In-vitro and ex-vivo Hemodynamic Testing of an Innovative Occluder for Paravalvular Leak after Transcather Aortic Valve Implantation

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ABBREVIATIONS

CO = Cardiac output

HR = Heart rate

p_{Ao} = Mean aortic pressure

PVL = Paravalvular leakage

RF = Regurgitant fraction

RV = Regurgitant volume

SV = Stroke volume

TAV = Transcatheter aortic valve

TAVI = Transcatheter aortic valve implantation

ΔP = Mean diastolic transvalvular pressure

η = Device efficiency

ABSTRACT (words number: 150)

This study aims at achieving a proof-of-concept for a novel device designed to occlude the orifices that may form between transcatheter valves and host tissues after TAVI. The device effect on the performance of a Sapien XT with a paravalvular gap was assessed into an in-vitro and ex-vivo pulse duplicator. The in-vitro tests were performed complying with the standard international regulations, measuring the trasvalvular pressure and regurgitant volumes with and without the paravalvular gap, and with the occluder correctly positioned into the gap. In the second series of tests, the leakage reduction due to the presence of the occluder was assessed for the same setup, into a beating swine heart. The occluder implantation decreased the regurgitant fraction of about 50% for the in-vitro assessment and 75% for the ex-vivo test, under rest operating conditions. These results suggest that suitably design occluders can lead to important benefit in the PVL treatment.

Clinical Relevance

Addressing PVL is still an unmet need to reduce the main adverse complications related to TAVI and support the expansion of the treatment of lower-risk patients. This work presents the in-vitro and ex-vivo assessment of a new endovascular occluding device, specifically designed to mitigate PVL by obstructing the ventricle backward flow.**Key words:** Transcatheter aortic valve implantation (TAVI), transcatheter aortic valve replacement (TAVR), paravalvular leakage (PVL), aortic regurgitation, vascular plugs.

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) avoids the needs for open-heart surgery and, therefore, it has established as the treatment of preference for severe aortic stenosis in high and intermediate risk patients[1]. In the last decade the number of patients treated with TAVI has rapidly increased, and it is foreseen that this number will further enlarge in the years to come, due to the continuous aging of the population[2–4].

As a result, the available typologies of transcatheter aortic valves (TAVs) have progressively expanded in terms of design and materials, so that several families of devices are now routinely used[5]. However, the main risks and complications mainly associated with stroke, atrioventricular block and PVL[1], still need to be fully addressed. In particular, PVL remains the major complication, reducing the safety and the efficacy of TAVI[5–9], and it is the drawback for extending TAVI to patients at lower risk[10–12] if compared to conventional aortic valve replacement[13].

There is agreement on the sources of PVL, which is typically attributed to: i) dimensional mismatch between prosthesis and host region due to undersizing or incomplete expansion of the TAV; ii) incorrect release and positioning of TAV into the host region; and iii) the irregular annulus shape and/or leaflets calcification that determine the incomplete apposition of the TAV on the native host tissues[14, 15]. The first and second sources can be limited by balloon overfilling, valve in valve, and post dilatation of the valve[16, 17]; whereas in the last case, which is the most frequent, the presence of gaps between the native annulus and the prosthetic valve can be treated by sealing the paravalvular orifices by means of occluding devices[18–20].

A number of devices have been employed off-the-shelf for PVL closure, typically belonging to the AMPLATZER family (e.g. as AMPLATZER™ PDA, AMPLATZER™ VSD, AMPLATZER™ vascular plugs, Abbott, USA), or coil systems (e.g. Gianturco or Flipper coils,

Cook Medical, USA)[21]. However, the implants have been characterized by significant incidence of procedural failure and clinically unsatisfactory mitigation of the leakage. Procedure failure is commonly associated with the inability to cross the paravalvular orifice with a wire or delivery catheter, dislodgement/embolization of the device, incomplete closure of the defect, or interference of the device with the prosthetic valve function[22–26].

Recently, an in-vitro study analyzing and quantifying the efficacy of AMPLATZER™ vascular plug II and III (two of the most adopted devices to occlude paravalvular orifices after TAVI) to reduce PVL indicated that the paravalvular orifice occlusion with these solutions is far from being satisfactory, at least in the short term[27]. In particular, defining the efficiency of the occluders as the ratio between the reduction of regurgitant volume after the plugs implantation and the total regurgitant volume passing through the defect free from the device, efficiencies of about 30% and less than 10% were estimated for the AMPLATZER™ vascular plug II and III, respectively. Moreover, in the case of the AMPLATZER™ vascular plug II, cyclic mechanical interaction between the leaflet and the device is observed, which may result into leaflet damage by wearing. The limits of these devices can partially to be attributed to their improper use, as they are not specifically designed for the mitigation of PVL after TAVI[27, 28].

The present work describes a new device purposely developed to occlude the paravalvular orifice after TAVI, and the preliminary assessment of its efficiency, by means of in-vitro and ex-vivo testing in a hydromechanical pulse duplicator and in an isolated beating swine heart.

