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Research Article

The End of Repeated Reoperations for Degenerated Bioprosthesis? Hydrodynamic *In-Vitro* Analysis for Sequential Valve-in-Valve Feasibility

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ABSTRACT

Objective: To develop a therapeutic guide for the implantation of Braile Inovare transcatheter valves within valve-in-valve sets (including valve-in-valve-in-valve and sequential valve-in-valve configurations), based on hydrodynamic testing. The guide aims to establish therapeutic limits and recommend optimal sizes for transcatheter valves.

Materials and Methods: Hydrodynamic testing was performed using the pulse duplicator to measure the effective orifice area in square centimeter and the mean transvalvular gradient in millimetres of mercury of various valve sets. The tests adhered to Food and Drug Administration (FDA) and International Organization for Standardization (ISO) regulations, specifically ISO 5840. For sequential valve-in-valve testing, each selected valve-in-valve set was evaluated with a transcatheter valve smaller than the previously implanted valve. Each valve set was assembled in triplicate and each configuration underwent three pulse duplicator cycles in accordance with Food and Drug Administration (FDA) guidelines.

Results: The use of progressively smaller transcatheter valves in sequential implantation was informed by experiments that demonstrated stable prosthesis placement and reliable hemodynamic performance.

Sequential aortic valve-in-valve: Implantation of a 22 millimeters transcatheter valve inside a 25 millimeters bioprosthesis with a 24 millimeters transcatheter valve resulted in an effective orifice area of 0.99 square centimeter and a mean transvalvular gradient of 13.59 millimeters of mercury. Using a 20 mm transcatheter valve in the same set produced an effective orifice area of 0.84 square centimeter and a mean transvalvular gradient of 15.31 millimeters of mercury.

Sequential mitral valve-in-valve: Deployment of a 28 millimeters transcatheter valve inside a 31 millimeters bioprosthesis with a 30 millimeters transcatheter valve yielded an effective orifice area of 2.1 square centimeter and a mean transvalvular gradient of 3.6 millimeters of mercury. Sequential implantation of a 26 millimeters transcatheter valve in this set resulted in an effective orifice area of 1.99 square centimeter and a mean transvalvular gradient of 3.71 millimeters of mercury. Further implantation of a 24 millimeters transcatheter valve produced an effective orifice area of 1.67 square centimeter and a mean transvalvular gradient of 5.04 millimeters of mercury. Finally, deployment of a 22 millimeters transcatheter valve led to an effective orifice area of 1.07 square centimeter and a mean transvalvular gradient of 11.42 millimeters of mercury.

Conclusion: Sequential aortic valve-in-valve procedures are feasible and demonstrate satisfactory hydrodynamic performance with Braile Inovare transcatheter valves up to 22 millimeters in diameter. For sequential mitral valve-in-valve procedures, a cautious approach is recommended with 27 millimeters bioprostheses. The best hydrodynamic outcomes were observed with 29 millimeters and 31 millimeters bioprostheses, using a transcatheter valve size that is 1 millimeter smaller than the nominal size. Implantation of a 26 millimeters transcatheter valve in the sequential mitral valve-in- valve configuration is feasible with satisfactory performance, while the 24 millimeters transcatheter valve should be used with caution due to borderline transvalvular gradients and effective orifice area.

Keywords: Aortic valve; Mitral valve; Valve replacement; Transcatheter; Cardiopulmonary bypass; Biologic prosthesis; Hydrodynamic models

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INTRODUCTION

The origin of transcatheter valves can be traced to the relentless pursuit of an alternative to conventional valve replacement, particularly for aortic valve stenosis, through a less invasive procedure. Cribier described the first implantation of a transcatheter valve in the aortic position in a human [1]. With the increasing use of transcatheter valves for treating aortic valve stenosis, attention has shifted towards using these devices for treating degenerated conventional bioprostheses. Implanting a transcatheter valve within a bioprosthesis is referred to as a "valve-in-valve" procedure.

Wenaweser, et al., performed the first human implantation of a transcatheter valve within a conventional degenerated bioprosthesis in an 80-year-old patient with two prior cardiac surgeries, pulmonary hypertension, left ventricular dysfunction and coronary atherosclerotic disease, presenting with a logistic Euroscore of 35.6% for perioperative mortality [2].

This approach presents significant prospects. Due to the advantages of bioprostheses over mechanical prostheses, particularly concerning biocompatibility and the avoidance of oral anticoagulation with coumarins, despite their associated drawbacks and risks [3,4], there is a growing use of these devices. It is estimated that in the United States of America, between 2007 and 2011, 63.6% of prosthetic valve devices were made from bovine pericardium, reflecting a 100% increase compared to the period from 1998 to 2001 [5].

Nevertheless, the implantation of transcatheter valves is progressively increasing. Given the satisfactory outcomes, the indications for transcatheter valve implantation in the aortic position have expanded over the past two decades, now including not only patients with prohibitive conventional surgical risk but also high-risk patients, octogenarians and increasingly, studies on intermediate-risk and low-risk patients, with notable research such as the evolut low risk trial and partner 3 Trial [3,4,6-9].

However, both conventional bioprostheses and transcatheter valves have limited durability, despite the absence of anticoagulation requirements. The major limiting factor for bioprostheses durability is the structural degeneration of the valve [10-14], either due to dystrophic calcification of cusps made from heterologous pericardium or mechanical degeneration, primarily due to shear stress on the leaflets [12,15-18].

