluid. Pressures in the aortic and ventricular chambers were measured using Millar Mikro-tip pressure catheters (Millar Instruments, Inc., Houston, TX, USA), and the flow through the valve was monitored with an electromagnetic flowmeter (Carolina Medical Electronics, Inc., East Bend, NC, USA). The fifteen total combinations of functional parameters used for each testing configuration are summarized in Table 1. During the experiments a high-speed camera (1200 frames per second) was used to record the valve dynamics during the cardiac cycle, and its interactions with the occluding devices.

The described tests were repeated for four different configurations: *i*) open leak (Fig. 2a), *ii*) partially occluded leak by *Amplatzer plug II* (Fig. 2b), *iii*) partially occluded leak by *Amplatzer plug III* (Fig. 2c) and *iv*) fully occluded hole (i.e. a solid block fitting into axial groove was positioned into the leakage hole, restoring an ideally cylindrical valve orifice, see Fig. 2d).

For each test condition, the instantaneous pressures in the aortic and ventricular chambers and the flow rate through the valve were measured during the entire cycle (see supplemental material).

Data were averaged over 10 consecutive cycles and used to extract the following quantities: *i*) mean diastolic pressure difference (Δp); *ii*) regurgitant volumes (RV); and *iii*) percentage regurgitant fraction through the valve (RF) (expressed as the ratio between the RV and the Stroke Volume (SV); i.e. the percentage of the ejected fluid that leaks back in the ventricle).

To allow direct comparison of the test results, the *reduction of the paravalvular regurgitant volume* was defined as:

$$\Delta RV = RV - RV_{occl}; \quad (1)$$

where RV_{occl} corresponds to the regurgitant volume with completely occluded hole (configuration represented in Fig. 2b), calculated at the specific test conditions.

The device efficiency (η) was expressed as:

$$\eta = \frac{RV - RV_{occl}}{RV_{open} - RV_{occl}} = \frac{\Delta RV}{\Delta RV_{max}}; \quad (2)$$

where ΔRV_{max} corresponds to the difference between the regurgitant volume measured with the open leak (RV_{open}), and the regurgitant volume measured with the occluded leak (gives the maximum reduction of regurgitant volume achievable with an occluding device), calculated at the specific test conditions. This equation gives a total efficiency equal to 1 (i.e. 100%) when the effect of the device is equivalent to the solid block (completely occluded hole); and an efficiency equal to zero when the effect of the device is equivalent to the completely open hole.

Finally, to quantify the hydrodynamic benefits of the procedure, the *mean flow velocity in the leak during diastole* (\bar{U}_{leak}), was defined as:

$$\bar{U}_{leak} = \frac{\Delta RV}{T_{diast} \cdot A} \quad (3)$$

where T_{diast} is the diastolic duration and A is the paravalvular orifice area

RESULTS

The regurgitant fraction measured for all testing configurations, at $HR = 70$ bpm, $\bar{p}_{Ao} = 100$ mmHg and variable CO is represented in Figure 3a. The efficiency η for the two occluders with equation (2) is plotted in Figure 3b. The *Amplatz plug II* was associated with an estimated efficiency (η) ranging from 20% to 60%, with of 30-40% at normal physiological CO of 4 – 5 l/min, and minimum performance at the largest CO (7 l/min), when the efficiency of reduces to 20%. The *Amplatz plug III* shows an estimated efficiency (η) ranging from 0 to 25%, with the efficacy lower than 10% for CO s higher than 4 l/min.

Figures 4a₁, 4b₁ and 4c₁ show the RF measured in the additional tests performed at constant $CO = 4$ l/min, at different values of HR and \bar{p}_{Ao} , while the respective curves of the efficiency for the two devices are reported in column Figures 4a₂, 4b₂ and 4c₂. For the studied HR s the measured RF raises when \bar{p}_{Ao} increases, while no monotonic trend was observed in terms of device efficiency.