MATERIALS AND METHODS

Prototype of the device

The test device consists of a nitinol winding contained inside a flexible polymeric sac, as shown in Figure 1. The winding is a closed wire-frame of 0.15 mm diameter, obtained from a pair of

specular elliptical helices whose spirals progressively enlarge moving from the two ends of their axis to the mid-span, so that the enveloped shape resembles a spinning top of elliptical cross section. In the case of the test prototype, the two helices included 5 spirals each, joined at the proximal and distal extremities. The occluder's axial length was 4.0 mm and the minor and major diameters at the largest cross section were 7.0 and 6.0 mm, respectively. The sac is designed to cover the whole nitinol frame with the exception of the proximal portion of the device, in order not to impede the easy collapse of the device and allow its adaptation to the hosting paravalvular orifice (see Figure 1). In the tested prototype, this component was made of medical grade silicone (MED10-6607, Nusil, Carpinteria, CA, USA) by dip coating, achieving a thickness of about 0.2 mm. The occluder is designed to be collapsed by winding up the nitinol coil about its axis, thus reducing its loaded diameter to less than 6 Fr while maintaining its axial length.

The manufacturing approach can be easily modified to achieve dimensions conforming most paravalvular orifices.

In-Vitro assessment

The performance of the proposed occluder was assessed by means of in-vitro testing on a hydro-mechanical pulse duplicator (*ViVitro System, ViVitro Labs Inc*.). A silicone housing identical to the one described in Burriesci *et al*.[27] and Peruzzo *et al*. [29], replicating a cylindrical host region of 23 mm diameter with a paravalvular orifice of semielliptical shape of major and minor axis of 6 and 5 mm, respectively, was used to host an Edward SAPIEN XT of nominal size 26 mm. Phosphate buffered saline solution at 37 °C, was used as testing fluid. Hydrodynamic parameters of interest, i.e. pressures in ventricular and aortic chamber and aortic flowrate, were measured using Millar Mikro-tip pressure catheters (Millar Instruments, Inc., Houston, TX, USA) and an electromagnetic flowmeter (Carolina Medical Electronics, Inc., East Bend, NC, USA), respectively.

The valve regurgitant volume was estimated at cardiac outputs (*CO*) from 2 to 7 l/min, with increments of 1 l/min, at a normal heart rate (*HR*) of 70 bpm and a constant cycle-averaged aortic pressure (p_{Ao}) of 100 mmHg, as required by international standard ISO 5840-3:2013. Further nine experiments were conducted at a *CO* of 4 l/min, for combinations of three different *HR* (45, 70 and 120 bpm) and three p_{Ao} (80, 120 and 160 mmHg).

Data were averaged over 10 consecutive cycles and used to extract the following quantities: *i)* mean diastolic transvalvular pressure difference (ΔP); *ii)* regurgitant volumes (*RV*); and *iii)* percentage regurgitant fraction through the valve (*RF*), which is 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.

The fifteen tests described above were repeated for three different configurations. In the first configuration the paravalvular orifice was free from the occluder, thus simulating the maximum leakage of the system. In the second configuration the paravalvular orifice was completely occluded by a solid block, designed to fit ideally into the gap, thus reducing the leakage of the apparatus to the minimum achievable value (corresponding to the distributed leakage through the stent periphery). Finally, in the third configuration the orifice was partially occluded by the implanted device (see Figure 2a-c).

The efficiency of the occluder was determined by the following expression:

$$\eta = 1 - \frac{RV - RV_C}{RV_O - RV_C} \cdot 100\% \qquad (1)$$

where RV is the measured regurgitant volume when the orifice is occluded by the device, RV_C is the regurgitant volume when the defect is filled by the solid block, and RV_O the estimate regurge when the orifice is completely open. The efficiency η ranges from 0 to 100%.

Ex-Vivo assessment

In order to test the device in a more physiological environment, additional ex-vivo experiments were conducted in a suitably designed platform that consists in a pump feeding a circuit in which heparinized blood flows through a left ventricle and ascending aorta of a pig, usually employed for preoperative training and for testing percutaneous procedures[30, 31]. A detailed description of the setup of the apparatus and the preparation of the pig heart is provided by de Hart *et al*.[32]. Similarly to the in-vitro experiment, a silicone housing of the same lumen and paravalvular orifice was manufactured and used to host the same transcatheter valve used in the pulse duplicator. The periphery of the housing was covered with fabric, to enable its suturing to the annulus of the porcine aortic root. To prevent dislodgement during manipulation, the valve was tied to the housing with three suture knots (see Figure 2d-f). Then, the occluder was manually inserted inside the paravalvular orifice (see Figure 2f), maintaining a tether which could be passed through a hole in the aortic root and pulled during the test, to disengage the device from the orifice.

The block was then positioned above of the aortic sinotubular junction, after removal of the native leaflets and coronary arteries occlusion, as shown in Figure 2g-i, using three pairs of wires passed through the fabric in the housing, and a set of pledgets.