With improvements in healthcare leading to an aging population, there is a growing likelihood of bioprosthesis dysfunction and potentially higher operative risks [15,19,20]. Considering the positive clinical outcomes achieved so far, there is a trend towards expanding the indications for valve-in-valve procedures [21,22]. Additionally, a new perspective is emerging with the concept of valve-in-valve-in-valve, or sequential valve-in-valve, for treating degenerated transcatheter valves previously implanted in the valve-in-valve modality.

The first report of sequential valve-in-valve implantation in a degenerated transcatheter valve, which was initially implanted within a bioprosthesis, was presented in 2016 by Leung et al. [23]. This involved a 64-year-old patient with advanced idiopathic liver cirrhosis who had undergone aortic valve replacement with a bioprosthesis (Perimount Edwards 23 mm) at 54 years of age, followed by a valve- in-valve procedure at 60 years of age due to bioprosthesis stenosis and then a sequential implantation of another transcatheter valve due to early stenosis of the previous transcatheter valve.

Looking towards the future, as the use of conventional bioprostheses, transcatheter aortic valve implantation and transcatheter valve-in-valve procedures continues to expand and as life expectancy increases, there will likely be a growing number of patients with transcatheter valve dysfunction who will require alternatives to conventional surgical valve replacement. These patients will inevitably present with even higher surgical risks compared to those undergoing the initial valve-in-valve implantation.

Therefore, studies are essential to evaluate the feasibility of sequential implantation, determine the optimal valve size, predict the reduction in effective valve area and increase in transvalvular gradient with sequential implantation (patient-prosthesis mismatch) and establish the limits for sequential implantation. Research into the feasibility of sequential implantation may also impact the expanding use of transcatheter implantation, particularly for aortic valve diseases in younger patients with lower surgical risks compared to conventional valve replacement. To date, there are no studies on *in vitro* hydrodynamic performance or oversizing analysis for human implantation in the literature, with only exceptional and specific case reports available.

MATERIALS AND METHODS

To assess the performance of transcatheter valves in valve-in-valve-in- valve configurations, we utilised aortic and mitral bioprostheses made from bovine pericardium provided by Braile Biomédica, as well as transcatheter valves from Braile Inovare expandable balloons. The pulse duplicator ViVitro® (Canada) was employed for this research, located in Braile Biomédica's research laboratory in São José do Rio Preto, São Paulo, Brazil (Figure 1).

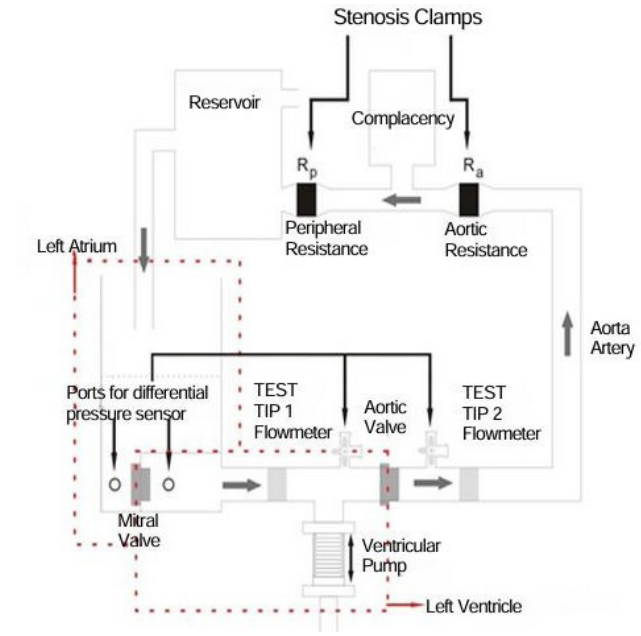


Figure 1: Schematic representation of the pulse duplicator system. Dashed rectangles represent the ventricles and left atrium, with grey arrows indicating the direction of flow.

The pulse duplicator® is an acrylic system with 2 chambers (simulating atrium and ventricle), pressure transducers,

electromagnetic flow meters, heat exchanger, centrifugal pump, data acquisition system and software for interpretation and presentation of results called LabVIEW, which through the generation of pulse waves and flows, allows prosthetic valve devices tests, generating results of mean transvalvular gradient, allowing the calculation of effective orificial area. The tests followed the pulse duplicator manual specifications.

In addition, cardiac output (Litres Per Minute) and mean arterial pressure (millimeters of mercury.) followed the standards established for heart prosthetic valves tests by the Food and Drug Association (FDA) and International Organization for Standardization (ISO) (resolution number 5840), representing, respectively, 5 litres per minute and 100 millimeters of mercury and the measurements were performed with heart rate simulation ranging between 70, 80, 90, 100, 110 and 120 beats per minute, accordingly to the aforementioned standardization.

Pressure and flow data through the valves were captured by sensors and from these data the transvalvular pressure gradient and effective orificial area were calculated.

The device aims to simulate the *in vivo* hydrodynamic behaviour to which the valve prostheses are submitted and thus determine the transvalvular pressure and flow parameters through the sensors. In the equipment, the complexes formed by the valves were immersed in a solution of 0.9% sodium chloride and 1% benzyl alcohol, seeking viscosity close to that of the blood (between 4 and 5 milliPascals per second), in accordance with the aforementioned regulations, as shown in Figure 2.

