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1 **Characterization of the Effective Orifice Areas of Mitral Prosthetic Heart**  
2 **Valves: An In Vitro Study.**

3

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23

24

25 **Abstract**

26 **Objectives:**

27 Reference values of hemodynamic parameters for the assessment of prosthetic heart valves are  
28 necessary and ideally need to be provided by entities independent of valve manufacturers. The aim of  
29 this in vitro study was thus to provide normal reference values of effective orifice area (EOA) for  
30 different models and sizes of mitral prosthetic valves and to assess the determinants of EOA and mean  
31 transvalvular pressure gradient (mTPG).

32 **Methods:**

33 We tested 4 models of mechanical prostheses (1 mono-leaflet and 3 bi-leaflet) and 4 models of  
34 bioprostheses (2 bovine pericardial and 2 porcine) on a double activation pulsed duplicator specifically  
35 designed and optimized for the assessment of the hemodynamic performance of mitral prosthetic  
36 valves. The hemodynamic conditions were standardized and included for bioprostheses: two mitral  
37 flow volumes, three mean aortic pressure, two heart rates and three E/A ratios. The EOAs were  
38 measured by Doppler-echocardiography using the same method (continuity equation) as the one used  
39 in the clinical setting. Overestimation in term of EOA was defined according with guidelines as >  
40  $0.25\text{cm}^2$ .

41 **Results:**

42 EOA reference values were: for mono leaflet prosthesis (Medtronic Hall 7700, size 25 to 31mm): 2.29  
43 and 3.49, for bi-leaflet prosthesis (St. Jude Medical Master and Master HP, sizes 25 to 33mm, On-X  
44 valve, sizes 27-29mm): 1.34 and  $4.74\text{ cm}^2$ ; for porcine bioprostheses (Medtronic Mosaic CINCH, sizes  
45 25 to 31mm, St. Jude Epic 100, sizes 25 to 33mm): 1.35 and  $3.56\text{ cm}^2$ ; for bovine pericardial  
46 bioprosthetic valves (Edwards Perimount 6900P and Magna Ease 7300, sizes 25 to 33mm): 1.67 and  
47  $2.36\text{ cm}^2$ . There were some discrepancies between the normal reference EOAs measured in this study  
48 versus those provided by prosthesis manufacturers or by literature. The bioprosthesis EOAs were  
49 found lower than the manufacturers' values in 32% by  $0.57\pm 0.28\text{cm}^2$  in average vs in 7% when  
50 compared to values presented in the literature by  $0.43\pm 0.17\text{cm}^2$ . The relationship between EOA and  
51 the internal orifice area (IOA) varied according to the type of prosthesis. The EOA was close to the

52 IOA in mechanical valves (regression slopes 0.87 to 0.99) but much smaller than IOA in bioprosthetic  
53 valves (slopes 0.25-0.30). The EOA was influenced by prosthesis diameters, prosthesis stent diameter  
54 and height and mTPG was influenced by EOA and heart rate.

55 **Conclusion:**

56 This study provides normal reference values of EOAs for several frequently used mitral prostheses.

57 This information may be helpful to identify and quantify a prosthetic valve dysfunction and prosthesis-  
58 patient mismatch.

59

## 60 **Introduction**

61 The valve effective orifice area (EOA) is a key parameter to assess the hemodynamic function of  
62 native and prosthetic mitral valves <sup>1</sup>. While mean transvalvular pressure gradient (mTPG) is also often  
63 measured, the clinical utility of this parameter is more limited due to its high dependence on heart rate  
64 and flow rate. EOA can be accurately measured by Doppler-echocardiography with the use of the  
65 continuity equation method. The presence of prosthetic valve stenosis can be assessed by comparing  
66 the EOA measured by echocardiography with the normal reference value of EOA<sup>2</sup>. A measured EOA  
67 that is significantly smaller than the normal EOA suggests pathologic obstruction of the prosthetic  
68 valve <sup>1</sup>. However, the normal value of EOA differs markedly depending on the model and size or  
69 prosthetic valve. It is thus crucial to establish normal reference values for the models and sizes of  
70 prosthetic valves that are used clinically. Furthermore, the normal reference values of EOA can be  
71 used to calculate the predicted indexed EOA (i.e. normal EOA for the model and size implanted in  
72 the patient divided by the patient's body surface area), which in turn allows identification and  
73 quantitation of prosthesis-patient mismatch<sup>3</sup>. The primary objective of this in vitro<sup>3</sup> study was to  
74 provide normal EOA reference values for some of the most frequently implanted mitral prostheses  
75 using highly standardized hemodynamic conditions. The secondary objective of this study was to  
76 assess the effects of prosthesis geometric parameters and of the hemodynamic parameters on the EOA  
77 and mTPG.