Tests were carried out to evaluate the hemodynamic performance of the system with and without the device positioned within the paravalvular defect. Three series of tests were devised for each of the two configurations, in order to investigate the PVL and its reduction as a function of the cardiac output, heart rate and aortic mean pressure. Specifically, the first series the cardiac output was performed at COs of 4.0, 5.0 and 6.0 l/min, with p_{Ao} = 100 mmHg and HR = 70 bpm. In the second series, the performance of the systems was analyzed at three heart rates, i.e. 60, 70 and 90 bpm, with p_{Ao} = 100 mmHg and CO = 5.0 l/min; whereas in the last series we considered three mean aortic pressures equal to 80, 100 and 120 mmHg with CO = 5.0 l/min and HR = 70 bpm.

Consistently with the in-vitro analysis, data were averaged over 10 cycles to estimate the characteristic hemodynamic parameters, i.e.; Δp, RV, and RF.

Two additional tests were carried out imposing CO = 5.0 l/min; p_{Ao} = 100 mmHg and HR = 70 bpm in the plugged configuration, and maintaining the same stroke volume, beat-rate and systemic resistance after removal of the plug. The flow through the defect was analyzed by means of Echo-Doppler acquisition, for the two scenarios i.e. with the paravalvular orifice either occluded or free.

RESULTS

Results from the in-vitro assessment

Diagrams of the regurgitant fraction estimated in the in-vitro tests at the different operating conditions are summarized in Table 1 and represented in Figure 3.

RF consistently decreases with increasing *CO* for all analyzed configurations (see Figure 3a). In particular, when the paravalvular orifice is unobstructed, *RF* reduces from about 35% for *CO* = 2.0 l/min to about 13% for *CO* = 7.0 l/min. These values reduce to about 20% and 9%, respectively, by occluding the paravalvular orifice either with the solid block or the occluder. The regurgitant fraction increases with p_{Ao} and with *HR* as shown in the panels b-d and e-g of Figure 3, respectively. As expected, the largest values of *RF* are observed when the orifice is open. Occluding the orifice results in a reduction in the *RF* of 30% ± 5%. The presence of the device results in an intermediate behavior at the less severe operating conditions (when *CO*, p_{Ao} and *HR* are low), becoming equivalent to the case where the orifice is totally occluded at higher values of CO, p_{Ao} and *HR*, more representative of the normal physiological functioning. This is reflected in the device efficiency, η, estimated by equation (1) and reported in the last column of Table 1. The average efficiency estimated for all tested configurations is above 90%, with lower values only for

combinations of low cardiac outputs (3 and 4 l/min) and low mean aortic pressure (80 mmHg) at the beat rates inferior to 120 bpm.

Results from the ex-vivo assessment

The valve performances from the ex-vivo tests are summarized in Table 2. The occluder into the defect limited the measured Regurgitant Volume and, thus, the Regurgitant Fraction. The PVL reduction is represented in the diagrams in Figure 4, where the RF for both scenarios is reported at varying CO (panel a), HR (panel b), and p_{Ao} (panel c). RF varies monotonically in the three series and an almost constant difference $\Delta RF \approx 20\%$ persists between unplugged and plugged conditions.

A qualitative description of the leakage is finally shown in Figure 5, where the diastolic blood flow in the ventricle is measured by color echo-Doppler in both the open leak and implanted device scenarios. When the orifice is open (panel a) a jet is recognizable in yellow, and the ascribed flow is estimated greater than 0.5 m/s; while no jet is observed in the same region when the occluder is implanted into the paravalvular defect (panel b).

DISCUSSION

The present work focuses on a suitably designed device to occlude paravalvular leakage. The solution was assessed by means of in-vitro testing, on a commercial TAVI device (Sapien XT) with a lateral orifice, simulating the presence of a paravalvular defect. The mitigation of PVL due to the device was quantified by considering the leakage through i) the free paravalvular orifice, ii) the completely closed paravalvular orifice, and iii) the orifice occluded by the device. Results indicate a clear benefit introduced by the implant, which was able to seal the defect for most of the tested operating conditions, approximating the configuration with no defect.

The average efficiency of the occluder was about 90%. This is substantially larger than that previously estimated for the Amplatzer Plug II and III in equivalent testing conditions[27], which is reported to be respectively equal to 30% and 7%.

In some cases, mostly associated with large transvalvular pressures, the computed η exceeded the maximum expected value of 100%. This could be explained by the presence of the deformable polymeric cuff, which might penetrate between the mesh of the prosthetic stent, providing a better seal than the block used to test the configuration with no paravalvular defect. On the contrary, in commonly adopted solutions, such as the Amplatzer plugs, blood is blocked by meshes which work as porous barriers, allowing a residual leakage persisting through preferential paths within the lumen[27].

Visual access to the valve block allowed us to verify that for all tests the occluder remained securely anchored inside the lumen, experiencing only small displacements during the cardiac cycle as effect of the change of transvalvular pressure difference.

Tests carried out on the ex-vivo model confirmed the findings from the in-vitro evaluation. In this case, the regurgitant fraction estimated for the free orifice was higher than that determined in-vitro. This difference could be intrinsic to the apparatus, inasmuch is unattainable the perfect coupling between the device (and the occluder) and the surrounding tissues, mainly due to the presence of the fabric coating incorporated at the periphery of the silicone housing used for the ex-vivo assessment, to allow the surgical stitching of the block. This determines some reduction in the compliance of the host region, which may result in lower interference between the prosthesis and the silicone annulus[33]. Manipulation of the block during the implant, may have further contributed to decrease the radial force exchanged between the two components.