Figure 5 shows a typical sequence of frames acquired with the high-speed camera during the test. The sequence is relative to the case of presence of the occluding device into the leak. Red dashed line highlights the contact area between the occluder and the leaflet.

The main input and output parameters of the study are summarized in table 1. Efficiency η for the two amplatzer for each working conditions are finally shown in table 2. For the first series of tests, with varying CO , the *Amplatzer plug II* and *Amplatzer plug III* efficiency ranges from 14% to 56% and from -19% to 16% respectively. In the additional tests prescribed by the international standard ISO 5840-3:2013 for the leakage assessment, the *Amplatzer plug II* ranges from 5% to 51%, while the *Amplatzer plug III* efficiency ranges between -3% and 38%.

DISCUSSION

The present study represents the first attempt to quantify the benefit of *Amplatzer* vascular plug implantation in order to mitigate the PVL after TAVI. Results underline that both devices fail to completely occlude the leak. The *Amplatzer plug III* shows lower or no efficacy, with unexpected negative values of the efficiency for large CO s, i.e. the leakage is worsened by the device. This may be due to higher rigidity of the plug frame, that may have produced an expansion of the cross section of the paravalvular side orifice.

Difference in the *Amplatzer* performance may also be due to the selected orifice shape and the different mesh-density of the two devices (see Fig. 6). In fact, the blockage factor of the mesh, defined as the percentage of the nominal surface obstructed by the mesh filaments, varies from 100% in proximity of the platinum caps, to less than 35% at the periphery (see Fig 6a). This is probably due to the fact that the devices are designed expand only partially within blood vessels which are about 30% smaller than their unloaded diameter. Under these conditions, the coarse regions of the mesh adhere to the vascular walls, while the dense central regions close to their axis occupy the lumen. On the contrary, when used to occlude paravalvular leakage, the distal and proximal peripheral regions of the device are entirely exposed to the fluid. This represents a more critical problem in the case of the *Amplatzer plug III*, which forms bulges at the inlet and outlet ends, offering the coarse flanks to the flow and providing an easy route to the blood (see Fig. 6.b). Conversely, the end flanges of the *Amplatzer plug II* can expand fully and form occlusive planes that cling on each other, positioning their region with higher blockage factor at

the inlet and outlet of the orifice (see Fig. 6.c). However, the outflow flare can find access between the distal zigzag ribs of the valve stent, occupying a portion of the valve lumen and contacting one of the prosthetic leaflets at each opening cycle.

For all testing configurations, the increase of CO reduces the RF (see Fig. 3a) as direct consequence of the definitions of these parameters. This is due to the fact that, as the SV increases, the flow volume ejected at each cycle rises with respect to the RV , that keeps about constant. For all testing configurations, RF increases both with the mean aortic pressure \bar{p}_{Ao} and HR (see Fig. 4). Proportionality with the mean aortic pressure is expected, as its increase is associated with higher mean pressure difference across the closed valve, driving the fluid during diastole. The relationship with the heart rate is somewhat less intuitive and apparently in contrast with clinical studies [16]. As observed in the clinical experience, with faster heart rates the regurgitant volume decreases (see table 1). However, as the portion between the systolic and diastolic time is kept unchanged in the tests, the same CO is achieved with lower ejection volumes per cycle. As a result, the reduction in stroke volume is larger than that of the regurgitant volume, resulting in a global increase in the regurgitant fraction, as demonstrated in appendix A (see supplemental material). The discrepancy with clinical reports is probably due to the fact that the international standard adopted for the presented *in vitro* tests does not model the reduction in diastolic/systolic time ratio that is typically observed in patients at increasing HR [33]. This may reduce the time during which leakage occurs, resulting in a global reduction of the regurgitant fraction.

The diagrams in Fig. 4 show that both Amplatzer achieve the maximum efficiency at lower \bar{p}_{Ao} when HR increases.

