A design for human variability (DfHV) approach to predicting appropriate dimensions for pediatric-sized prosthetic heart valves

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Heart valve malformations are a common form of congenital heart disease with a prevalence rate of approximately 15 / 1,000 live births. Despite the large number of artificial valves available for adult patients, treatment options for smaller patients remain limited. In the United States (US), only one prosthetic valve is authorized for placement in pediatric patients (Melody\textsuperscript{e}, Medtronic, Minneapolis, MN). Furthermore, adult valves are usually prohibitively large for use in infants and children. In a previous study, it was suggested that a logical approach to designing pediatric valves would be to scale down current valve designs to sizes appropriate for the pediatric population. However, appropriate sizes for pediatric valves were not recommended. It is therefore the objective of this study to provide a method for determining the appropriate size of heart valves for pediatric patients. Pulmonary valve diameters were synthesized for the US pediatric population using NHANES data and a published regression model correlating valve size and body surface area (BSA). Variation in pulmonary valve size not related to anthropometry was modeled by the addition of a residual variance term to the regression model. Variations in the prevalence of congenital pulmonary valve disease with ethnicity and gender were also considered based on data from literature. Accommodation was then estimated for virtual prototype valves based on the ratio of the diameters of the prototype valves to the diameters synthesized for the pediatric population. The presented model predicts that the three existing sizes of the Medtronic Melody valve accommodate 40% of the full pediatric population (age 0-21) and 52% of a younger sub-population (age 0-12). The addition of three virtual prototype valves with smaller valve diameters (12.6mm, 14.4mm, and 16.3mm) is predicted to increase accommodation by 20 percentage points for the full pediatric population (age 0-21) and 34 percentage points for a younger sub-population (age 0-12). In future work, similar analyses could be performed to predict the proper sizing of other pediatric medical devices.

Practitioner Summary:
Optimal dimensions for pediatric-sized prosthetic pulmonary valves were predicted using a numerical model based on NHANES anthropometry data and clinical data from literature. The addition of three small prosthetic pulmonary valve sizes was predicted to increase the accommodation of pediatric patients (age 0-12) by 34 percentage points. Similar methods could be used for sizing other medical devices.

Keywords: Design for Human Variability, Prosthetic Heart Valve, Pediatric Medical Devices.

1. INTRODUCTION

1.1 Congenital heart valve disease
Heart valve defects are a common form of congenital heart disease, affecting approximately 15 / 1,000 live births [1]. Common valve abnormalities include stenosis, atresia, and regurgitation [2]. Stenotic valves are narrower than healthy valves, thus restricting flow and increasing the load on the heart. Atretic valves instead lack a valve orifice entirely and are usually associated with other abnormalities in the cardiac circulation (e.g., septal defects or “holes”) which compensate for the lack of blood flow between the chambers of the heart.
Regurgitation occurs when valve leaflets are present but do not close properly, resulting in excessive backward flow across the valve. All of these valvular abnormalities can be life-threatening.

Surgeons may perform valve replacement or repair surgeries to treat valvular defects when they are severe. New percutaneous devices for adults have also been developed in recent years which reduce patient hospitalization and recovery times and, potentially, lower procedure costs. Unfortunately, however, treatment options for pediatric patients remain limited [2]. Thus, pediatric patients often receive valves that are too large and thus fit poorly in their vasculature, or undergo valve repair surgeries when a valve replacement would be preferred but is not possible due to the lack of a suitable pediatric prosthetic device. Accordingly, new, pediatric-sized artificial heart valves are needed.

1.2 Objective
In a previous study [2], it was suggested that a logical approach to designing pediatric valves would be to scale down current valve designs to sizes appropriate for the pediatric population. However, appropriate sizes for pediatric valves were not recommended. It is therefore the objective of this study to provide a method for determining the appropriate size of heart valves for pediatric patients. Specifically, the proper sizing of a stent-framed percutaneous pulmonary heart valve is investigated. Accommodation is then estimated for currently-existing artificial pulmonary valves, and new valve sizes are proposed to increase the accommodation for smaller pediatric patients.

2. METHODS
2.1 Anthropometry data
Anthropometry data from the National Health and Nutrition Examination Survey (NHANES) [3] were used to synthesize pulmonary valve diameters for pediatric populations in the United States (US). The NHANES data are a biannual sample of approximately 10,000 participants. The study is designed such that underrepresented groups are oversampled. Sample weights accompany the NHANES data, allowing for the reweighting of the data to represent the population of interest.