Conversely, the reduction of regurgitant fraction produced by the presence of the occluder results larger than in the in-vitro tests, suggesting a more effective function of the device. This is probably

due to the significantly greater viscosity of the real blood used in the ex-vivo test, compared to the saline solution preferred in the pulse duplicator, which would reduce the diffusive leakage. However, the effect of the different fluid viscosity on the diffusive leakage may have played some role in the results. The overall result is a larger relative reduction of *RF* due to the device that, referring to the physiological work condition (CO = 5 l/min, p_{Ao} = 100 mmHg and HR = 70 bpm), varies from the 35% for the in-vitro test to the 73% for the ex-vivo platform.

The interpretation of the performance indicated by the ex-vivo tests shall take into account that this is based on a single experiment, whilst a large number of hearts would be required to assess the efficacy of the device with this type of study [34, 35].

However, independently of the platform employed for the tests, the dependency of the regurgitant fraction on the hydrodynamic parameters, i.e. CO, HR and p_{Ao}, is in agreement with previous experiments reported by Burriesci et al.[27].

The comparison between the aortic valve performance obtained from the two additional ex-vivo tests, before and after removing the occluder, provides useful information on the benefit of the occluder implant in a hypothetical patient affected by moderate PVL. In this scenario, the occlusion of the defect reduces considerably the aortic regurgitant volume from 20.3 ml (RF= 25.0%) to 5.3 ml (RF= 7.1%), i.e. PVL grade mild-trace. In addition, the best performance of the valve in diastole promotes a gain in the mean aortic pressure and cardiac output of 12 mmHg (87 vs 99 mmHg) and 624 ml/min (4.251 l/min vs 4.875 l/min), respectively, i.e. an improvement of the cardiac performance of almost 15%.

The epicardial echo acquisitions confirm the effective function of the occluder, with the paravalvular jet clearly localized in diastole through the free orifice and totally absent when the occluder is correctly placed into the defect. Although the entrapment of air bubbles into the circuit has introduced significant noise in a measurement which already presents difficulties in achieving

accurate quantifications of the leakage, this test provides a clinical perspective about the measured PVL mitigation.

The main limitations of the present study are the use of fluids precluding or inhibiting the coagulation and the simplified anatomy of the orifice as well as the cardiovascular apparatus. The former should affect the mid-long term performance of the device, since coagulation promotes the occlusion of the orifice and thus an additional reduction of the measured leakage. However, the residual leakage observed in the present analysis when the occluder is implanted is precautionary and suggests that the treatment of PVL is effective also in adverse conditions, namely, in patients following anticoagulant therapy. Concerning the second limitation, it is likely that the idealized cylindrical defect, here modeled, favors the sealing between the hosting region and the silicone cuff. In general, we expect that the anatomy of the paravalvular orifice and the adaptability of the device into the housing region play a key role in the total efficiency. In particular, very complex lumen shapes and/or the coarseness of calcified regions may limit the efficacy of the device. This aspect needs to be further investigated, possibly reproducing patient-specific paravalvular orifices, also taking into account the different types of balloon- and self-expandable valves.

Finally, the use of in-vitro and ex-vivo apparati, whilst essential to allow the accurate control of the working conditions of the experiments, does not reproduce all factors which may intervene in a physiological environment. Such a limitation is hard to address, since standard animal models do not present calcified tissues in the left ventricular outflow tract. For these reasons, the direct application of the present outcomes to clinical cases should be prudential. In this context, it is worth underlining that there are no recommendations in currently available regulatory standards on the in-vitro modeling of paravalvular leakage. Hence, the present work represents a first attempt to propose a systematic experimental approach, which allows the comparison between alternative corrective solutions.

The experiments confirm the efficacy of the new occluding device, based on a nitinol winding core supporting a polymeric sac, and enlightens the substantial functional advantages that design solutions targeted to address specific problems may bear, compared to generic or off-the-shelf devices. This operating principle is suitable to be expanded to other sealing devices, such as vascular plugs in general.

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Ethical Approval: This article does not contain any studies with human participants or animals performed by any of the authors.

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Figure Legends

Figure 1. Description of the prototype made by a NiTi wireframe and covered by the silicone bag. Distances are expressed in mm.

Figure 2. Rubber holder in presence of the orifice and SAPIEN valve in the in-vitro tests: (a) no occlusion of the leak, (b) complete occlusion of the leak by a solid filler, and (c) occlusion of the leak with the proposed device. Implantation of the Sapien XT and the occluder into the silicone ring in the ex vivo tests: (d) expansion of the valve by balloon filling, (e) fixing of the valve to the annulus by sutures, and (f) implantation of the occluder into the defect, red circle highlights the wire used to pull out the device during the tests. Implantation of the block into the pig heart: (g) Removal of native aortic valve, (h) insertion of aortic block into the pig heart, and (i) Block implantation by mean of pladgets.