78

79

## 80 **Methods**

### 81 *In vitro simulation*

82 The pulse duplicator used in this study is a double activation duplicator in which left ventricle and  
83 atrium are anatomically shaped and has been previously described <sup>4</sup>. Left cavities flow is generated by  
84 gear pumps inside the two activation boxes control the contraction and dilatation of both the LA and  
85 LV cavities. The aortic and pulmonary native valves are simulated by two Biocor 23mm valves. Right  
86 ventricular flow is generated by a third pump. Compliance and resistance assemblies enable to model  
87 both pulmonary and systemic circulation using a hybrid Windkessel and lumped element modeling  
88 approach. Validation of pressure volume loop as well as a harmonic analysis have been previously  
89 performed for general validation of the duplicator <sup>5</sup>. Previous results show that regurgitation volumes  
90 remain within sensors precision range ( $\pm 0.1$ L/min, range 0.5mL/min to 10L/min).

91

### 92 *Tested Prosthetic Valves*

93 Nine types of bioprostheses and mechanical heart valves (MHV) from 4 manufacturers were tested in  
94 this study: 1) Mono-leaflet mechanical valve Medtronic Hall 7700 (sizes 25/27/29/31mm), 2) Bileaflet  
95 mechanical valves: St. Jude Medical Master (sizes 25/29/33mm); St-Jude Medical Master HP (sizes  
96 25/27mm); On-X (sizes 27-29mm). 3) Porcine bioprosthetic valves: Medtronic Mosaic CINCH (sizes  
97 25/27/29/31mm); St. Jude Epic 100 (sizes 25/27/29/31/33mm). 4) Bovine pericardial bioprostheses:  
98 Edwards Perimount 6900P (sizes 25/27/29/31mm); Edwards Magna Ease 7300 (sizes  
99 25/27/29/31/33mm).

100

### 101 **Measurements of Prosthesis Geometric Parameters**

102 Figure 1, A illustrates how the internal diameter, height and opening angle of MHVs were measured.  
103 For bioprostheses, the reference measurement of internal orifice diameter provided by the  
104 manufacturer corresponds to the internal diameter of the metal structure of the stent without  
105 consideration of the space occupied by the leaflets and sutures attaching those leaflets (Figure 1,B).  
106 Measurements performed by the authors are also provided in Supplement Table 1. In brief, the internal

107 diameters at three levels of the prosthesis using a contactless measurement system (Smart Scope,  
108 Optical Gaging Pty Ltd, Singapore) (Figure 1). The internal orifice area (IOA) of the prosthesis was  
109 calculated from the internal diameter measured at the inflow level of the prosthesis (Figure 2).

110

### 111 *Hemodynamic Conditions for Prostheses Testing*

112 We tested all prostheses under the following hemodynamic conditions: sinus rhythm, heart rate 70  
113 bpm, mitral flow volume (MFV) of 70mL, a systolic time interval of 35% of the cardiac cycle, E  
114 wave/A wave velocities ratio of 1.5, aortic pressure of 100mmHg. These parameters have been  
115 previously validated elsewhere<sup>5</sup>.

116 For bioprostheses, we tested using additional conditions in order to assess the effect of different  
117 hemodynamic factors on the valve EOA and mTPG: MFVs of 70 and 90mL; heart rates of 45, 70 and  
118 120 beats per minute; E/A ratio of 0.5, 1.0 and 1.5.

