Transcatheter aortic valve implantation (TAVI) has emerged in Canada and worldwide as a valid alternative to surgical aortic valve replacement in high-risk patients with severe aortic stenosis. The most frequent complication of TAVI is the occurrence of paravalvular regurgitation. Moderate to severe paravalvular regurgitation indeed occurs in 5%-20% of patients and is associated with a 2-fold increase in mortality. Moderate transcatheter heart valve (THV) oversizing is routinely used to prevent paravalvular regurgitation after TAVR. However, there are very few data about the impact of oversizing and ensuing underdeployment of the THV on valve kinetics and hemodynamic performance. In vivo, it is very difficult or impossible to assess the valve leaflet kinetics and mechanical stress. Moreover, several factors besides the degree of THV oversizing may influence THV hemodynamics. In vitro experiments provide a unique opportunity to delineate the effect of THV oversizing on valve hemodynamics and kinetics in a controlled and standardized environment.

The objective of this in vitro study was to assess the effect of aortic annulus size and prosthesis size on the valve.
hemodynamics and leaflet bending stress of the SAPIEN balloon-expandable THV (Edwards Lifesciences, Irvine, CA).

**Methods**

**In vitro model**

For the purpose of this study, a left heart duplicator system was used (Left Heart Simulator; ViVitro Labs, Victoria, BC). This simulator is capable of reproducing physiological pressure and flow waveforms. Briefly, it is composed of a piston-in-cylinder pulsatile pump, rigid models of the left atrium and ascending aorta, and elastic model of the left ventricle. The aortic flow rate is measured using an electromagnetic flow probe (Carolina Medical Electronics, East Bend, NC; accuracy within 10%, full scale) and aortic and left ventricular pressures using Millar catheters (MPR-500; Millar Instruments, Houston, TX; accuracy of ± 0.025%, full scale).

Two sizes of 1 THV model were tested in the pulse duplicator: the 23-mm Edwards SAPIEN (SAP23 mm) and the 26-mm Edwards SAPIEN (SAP26 mm). The valves were implanted using balloon expansion within rubber tubes (DM9865 material with a durometer of A65), with internal diameter varying between 19 and 25 mm to simulate the range of aortic annulus size in which these valves are implanted within rubber tubes (DM9865 material with a durometer of A65), with internal diameter varying between 19 and 25 mm to simulate the range of aortic annulus size in which these valves are implanted using balloon expansion within rubber tubes (DM9865 material with a durometer of A65), with internal diameter varying between 19 and 25 mm to simulate the range of aortic annulus size in which these valves are implanted using balloon expansion within rubber tubes (DM9865 material with a durometer of A65), with internal diameter varying between 19 and 25 mm to simulate the range of aortic annulus size in which these valves are implanted using balloon expansion within rubber tubes (DM9865 material with a durometer of A65), with internal diameter varying between 19 and 25 mm to simulate the range of aortic annulus size in which these valves are implanted using balloon expansion within rubber tubes (DM9865 material with a durometer of A65), with internal diameter varying between 19 and 25 mm to simulate the range of aortic annulus size in which these valves are implanted using balloon expansion within rubber tubes (DM9865 material with a durometer of A65), with internal diameter varying between 19 and 25 mm to simulate the range of aortic annulus size in which these valves are implanted using balloon expansion within rubber tubes (DM9865 material with a durometer of A65), with internal diameter varying between 19 and 25 mm to simulate the range of aortic annulus size in which these valves are implanted using balloon expansion within rubber tubes (DM9865 material with a durometer of A65), with internal diameter varying between 19 and 25 mm to simulate the range of aortic annulus size in which these valves are implanted using balloon expansion within rubber tubes (DM9865 material with a durometer of A65), with internal diameter varying between 19 and 25 mm to simulate the range of aortic annulus size in which these valves are implanted using balloon expansion within rubber tubes (DM9865 material with a durometer of A65), with internal diameter varying between 19 and 25 mm to simulate the range of aortic annulus size in which these valves are implanted using balloon expansion within rubber tubes (DM9865 material with a durometer of A65), with internal diameter varying between 19 and 25 mm to simulate the range of aortic annulus size in which these valves are implanted using balloon expansion within rubber tubes (DM9865 material with a durometer of A65), with internal diameter varying between 19 and 25 mm to simulate the range of aortic annulus size in which these valves are implanted using balloon expansion within rubber tubes (DM9865 material with a durometer of A65), with internal diameter varying between 19 and 25 mm to simulate the range of aortic annulus size in which these valves are implanted using balloon expansion within rubber tubes (DM9865 material with a durometer of A65), with internal diameter varying between 19 and 25 mm to simulate the range of aortic annulus size in which these valves are implanted using balloon expansion within rubber tubes (DM9865 material with a durometer of A65), with internal diameter varying between 19 and 25 mm to simulate the range of aortic annulus size in which these valves are implanted using balloon expansion within rubber tubes (DM9865 material with a durometer of A65), with internal diameter varying between 19 and 25 mm to simulate the range of aortic annulus size in which these valves are implanted using balloon expansion.
**Results**