Figure 3. Benefit of occluder implantation on leakage in in-vitro tests. a) Regurgitant Fraction, *RF*, for HR= 70 bpm and $\boldsymbol{p_{Ao}}$= 100 mmHg with *CO* for the three scenarios analyzed, b-d) *RF* with $\boldsymbol{p_{Ao}}$ for *HR*= 45, 70 and 120 bpm at *CO*= 4.0 l/min, and e-f) *RF* with *HR* for $\boldsymbol{p_{Ao}}$= 80, 120 and 160 mmHg at *CO*= 4.0 l/min. Red, blue and green lines represent the free leak (Open), the fully occluded leak (Closed), and the leakage with the device implanted (Device), respectively. Experimental data are indicated by square (open leak), circle (occluded leak) and tringle (implanted device) markers.

Figure 4. Effect of occluder implantation on leakage in ex-vivo platform. a) Regurgitant Fraction, *RF*, for *HR*= 70 bpm and $\boldsymbol{p_{Ao}}$= 100 mmHg with *CO* varying, b) *RF* with *HR* varying for $\boldsymbol{p_{Ao}}$ = 100

mmHg and *CO*= 5.0 l/min, and c) *RF* with $\boldsymbol{p_{Ao}}$ varying for *HR*= 70 bpm and *CO*= 5.0 l/min. The open and implanted device conditions are represented by red solid line and blue solid line, respectively. Experimental data are shown by squares (open condition) and circles (device condition).

Figure 5. Epicardial color echo-doppler of the ventricle flow pattern in diastole measured in absence (a) and in presence (b) of the occluder into the paravlvular orifice. Both the acquisitions are referred to the case having CO= 5.0 l/min, HR= 70 bpm, and the same pherifery resistance.

Tables

Table 1. Summay of in-vitro experimental work conditions and main postprocessing data.

Work conditions			*Open leak*			*Occluded leak*			*Implanted device*			
HR	*CO*	p_{Ao}	*RV*	*RF*	ΔP	*RV*	*RF*	ΔP	*RV*	*RF*	ΔP	η
bpm	*l/min*	*mmHg*	*ml*	*%*	mm_{Hg}	*ml*	*%*	mm_{Hg}	*ml*	*%*	mm_{Hg}	*%*
70	2	100	15.0	34.6	-94.3	7.1	19.7	-99.3	7.8	21.7	-96.7	91
	3		13.8	24.5	-98.0	8.0	15.5	-97.4	8.8	17.1	-96.1	86
	4		14.1	20.1	-94.6	8.1	12.5	-99.3	11.5	16.8	-96.9	43
	5		15.2	17.8	-95.1	8.7	11.2	-97.9	9.3	11.6	-97.6	91
	6		16.9	16.7	-92.2	10.1	10.8	-97.4	10.3	10.8	-97.5	97
	7		15.4	13.4	-94.0	9.5	8.7	-101.0	9.4	8.7	-98.7	102
45	4	80	17.3	16.4	-74.5	10.8	10.5	-75.7	12.5	12.4	-74.5	74
		120	19.6	18.0	-111.2	11.2	11.2	-114.0	11.5	11.5	-115.7	96
		160	21.8	20.1	-148.2	14.8	14.5	-150.6	13.7	13.8	-151.4	116
70	4	80	11.8	17.5	-75.6	8.3	12.6	-75.6	10.0	14.9	-77.3	51
		120	13.6	18.6	-116.5	9.7	14.3	-116.0	9.1	14.0	-117.0	115
		160	16.0	22.2	-150.3	10.8	16.2	-154.0	10.8	16.2	-156.7	100
120	4	80	8.5	20.6	-73.9	5.8	14.6	-73.8	5.7	14.8	*-78.0*	104
		120	10.9	25.3	-114.2	6.7	16.3	-116.2	6.6	16.7	-115.9	102
		160	11.1	25.0	-150.5	7.5	18.2	-157.0	7.5	18.5	-156.2	100

Table 2. Summay of ex-vivo experimental work conditions and main postprocessing data.

Work conditions			*Open leak*			*Implanted device*.		
HR	*CO*	p_{Ao}	*RV*	*RF*	*ΔP*	*RV*	*RF*	*ΔP*
bpm	*l/min*	*mmHg*	*ml*	*%*	mm_{Hg}	*ml*	*%*	mm_{Hg}
	4		28.2	33.4	-49.6	6.9	10.7	-55.4
70	5	100	26.4	26.9	-51.3	5.3	7.1	-51.2
	6		24.9	23.0	-48.3	2.8	3.1	-47.0
60			30.8	27.3	-49.8	6.4	7.3	-52.7
70	5	100	26.4	26.9	-51.3	5.3	7.1	-51.2
90			26.3	32.3	-53.0	6.3	9.9	-50.0
		80	16.8	18.9	-36.7	2.1	3.0	-41.3
70	5	100	26.4	26.9	-51.3	5.3	7.1	-51.2
		120	33.6	31.9	-61.5	12.1	14.5	-63.2