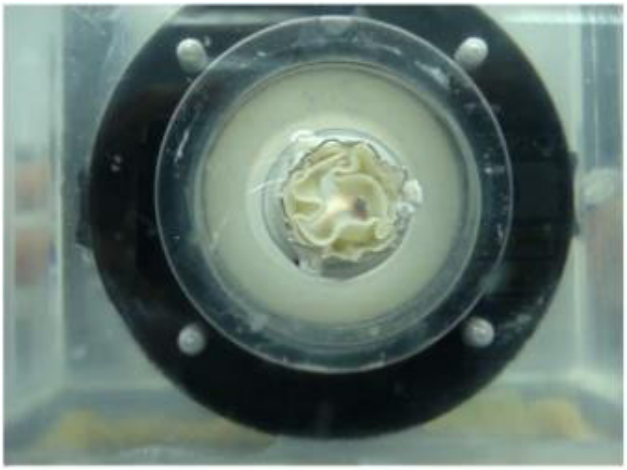


Figure 2: Pulse Duplicator (Vivitro) with a valve-in-valve set. It is noteworthy that this transcatheter valve is excessively oversized in relation to the valve prosthesis ring, resulting in incomplete expansion of the leaflets.

For each proposed valve-in-valve-in-valve test, ten sets were replicated (in accordance with ISO 5840 guidelines for testing new prosthetic devices intended for human use) and each set was subjected to three successive cycles in the pulse duplicator simulation. Thus, for each simulated heart rate, 180 values were obtained for both the transvalvular gradient and the effective orifice area. Regarding the implantation of the transcatheter valve, the prosthesis was initially crimped onto a 30 mm valvuloplasty balloon catheter using a specific crimping device and then expanded within the bioprosthesis, as shown in Figures 3 and 4.

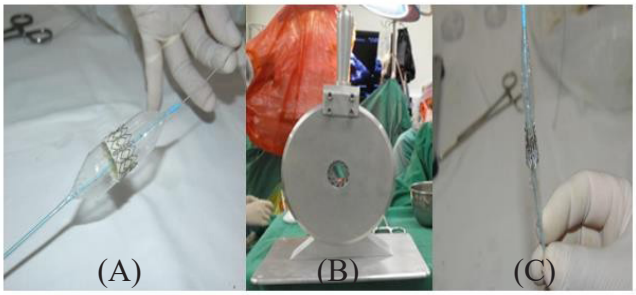


Figure 3: Image depicting the homogeneous crimping of the transcatheter valve onto an expandable balloon catheter. **Note:** (A): Placement of the transcatheter valve into the inflated balloon catheter; (B): Crimping device for valve compaction over the balloon catheter; (C): Final result of transcatheter valve crimping within the deflated balloon catheter.

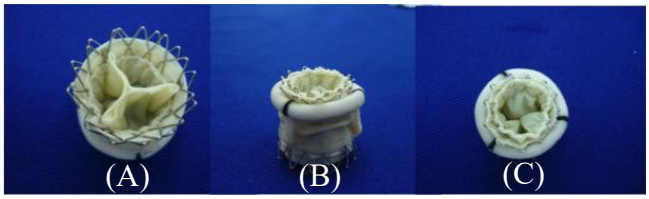


Figure 4: Image showing the structure composed of the superimposition of a 23 millimeters bioprosthesis with a 22 millimeters transcatheter prosthesis and a subsequent 20 millimeters transcatheter valve. **Note:** (A): Oblique view; (B): Side view; (C): Bottom view.

The position of the transcatheter valve relative to the bioprosthesis was carried out according to the manufacturer's recommendations, with the lower portion of the transcatheter valve covering the suture ring of the bioprosthesis. The implant height was maintained between 0 mm and 2 mm above the plane of the bioprosthesis ring [24,25]. The valve-in-valve assemblies designated for the implantation of a given transcatheter valve were determined based on previous studies involving the mentioned prosthetic valve devices.

For the sequential implantation, the transcatheter valve had a nominal size immediately smaller than the previously implanted transcatheter valve, positioned at the same height. At each stage of the sequential implantation in the valve-in-valve set, three cycles of hydrodynamic tests were conducted using the pulse duplicator (Figure 5).

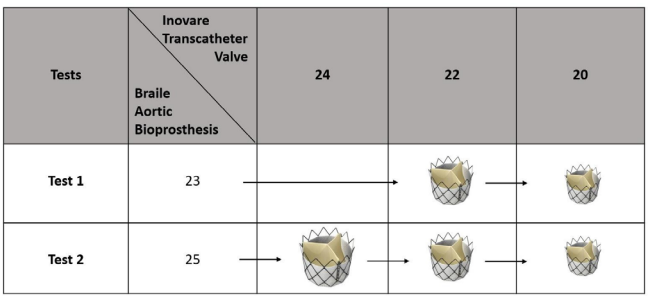


Figure 5: Schematization of proposed tests for the evaluation of the sequential aortic valve-in-valve.

To assess the hydrodynamic behaviour in aortic valve-in-valve scenarios, the following experimental assemblies were performed.

Test 1: A 22 millimeters transcatheter prosthesis was implanted

inside a 23 millimeters aortic bioprosthesis, followed by sequential implantation of a second 20 millimeters transcatheter valve prosthesis.

Test 2: A 24 millimeters transcatheter prosthesis was implanted inside a 25 millimeters aortic bioprosthesis, followed by the sequential implantation of a 22 millimeters transcatheter valve prosthesis and subsequently a third 20 millimeters transcatheter valve.

Similarly, to the above, the following tests were performed for the mitral position as shown in Figure 6.

