INTRODUCTION

Reconstruction of the right ventricular outflow tract (RVOT) is an important step in the repair of complex conotruncal defects. Although numerous alternatives for reconstruction of the RVOT continuity exist, to date no ideal right ventricular to pulmonary artery conduit has been found. In addition to the homograft, the bovine jugular vein conduit graft (Contegra graft, Medtronic, Inc., Minneapolis, MN, USA) is ‘state-of-the-art’ in surgical reconstruction of the RVOT. The Contegra graft is a ready-to-use conduit, available in a wide range of sizes and has been considered as an excellent substitute for the pulmonary valve. After initial enthusiasm, however, a high reintervention rate in the short-term became evident [1]. Age, small body surface and small graft size of the conduit were identified as predictive factors [1, 2]. It is obvious that age and graft size are in reverse relation and indicate the impact of somatic growth in this pathology. To avoid this phenomenon, graft oversizing was advocated [1, 2]. However, evidence exists that somatic growth is not the primary reason for the relatively high reintervention rates [3, 4]. Degeneration and structural deterioration of the implanted valve, a stenotic process at the pulmonary artery and at distal anastomosis are the most frequent reasons for reintervention [4]. As such, the exact mechanisms and details around conduit failure are unclear. It also appears that intimal hyperplasia, as a consequence of local haemodynamical conditions, is one of the most important elements in this pathology [5–7]. Despite the fact that local haemodynamical elements may trigger the activation of a proatherogenic process in the vascular wall, to date, there has been no assessment of local shear stress and pressure conditions in oversized RVOT.

Our 12 mm RVOT haemodynamical model identified the shear stress and pressure profile prone for endothelial remodelling at the pulmonary artery bifurcation and at the ostia of pulmonary arteries [8]. Since oversizing the RVOT with valved conduits is
well established in reconstruction of the conotruncal defect, the aim of this experimental study was to provide an oversized 12-mm RVOT (for 4, 6 and 8 mm) to identify local haemodynamical conditions that may contribute to early wall degeneration and conduit failure. This approach may elucidate and allow for prediction of the optimal grade of conduit oversizing in a given RVOT.

MATERIAL AND METHODS

Animal protocol
The protocols described were reviewed and approved by the Committee on Animal Care, Office Vétérinaire Cantonal, Lausanne. Twenty domestic pigs were used with a mean body weight of 24.8 ± 0.78 kg. Relatively small animals were chosen with a mean body surface of 0.82 ± 0.01 m² and an RVOT diameter of 1.3 ± 0.17 cm in order to simulate conditions in paediatric cardio-surgical scenarios. After general anaesthesia with volatile anaesthetics was established, baseline haemodynamical parameters were monitored by central venous catheter in the jugular vein and arterial pressure, using a femoral arterial catheter. Heart rhythm was evaluated by a five-lead electrocardiography (ECG).

Steady-state measurements
The pulmonary root, pulmonary artery, pulmonary artery bifurcation and left and right pulmonary arteries were dissected. Flow measurements (Vascular probe size of 12 mm, Medistim, Oslo, Norway) under steady-state conditions, with an arterial pressure of 120/80 mmHg, and heart rate at 90 beats per minute, were taken at the pulmonary trunk and left and right pulmonary arteries. Invasive pressure measurements (direct intravascular hydrostatic pressure measurements) were taken from the pulmonary root at the infravalvular and supravalvular positions, the pulmonary artery, the bifurcation of the pulmonary artery and the left and right pulmonary arteries [8].