Figure 1

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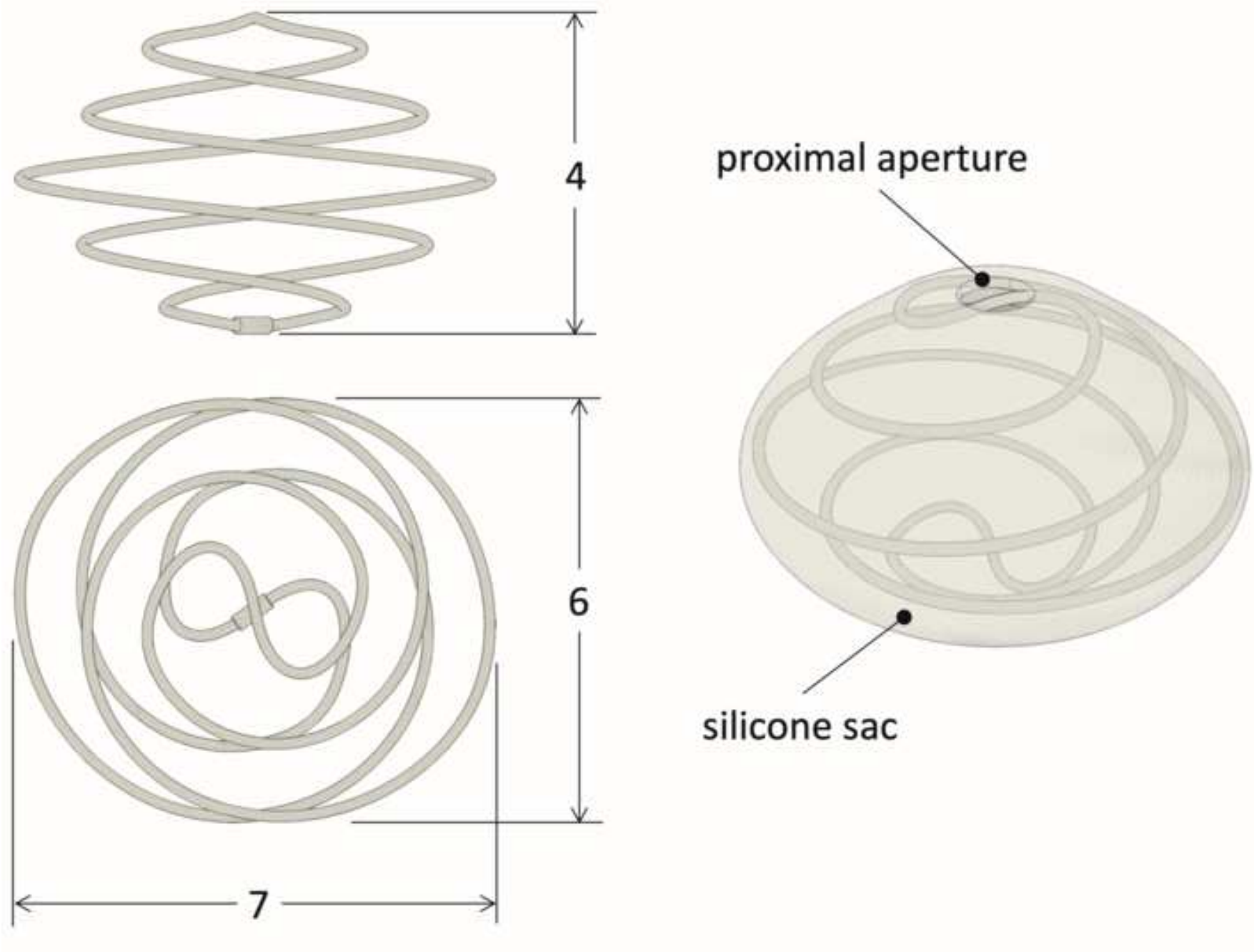