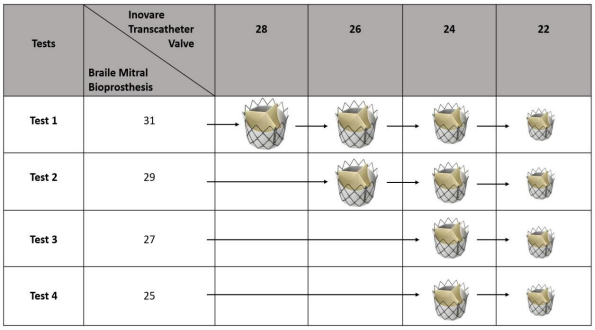


Figure 6: Schematization of proposed tests for the evaluation of mitral sequential valve-in-valve.

Test 1: A 30 millimeters transcatheter prosthesis was implanted inside the 31 millimeters mitral bioprosthesis and a second 28 millimeters transcatheter valve prosthesis was sequentially implanted; afterwards, a third 26 millimeters transcatheter valve was implanted; then, a fourth transcatheter valve of size 24 millimeters was implanted and finally, to this established set, a fifth transcatheter valve of size 22 millimeters.

Test 2: Inside the 29 millimeters mitral bioprosthesis, a 28 millimeters transcatheter prosthesis was implanted and a second 26 millimeters transcatheter valve prosthesis was sequentially implanted, a third 24 millimeters transcatheter valve prosthesis and finally a fourth 22 millimeters transcatheter valve was implanted.

Test 3: A 26 millimeters transcatheter prosthesis was implanted inside the 27 millimeters mitral bioprosthesis and a second 24 millimeters transcatheter valve prosthesis was sequentially implanted and then a 22 millimeters transcatheter valve was implanted.

Test 4: A 24 millimeters transcatheter prosthesis was implanted inside the 25 millimeters mitral bioprosthesis, followed by another 22 millimeters transcatheter valve.

RRESULTS

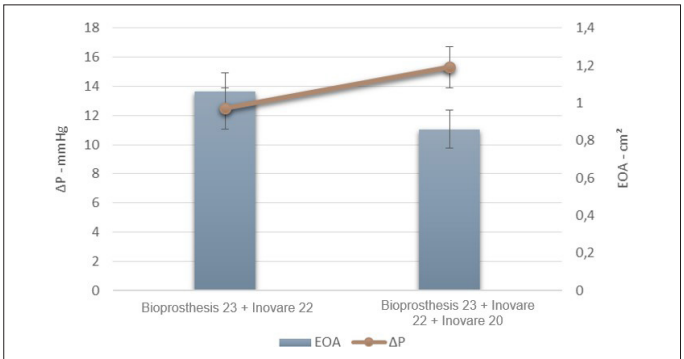
The decision to use progressively smaller transcatheter valves in a sequential implantation within a bioprosthesis, as outlined by the Food and Drug Administration and International Organization for Standardization (ISO resolution 5840), was based on the outcomes of all proposed experimental groups, following the preliminary tests described in the methodology. No migration of the prostheses was observed in any of the tests and the parameters for cardiac output (ranging from 4.897 litres to 5.188 litres per minute) and mean arterial pressure (100 millimetres of mercury) were consistently maintained across all simulated heart rates (ranging from 70 beats to 120 beats per minute). Effective orifice area (in square centimetres) and transvalvular gradient (in millimetres of mercury) data were collected.

Aortic sequential valve-in-valve

In the sequential valve-in-valve modality using 23 millimeters aortic bioprosthesis, a transcatheter valve with a nominal size of 22 millimeters was initially implanted, followed by the sequential implantation of a 20 millimeters transcatheter valve. This configuration resulted in an effective orifice area of 0.86 (SD ± 0.01) square centimetres and a transvalvular gradient of 15.32 (SD ± 0.21) millimetres of mercury, as shown in Table 1 and Graph 1.

Table 1: Values obtained in the tests using a 23 millimeters aortic bioprosthesis, with initial 22 mm transcatheter valve implantation, followed sequentially by a 20 millimeters transcatheter valve implantation.

	Bioprosthesis 23+Inovare 22		Bioprosthesis 23+Inovare 22+Inovare 20	
		SD		SD
EOA	1,06	0,05	0,86	0,01
ΔP	12,50	0,20	15,32	0,21

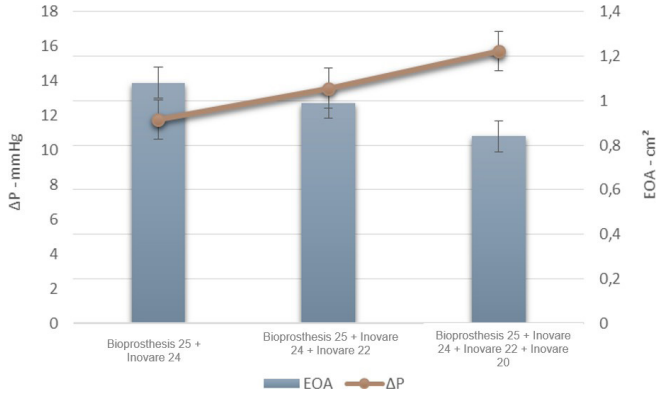


Graphic 1: Correlation between the progressive reduction of the Effective Orificial Area (EOA) and the elevation of the transvalvular gradient (ΔP) in the case of sequential valve-in-valve implantation in a 23 millimeters aortic bioprosthesis.