119

### 120 *Pressure, Flow and Doppler Measurements*

121 An electromagnetic flowmeter was placed immediately before the prosthesis. Its internal diameter did  
122 not interfere with flow (Carolina Medical Probe 95, internal diameter 30.24mm). Pressure  
123 measurements were acquired in left atrium, left ventricle, pulmonary artery and in aorta using Millar  
124 MPR 500 catheters (accuracy full range  $\pm 0.5\%$ , -50 to 300 mmHg). Both systems, flow meter and  
125 pressure acquisition chains, have been previously calibrated. Closing, leakage and regurgitant volumes  
126 were calculated for each prosthesis using the flow signal variations<sup>6</sup>.

127 The mTPG was measured by continuous wave Doppler using the Bernoulli formula as described in  
128 our previous study<sup>4</sup>. EOA was calculated using the continuity equation by dividing flow meter  
129 derived MFV by the velocity time integral of the transprosthetic velocity obtained by continuous-wave  
130 Doppler. Catheter measurements of transvalvular pressure were also obtained.

131

### 132 *Statistical analyses*

133 All described values are given as mean value  $\pm$  standard deviation and a Wilcoxon test was performed  
134 to test statistical significance between groups when appropriate using R software. Univariate and

135 multivariate linear regression analyses were performed to evaluate which parameters are associated  
136 with EOA and mTPG. Statistical significant was defined as  $p < 0.05$ .

137

## 138 **Results**

### 139 *EOA Reference Values*

140 EOA reference values are reported in Table 1: 1) Mono-leaflet mechanical valves: the EOA was  
141 between 2.29 and 3.49  $\text{cm}^2$  for Medtronic Hall 7700 (sizes 25/27/29/31mm); 2) Bileaflet mechanical  
142 valves, EOA was between : 1.34 and 2.18  $\text{cm}^2$  for the St. Jude Medical Master (sizes 25/29/33mm),  
143 2.11 and 4.74  $\text{cm}^2$  for the St-Jude Medical Master HP (sizes 25/27mm) and 2.53  $\text{cm}^2$  for the On-X  
144 valve (sizes 27-29mm);3) Porcine bioprosthetic valves: the EOA was between 1.35 and 1.94  $\text{cm}^2$  for  
145 the Medtronic Mosaic CINCH (sizes 25/27/29/31mm); 3.08 and 3.56  $\text{cm}^2$  for St. Jude Epic 100 (sizes  
146 25/27/29/31/33mm); 4) Bovine pericardial bioprosthetic valves: EOA was between 1.69 and 2.36  $\text{cm}^2$   
147 for the Edwards Perimount 6900P (sizes 25/27/29/31mm); 1.67 and 2.25  $\text{cm}^2$  for the Edwards Magna  
148 Ease 7300 (sizes 25/27/29/31/33mm). Additionally, regurgitant volumes were reported in Table 2 and  
149 found below 10% of the SV in all tests.

150 We compared the values of EOAs obtained in this standardized in vitro study with the normal values  
151 of EOAs reported by valve manufacturers and also with those reported in the literatures (see Table 3).  
152 Manufacturers EOAs and literature-derived EOAs overestimated the EOAs obtained in the present  
153 study by  $>0.25 \text{ cm}^2$  (difference considered significant in 2016 EACVI guidelines) in 32% and 7% of  
154 the cases, respectively and with an average overestimation of respectively  $0.57 \pm 0.28 \text{ cm}^2$  and  
155  $0.43 \pm 0.17 \text{ cm}^2$ . When the analysis restricted to bioprostheses, the manufacturer and literature EOAs  
156 overestimated the present EOAs by  $> 0.25 \text{ cm}^2$  in 44 % and 4% of the cases, respectively and with an  
157 average overestimation of respectively  $0.48 \pm 0.16 \text{ cm}^2$  and  $0.55 \text{ cm}^2$ . Underestimation ( $>0.25 \text{ cm}^2$  )  
158 compared to the reported EOA values happened in all case of bi-leaflet valves with manufacturer  
159 values (average value  $1.5 \pm 0.62 \text{ cm}^2$ ) and in 6% of bioprostheses (average value  $0.67 \text{ cm}^2$ ). Respectively  
160 in literature, EOA was underestimated ( $>0.25 \text{ cm}^2$ ) the reported EOA values by in all case of bi-leaflet  
161 valves (average value  $1.2 \pm 1.1 \text{ cm}^2$ ) and in 44% of bioprostheses (average value  $0.28 \pm 0.38 \text{ cm}^2$ ).