For the present study, two NHANES datasets were combined (2007–08 and 2009–10; [3]) according to the statistical analysis procedures guidelines published with the data. All analyses were performed using the statistical software package R [4].

2.2 Target populations
Pediatric patients age 0-21 years were considered in the present study. Additionally, because many of the older pediatric patients may be accommodated by existing prosthetic valves designed for the adult population, a younger sub-population of the pediatric group from age 0-12 was also considered. These are the approximate ages of sub-populations previously used in related valve design work (e.g., Yoganathan [2]).

The NHANES weights were adjusted to account for the difference in prevalence rates of pulmonary valve stenosis among different sexes and ethnicities. Based on a study of approximately 1.2 million live births in Florida from 1998–2003 [5], the prevalence rate of congenital pulmonary valve stenosis is nearly twice as high in Blacks compared with Whites and Hispanics (Table 1). Accordingly, the NHANES data were modified by multiplying the NHANES weights by these prevalence rates [5].

<table>
<thead>
<tr>
<th>Gender</th>
<th>White (non-Hispanic)</th>
<th>Black (non-Hispanic)</th>
<th>Hispanic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>8.85/10,000</td>
<td>14.47/10,000</td>
<td>8.59/10,000</td>
</tr>
<tr>
<td>Male</td>
<td>8.69/10,000</td>
<td>14.98/10,000</td>
<td>9.21/10,000</td>
</tr>
</tbody>
</table>
2.3 Pulmonary valve diameter synthesis

Pulmonary valve diameters (PVD) were synthesized for the pediatric target populations using a nonlinear correlation between body surface area (BSA) and PVD [6]. Because BSA data were not measured in NHANES, BSA was first estimated using a correlation between height and weight (from NHANES) and BSA developed by Haycock et al. [7]:

\[
BSA = 0.024265 \times W^{0.5378} \times H^{0.3964}
\]  

(1)

where \( H \) is height and \( W \) is weight. For pediatric individuals younger than two years old, the recumbent length from NHANES was substituted for height. According to Haycock et al., Eqn. (1) is valid for infants, children, and adults \( (R^2 = 0.998) \).

Pulmonary valve diameters for males and females were then synthesized using nonlinear regression models from literature [6] based on measurements from 3,000 patients \( (R^2 > 0.8) \):

\[
PVD_{\text{male}} = \exp(2.936 + 0.4455 \times \log(\text{BSA}))
\]  

(2)

\[
PVD_{\text{female}} = \exp(2.913 + 0.4425 \times \log(\text{BSA}))
\]  

(3)

In order to capture the variability in PVD not attributable to anthropometry, a stochastic term was added to the regression models in Eqns. (2) and (3):

\[
PVD_{\text{male}} = \exp(2.936 + 0.4455 \times \log(\text{BSA})) + rnorm(0, \sigma_{\text{male}})
\]  

(4)

\[
PVD_{\text{female}} = \exp(2.913 + 0.4425 \times \log(\text{BSA})) + rnorm(0, \sigma_{\text{female}})
\]  

(5)

where \( rnorm(0, \sigma) \) is the R function for generating a random number from a Gaussian distribution with a mean of 0 and a standard deviation of \( \sigma \). See Garneau and Parkinson [8] for the details of this method.

The standard deviation \( \sigma \) was defined as a nonlinear function of BSA based on the data in Capps et al. [6]. Specifically, because \( \sigma \) in PVD was not explicitly provided in Capps et al. [6], the standard deviation in the PVD was estimated for different BSA values. Assuming that the data are normally distributed, the difference between the 95th percentile PVD and the 50th percentile PVD is approximately equal to twice the standard deviation of the PVD. The estimated standard deviation of the PVD was calculated as:

\[
\sigma(\text{BSA}) \approx \frac{PVD_{0.95}(\text{BSA}) - PVD_{0.50}(\text{BSA})}{2}
\]  

(6)

for approximately 25 BSA values between 0.2m\(^2\) and 3.5m\(^2\). An exponential regression was then performed on the resulting standard deviation values for the male and female data yielding the following equations \( (R^2 > 0.99) \):

\[
\sigma_{\text{male}}(\text{BSA}) = 1.85 \times \text{BSA}^{0.454}
\]  

(7)

\[
\sigma_{\text{female}}(\text{BSA}) = 1.89 \times \text{BSA}^{0.448}
\]  

(8)