In the aortic bioprosthesis with a nominal size of 25 millimeters, a transcatheter valve number 24 millimeters was implanted and the transcatheter valve with a nominal size of 22 millimeters was sequentially implanted, observing in the set effective orificial area 0.99 (SD ± 0.03) square centimeters and transvalvular gradient 13.59 (SD ± 0.54) millimetres of mercury; finally, with the transcatheter valve of nominal size 20 millimeters implanted sequentially to the previously assembled set, effective orificial area was obtained at 0.84 (SD ± 0.01) square centimeters and transvalvular gradient 11.42 (SD ± 0.21) millimetres of mercury. The values obtained in the sequential valve-in-valve tests for the aortic position are shown in Table 2 and in Graph 2.

Table 2: Values obtained in test 2, with 25 millimeters aortic bioprosthesis with 24 millimeters, 22 millimeters and 20 millimeters transcatheter valve sequential implantation.

	Bioprosthesis 25+Inovare 24		Bioprosthesis 25+Inovare 24+Inovare 22		Bioprosthesis 25+Inovare 24+Inovare 22+Inovare 20	
		SD		SD		SD
EOA	1,08	0,0018	0,99	0,03	0,84	0,01
ΔP	11,76	0,55	13,59	0,54	15,71	0,21



Graphic 2: Correlation between the progressive reduction of the Effective Orificial Area (EOA) and the elevation of the transvalvular gradient (ΔP) in the case of sequential valve-in-valve implantation in a 25 millimeters aortic bioprosthesis, with 24 millimeters, 22 millimeters and 20 millimeters transcatheter valves.

Mitral sequential valve-in-valve

In the sequential valve-in-valve modality using a 31 millimeters mitral bioprosthesis (Test 1), a 30 millimeters transcatheter valve was initially implanted, followed sequentially by transcatheter valves of 28 millimeters, 26 millimeters, 24 millimeters and finally 22 millimeters nominal sizes. The results observed were as follows:

- With the 30 millimeters transcatheter valve, the effective orifice area was 2.1 (SD ± 0.02) square centimeters and the transvalvular gradient was 3.6 (SD ± 0.05) millimeters of mercury.
- With the 26 millimeters transcatheter valve, the effective orifice area was 1.99 (SD ± 0.01) square centimeters and the transvalvular gradient was 3.71 (SD ± 0.03) millimeters of mercury.
- With the 24 millimeters transcatheter valve, the effective orifice area was 1.67 (SD ± 0.01) square centimeters and the transvalvular gradient was 5.04 (SD ± 0.06) millimeters of mercury.
- With the 22 millimeters transcatheter valve, the effective orifice area was 1.07 (SD ± 0.03) square centimeters and the transvalvular gradient was 11.42 (SD± 0.67) millimeters of mercury.

The results are shown in Table 3 and Graph 3.

Mitral sequential valve-in-valve

In the sequential valve-in-valve modality using a 29 millimeters mitral bioprosthesis, a 28 millimeters transcatheter valve was implanted initially, followed by a 26 millimeters transcatheter valve. The results were as follows:

- With the 28 millimeters transcatheter valve, the effective orifice area was 1.92 (SD ± 0.02) square centimeters and the transvalvular gradient was 3.71 (SD ± 0.03) millimeters of mercury.
- With the 26 millimeters transcatheter valve, the effective orifice area was 1.49 (SD ± 0.01) square centimeters and the transvalvular gradient was 6.38 (SD ± 0.08) millimeters of mercury.
- Finally, with the 22 millimeters transcatheter valve, the effective orifice area was 1.10 (SD ± 0.10) square centimeters and the transvalvular gradient was 11.06 (SD ± 0.15) millimeters of mercury.

The results are shown in Table 4 and Graph 4.

With the bioprosthesis of nominal size 27 millimeters, with transcatheter valve implantation of size 26 millimeters and, successively, with the transcatheter valve size of 24 millimeters, effective orifice area is 1.35 (SD ± 0.01) square centimeters and transvalvular gradient 6.98 (SD ± 0.09); and with a transcatheter valve size of 22 millimeters implanted sequentially, effective orifice area was 0.85 (SD ± 0.01) and transvalvular gradient 17.04 (SD ± 0.38).

The results are shown in Table 5 and Graph 5.

Finally, in a bioprosthesis with a nominal diameter of 25 millimeters, sequential implantation of a 24 millimeters transcatheter valve followed by a 22 millimeters transcatheter valve resulted in an effective orifice area of 0.97 (SD ± 0.01) square centimeters and a transvalvular gradient of 13.46 (SD ± 0.22) millimeters of mercury.

The results are shown in Table 6 and Graph 6.

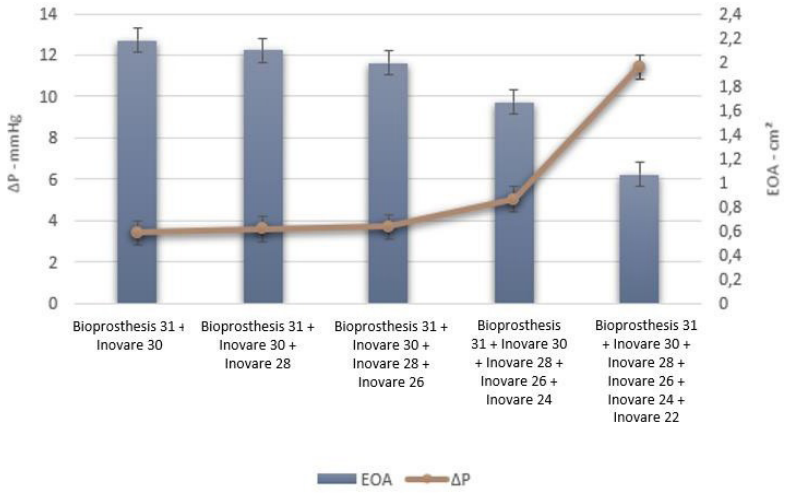
As demonstrated in the results, sequential implantation leads to a progressive reduction in the effective orifice area, resulting in increased transvalvular gradients.

