Evaluation of pulmonary artery stenosis in congenital heart disease patients using functional diagnostic parameters: An in vitro study

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Congenital pulmonary artery (PA) stenosis is often associated with abnormal PA hemodynamics including increased pressure drop (Δp) and reduced asymmetric flow (Q), which may result in right ventricular dysfunction. We propose functional diagnostic parameters, pressure drop coefficient (CDP), energy loss (Eloss), and normalized energy loss (Eloss,LPA) to characterize pulmonary hemodynamics, and evaluate their efficacy in delineating stenosis severity using in vitro experiments. Subject-specific test sections including the main PA (MPA) bifurcating into left and right PAs (LPA, RPA) with a discrete LPA stenosis were manufactured from cross-sectional imaging and 3D printing. Three clinically-relevant stenosis severities, 90% area stenosis (AS), 80% AS, and 70% AS, were evaluated at different cardiac outputs (COs). A benchtop flow loop simulating pulmonary hemodynamics was used to measure Q and Δp within the test sections. The experimental Δp-Q characteristics along with clinical data were used to obtain pathophysiologic conditions and compute the diagnostic parameters. The pathophysiologic Q_{LPA} decreased as the stenosis severity increased at a fixed CO. CDP_{LPA}, E_{LPA} (absolute), and E_{LPA,abs} (absolute) increased with an increase in LPA stenosis severity at a fixed CO. Importantly, CDP_{LPA} and E_{LPA,abs} had reduced variability with CO, and distinct values for each LPA stenosis severity. Under variable CO, a) CDP_{LPA} values were 14.5–21.0 (70% AS), 60.7–22.2 (80% AS), ≥261.6 (90% AS), and b) E_{LPA,abs} values (in mJ) per Q_{LPA} were −501.9 to −1023.8 (70% AS), −1247.6 to −1773.0 (80% AS), −1934.5 (90% AS). Hence, CDP_{LPA} and E_{LPA,abs} are expected to assess the true functional severity of PA stenosis.

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1. Introduction

Congenital pulmonary artery (PA) stenosis in isolation, or combined with other congenital heart diseases (CHDs) such as tetralogy of Fallot (TOF) is a significant lesion causing cardiopulmonary dysfunction in CHD patients (Bergersen et al., 2006; Franch et al., 1963; Hoffman et al., 2002; Yacoub et al., 2014). Specifically, a residual unilateral PA stenosis after TOF repair (a) impairs exercise capacity likely secondary to abnormal differential pulmonary blood flow (Clark et al., 1995; Rhodes et al., 1998; Wessel et al., 1980), and (b) worsens pulmonary insufficiency that may accelerate adverse right ventricular (RV) remodeling (Harrild et al., 2009; Maskatia et al., 2013; Miyazaki et al., 2009; Petit et al., 2009). Hence, it is necessary to accurately measure the stenosis severity and determine the need for intervention to minimize patient risk.

Although catheterization enables direct measurement of transstenotic pressure gradient, it poses risks to pediatric patients due to its invasive nature (Vitiello et al., 1998; Yilmazer et al., 2012). Further, non-invasive echocardiography, cardiac magnetic resonance imaging (MRI), and computed tomography (CT) provide data that are limited to vessel measurements (diameter and length) and flow assessment only, and do not fully characterize the PA hemodynamics.

Unilateral left or right PA (LPA or RPA) stenosis presents additional resistance to flow in that side of the pulmonary circulation. Beyond the auto-regulatory capacity, impairment of pulmonary flow reserve occurs causing flow reduction and pressure drop in the affected PA. Interestingly, as the stenosis severity increases, reduced flow will lead to reduced pressure drop across a stenosis. Additional decrease in total PA flow may be due to other independent factors including pulmonary microvascular dysfunction (Ilslar et al., 2010), hypoplastic RV (Pinsky, 2016), or inherently low
cardiac output (Dumesnil et al., 2010). The decreased flow causes a lower measured pressure drop even for a highly stenotic artery, thus masking the true stenosis severity. The hemodynamic significance of a stenosis based on commonly used trans-stenotic pressure gradient may be underestimated. The possibility of clinical misdiagnosis when using trans-stenotic pressure gradient alone has been observed previously (Clavel et al., 2017; D’Souza et al., 2014; Garcia et al., 2000; Peelukhana et al., 2009). Thus, there is a need to evaluate the complex effect of an LPA or RPA stenosis of increasing severity on the pathophysiologic hemodynamics using comprehensive pressure-flow diagnostic parameters.

Energy-based diagnostic endpoints have been proposed for monitoring right heart dysfunction in CHD patients, especially those with repaired TOF and Fontan-based anatomies (Das et al., 2010; Ensley et al., 1999; Lee et al., 2013a; Milnor et al., 1966; Schiavazzi et al., 2015). Evaluation of these endpoints has been augmented by analytical, computational fluid dynamics, and 4D MRI techniques (Dasi et al., 2009; Lee et al., 2013b; Pekkan et al., 2005a; Pennati et al., 2013; Roldán-Alzate et al., 2015).