2.4 Estimating accommodation

Valve accommodation levels were estimated using details from a clinical study on optimal valve sizing by Schwarz et al. [9] in which valve performance was evaluated in 116 patients receiving the Edwards SAPIEN XT (Edwards Lifesciences Corporation, Irvine, CA) stent-framed aortic heart valve. Valve performance was characterized by measuring transvalvular pressure gradients via balloon catheter and valve regurgitation levels via computed tomography-angiography. Using this approach, cut-off values were determined for optimal valve sizing (Fig. 1).
In the present study, the cut-off values from Schwarz et al. [9] were used to determine high and low limits on the prosthesis-to-patient diameter ratio, which were then used to predict accommodation for existing stent-framed valves and proposed virtual prototype valves. For example, comparing the smallest prosthetic valve diameter to the cut-off value for small versus medium sized valves (23mm vs. 22.5mm) yields a lower limit to the prosthesis-to-patient ratio of approximately 1.02 (Fig. 2). In contrast, comparing the largest prosthetic valve diameter to the cut-off value for the medium versus large sized valves (29mm vs. 25.5mm) yields an upper limit to the prosthesis-to-patient ratio of approximately 1.1 (Fig. 2). Analysis comparing the medium prosthetic valve diameter to the small versus medium and medium versus large cut-off values yields similar results (prosthesis-to-patient ratio from 1.02–1.16; see Fig 2). Therefore, accommodation was defined as a prosthesis-to-patient ratio of more than 1.02 and less than 1.16.

### 2.5 Currently-existing prosthetic pulmonary valves

Accommodation ranges were calculated for two currently-existing artificial pulmonary valves: the Edwards SAPIEN Pulmonic valve (Edwards Lifesciences Corporation, Irvine, CA) and the Melody Transcatheter Pulmonary Valve (Medtronic, Minneapolis, MN).

The Edwards SAPIEN Pulmonic valve has not yet been evaluated for use in the US by the US Food and Drug Administration (FDA) but is CE-marked for clinical use in Europe. Two valve sizes are available: 23mm and 26mm (Fig. 3). The literature indicates that the 23mm valve can be safely placed in patients with native pulmonary conduits of 21-23mm, while the 26mm valve can be placed in patients with native pulmonary conduits of 23-26mm [11].
The Melody Transcatheter Pulmonary Valve (Medtronic, Minneapolis, MN) is the only prosthetic valve authorized for placement in pediatric patients in the US (approved under the Humanitarian Device Exemption (HDE) program by the FDA). Three sizes are available: 18mm, 20mm, and 22mm (Fig. 4). The Melody valve is made from a bovine jugular venous valve sutured into a metal stent. A clinical study from the literature [13] suggests that the Melody valves may be safely placed in patients with native pulmonary conduits larger than 16mm but smaller than 22mm.

2.6 Virtual prototype valves

Three new prosthetic valve sizes were proposed to increase the accommodation of the pediatric population. Accommodation was predicted based on the optimal prosthesis-to-patient ratios developed previously. Prototype valve diameters were calculated such that the overlap in accommodation among the three prototype valve sizes and the currently-existing valves (i.e., the Edwards SAPIEN Pulmonary and Medtronic Melody valves) was minimized, thus maximizing the increase in accommodation.

2.7 Virtual fitting trials

Virtual fitting trials were performed to predict the percent accommodation of the pediatric population by the currently-existing valves (i.e., the Edwards SAPIEN Pulmonary and Medtronic Melody valves) and the proposed prototype valves. Accommodation was calculated by comparing the synthesized PVDs for the pediatric population to the accommodation ranges estimated for each of the valves considered.

3. RESULTS

3.1 Synthesized pulmonary valve diameters for the pediatric population

Pulmonary valve diameters synthesized from BSA for the US pediatric population ranged from approximately 7.7mm to 36.5mm for the full pediatric population (age 0-21), and from 7.7mm to 31.7mm for the younger sub-population (age 0-12). The synthesized PVDs increased nonlinearly with BSA in agreement with the original data from Capps et al. [6]. Valve diameters synthesized using residual variance also show the same trend as in Capps et al. [6], with the variance in valve diameter increasing nonlinearly with BSA for both males and females (Fig. 5).
3.2 Accommodation ranges for currently-existing prosthetic pulmonary valves

Using the optimal prosthesis-to-patient ratio limits calculated using data from the clinical study by Schwarz et al. [9] (1.02–1.16), predicted accommodation ranges were found (Tables 2 & 3). The small Melody valve was predicted to accommodate the smallest patients, the smallest accommodated PVD being 15.5mm (Table 3). The predicted accommodation ranges for the Edwards SAPIEN Pulmonic and Medtronic Melody valves were close to actual accommodation ranges reported in literature (Tables 2 and 3).