Figure 2

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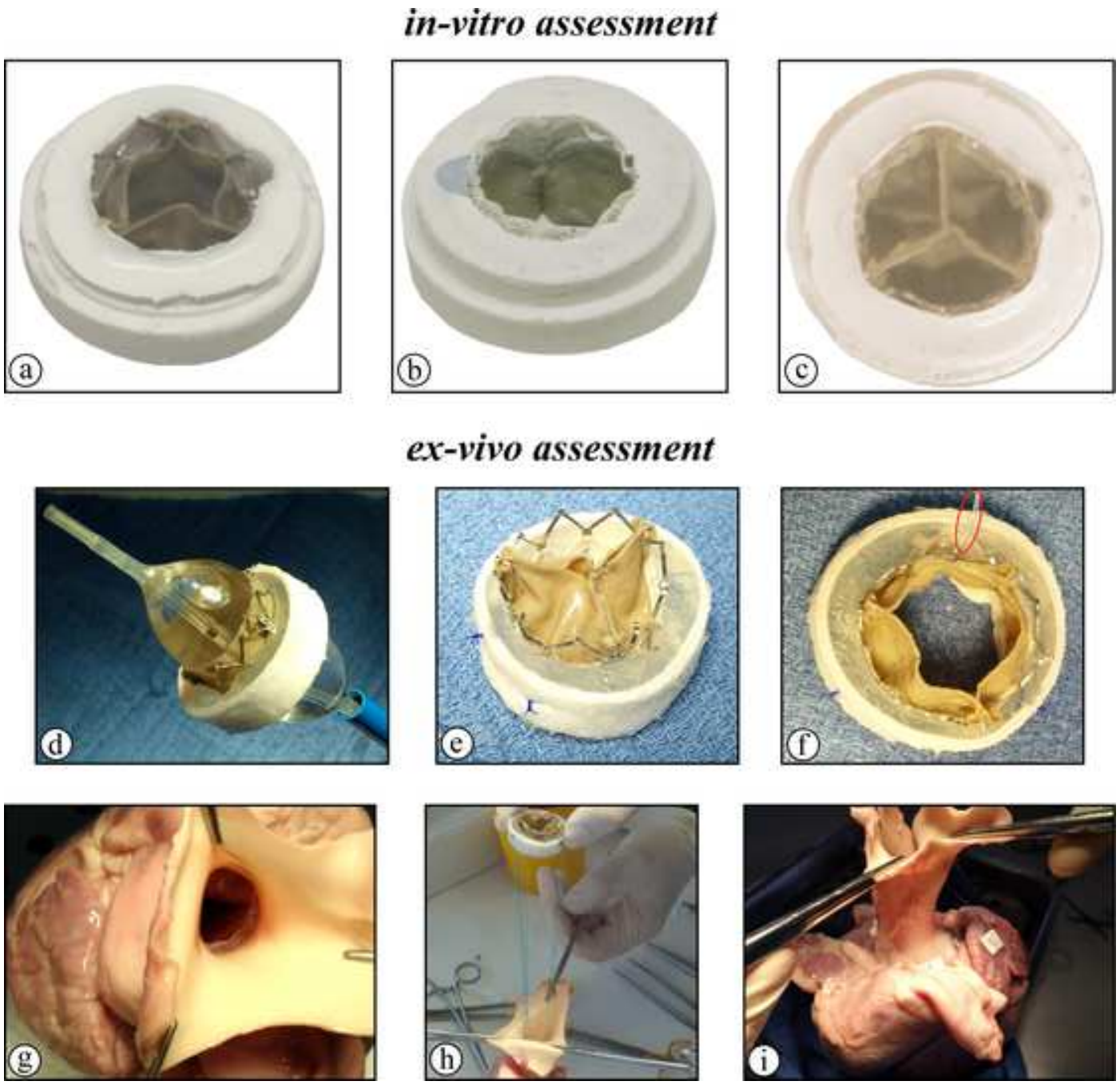

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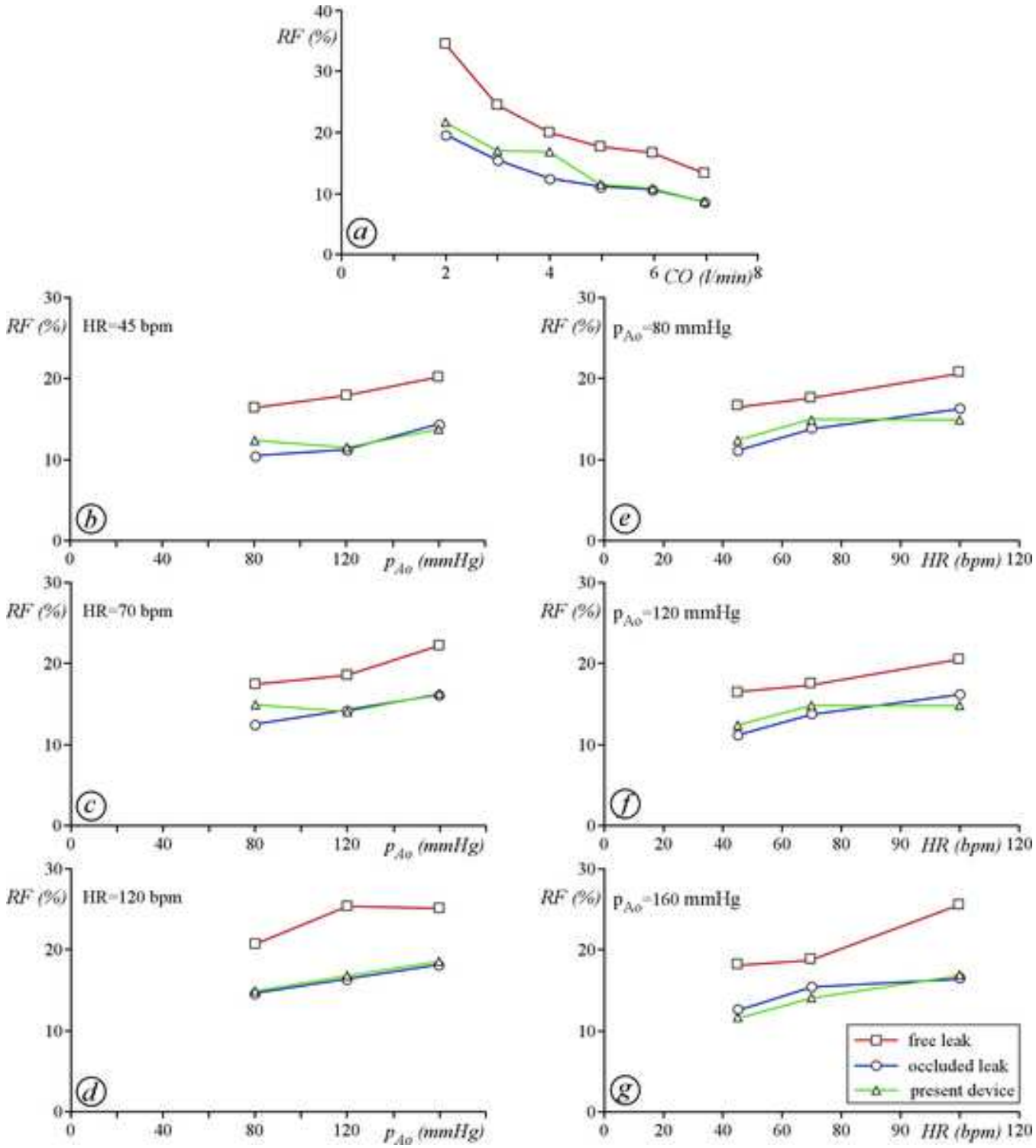