Besides energy-based parameters, combined pressure-flow diagnostic endpoints (Banerjee et al., 2007) have been developed based on fundamental fluid dynamics principles for evaluating flow through constricted geometries. The efficacy of these parameters in accurately delineating the severity of epicardial coronary lesions has been investigated pre-clinically (Banerjee et al., 2008; D’Souza et al., 2014; Kolli et al., 2012; Peelukhana et al., 2009) and clinically (Effat et al., 2016; Kolli et al., 2016; Paul et al., 2015; Peelukhana et al., 2017). The energy-based and pressure-flow diagnostic endpoints have not been evaluated in CHD patients with unilateral PA stenoses of varying severities under pathophysiologic conditions. Thus, in the present study, an in vitro methodology was used for evaluating the pathophysiologic hemodynamics of a PA stenosis having varying degrees of severity under subject-specific conditions. Further, the functional endpoints, pressure drop coefficient (CDP), energy loss (E_loss), and normalized energy loss (E_norm) were evaluated to better delineate the stenosis severity.

2. Methodology

Details of the in vitro experimental setup, procedure for evaluating the pathophysiologic hemodynamics of LPA stenoses, and the functional diagnostic parameters are reported in this section.

2.1. Clinical data acquisition

De-identified imaging data of a normal pediatric patient acquired under IRB approval, was used for designing the in vitro test sections. The subject (female, 8 months old, body surface area (BSA) = 0.3 m²) underwent echocardiography and CT angiography (CTA) secondary to respiratory distress. The evaluations showed normal cardiopulmonary anatomy. Using pulsed wave Doppler data and the continuity equation, the subject’s cardiac output (CO) was determined to be 3.74 LPM. The CTA images (spatial resolution = 0.06 mm³) were used for creating the subject-specific PA test sections.

2.2. Experimental setup

Subject-specific stenotic PA benchtop test sections were created from CTA images and clinical observations using image processing, computer-aided design (CAD), and 3D printing, as shown in Fig. 1. A single, central, and discrete stenosis (Franch et al., 1963) of the LPA with varying anatomical severities (Schiavazzi et al., 2015) – (a) mild (~70% area stenosis (AS)), (b) moderate (~80% AS), and (c) severe (~90% AS) – was evaluated. Fig. 2 shows a schematic of the typical stenosis geometry (dimensions provide in Table 1), comprising of a converging and diverging section separated by a throat region. The regions proximal and distal to the stenosis are denoted by ‘e’ and ‘r,’ respectively. In vitro experiments were conducted on the stenotic PA test sections under pathophysiologic conditions using the benchtop MCL, shown in Fig. 3. The MCL, along with blood analog fluid (BAF) circulated through it, was designed based on previous studies conducted in our laboratory (Ashtekar et al., 2007; Banerjee et al., 2008; D’Souza et al., 2014; Peelukhana et al., 2009). Details of the experimental setup including the test section manufacturing process and the MCL are provided in Appendix A.

2.3. Pressure and flow measurements

Testing at the subject-specific CO of 3.74 LPM was not feasible due to the limited capability of the in vitro system (see Appendix A). Hence, the stenotic LPA’s were experimentally tested at alternate and lower COs of 1, 1.5, 2, and 3 LPM. Results at the subject-specific CO were then extrapolated. Since a pediatric subject’s PA anatomy was used for this study, COs of 2 and 3 LPM are also physiologic and clinically relevant to this study. For a small patient with BSA = 0.5 m², these flows would represent normal car-
diac indices of 4 and 6 LPM/m², respectively (Cattermole et al., 2017).

The pathophysiologic LPA flow splits \( Q_{LPA} = Q_{MPA} \) corresponding to a unilateral 70%, 80%, and 90% AS have not been reported before. Hence, pressure and flow recordings were made at four different \( Q_{LPA} = Q_{MPA} \) values ranging between 22–40%, 18–30%, and 15–27% for the 70%, 80%, and 90% AS LPAs, respectively (Schiavazzi et al., 2015), at each CO. The large constriction in the 90% AS LPA caused a \( \Delta p \) of 40 mmHg pressure drop when the LPA flow rate was 15% of the 3 LPM CO. This led to the instantaneous pressure values, distal to the stenosis, to fall below the negative pressure sensing limit of the pressure scanner (\( \Delta p \) of 55 mmHg). Hence, pressure data for the 90% AS LPA at 3 LPM was not recorded. Three sets of benchtop experiments were conducted in order to account for random experimental error.

Representative experimental pulmonary flow and pressure pulses are shown in Fig. 4. The cardiac cycle duration (T cycle) in all cases was approximately 0.9 s (T systole \( \sim 0.4 \) s, T diastole \( \sim 0.5 \) s), representing an in vivo condition (Alkon et al., 2010). The pressure and flow values were first averaged over the cardiac cycle to obtain ‘mean’ values. Subsequently, a statistical average of the mean values of the three experimental datasets was computed. The averaged pressure-flow data was used to obtain pressure drop-flow rate (\( \Delta p - Q \)) characteristic curves (described in Appendix B). The characteristics were used in conjunction with clinical data (described in the Results) to obtain the pathophysiologic hemodynamics, and subsequently compute the functional diagnostic parameters.

2.4. Diagnostic parameters

The proposed diagnostic parameters, pressure drop coefficient \( (CDP_{LPA}) \), energy loss \( (E_{loss,LPA}) \), and normalized energy loss \( (E_{norm,LPA}) \) for evaluating the functional severity of LPA stenoses are defined below. The functional stenosis severity evaluated using \( CDP_{LPA}, E_{loss,LPA}, \) and \( E_{norm,LPA} \) is hereafter referred to as stenosis severity.