**Effect of aortic annulus diameter, prosthesis size, and flow on valve EOA**

For each prosthesis and annulus size, the EOA increased significantly with flow (Fig. 1 and Table 1). The smallest value of EOA for the SAP23 mm (1.01 ± 0.06 cm²) was obtained in an aortic annulus of 19 mm with a stroke volume of 20 mL and the largest value (2.02 ± 0.15 cm²) in the 22-mm annulus with a stroke volume of 80 mL (Fig. 1A). Using the same flow range and with an aortic annulus diameter varying from 22-25 mm, the EOA of the SAP26 mm increased from 1.18 ± 0.08 cm² to 2.45 ± 0.08 cm² (Fig. 1B). The EOA also increased with annulus size for a given stroke volume. Figure 1C shows the average values of the EOA obtained in the different flow conditions as a function of the aortic annulus diameters. For SAP23 mm, the EOA increased (**P** = 0.001) from 1.37 ± 0.30 cm² to 1.66 ± 0.31 cm² (+21% increase) with the aortic annulus diameter increasing from 19-22 mm. For the SAP26 mm, the EOA increased (**P** = 0.008) from 1.75 ± 0.45 cm² to 2.03 ± 0.32 cm² (+16% variation), with the aortic annulus diameter increasing from 22-25 mm.

Figure 2 shows the comparison between the EOAs obtained in the present study and those reported in the *in vivo* study of Clavel et al.8 for each annulus size. There was good agreement between our *in vitro* EOA data (Table 1) and the data measured *in vivo* by Doppler echocardiography in the Clavel et al. study. When pooling all experimental conditions together, the EOA of the SAP26 mm was significantly larger than the EOA of the SAP23 mm (1.92 ± 0.38 vs 1.51 ± 0.32; **P** < 0.001). However, the EOA of the SAP23 mm and SAP26 mm were similar (1.66 ± 0.31 vs 1.73 ± 0.45; **P** = 0.24) when these 2 valves were implanted in the same 22-mm annulus diameter.

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**Figure 1.** Effective orifice area of the 23-mm SAPIEN (A) and the 26-mm SAPIEN (B) as a function of stroke volume and aortic annulus diameter (C). The error bars represent standard error of the mean. % OS, percentage of oversizing. *Significant difference (**P** value < 0.05) with the 23-mm SAPIEN. †Significant difference (**P** value < 0.05) with the 26-mm SAPIEN.

**Figure 2.** Comparison between effective orifice areas obtained in this *in vitro* study vs *in vivo* data reported by Clavel et al.8
Table 1. Effective orifice area (cm²) for the 23-mm and 26-mm SAPIEN valves as a function of aortic annulus diameter (mm) and stroke volume (mL)

<table>
<thead>
<tr>
<th>Stroke volume (mL)</th>
<th>Effective orifice area (cm²) for 23-mm SAPIEN aortic annulus diameter (mm)</th>
<th>Effective orifice area (cm²) for 26-mm SAPIEN aortic annulus diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke volume</td>
<td>19 mm</td>
<td>20 mm</td>
</tr>
<tr>
<td>19 mm</td>
<td>1.65 ± 0.07</td>
<td>1.71 ± 0.02</td>
</tr>
<tr>
<td>20 mm</td>
<td>1.66 ± 0.07</td>
<td>1.67 ± 0.11</td>
</tr>
<tr>
<td>21 mm</td>
<td>1.41 ± 0.14</td>
<td>1.55 ± 0.10</td>
</tr>
<tr>
<td>22 mm</td>
<td>1.12 ± 0.02</td>
<td>1.21 ± 0.06</td>
</tr>
<tr>
<td>Mean ± SD (cm²)</td>
<td>1.37 ± 0.30</td>
<td>1.44 ± 0.29</td>
</tr>
</tbody>
</table>