For the aortic position, the sequential modality shows adequate parameters: Sequential implantation with a transcatheter valve that is immediately smaller than the previously implanted valve up to a nominal diameter of 22 mm. When the sequential implantation extends to a transcatheter valve with a nominal diameter of 20 mm, the effective orifice area falls below 1 cm^2, though the transvalvular gradient remains adequate, indicating a recommendation with reservations.

Conversely, in the mitral position, the sequential valve-in-valve results are satisfactory up to a transcatheter valve with a nominal diameter of 26 mm, but caution is advised when using a transcatheter valve with a nominal diameter of 24 mm, given the effective orifice area approaches 1.5 cm^2.

Table 3: Values obtained in Test 1 with a 31 mm mitral bioprosthesis and sequential transcatheter valve implantation of 30 millimeters, 28 millimeters, 26 millimeters, 24 millimeters and 22 millimeters.

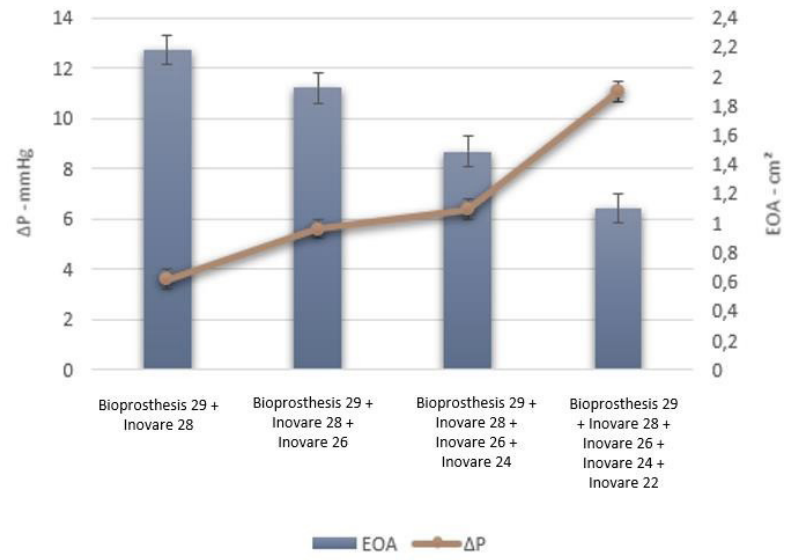
	Bioprosthesis 31+Inovare 30		Bioprosthesis 31+Inovare 30+28		Bioprosthesis 31+Inovare 30+28+26		Bioprosthesis 31+Inovare 30+28+26+24		Bioprosthesis 31+Inovare: 30+28+26+24+22	
		SD		SD		SD		SD		SD
EOA	2,18	0,018	2,1	0,02	1,99	0,01	1,67	0,01	1,07	0,03
ΔP	3,41	0,045	3,6	0,05	3,71	0,03	5,04	0,06	11,42	0,67



Graphic 3: Correlation between the progressive reduction of the Effective Orificial Area (EOA) and the increase in the transvalvular gradient (ΔP) with sequential valve-in- valve implantation in mitral bioprosthesis 31 millimeters, with transcatheter valves 30 millimeters, 28 millimeters 26 millimeters, 24 millimeters and 22 millimeters.

Table 4: Values obtained in the sequential implantation test with a 29 millimeters mitral bioprosthesis and transcatheter valves of 28 millimeters, 26 millimeters and 22 millimeters.

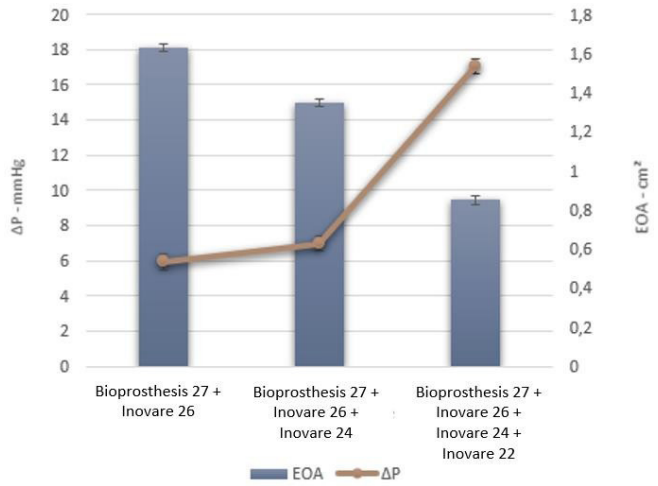
	Bioprosthesis 29+Inovare 28		Bioprosthesis 29+Inovare 28+26		Bioprosthesis 29+Inovare 28+26+24		Bioprosthesis 29+Inovare 28+26+24+22	
		SD		SD		SD		SD
EOA	2,18	0,02	1,92	0,02	1,49	0,01	1,1	0,1
ΔP	3,61	0,071	5,61	0,05	6,38	0,08	11,06	0,15



Graphic 4: Correlation between the progressive reduction in the Effective Orifice Area (EOA) and the increase in the transvalvular gradient (ΔP) with sequential valve-in- valve implantation in a 29 millimeters mitral bioprosthesis, using 28 millimeters, 26 millimeters, 24 millimeters and 22 millimeters transcatheter valves.