### Table 1

<table>
<thead>
<tr>
<th>Stenosis severity</th>
<th>( L_c, L_t, L_d ) (mm)</th>
<th>Throat area, ( A_t ) (mm²)</th>
<th>Actual area stenosis, AS (%)</th>
<th>Diameter stenosis, DS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild – 70% AS</td>
<td>2</td>
<td>17.94</td>
<td>71</td>
<td>46</td>
</tr>
<tr>
<td>Moderate – 80% AS</td>
<td>2</td>
<td>10.99</td>
<td>82</td>
<td>55</td>
</tr>
<tr>
<td>Severe – 90% AS</td>
<td>2</td>
<td>5.68</td>
<td>91</td>
<td>70</td>
</tr>
</tbody>
</table>

Area of native vessels: \( A_{MPA} = 220 \) mm²; \( A_{LPA} = 61 \) mm²; \( A_{RPA} = 70 \) mm².

![Fig. 3. A schematic of the benchtop mock circulatory flow loop (MCL).](image)

![Fig. 4. (A) Representative experimental flow pulses (B) Representative experimental pressure pulses.](image)

**Pressure drop coefficient.** \( CDP_{LPA} \) is defined as the ratio of the pressure drop across the LPA stenosis to the dynamic pressure proximal to the stenosis (Banerjee et al., 2007).

\[
CDP_{LPA} = \frac{\Delta p_{LPA}}{0.5 \times \rho \times u_{LPA} \times u_{LPA}}
\]

where \( \Delta p_{LPA} \) is the mean pressure drop across the LPA stenosis, \( p_{LPA} \) and \( p_{MPA} \) are the pressures proximal and distal to the LPA stenosis, respectively, \( \rho \) (kg/m³) is the fluid density, and \( u_{LPA} \) (m/s) is the mean proximal LPA velocity.

**Energy loss.** By applying the conservation of energy and mass to a control volume represented by the MPA, LPA, and RPA, the \( E_{loss,LPA} \) (J) can be defined as the sum of the difference in pressure-flow and kinetic energies between the LPA and MPA (Lee et al., 2013b).

\[
E_{loss,LPA} = (p_{LPA} - p_{MPA})Q_{LPA} + \frac{1}{2} \rho (u_{LPA}^2 - u_{MPA}^2)Q_{LPA}
\]
where $p$ (Pa), $Q$ (m$^3$/s), and $u$ (m/s) are the pressure, flow rate, and velocity, respectively, of the MPA (subscript 'MPA') and LPA (subscript 'LPA').

Normalized energy loss. The $E_{loss_{LPA}}$ (J per $Q_{LPA}$) is defined as the ratio of energy loss in the LPA (J) to the LPA flow rate (m$^3$/s).

$$E_{loss_{LPA}} = \frac{E_{loss_{LPA}}}{Q_{LPA}}$$

3. Results

The pathophysiologic $Q_{LPA}/Q_{MPA}$ and $p_{LPA}$, obtained using experimental and clinical data, are reported first below. Subsequently, the proposed diagnostic parameters, $CDP_{LPA}$, $E_{loss_{LPA}}$, and $E_{loss_{LPA}}/C_0$ are quantified for the three severities of LPA stenosis at multiple COs.

3.1. Determination of pathophysiologic LPA hemodynamics using experimental and clinical ($Q_{LPA}/Q_{MPA}$) – $p_{LPA}$ data

The relationship between the $Q_{LPA}/Q_{MPA}$ and the corresponding $p_{LPA}$ for pediatric subjects with pulmonary dysfunction was obtained from previous clinical studies and is shown in Fig. 5. The $Q_{LPA}/Q_{MPA}$ of subjects with normal cardiopulmonary function and anatomy was measured to be 47% (see * in Fig. 5) (Friedman et al., 1968). From another clinical study (Shafter et al., 1959), the $p_{LPA}$ of a similar group of normal subjects was measured to be 17 mmHg (see + in Fig. 5). The $Q_{LPA}/Q_{MPA}$ and $p_{LPA}$ values obtained from these studies represent the physiologic hemodynamic conditions of a normal pediatric subject, and are thus, the maximal values (in the context of this study). A pulmonary occlusion pressure, $p_o$, of 7 mmHg (Franch et al., 1963; Shafter et al., 1959) has been clinically recorded by occluding the distal pulmonary vasculature in order to achieve a 0% $Q_{LPA}/Q_{MPA}$ (see # in Fig. 5). Assuming a constant arterial resistance (Borst et al., 1956; Shafter et al., 1959; Wilson et al., 1988), a straight line was constructed on the $(Q_{LPA}/Q_{MPA})$ vs. $p_{LPA}$ plot using the data point representing the physiologic hemodynamic condition (47%, 17 mmHg) and that representing the occluded artery condition (0%, 7 mmHg). This unique line represents the clinical LPA flow split-distal perfusion pressure line $[(Q_{LPA}/Q_{MPA}) - p_{LPA}]$ observed in pediatric subjects with varying degrees of pulmonary dysfunction. More importantly, the clinical data line accounts for the auto-regulation of the pulmonary vasculature in the presence of a stenosis. Points on the line between the physiologic (47%, 17 mmHg) and occluded artery (0%, 7 mmHg) conditions represent a diseased state indicating loss of pulmonary vascular reserve.