The estimation of η in both Fig. 3b and Fig. 4b is affected by not negligible uncertainty due to the error propagation in postprocessing data. Interval confidence analysis of 70 % (error bars in Fig 3b and in Fig. 4b) provides the follow additional information: *i*) negative efficiency values estimated for *Amplatzer plug III* (except the case for $CO= 7$ l/min in Fig. 3b) is fully explained by the measurements uncertainty and *ii*) also in the most favorable case (upper bars in Fig. 3b and in Fig. 5b) both devices fail to completely occlude the lumen. For example for $CO = 4-5$ l/min efficiency estimated is lower than 50 % (see Table 2).

The benefits due to occluder implantation may also concern flow velocity through the hole. As well known the reduction of the velocity enhances the hemodynamics of the patient, since low velocity through the hole favours platelet activation enhancing occlusion of the orifice. Similarly as for η , slight differences of mean flow velocity in the leak during diastole were estimated between *Amplatzer plug III* and open leak condition, whereas reduction of velocity was computed in *Amplatzer plug II* (see table 1). Video analysis did not reveal any substantial impairment of the valve dynamics, or plug embolization. However, a strong mechanical interaction between *Amplatzer plug II* and valve leaflets was observed during the tests, with one of the valve leaflets cyclically impacting on the plug outflow flared portion. This can be observed in the sequence of acquisitions reported in fig. 5 (and supplemental material movie). The phenomenon, over time, might result into wear, puncture or tearing of the prosthetic leaflet and high cycle tests would be recommended to further investigate it. This problem is described in recent clinical reports with the *Edwards Sapien* and the *Medtronic CoreValve* [34, 35]. In particular, with this last device, the anchoring of the distal flange of the prosthesis to the ascending aorta necessitates the crossing of the stent wall to access the leak, with higher probability of leaflets interaction [35].

The main limitations of the present study are *i)* the use of saline solution instead of a fluid with the closer rheological property to blood and *ii)* the simplified geometry adopted for the housing and paravalvular orifice. The coagulation process inside the hole due to the Amplatzer, which should play a fundamental role in the medium-long term period for reduction of the leakage, cannot be reproduced in these acute experiments. However, the adoption of saline solution is in accordance with ISO standards. The geometry adopted in the model is strongly idealized and the efficiency of the devices may change with the shape of the leak. Also, the cylindrical valve housing provides an idealized anchoring region, which does not accurately model the potential interaction between the prosthesis and the diseased host tissues. Therefore, caution should be taken to directly extend the conclusions to clinic cases.

However, our study provides a deeper insight into the biomechanical implications of the treatment, suggesting potential justifications for the cases where clinical inadequacy of therapy has been observed. The results reveal that the use of vascular plugs is not *per se* sufficient to produce an effective or

substantial reduction in PVL, and may otherwise compromise the structural integrity of the valve implant. The study considers only two of the most adopted solutions, whilst other type of vascular plugs, such as the *Amplatzer Plug IV*, have recently been used for PVL occlusion [36]. However, no reports are currently available on the medium and long-term outcome with this device. Furthermore, the reported evidence is relative to an idealized *in vitro* test, and therefore it may be different from specific clinical cases. Moreover, devices based on similar design solutions, such as the *Amplatzer plug II* and *III*, can result into substantially different operating configurations and efficiencies.

Besides, the results open several questions on the improper use of medical devices. The efficiency of the two tested Amplatzer strongly depends on the operating parameters (e.g. \bar{p}_{Ao} , *HR* and *CO*) and this may imply that their efficacy depends on their specific physiological conditions. What said above highlights that more extensive studies are necessary in order to ensure the effectiveness and safety of this percutaneous solution in applications for PVL reduction. Also, it appears evident the need to improve the vascular plugs currently in use or to develop new specifically designed devices that could guarantee an effective and safe treatment of PVL, avoiding physical interaction with the functional components of the transcatheter prosthesis. This would ideally be complemented by the development of more specific guidances, regulating the evaluation of the safety and efficacy of prostheses used for this application.

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