Table 5: Values obtained in test 3, with 27 millimeters mitral bioprosthesis with 26 millimeters, 24 millimeters and 22 millimeters transcatheter valve sequential implantation.

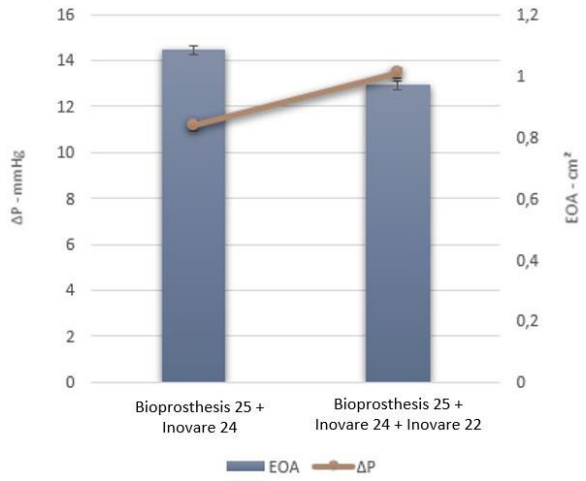
	Bioprosthesis 27+Inovare 26		Bioprosthesis 27+Inovare 26+25		Bioprosthesis 27+ Inovare 26+24+22	
		SD		SD		SD
EOA	1,63	0,013	1,35	0,01	0,85	0,01
ΔP	5,95	0,11	6,98	0,09	17,04	0,38



Graphic 5: Correlation between the progressive reduction in the Effective Orifice Area (EOA) and the increase in the transvalvular gradient (ΔP) with sequential valve-in- valve implantation in a 27 millimeters mitral bioprosthesis, using 26 millimeters, 24 millimeters and 22 millimeters transcatheter valves.

Table 6: Values obtained in Test 4, with a 25 millimeters mitral bioprosthesis and sequential transcatheter valve implantation of 24 millimeters and 22 millimeters.

	Bioprosthesis 25+Inovare 24		Bioprosthesis 25+Inovare 24+22	
		SD		SD
EOA	1,085	0,013	0,97	0,01
ΔP	11,17	0,25	13,46	0,22



Graphic 6: Correlation between the progressive reduction in the Effective Orifice Area (EOA) and the increase in the transvalvular gradient (ΔP) with sequential valve-in- valve implantation in a 25 millimeters mitral bioprosthesis, using 24 millimeters and 22 millimeters transcatheter valves.

DISCUSSION

The successful expansion and anchoring of a transcatheter valve over another valve within a bioprosthesis ring depend critically on appropriate oversizing. Oversizing is assessed by comparing the external area of the transcatheter valve to be implanted with the internal area of the previously implanted valve (derived from its internal diameter, or true ID) for balloon-expandable transcatheter valves. Insufficient oversizing can lead to valve migration, while excessive oversizing may result in inadequate expansion, particularly of the pericardial leaflets.

This inadequate expansion can increase transvalvular gradients compared to a properly expanded valve and potentially compromise the long-term durability of the transcatheter valve by increasing shear stress on the valve leaflets.

Due to the variety of available bioprostheses and transcatheter valves, an IOS application called valve-in-valve, developed in collaboration with UBQO and Vinayak Bapat (St Thomas' Hospital, London, UK), provides technical data on specific bioprostheses and recommends appropriate sizes for transcatheter valves in valve-in- valve procedures. However, this application does not include data for Braile bioprostheses or Braile Inovare transcatheter valves.

In tests involving sequential transcatheter valve implantation, the transcatheter valve chosen for implantation was one size smaller

than the previously implanted valve. In all experimental tests, no migration of the newly implanted transcatheter valve into another transcatheter valve was observed.

For the sequential aortic valve-in-valve procedure, the implantation of a 20 mm Braile Inovare transcatheter valve within a 22 mm transcatheter valve (previously implanted in a 23 mm conventional Braile bioprosthesis) resulted in an oversizing of 10.80%. When a 22 mm transcatheter valve was implanted inside a 24 mm transcatheter valve, the oversizing was 9.77%.

For the sequential mitral valve-in-valve procedure, the implantation of a 24 mm transcatheter valve into a 26 mm transcatheter valve resulted in an oversizing of 8.90%. Implantation of a 26 mm transcatheter valve within a 28 mm transcatheter valve produced an oversizing of 8.16%. Finally, when a 28 mm transcatheter valve was implanted inside a 30 mm transcatheter valve, the oversizing was 7.55%.

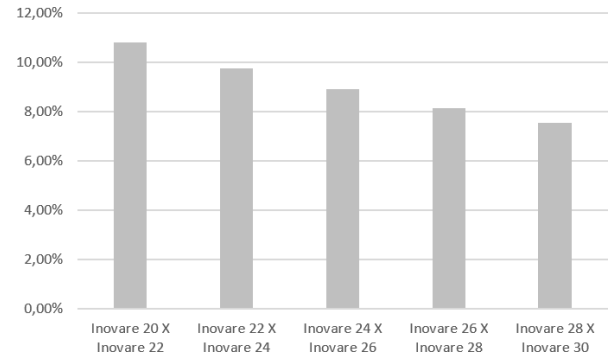
Oversizing plays an essential role in ensuring proper expansion and anchoring of the transcatheter valve. Oversizing in balloon expansible transcatheter valves refers to the ratio of the external diameter of the transcatheter valve to the internal diameter of the valve it is being implanted into. It is important to achieve a balance: Insufficient oversizing can lead to migration or incomplete expansion of the transcatheter valve, whereas excessive oversizing can cause inadequate leaflet expansion and increased transvalvular gradients.