The pathophysiologic $Q_{LPA}/Q_{MPA}$ and $p_{LPA}$ (Operating point in Fig. 5) for the 70%, 80%, and 90% AS LPAs were determined by intersecting the experimental $(Q_{LPA}/Q_{MPA}) - p_{LPA}$ values with the clinical data line, as shown in Fig. 5. The solid black lines represent

![Fig. 5](image-url) A plot showing the intersection of the clinical LPA flow split-distal perfusion pressure line and experimental curves to obtain pathophysiologic operating conditions for a specific LPA stenosis (A) Cardiac output (CO) = 1 LPM (B) CO = 1.5 LPM (C) CO = 2 LPM (D) CO = 3 LPM.
experimental \((Q_{\text{LPA}}/Q_{\text{MPA}}) - p_{\text{LPA}}\) data that falls within the range of experimentally-tested LPA flow splits (marked by solid squares, circles, and triangles), while the dashed lines represent extrapolated data. Experimental \(p_{\text{LPA}} = p_{\text{MPA}} - \Delta p_{\text{LPA-MPA}}\) were computed where the mean pressure drop from the MPA to LPA (distal to stenosis), \(\Delta p_{\text{LPA-MPA}}\), were obtained at different %QLPA/QMPA values using the experimental \(\Delta p - Q \) characteristics (see Appendix section) and clinically-recorded \(p_{\text{MPA}}\). Based on a case study of a CHD patient treated for single-vessel, discrete PA stenosis (Shafter et al., 1959), the \(p_{\text{MPA}}\) for the 90% (pre-operation case) and 70% (post-operation case) AS LPA were 26 and 21 mmHg, respectively. The \(p_{\text{MPA}}\) for the 80% AS LPA was assumed to be 24 mmHg.

The \(Q_{\text{LPM}}/Q_{\text{MPA}}\) and \(p_{\text{LPA}}\) values were higher and out of bounds in reference to the maximal physiologic \((Q_{\text{LPM}}/Q_{\text{MPA}}) - p_{\text{LPA}}\) condition for the 70% and 80% AS LPA cases at 1 LPM (see @ in Fig. 5 A), and the 70% AS LPA case at 1.5 LPM (see @ in Fig. 5 B). This is possibly due to the fact that 1 and 1.5 LPM are low and less physiologic COs, that were primarily used for data extrapolation at the subject-specific CO. Hence, for further discussion of results, only the clinically-relevant COs (>1.5 LPM) have been used.

The pathophysiologic \(Q_{\text{LPM}}/Q_{\text{MPA}}\) and \(p_{\text{LPA}}\) decreased with an increase in LPA stenosis severity at a fixed CO (Fig. 5C and D and Table 2). For example, at CO = 2 LPM (Fig. 5C), the \((Q_{\text{LPA}}/Q_{\text{MPA}}) - p_{\text{LPA}}\) values were [47%, 17.1 mmHg], [36%, 14.6 mmHg], and [21%, 11.5 mmHg] for the 70%, 80%, and 90% AS LPAs, respectively. The pathophysiologic \(Q_{\text{LPA}}/Q_{\text{MPA}}\) at the subject-specific CO of 3.74 LPM (data points marked by asterisk symbols in Fig. 6) was obtained for the different LPA stenosis severities by extrapolating the pathophysiologic \(Q_{\text{LPA}}/Q_{\text{MPA}}\) at lower COs (Fig. 6).

### 3.2. Pathophysiologic LPA flow split

Fig. 7A shows a bar graph of the variation of pathophysiologic \(Q_{\text{LPM}}/Q_{\text{MPA}}\) with varying severities of LPA stenosis at COs of 2, 3, and 3.74 LPM. At a fixed CO, the \(Q_{\text{LPM}}/Q_{\text{MPA}}\) decreased below the physiologic value (dash-dot line indicating 47%) with an increase in LPA stenosis severity. For example, at the subject-specific CO of 3.74 LPM, the \(Q_{\text{LPM}}/Q_{\text{MPA}}\) decreased from 29% to 18% when the LPA stenosis severity increased from 70% AS to 80% AS. The 90% AS resulted in ~0% \(Q_{\text{LPM}}/Q_{\text{MPA}}\) (Fig. 6) or no flow through the LPA, indicating a blocked/collapsed artery. The values above the bars in Fig. 7A represent the % reduction \((E_{\text{LPA}})\) in LPA flow from the physiologic value. For example, at the subject-specific CO of 3.74 LPM, a 38% and 61% reduction in LPA flow was observed in the presence of the 70% and 80% AS, respectively.

### 3.3. Diagnostic parameters

The pathophysiologic \(Q_{\text{LPM}}/Q_{\text{MPA}}\) and \(p_{\text{LPA}}\) values, reported in Table 2, were used to compute the functional diagnostic parameters. The variation of CDP\(LPA\), \(E_{\text{loss,LPA}}\), and \(E_{\text{loss,LPA}}\) with LPA stenoses at different COs is presented in Fig. 7B, 7C, and 7D, respectively, and Table 3.