162 ***Effect of hemodynamic and prosthesis design parameters on EOA and mTPG***

163 Prosthetic valve EOA increased and mTPG decreased with increasing internal prosthesis diameter or  
164 IOA (Figure 3). EOA also increased and mTPG decreased with increasing prosthesis height (Figure 3).  
165 With regards to hemodynamic parameters, EOA increased with increasing mitral flow volume and  
166 decreases with mean aortic pressure without reaching significance, whereas mTPG increased with  
167 increasing mitral flow volume (ns) and heart rate ( $p < 0.05$ ) (Figure 4).

168 ***Relationship between EOA, IOA, and mTPG***

169 Figure 5 shows the relationship between EOA and IOA (A) and and between EOA mTPG (B). The  
170 correlation between EOA and IOA was stronger in mechanical valves than in bioprosthetic valves.  
171 The regression slopes were much steeper in mechanical valves than in prosthetic valves: pericardial  
172 bioprostheses: slope=0.253 (unit),  $r=0.94$ , porcine bioprostheses: slope=0.297 (unit),  $r=0.91$ , vs.  
173 mono-leaflet mechanical valves: slope=0.866 (unit),  $r=0.95$ , bi-leaflet mechanical valves: slope=0.99,  
174  $r=0.79$ . There was a modest relationship between EOA and mTPG  $= -1.44 + 12.42 \cdot \exp(-0.599 \cdot \text{EOA})$   
175 (mean square error=2.305,  $r=0.62$ ).

176

## 177 **Discussion**

178 This in-vitro study reports for the first time normal reference values of EOAs for several models and  
179 sizes of mitral prosthetic valves. These in vitro EOA values were close to the in vivo values reported  
180 in the literature but smaller when compared with normal EOAs reported by prostheses manufacturers.  
181 mTPG was found to be more sensitive than the EOA to patient hemodynamic conditions. Both mTPG  
182 and EOA were influenced by prosthesis diameters and heights.

### 183 *In-vitro EOA as a reference values for prosthesis valve function assessment*

184 The graphs of EOA according to body surface area (BSA) have the advantage to take into  
185 consideration patient specific parameters related to hemodynamic through cardiac index. Such graphs  
186 do not take into consideration neither pressure conditions neither mitral flow profile (as a surrogate of  
187 diastolic function), and in-vitro EOA appears to give a full image of mitral valvular prostheses  
188 performance when properly tested. The results of this study showed the influence of hemodynamic  
189 conditions (heart rate, mean aortic pressure and E/A ratio) on continuity equation EOA and mTPG  
190 (Figure 4). As such, it seems indispensable to complete the EOA/BSA graphs have with minimum and  
191 maximum range of EOA for various heart rates, mean aortic pressures, mitral flow profiles and mitral  
192 flow volumes (for identical cardiac index).

193 Such parameters as IOA should be given to the clinician knowledge for a complete assessment of  
194 valvular prostheses. Internal diameters provided by manufacturers are usually internal diameters of the  
195 prosthesis structure without additional part (and measurement levels of such measurements are mostly  
196 not provided). Internal diameter at the entry level of the prosthesis should be preferred as constraining  
197 the flow without depending of the leaflet opening. The prosthesis height, limitedly studied and  
198 reported so far, as duration of the flow constriction through the valve, is reported here to influence  
199 both EOA and mTPG.

200

### 201 *EOA influenced by prosthesis type, design and hemodynamic conditions*

202 Correlations between EOA and IOA have been showed to be significantly different between  
203 bioprostheses and MHV: reduction between IOA and EOA is much higher in bioprostheses than in

204 MHV (slopes of 0.87 and 0.99 for MHV vs 0.25 and 0.3 for bioprosthesis). Reduction of the area  
205 between IOA to EOA was more pronounced for bioprostheses and EOA values were found smaller  
206 than in MHV (Figure 5). Difference between the IOA/EOA correlation slopes between pericardial and  
207 porcine prostheses may be related to prosthesis design differences. Indeed, prosthesis parameters  
208 influences on EOA and mTPG were highlighted in the results (Figure 3).