Cardiopulmonary bypass and perfusion protocol
The superior and inferior vena cava were cannulated using 16 and 18 Fr venous cannulas, respectively (DLP®, Medtronic, Inc.). Arterial cannulation at the ascending aorta was carried out with 14 Fr cannula (Jostra® cannula, Maquet Gmbh, Hirrlingen, Germany). Full systemic heparinization (heparin loading dose 300 units/kg body weight with activated clotting time >480 s) was used throughout the procedure. After the maximal stable pump flow of 14 Fr cannula (Jostra® cannula, Maquet Gmbh, Hirrlingen, Germany). Full systemic heparinization (heparin loading dose 300 units/kg body weight with activated clotting time >480 s) was used throughout the procedure. After the maximal stable pump flow of 14 Fr cannula (Jostra® cannula, Maquet Gmbh, Hirrlingen, Germany). Full systemic heparinization (heparin loading dose 300 units/kg body weight with activated clotting time >480 s) was used throughout the procedure. After the maximal stable pump flow of 14 Fr cannula (Jostra® cannula, Maquet Gmbh, Hirrlingen, Germany). Full systemic heparinization (heparin loading dose 300 units/kg body weight with activated clotting time >480 s) was used throughout the procedure. After the maximal stable pump flow of the total cardiopulmonary bypass was achieved, the pulmonary trunk was removed. Continuity between RVOT and pulmonary artery was established in an end-to-end straight fashion using 12, 16, 18 and 20 mm bovine jugular vein grafts [7] with proximal anastomosis at the RVOT and distal anastomosis [8]. Five animals were used for each graft size.

For each Contegra graft size (12, 16, 18 and 20 mm), after anastomosis was completed, CPB was stepwise augmented from 75 to 100 and 125% of the steady-state flow. At each flow level, pressure and flow were measured. Invasive pressure was measured at the RVOT, in the Contegra graft at the infravalvular and supravalvular area, at the pulmonary trunk, at its bifurcation and at the left and right pulmonary arteries. A flow probe of 10 mm was used to determine the flow for pulmonary arteries, a 12 mm probe for the pulmonary trunk, and 16, 18 and 20 mm for the Contegra graft area. The strategy of stepwise flow augmentation was chosen to evaluate the haemodynamical conditions of shear stress, pressure and flow relations over the pulmonary tract under low, normal and high flow conditions.

Pulmonary artery geometry
After invasive measurements were taken, the animals were euthanized and the RVOT and pulmonary arteries were explanted. Circumference was measured at the pulmonary root at the infra- and supravalvular positions, at the pulmonary artery, at the bifurcation of the pulmonary artery and at the left and right pulmonary arteries, as mentioned in our previous work [8, 9].

Computational fluid dynamics model
Computed fluid dynamics (CFD) simulation was established for each Contegra size (12, 16, 18 and 20 mm), from the RVOT up to the pulmonary artery bifurcation. Geometric interpretation of the RVOT, pulmonary root and bifurcation was based in part on our previous results [8] and in part on results obtained following autopsy [8]. Computational fluid modelling of the pulmonary trunk was done as mentioned previously [8]. In brief, blood was modelled as a Newtonian fluid with a viscosity of 4 × 10⁻³ Pa s and a density of 1060 kg/m³. No-slip boundary conditions were imposed on the artery walls and the valve leaflets. Atmospheric pressure conditions (101 325 Pa) were set at the two artery outlet regions. At the inlet of the pulmonary artery, various boundary conditions were applied according to the case being considered. A steady velocity flat profile with an open pulmonary valve was applied according to the measured flow rates of 1.5, 2.0 and 2.5 l/min. The Navier–Stokes multiblock solver (NSMB) flow solver uses a cell-centred finite volume method to solve the compressible Navier–Stokes equations. The spatial discretization was ensured by a fourth-order central scheme, whereas the time discretization was resolved by an implicit scheme. The ANSYS ICEM CFD (ANSYS, Inc., PA, USA) is a preprocessor tool used to generate the multiblock structured grid needed by the NSMB flow solver. An O-grid topology was employed to refine the mesh close to the walls to correctly capture the laminar boundary layers in these regions. The grid for the smooth PA comprises 19 structured blocks for approximately 365 000 cells [8]. Experimental data (e.g. flow and pressure) were used as boundary conditions for the CFD model. The CFD model evaluated the pressure, velocity and shear stress profiles, which were estimated, and values from the subvalvular position in the RVOT were compared with those from the outlet of the left and right pulmonary arteries in three different inlet velocity profiles [8]. For computational fluid dynamics data, velocity profile, shear stress profile and flow were averaged over the cross section and time at the RVOT, infravalvular region, supravalvular region, pulmonary artery, bifurcation and at both pulmonary arteries for all three flow rates and in all four oversized geometries.