#### Pressure drop coefficient

The \(E_{\text{loss,LPA}}\) values of a specific case of LPA stenosis was not distinct, and overlapped with those obtained for other stenosis severities (Fig. 7C). Thus, \(E_{\text{loss,LPA}}\) could possibly lead to clinical misdiagnosis of the severity of PA stenosis. Consequently, \(E_{\text{loss,LPA}}\) which accounts for the decrease in LPA flow due to an increase in stenosis severity, has been evaluated as an alternate diagnostic parameter. The \(E_{\text{loss,LPA}}\) (absolute) increased with an increase in LPA stenosis severity (Fig. 7D). For example, at 3.74 LPM, the \(E_{\text{loss,LPA}}\) (absolute) values increased from 1023.8 mJ per \(Q_{\text{LPA}}\) to 1773.0 mJ per \(Q_{\text{LPA}}\) as the stenosis severity increased from 70% AS to 80% AS. At the same CO, the 90% AS LPA produced an impractical (high) \(E_{\text{loss,LPA}}\) value due to no flow. Similar to CDP\(LPA\), for a specific LPA stenosis severity, the \(E_{\text{loss,LPA}}\) (absolute) increased with an increase in CO; \(E_{\text{loss,LPA}}\) increased within 31% for the 70% AS LPA, and within 34% for the 80% AS LPA as the CO increased from 2 LPM to 3.74 LPM. However, a distinct and non-overlapping range (70% AS: 14.5–21.0; 80% AS: 60.7–92.2; 90% AS: 261.6) of \(E_{\text{loss,LPA}}\) values was observed for each case of LPA stenosis under variable CO.

#### Energy loss

The \(E_{\text{loss,LPA}}\) values of a specific case of LPA stenosis was not distinct, and overlapped with those obtained for other stenosis severities (Fig. 7C). Thus, \(E_{\text{loss,LPA}}\) could possibly lead to clinical misdiagnosis of the severity of PA stenosis. Consequently, \(E_{\text{loss,LPA}}\), which accounts for the decrease in LPA flow due to an increase in stenosis severity, has been evaluated as an alternate diagnostic parameter. The \(E_{\text{loss,LPA}}\) (absolute) increased with an increase in LPA stenosis severity (Fig. 7D). For example, at 3.74 LPM, the \(E_{\text{loss,LPA}}\) (absolute) values increased from 1023.8 mJ per \(Q_{\text{LPA}}\) to 1773.0 mJ per \(Q_{\text{LPA}}\) as the stenosis severity increased from 70% AS to 80% AS. At the same CO, the 90% AS LPA produced an impractical \(E_{\text{loss,LPA}}\) value due to no flow. Similar to CDP\(LPA\), for a specific LPA stenosis severity, the \(E_{\text{loss,LPA}}\) (absolute) increased with an increase in CO; \(E_{\text{loss,LPA}}\) (absolute) increased within 31% for the 70% AS LPA, and within 34% for the 80% AS LPA as the CO increased from 2 LPM to 3.74 LPM. However, a distinct and non-overlapping range (70% AS: 14.5–21.0; 80% AS: 60.7–92.2; 90% AS: 261.6) of \(E_{\text{loss,LPA}}\) values was observed for each case of LPA stenosis under variable CO.

### Table 2

<table>
<thead>
<tr>
<th>LPA stenosis severity</th>
<th>(Q_{\text{LPA}}/Q_{\text{MPA}}(%)) - (p_{\text{LPA}}) (mmHg)</th>
<th>(Q_{\text{LPM}}/Q_{\text{MPA}}(%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO = 1 LPM</td>
<td>(70% ) AS</td>
<td>61% - 19.9 mmHg</td>
</tr>
<tr>
<td></td>
<td>(80% ) AS</td>
<td>57% - 19.1 mmHg</td>
</tr>
<tr>
<td></td>
<td>(90% ) AS</td>
<td>40% - 15.5 mmHg</td>
</tr>
<tr>
<td>CO = 1.5 LPM</td>
<td>(70% ) AS</td>
<td>53% - 18.3 mmHg</td>
</tr>
<tr>
<td></td>
<td>(80% ) AS</td>
<td>46% - 16.9 mmHg</td>
</tr>
<tr>
<td></td>
<td>(90% ) AS</td>
<td>30% - 13.3 mmHg</td>
</tr>
<tr>
<td>CO = 2 LPM</td>
<td>(70% ) AS</td>
<td>47% - 17.1 mmHg</td>
</tr>
<tr>
<td></td>
<td>(80% ) AS</td>
<td>36% - 14.6 mmHg</td>
</tr>
<tr>
<td></td>
<td>(90% ) AS</td>
<td>21% - 11.5 mmHg</td>
</tr>
<tr>
<td>CO = 3 LPM</td>
<td>(70% ) AS</td>
<td>36% - 14.7 mmHg</td>
</tr>
<tr>
<td></td>
<td>(80% ) AS</td>
<td>25% - 12.4 mmHg</td>
</tr>
<tr>
<td></td>
<td>(90% ) AS</td>
<td>---</td>
</tr>
<tr>
<td>CO = 3.74 LPM</td>
<td>(70% ) AS</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>(80% ) AS</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>(90% ) AS</td>
<td>0</td>
</tr>
</tbody>
</table>
4. Discussion