209 Regarding mTPG, the relationship between EOA and mTPG is described by Gorlin relation in aortic  
210 position for EOA calculation:  $EOA = Q_{rms} / (50.4 * \sqrt{mTPG})$ . Thus, model to be expected to fit was  
211 an inverse root squared model, however best results were found with exponential model when express  
212 through Gorlin. Such exponential model are more adaptive and in-vitro results presented here are  
213 consistent with clinically reported values<sup>7,8</sup>. Such relationship between EOA and mTPG, even though  
214 non-linear, could explain the higher sensitivity of mTPG to hemodynamic conditions

#### 215 ***Discrepancies between manufacturers, literature and in-vitro EOA***

216 Reference EOA values provided here were found lower than EOA values from manufacturer and  
217 literature when overestimation was considered as  $> 0.25\text{cm}^2$  (32% for manufacturers' values and 7%  
218 for literature, respectively by  $0.57 \pm 0.28\text{cm}^2$  and  $0.43 \pm 0.17\text{cm}^2$  in average). Those differences were  
219 significantly influenced by prosthesis types. The lack of reference values for mechanical prostheses  
220 and the inability of the in-vitro values to be used in patients were underlined. Whenever MHV are  
221 concerned, guidelines advice careful diagnosis on changes in EOA values between two  
222 echocardiographic prosthesis assessments rather than comparison to provided MHV reference values.  
223 Furthermore, in the context of MHV assessment, the use of continuity equation could be questioned as  
224 mentioned in guidelines<sup>2</sup>.

225 Manufacturers provide internal diameters of the different prosthesis sizes they produce. In some cases,  
226 they sometime described reference values of EOAI in relation to patient BSA, while in vitro testing  
227 setting and testing conditions are rarely provided. As the present work showed that EOA values  
228 change with hemodynamic conditions (Figure 4), description of testing systems and conditions as well  
229 as results of one reference prosthesis in this setting should be a norm requirement for mitral valvular  
230 prostheses.

231 The main objection to the use of in-vitro values are based on that EOA values obtained clinically  
232 would generally be preferred for patient prosthesis mismatch (PPM) assessment and prospective  
233 preventive strategy<sup>9</sup>. However as literature values are derived from clinical studies, characteristics of  
234 the studied population may wronged reference values. Differences between in vitro values and the  
235 literature ones can be explained by the finite number of patients compare to the larger panel of testing  
236 conditions which simulate a probably larger range of hemodynamic conditions. The advantages of in  
237 vitro testing are to enable the test of the whole range of hemodynamic conditions possibly found in  
238 patients who underwent mitral valve replacement.

### 239 *Consequences on echocardiographic criteria*

240 The threshold values for prosthesis dysfunction diagnosis will depend of the prosthesis model and size  
241 and is defined for a value lower than « reference EOA value » - 1SD for a probable dysfunction and  
242 « reference EOA value » - 2SD for a most probable prosthesis dysfunction. The EOA values provided  
243 here are averaged on all testing conditions that depict the wide range of hemodynamic conditions in  
244 which a patient could be. The SDs provide information on what could be the differences from one  
245 patient to another with the same prosthesis model and size.

246 For prognostic and diagnosis, EOAI and mTPG comparison with reference values aims to avoid PPM  
247 resulting of prejudiced prosthesis choice. Hemodynamic reference values provided here enable to  
248 anticipate post-surgery EOA and geometric reference values could be used to determine which  
249 transcatheter valve size should be implanted whenever a valve-in-valve procedure is considered.

250

### 251 **Limitations**

252 Further study on MHV EOA could investigate the relationship with mTPG and leads to correction of  
253 EOA formulation by continuity equation. Moreover tissue characterization of each prosthesis leaflet  
254 type could complete and explain difference between porcine and pericardial prostheses presented here  
255 (influence on opening, partial closing and closing time of the prosthesis). Design prosthesis influence  
256 could be studied with numerical models simulating similar testing conditions. Other echocardiographic

257 diagnosis criteria include maximal velocity, Doppler velocity index (DVI,) acceleration time and PHT.  
258 Those parameters were not described here.