Table 2. Univariable and multivariable determinants of in vitro transcatheter heart valve effective orifice area

<table>
<thead>
<tr>
<th>Stroke volume (mL)</th>
<th>Standard β coefficient ± SE</th>
<th>$R^2$</th>
<th>$P$ value</th>
<th>Standard β coefficient ± SE</th>
<th>Δ$R^2$*</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke volume</td>
<td>0.79 ± 0.10</td>
<td>0.63</td>
<td>&lt; 0.001</td>
<td>0.79 ± 0.03</td>
<td>0.63</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Aortic annulus diameter (mm)</td>
<td>0.57 ± 0.13</td>
<td>0.33</td>
<td>&lt; 0.001</td>
<td>0.44 ± 0.06</td>
<td>0.33</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Prosthesis size (mm)</td>
<td>0.52 ± 0.14</td>
<td>0.27</td>
<td>0.001</td>
<td>0.17 ± 0.06</td>
<td>0.01</td>
<td>0.004</td>
</tr>
<tr>
<td>Oversizing (%)</td>
<td>−0.33 ± 0.015</td>
<td>0.33</td>
<td>0.037</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

SE, standard error.

*The $ΔR^2$ coefficient represents the independent contribution of the variable to the variance of the effective orifice area. The total $R^2$ of the multivariable model was 0.96.

Discussion

The main findings of this study are as follows:

1. As in native aortic valves and surgical bioprosthetic valves, the EOA in THVs is dependent on flow, ie, low flow condition may result in incomplete opening of the valve leaflets and thus smaller EOA.
2. For a given flow rate, the EOA of the balloon-expandable THVs is determined by the aortic annulus size.
3. Prosthesis oversizing (up to 20% in area) has no significant effect on valve EOA.
4. Prosthesis oversizing increases the leaflet bending stress during systole.

Effect of aortic annulus diameter and prosthesis size on THV hemodynamics

Patients with a small aortic annulus (ie, ≤ 21 mm) undergoing surgical AVR require the implantation of small-sized prosthetic valves, which generally have suboptimal hemodynamics and EOAs and are therefore often associated

In the dataset including the results of all experimental conditions, the valve EOA correlated significantly and positively with stroke volume, aortic annulus diameter, and prosthesis size (Table 2). There was a weak and inverse relationship between valve EOA and % OS. On multivariable analysis, stroke volume and aortic annulus diameters were found to be the 2 main independent determinants of valve EOA (Table 2). These 2 variables together explained about 96% of the variance of EOA. The prosthesis size was also an independent determinant of the EOA but with minimal incremental contribution (1%) to the variance. The % OS was not an independent determinant of valve EOA.

Effect of aortic annulus diameter and prosthesis size on valve leaflet kinetics and bending stress

Supplemental Figure S2 shows THV leaflets at peak systole (maximum opening) and during diastole as recorded by the high-speed camera. The images in this figure show that greater valve oversizing, ie, higher % OS, is associated with more pronounced leaflet distortion at peak systole and during diastole. Supplemental Figure S3 shows the effect of valve oversizing on the bending stress of the free edges of valve leaflets. Marked oversizing (% OS of 15%-21%) was associated with higher (P < 0.001) leaflet bending stress compared with modest oversizing (% OS of 4%-13%): 0.98 ± 0.87 vs 0.61 ± 0.14 MPa, respectively. On multivariable analysis, larger % OS, and to a lesser extent smaller annulus size and prosthesis size, were independently associated with higher leaflet bending stress during systole, whereas stroke volume was not (Table 3). Furthermore, Supplemental Figure S2 shows evidence of “pinwheeling” of the leaflets during diastole in the configurations with important oversizing.
with a high incidence of prosthesis-patient mismatch. For both the SAP23and SAP26 valves, the EOA was lower when the valve was deployed in the smaller annulus. This is consistent with the fact that the patient’s annulus size is the main anatomic factor limiting the expansion of the THV and thus its EOA. Nevertheless, the EOAs of the THVs implanted in the small annuli were excellent and appear to be better than those (1.0-1.4 cm²) generally obtained with surgical bioprostheses in such conditions. These findings suggest that TAVI could be a good alternative to surgical AVR in patients with a small aortic annulus. They are also consistent with recent clinical studies showing that TAVI is associated with larger EOAs and lower incidence of prosthesis-patient mismatch compared with surgical AVR and that this difference is more pronounced in patients with a small aortic annulus. Modest prosthesis oversizing has been recommended to prevent paravalvular regurgitation after TAVI. In the present study, marked oversizing (up to 20% in area) had no significant effect on valve EOA, even when the valve was implanted in a small aortic annulus.