PA hemodynamics, evaluated in a controlled environment using \(\textit{in vitro}\) experiments under subject-specific conditions, prove to be useful in understanding the pathophysiology of PA stenoses. Translating the experimentally-recorded hemodynamic data to clinically relevant information requires the use of physiologic data. The clinical \((Q_{\text{LPA}}/Q_{\text{MPA}}) = \frac{Q_{\text{LPA}}}{Q_{\text{MPA}}}/C_0\) pr \(\text{LPA}\) line in the present study shows close resemblance with pulmonary pressure-flow characteristics reported in past animal studies (Kondo et al., 2003; Linehan et al., 1985; Shoukas, 1975). Although, a slightly non-linear pressure-flow curve has been observed at lower flows (within \(\sim 400 \text{ ml/min}\)) due to vessel distensibility (Linehan et al., 1985), the curve is linear at higher flows. Further, the ohmic-Starling resistor model \((P_{\text{atm}} - P_{\text{venous}} = mQ + b)\), frequently assumed for characterizing pulmonary hemodynamics (Kondo et al., 2003; Linehan et al., 1985; Shoukas, 1975), fits the linear clinical \((Q_{\text{LPA}}/Q_{\text{MPA}}) - P_{\text{LPA}}\) line \((Q_{\text{LPA}}/Q_{\text{MPA}} = 4.7 \times P_{\text{LPA}} - 32.9)\) used for obtaining the pathophysiologic \(Q_{\text{LPA}}/Q_{\text{MPA}}\) in the present study.

Based on the \((Q_{\text{LPA}}/Q_{\text{MPA}}) - P_{\text{LPA}}\) results, the decrease in pathophysiologic \(Q_{\text{LPA}}\) below the physiologic level was observed only beyond a certain level of stenosis severity at a specific CO due to the auto-regulation of the pulmonary vasculature. These observations agree with previous clinical studies (Franch et al., 1963; Friedman et al., 1968; Shafter et al., 1959). However, the CO and stenosis severity (% AS) were not reported in these clinical studies. In a numerical study (Schiavazzi et al., 2015), stenosis of >65% vessel diameter reduction \((\sim 87\%\) AS) produced clinically significant levels of flow reduction \(<30\% Q_{\text{LPA}}/Q_{\text{MPA}}\) and pressure drop \((\Delta P > 3 \text{ mmHg})\). In the present study, at a CO of 2 LPM, a 70% AS produced a \(\Delta P_{\text{MPA- LPA}}\) of \(\sim 4 \text{ mmHg}\) and no \(Q_{\text{LPA}}\) reduction. This shows the auto-regulation of the downstream pulmonary vasculature to compensate for the increased stenotic resistance and maintain normal flow. In contrast, at a CO of 3 LPM, the same 70% AS

<table>
<thead>
<tr>
<th>LPA stenosis severity</th>
<th>Pressure drop coefficient, (\text{CDP}_{\text{LPA}})</th>
<th>Energy loss, (\text{E}_{\text{loss,LPA}}) (mJ)</th>
<th>Normalized energy loss, (\text{E}<em>{\text{loss,LPA}}/Q</em>{\text{LPA}}) (mJ per (Q_{\text{LPA}}))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CO = 2 LPM</td>
<td>CO = 3 LPM</td>
<td>CO = 3.74 LPM</td>
</tr>
<tr>
<td>70% AS</td>
<td>14.5</td>
<td>17.3(16%)</td>
<td>21.0(31%)</td>
</tr>
<tr>
<td>80% AS</td>
<td>60.7</td>
<td>65.6(7%)</td>
<td>92.2(34%)</td>
</tr>
<tr>
<td>90% AS</td>
<td>261.6</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Fig. 7. Bar graphs showing the effect of LPA stenosis on (A) \(Q_{\text{LPA}}/Q_{\text{MPA}}\) (values above the bars represent % reduction in \(Q_{\text{LPA}}\) from the clinical physiologic value) (B) \(\text{CDP}_{\text{LPA}}\) (C) \(\text{E}_{\text{loss,LPA}}\) (D) \(\text{E}_{\text{loss,LPA}}\) (*90% AS at 3 LPM data not available due to flow loop limitations; 90% AS at 3.74 LPM led to no flow in the LPA).
produced a $\Delta p_{\text{LPA}}$ of ~6 mmHg with 23% $Q_{\text{LPA}}$ reduction. A $Q_{\text{LPA}}$ reduction (24%), similar to the 70% AS at 3 LPM, was observed in the presence of an 80% AS ($\Delta p_{\text{LPA}}$ ~9 mmHg) at a 3 LPM CO. Thus, the effect of a stenosis on PA hemodynamics is highly dependent on both, CO and stenosis severity.

The proposed CDP $Q_{\text{LPA}}$ and $E_{\text{loss,LPA}}$ may be valuable in delineating the effect of CO and decreased LPA flow due to their distinct and non-overlapping ranges. These parameters are unique since the high significance paid to the LPA flow provides an increased ability to delineate the stenosis severity. Similar CDP ranges were observed in in vitro (Banerjee et al., 2008; D’Souza et al., 2014; Peelukhana et al., 2009) and in vivo (Effat et al., 2016; Kolli et al., 2016) studies evaluating coronary artery stenoses. Although, $E_{\text{loss,LPA}}$ has not been previously evaluated for a stenotic lesion, the $E_{\text{loss,LPA}}$ values (absolute values ~8–22 mW, see Table 3 and Fig. 3 in (Pekkan et al., 2005b)) in this study are comparable to those obtained for total cavopulmonary connections with LPA stenosis (~11–18 mW, Fig. 3 in (Pekkan et al., 2005b)).