In our study, the Braile Inovare transcatheter valve showed acceptable results with oversizing ranging from 7.55% to 10.80%, depending on the valve sizes used in sequential implantation. In the context of valve-in-valve procedures, several researches reveal that an ideal oversizing range for transcatheter valves typically falls between 10% and 20% [26-30]. This recommendation aligns well with the observations in our study using the Braile Inovare transcatheter valve, suggesting that similar oversizing principles apply across different valve types and brands.

Data related to oversizing analysis are shown in Table 7 and Graph 7.

Table 7: Analysis of oversizing (in percentage) during sequential valve-in-valve implantation, analyzing the oversizing of the transcatheter valve to be implanted versus the transcatheter valve that will receive the implant.

	Inovare 20 × Inovare 22	Inovare 22 × Inovare 24	Inovare 24 × Inovare 26	Inovare 26 × Inovare 28	Inovare 28 × Inovare 30
Oversizing	10,80%	9,77%	8,90%	8,16%	7,55%



Graphic 7: Analysis of oversizing in percentage for sequential valve-in-valve implantation, contrasting the transcatheter valve to be implanted versus the transcatheter valve that will receive the implant.

The transvalvular gradient and Effective Orifice Area (EOA) are critical indicators of valve performance. A higher transvalvular gradient suggests increased resistance to flow across the valve, which can result in symptoms of valve obstruction and reduced cardiac output. The EOA provides an estimate of the functional area through which blood flows, with a reduction in EOA indicating potential stenosis [31].

The clinical implications of sequential valve-in-valve implantation are significant. Excessive transvalvular gradients can lead to symptoms of heart failure and reduced patient quality of life. Additionally, long-term durability of transcatheter valves can be compromised by excessive shear stress and incomplete leaflet expansion. The study results suggest that careful consideration of valve sizes and oversizing is necessary to optimise clinical outcomes.

While valve-in-valve procedures are effective in treating degenerated bioprostheses, long-term follow-up studies are needed to assess the durability of transcatheter valves and the impact of oversizing on valve function. The progressive increase in transvalvular gradients observed in our study underscores the need for ongoing assessment and adjustment of valve sizing strategies [32,33].

Technological advancements are likely to improve the outcomes of valve-in-valve procedures. The development of more sophisticated sizing tools and imaging techniques can provide better pre-procedural planning and real-time adjustments during implantation. The absence of specific data for Braile bioprostheses and Braile Inovare transcatheter valves in existing applications, as noted in the study, highlights the need for dedicated tools and resources to guide valve sizing and placement.

Enhanced imaging and computational models could aid in predicting outcomes and tailoring interventions more precisely. Future research should focus on developing and validating these tools to improve the success rates and longevity of transcatheter valve procedures [34].

The *in vitro* hydrodynamic tests conducted in this study confirm the feasibility of employing the Braile Inovare transcatheter valve in the sequential valve-in-valve modality. These findings are consistent with the principles observed in other studies involving transcatheter balloon-expandable valves.

However, when considering the valve-in-valve-in-valve (or sequential valve-in-valve) modality, the literature lacks comprehensive studies on *in vitro* hydrodynamic performance and oversizing analysis prior to human implantation. Instead, available literature primarily comprises case reports addressing specific and exceptional scenarios. These case reports highlight several key issues.

Early degeneration of the transcatheter valve: There are documented cases where the transcatheter valve implanted within a bioprosthesis has experienced early degeneration. This phenomenon underscores the need for careful consideration of valve sizing and implantation strategies to prevent premature failure.

Cracking of the bioprosthesis annulus: Reports indicate that cracking, or the fracture of the annulus of the bioprosthesis, has been used as a strategy in certain situations [35-36]. This approach, although employed in specific cases, raises concerns about its potential impact on the longevity and functionality of both the bioprosthesis and the transcatheter valve.

Correction of paravalvular regurgitation: Another issue highlighted in the literature is the correction of paravalvular regurgitation resulting from valve-in-valve implantation [36]. This complication can compromise the effectiveness of the valve and necessitates careful procedural planning and execution.

Transcatheter valve endocarditis: Case reports also include instances where the transcatheter valve has been part of the treatment for endocarditis in patients with extreme fragility and critical clinical conditions [37]. This emphasise the complexity and challenges involved in managing such high- risk patients, where the choice of valve and implantation technique can significantly impact outcomes.

Based on these findings, it is feasible to develop a guidance document for selecting the appropriate transcatheter valve size for valve-in-valve and sequential valve-in-valve implantation modalities, informed by the experimental models proposed in this study, as shown in Figure 7.

CONCLUSION

Overall, while the *in vitro* results of this study support the use of the Braile Inovare transcatheter valve in sequential valve-in-valve procedures, the absence of comprehensive *in vitro* data for this modality in the literature highlights the need for further research. Future studies should aim to address these gaps, focusing on *in vitro* hydrodynamic performance and optimal oversizing strategies to enhance the safety and efficacy of sequential valve-in-valve procedures.

ETHICAL COMMITTEE CONSENT

The proposed study was approved by the Research Ethics Committee of the Federal University of São Paulo (Unifesp) on 17 July, 2016 with registration number 8345140716.

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