## 259 **Conclusion**

260 Objective in-vitro reference values are given here to clinicians to avoid PPM and improve prosthesis  
261 dysfunction diagnostic. Geometric parameters of the prosthesis have been additionally provided  
262 enabling best choice of the prosthesis by the clinician and in view of future valve-in-valve procedure  
263 in mitral prosthesis. This work highlighted an  $>0.25\text{cm}^2$  overestimation of the in-vitro EOA in  
264 comparison with current manufacturer's and literature provided values in respectively 32% and 7% of  
265 the bioprosthesis tests (  $0.57\pm 0.28\text{cm}^2$  and  $0.43\pm 0.17\text{cm}^2$  in average). Hemodynamic conditions and  
266 prosthesis design were found to influence EOA values. This implies necessity to detail testing  
267 conditions as well as testing set up in reference EOA reports. Additionally, provided SD EOA values  
268 depict the whole possible hemodynamic conditions find for patients with the given prostheses.

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271

272 **Figure Legends**

273 **[Figure 1] Geometric Measurements Acquired Bi-leaflet Mechanical Heart Valves (A) and**  
274 **Bioprostheses (B).**

275 **Legend:**

276 (A): bileaflet mechanical heart valve: D, internal diameter at the outflow side; H, height of the sewing  
277 ring without the hinges; a, distance between leaflet when fully opened at the outflow side (maximum  
278 distance); b, at the entry side (smallest). (B-C) : Bioprosthesis: d, outflow diameter at the post edges;  
279 D, internal diameter at the base of the leaflets; h, height of the sewing ring; H, height of the struts,  
280 IOD, internal orifice diameter at the entry level. (D): Medtronic Mosaic Cinch (E): St Jude Epic (F):  
281 Edwards Perimount (G): St Jude Masters (501 and 505) (H): OnX (I): Medtronic Hall.

282 **[Figure 2] Representation of the prosthetic valve EOA and IOA.**

283 **Legend:** LA: Left atrium; LV: Left ventricle; IOA: internal orifice area; EOA: effective orifice area;

284 **[Figure 3] EOA (A) and TPG (B) according to Bioprosthesis Type, Internal Diameter and**  
285 **Height.**

286 **Legend:** Type: prosthesis type (pericardial versus porcine); Diam : prosthesis diameter (mm); Height  
287 (prosthesis height (mm). Mean values are depicted in red. Red (plain and dashed) and blue lines depict  
288 respectively 2cm<sup>2</sup> EOA threshold, 1cm<sup>2</sup> EOA threshold and 5 mmHg mTPG threshold. p values were  
289 depicted by \* when p<0.05, \*\* when p<0.01 and \*\*\* when p<0.001.

290 **[Figure 4] EOA by Continuity Equation (A) and TPG (B) According to Mitral Flow Volume**  
291 **(MFV), E/A ratio, Mean Aortic Pressure (Pao), Heart Rate (HR).**

292 **Legend:** MFV : Mitral flow volume (mL) ; E/A : E wave/A wave velocities ; mPao : mean aortic  
293 pressure (mmHg) ; HR : Heart rate (bpm). Mean values are depicted in red. Red (plain and dashed)  
294 and blue lines depict respectively 2cm<sup>2</sup> EOA threshold, 1cm<sup>2</sup> EOA threshold and 5mmHg mTPG  
295 threshold. p values were depicted by \* when p<0.05, \*\* when p<0.01 and \*\*\* when p<0.001.

296

297 **[Figure 5] Relationship between EOA, IOA, and mTPG for all Tested Prostheses.**

298 **Legend:** A: Relationship between EOA and IOA for pericardial bioprostheses (red symbols and lines)

299 and porcine bioprostheses (pink), mono-leaflet mechanical prostheses (green), bileaflet mechanical

300 prostheses (blue) for the standard test condition (MFV=70mL, HR=70bpm, E/A=0.5 and

301 mPao=100mmHg). B: Relationship between EOA and mTPG.

302

303

304 **Table Legends**

305 **[Table 1] Normal Values of EOAs and mTPGs Measured by Doppler Echocardiography for the**  
306 **Tested Mitral Valve Prostheses.**

307 **[Table 2] Transvalvular Regurgitation of the Mitral Valve Bioprostheses.**

308 **[Table 3] Reference values for Effective Orifice Area Used in the Difference Computation from**  
309 **In-vitro Results.**

310 **[Supplement Table 1] Measurements of the Geometric Parameters of the Tested Prostheses.**

311