In addition to evaluating unilateral stenoses which may have a low hemodynamic significance, CDP $Q_{\text{LPA}}$ and $E_{\text{loss,LPA}}$ could also be applied to residual PA stenosis secondary to CHD repair, or even more complex bilateral stenosis. A residual unilateral or bilateral PA stenosis of a moderate to severe degree in repaired TOF patients may lead to increased pulmonary regurgitation and insufficiently, consequently accelerating adverse RV remodeling, indicated by RV pressure overload and smaller RV end-diastolic volume (Marx et al., 1988; Maskatia et al., 2013; Petit et al., 2009). Additionally, in the present study, the moderate (80% AS) and severe (90% AS) LPA stenosis caused a highly-skewed flow split to the right lung. Such a flow maldistribution may cause abnormal perfusion – ventilation matching (Clark et al., 1995; Rhodes et al., 1998; Wessel et al., 1980). Hence, even an isolated unilateral PA stenosis, if severe, may affect lung function, the effect being more pronounced during an exercise condition. The universal nature of CDP has been demonstrated in the past by its ability to accurately delineate serial (D’Souza et al., 2013, 2014) as well as collateral (Peelukhana et al., 2009) coronary stenosis. Thus, CDP, as well as $E_{\text{loss}}$, may be useful in accurately delineating the hemodynamic significance of a complex case of PA stenosis, irrespective of other associated lesions.

4.1. Limitations

Although the in vitro experiments were conducted within a controlled environment using subject-specific and clinically observed conditions, the results may not accurately represent a realistic in vivo condition due to study limitations, listed below. These limitations are either a result of maintaining conciseness and focus on the study objective, or inherent to the experimental system.

Stenosis geometry. Since the primary objective was to focus on the effect of stenosis of varying area reduction on flow and pressure, the LPA stenoses were modeled as discrete constrictions with a concentric shape, and fixed and equal axial dimensions (Franch et al., 1963; Schiavazzi et al., 2015). Although dimensional heterogeneity along the axial direction could produce variations in the results, the vessel area reduction has the primary influence on the pressure drop data (May et al., 1963). Thus, discrete stenoses may present a worst-case scenario with larger pressure drop due to change in momentum in comparison to the viscous effect that dominates diffuse stenoses.

Stenosis location. The LPA stenoses were located at around 10 mm from the PA bifurcation. In vivo, this location may vary, producing larger (closer to bifurcation) or smaller (farther away from bifurcation) hemodynamic disturbances, and consequently affecting the study results. However, the effect may not be significant since the total length of the LPA is quite small (~10–30 mm (Chern et al., 2012; Townsley, 2012)), thus limiting the location of the stenosis.

PA anatomy. Since the objective of this study was to evaluate PA stenoses with varying severities, a single subject’s anatomy was considered. However, the MPA-LPA-RPA branching angles as well as vessel area ratios show inter-subject variation. These parameters are known to affect PA hemodynamics (Chern et al., 2012) and may possibly change the study outcomes.

Further, straight extensions in the PA test section (Fig. 1) may lead to an unrealistic inlet velocity (spatial) profile at the MPA. Accurate simulation of the complex in vivo hemodynamics in vitro is challenging. However, the MPA pressure was measured in a region with partial flow disturbances, considering the flow was not allowed to fully develop (i.e. extension length (~5 cm) < entry length (at least 74 cm)). Additionally, the LPA pressure ports’ location enabled the capture of 3D blood flow effects in regions distal to the bifurcation and stenosis. Hence, the pressure drop values are expected to be like those observed in vivo.

Physiologic hemodynamics. The physiologic LPA hemodynamics used for predicting the pathophysiologic conditions in this study, were based on the most common in vivo values. Alternate and less common occlusion pressures ranging from 2 to 8 mmHg (Kondo et al., 2003; Linehan et al., 1983; Shafter et al., 1959; Shoukas, 1975) and asymmetric physiologic $Q_{\text{LPA}}/Q_{\text{MPA}}$ ranging from 30% to 47% (Borst et al., 1956; Friedman et al., 1968) may marginally alter the slope of the linear clinical $(Q_{\text{LPA}})/Q_{\text{MPA}}$ – $p_{\text{LPA}}$ line and consequently, the pathophysiologic conditions and diagnostic parameter values.

Experimental setup. The limitation of the in vitro benchtop setup in evaluating low pressure for the 90% AS LPA at 3 LPM may be insignificant since, the experimentally-observed pressure drop implies that the LPA flow would be much lesser than 15% of the CO due to loss in pulmonary vascular reserve. Also, the extrapolated data corresponding to the subject-specific CO is expected to be accurate based on the correlation coefficients ($R^2$ at least 0.993; Fig. 6).

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Conflict of interest statement

None of the authors have a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

Appendix A. Details of the experimental setup

To create subject-specific test sections, a 3D model of normal (representing a native anatomy) PAs of the CHD subject was first obtained by segmenting the 2D PA anatomy from the CTA images, and subsequently reconstructing it into a 3D stereolithographic (STL) volume (Mimics, Materialise, Inc.). The subject-specific PA model in conjunction with the stenosis geometry (Fig. 2 and Table 1), obtained from clinical evidence, was converted to a 3D print-
compatible stenotic PA model using computer-aided design (CAD). The stenosis geometry was incorporated into the subject-specific normal PA model with extensions (CAD image, Fig. 1) using a manual morphing technique (3-matic, Materialise, Inc.) to obtain the three LPA stenosis models representing 70%, 80%, and 90% AS. The virtual CAD models also included pressure ports for in vitro static pressure measurements. Polyjet 3D printing technology (Objet260 Connex3, Stratasys, Ltd.) was subsequently implemented to convert the virtual CAD models to physical test sections (3D printing image, Fig. 1). The subject-specific stenotic PA test sections were printed in a rigid clear acrylic-based material (VeroClear, Stratasys, Ltd.). The test sections were incorporated into the benchtop MCL with BAF (Fig. 3) for conducting hemodynamic tests in vitro.