<table>
<thead>
<tr>
<th>Table 2–Estimated PVD accommodation ranges for the Edwards SAPIEN Pulmonic valve based on prosthesis-to-patient ratio limits of 1.02–1.16 versus reported accommodation ranges from the literature.</th>
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<tbody>
<tr>
<td>Prosthetic Valve Diameter</td>
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<tr>
<td>Predicted Accommodation</td>
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<tr>
<td>Reported Accommodation [11]</td>
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<tr>
<th>Table 3–Estimated PVD accommodation ranges for the Medtronic Melody valve based on prosthesis-to-patient ratio limits of 1.02–1.16 versus reported accommodation ranges from the literature.</th>
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<tr>
<td>Reported Accommodation [13]</td>
</tr>
</tbody>
</table>

3.3 Virtual prototype valves

Three different sizes of virtual prototype valves were defined to increase accommodation for the pediatric population: 12.6mm, 14.4mm and 16.3mm (Fig. 6). With these valve sizes, the largest virtual prototype valve accommodates PVDs up to 16mm, which is the lower limit for the small Melody valve (16mm as reported in [13]; Table 3). Furthermore, overlap between the small, medium, and large virtual prototype valves is minimized (Table 4), thus maximizing total accommodation of the three valves.

<table>
<thead>
<tr>
<th>Table 4–Predicted PVD accommodation ranges for virtual prototype valves based on prosthesis-to-patient ratio limits of 1.02–1.16.</th>
</tr>
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</table>
### 3.4 Virtual fitting trials

Percent accommodation was calculated for the full pediatric population (age 0-21) and a younger subset of the pediatric population (age 0-12). According to the model, the two sizes of the Edwards SAPIEN Pulmonic valve accommodate 34% of the full pediatric population while the three sizes of the Medtronic Melody valve accommodate 40% (Fig. 7). With the addition of the three virtual prototype valves proposed in the present study, accommodation for the pediatric population is predicted to increase by 20 percentage points (Fig. 7).

![Figure 7](image1.png)

**Figure 7**–Accommodation plot for the full pediatric population, age 0-21. Note that the total accommodation is greater than 100% due to overlap between the Edwards SAPIEN Pulmonic and Medtronic Melody valves.

Considering only the younger subset of the pediatric population (age 0-12), the predicted accommodation levels are 17% for the two sizes of the Edwards SAPIEN Pulmonic valve and 52% for the three sizes of the Medtronic Melody valve (Fig. 8). With the addition of the three prototype valves proposed in the present study, accommodation is predicted to increase by 34 percentage points (Fig. 8).

![Figure 8](image2.png)

**Figure 8**–Accommodation plot for children, age 0-12. Note that the total accommodation is greater than 100% due to overlap between the Edwards SAPIEN Pulmonic and Medtronic Melody valves.
3.5 Study Limitations
In the present study, only one parameter, the synthesized PVD, was considered for predicting optimal valve sizes and corresponding accommodation levels. In practice, clinicians also use other parameter such as the valve effective orifice area (EOA) to determine proper valve selection. Furthermore, the optimal prosthesis-to-patient ratios may differ in small children due to the increased compliance of the pediatric vasculature. Despite these limitations, the accommodation ranges predicted by the presented model were close to those reported in literature (Tables 2 and 3). Therefore, we believe the presented approach is an appropriate first-step toward determining the proper sizing of smaller pediatric-sized heart valves.

4. SUMMARY & CONCLUSIONS
Prosthetic pulmonary heart valve sizing was considered for pediatric populations. Pulmonary valve diameters were synthesized using a correlation between PVD and BSA, with BSA calculated using height and weight measurements from the NHANES 2007-2010 data. The accommodation of existing valves and virtual prototype valves was then predicted using a ratio between the valve prosthesis diameter and the patient’s native valve diameter. Virtual fitting trials were performed to estimate accommodation levels.

The presented model predicts that the three existing sizes of the Medtronic Melody valve accommodate 40% of the full pediatric population (age 0-21) and 52% of a younger sub-population (age 0-12). With the addition of three virtual prototype valves with smaller valve diameters, accommodation was predicted to increase by 20 percentage points for the full pediatric population (age 0-21) and by 34 percentage points for a younger sub-population (0-12). In both cases, percent accommodation decreased with decreasing valve size.

In future work, the methods presented here could be used for predicting the proper sizing of other pediatric heart valves (e.g., aortic or mitral valves) or other pediatric medical devices.

References