Figure 4

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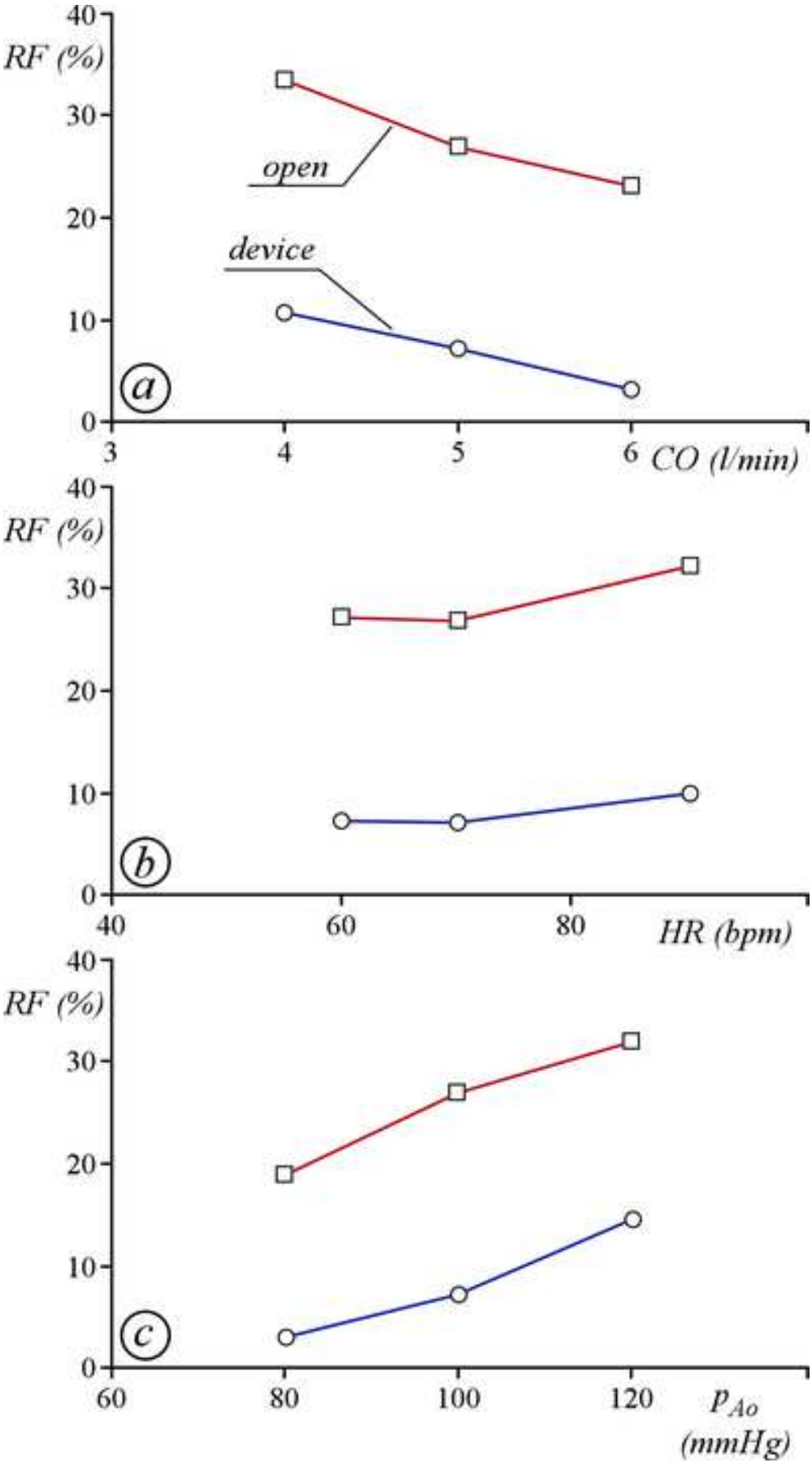

Figure 5

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