The BAF, which closely mimics the non-Newtonian behavior of blood, consisted of water (73%), glycerin (27%), and xanthan gum (0.009%) [composition by weight]. After curve fitting the experimental viscosity data to the standard Carreau curve (Cho et al., 1991), the following viscosity values were obtained: infinite shear viscosity, $\mu_{\infty} = 3.46$ cP, zero shear viscosity, $\mu_0 = 58$ cP. The fluid density was 1.057 g/cm$^3$.

A pulsatile blood pump (Model 1423, Harvard Apparatus), generating ventricular flow, was used to circulate the blood analog fluid through the MCL. The arterial wall compliance was simulated using air-filled compliance chambers, while the desired flow through each branch was achieved using flow control valves. Since pressure (or pressure drop) was the primary variable of interest, the compliance chamber and flow control valves were adjusted to obtain physiologic PA pressures (Franch et al., 1963) while compromising on the shape of the flow pulse (Fig. 4). The mean MPA pressures ($p_{\text{MPA}}$) were approximately maintained between 17 mmHg and 26 mmHg (Shafter et al., 1959). An ultrasound Doppler in-line flow sensor (ME-13PXN, Transonic Systems, Inc.), F1, was placed between the compliance chamber and test section (Fig. 3), and recorded the MPA flow rate (or CO). A second ultrasound Doppler clamp-on flow sensor (ME-9PX1, Transonic Systems, Inc.), F2, was placed at the exit of the test section in the LPA branch (Fig. 3 in the manuscript), and recorded the LPA flow rate. F1 and F2 were calibrated up to an accuracy of ±4% and ±10%, respectively. Signals from both the flow sensors were acquired and displayed using a digital flowmeter console (TS410, Transonic Systems, Inc.). Static pressure within the PA test section was recorded using a pressure scanner (DSA 3207, Scanivalve Corporation) consisting of 16 fluid-filled pressure sensors. The pressure scanner was calibrated up to an accuracy of ±0.20%. Data recorded by the flowmeter and pressure scanner was supplied to an analog input module (NI 9205, National Instruments Corporation) fitted within a data acquisition system (cDAQ-9174, National Instruments Corporation).

Appendix B. Pressure drop-flow rate characteristics

The mean pressure drop-flow rate ($\Delta p - Q$) characteristics have been represented by the dimensionless pressure drop from the MPA to LPA, $\Delta p_{\text{dim}} = \frac{\Delta p_{\text{MPA-LPA}}}{\rho q}$, and velocity ratio, $\frac{u_{\text{LPA}}}{u_{\text{MPA}}}$: where $\Delta p_{\text{MPA-LPA}}$ (Pa) is the mean pressure drop from the MPA to LPA (distal to stenosis), $\rho$ (kg/m$^3$) is the fluid density, $u_{\text{MPA}}$ (m/s) is the mean MPA velocity, and $u_{\text{LPA}}$ (m/s) is the mean proximal LPA velocity. Fig. A1 shows the $\Delta p_{\text{dim}}$ characteristics of the 70%, 80%, and 90% AS LPAs at varying $\frac{u_{\text{LPA}}}{u_{\text{MPA}}}$ and a specific CO. The solid symbols represent experimental data points and the grey dotted lines represent
trendlines obtained by fitting a polynomial curve to each dataset. Error bars for the dimensionless pressure drop were constructed using the standard error computed from the three experimental datasets, and are indicative of experimental repeatability. The standard error in $\Delta p_{\text{lim}}$ (error bars in Fig. A1) for all the cases was within 24.4, thus indicating highly repeatable experiments. The distinct characteristics observed for each LPA stenosis severity are similar to those reported in previous studies evaluating branched and stenotic vessels (Banerjee et al., 2007; de Zélicourt et al., 2005; Idelchik 2005; Pekkan et al., 2005b; Young et al., 1973). The $\Delta p_{\text{lim}}$ vs. $u_{\text{LPA}}/u_{\text{MPA}}$ characteristics are governed by a quadratic function, $\Delta p_{\text{lim}} = A \times (u_{\text{LPA}}/u_{\text{MPA}}) + B \times (u_{\text{LPA}}/u_{\text{MPA}}^2) + C$. The loss due to the change in momentum, which is primarily caused by the presence of a stenosis, is represented by the $A \times (u_{\text{LPA}}/u_{\text{MPA}})$ term in the equation, where $A$ is the loss coefficient. For higher % AS, loss due to momentum change is the primary contributing factor to the total pressure loss in the LPA. The non-linearity and slope of the $\Delta p_{\text{lim}}$ vs. $u_{\text{LPA}}/u_{\text{MPA}}$ curve (Fig. A1) increased with an increase in stenosis severity. This is due to the higher $A$ values obtained for the 90% AS LPA in comparison to the 80% and 70% LPAs. For example, at CO $= 2$ LPM (Fig. A1C), the $A$ values for the 90%, 80%, and 70% AS LPAs were 202.7, 94.1, and 19.1, respectively.

References