**Effect of annulus size and prosthesis oversizing on THV mechanical stress**

Because THV technology has been introduced recently and has been initially applied to patients with limited life expectancy, the long-term durability of this new type of valve has not yet been established. Good long-term durability of THVs is essential to allow expansion of this new technology to lower-risk and younger populations. Increased leaflet mechanical stress has been shown to play an important role in the structural degeneration of surgical bioprostheses. The results of the present study suggest that prosthesis oversizing > 10%-15% in area results in increased leaflet mechanical stress. This may, in turn, negatively impact the long-term durability of THVs. Hence, on the 1 hand, valve oversizing may be helpful to reduce paravalvular regurgitation, but on the other hand, it may limit valve durability by increasing leaflet mechanical stress. It should also be mentioned that introduction of new THV models has significantly limited the occurrence of paravalvular regurgitation. However, even with the new generation of THV, there still remain cases with higher than mild (7% with SAPIEN 3 and 34% with SAPIEN XT) or moderate (4% with SAPIEN 3 and 10% with SAPIEN XT) paravalvular leaks. Finally, the results of this study cannot be directly transposed to self-expandable valves.

**Limitations of study**

In this study, the impact of valve oversizing on hemodynamics and leaflet bending stress was investigated only for the first generation of the balloon-expandable transcatheter SA- PIEN valve. Hence, the results of this study cannot be directly transposed to the newer generations of this type of valve, ie, SAPIEN XT and SAPIEN 3, or to the other types of transcatheter valves (CoreValve, Portico, Directflow, JenaValve, and so on). Further studies are needed to assess the effect of valve sizing on valve hemodynamic performance and durability. In this in vitro study, we have used circular aortic annuli. However, in patients, the aortic annulus is not necessarily circular. Further studies are thus needed to determine whether the impact of oversizing on hemodynamic performance and leaflet mechanical stress is similar in circular annuli and oval annuli. Furthermore, the rubber tubes used in this study have low compliance for limiting, as much as possible, the expansion of the tube diameter caused by the radial expansion of the THV. We systematically measured the diameter of the tube after THV deployment, and the percent change in diameter was < 2% in all cases. Therefore, the % OS calculated using the nominal diameter of the tube before THV deployment adequately reflects the final % OS achieved after deployment. In vivo, the deployment of the THV may induce expansion of the aortic annulus in some patients, but this change is generally minimal. Finally, the THV stent was uniformly expanded or underexpanded over its whole length. In patients, the expansion of the stent is not necessarily uniform, and underexpansion, if any, may be more pronounced at the inflow level than at the mid- or outflow levels of the stent. Although we cannot exclude that this phenomenon may have an effect on the hemodynamic results of TAVI, it is probably minimal given that the EOAs we obtained in this in vitro study were highly consistent with those obtained in vivo with the SAPIEN THV.

**Conclusions**

This study shows that balloon-expandable THVs have excellent hemodynamics even when implanted in a small aortic annulus. Prosthesis oversizing (up to 20%) has no significant effect on valve hemodynamics but increases leaflet mechanical stress, which may accelerate structural valve degeneration and thus limit long-term valve durability of THVs.

**Impact on daily practice**

Prosthesis oversizing (up to 20%) has no significant effect on valve hemodynamics but markedly increases leaflet...
mechanical stress, which may accelerate structural valve degeneration and thus limit long-term valve durability of transcatheter heart valves.

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**Disclosures**
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**References**


**Supplementary Material**
To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at [www.onlinecjc.ca](http://www.onlinecjc.ca) and at [http://dx.doi.org/10.1016/j.cjca.2015.03.026](http://dx.doi.org/10.1016/j.cjca.2015.03.026).