RESULTS

Experimental data
Interventions on all 20 animals were successful. Results are presented as means and standard deviations. The mean measured
blood flow at the RVOT was 2.04 ± 0.51 l/min. After the CPB was established, the flow rate was increased to obtain 75, 100 and 125% of the steady-state flow. Corresponding flows were as follows: 1.5 ± 0.3 l/min for 75%, 2.2 ± 0.2 l/min for 100% and 2.47 ± 0.07 l/min for 125%, respectively. To simplify CFD modeling, flow ranges were determined as follows: 1.5 l/min for 75%, 2.0 l/min for 100% and 2.5 l/min for 125% of flow, respectively.

The measured circumference was 5.14 ± 0.4 cm at the subvalvular position, 3.84 ± 0.42 cm at the sinotubular junction and 3.68 ± 0.64 cm at the bifurcation, respectively. Velocity values were defined as previously [8]: 0.22 m/s, 0.29 and 0.36 m/s, corresponding to 1.5 l/min, 2.0 l/min and 2.5 l/min flow rates, respectively.

**Velocity profiles**

The velocity profiles for all three flow rates in all four Contegra graft diameters are given in Table 1. In the 12 mm graft, inflow velocity at a flow rate of 1.5 l/min was 0.22 m/s and remained constant to the bifurcation area where it was 0.21 m/s. In the right and left pulmonary arteries, inflow velocities were 0.21 m/s and 0.24 m/s, respectively. The same phenomenon of a constant velocity at a flow rate of 1.5 l/min was 0.22 m/s and remained constant to the bifurcation area where it was 0.21 m/s. In the right and left pulmonary arteries, inflow velocities were 0.21 m/s and 0.24 m/s, respectively. The same phenomenon of a constant velocity profile from RVOT to bifurcation was observed at flow rates of 2.0 l/min and 2.5 l/min, with a slight elevation in the left and right pulmonary arteries, inflow velocities were 0.21 m/s and 0.24 m/s, respectively. The same phenomenon of a constant velocity profile from RVOT to bifurcation was observed at flow rates of 2.0 l/min and 2.5 l/min, with a slight elevation in the left and right pulmonary arteries (Table 1). The following was observed in RVOT reconstructed with a 16 mm graft: inflow velocity augmented with inflow flow rate was from 0.21 m/s for 1.5 l/min, 0.28 m/s for 2 l/min and 0.35 m/s for 2.5 l/min. Passing the distal anastomosis, the velocity profile inside the graft showed lower values compared with the inflow area (Table 1). At the level of bifurcation, velocity reached 0.22 m/s for 1.5 l/min, 0.29 m/s for 2.0 l/min and 0.37 m/s for 2.5 l/min. These were almost similar values to those detected at the inflow area (Table 1). Similarly, as in the 12 mm graft, slight augmentation of velocity values was observed in the left and right pulmonary arteries. The same phenomenon of velocity reduction inside the Contegra graft was observed in the 18 and 20 mm grafts. The local velocity profiles are presented in Fig. 1. These velocity areas were averaged over the centre of the RVOT model. The velocity range was in the moderate range, between 0.2 and 0.4 m/s, independently from inflow velocity rate from the RVOT down to the bifurcation in all four graft sizes. Of note, the wall on left and right hands of the pulmonary trunk low velocity areas may be found independently from graft size and inflow velocity. This finding represents a narrow zone of the 12 and 16 mm grafts, but is brighter in 18 and 20 mm diameters. In all four dimensions, the ostia of the left and right pulmonary arteries were subject to high velocity area ranges between 0.4 and 0.6 m/s and, in some instances, with higher values at the right pulmonary artery. A prompt transition between the central high velocity areas and low velocity areas at the anterior wall of both pulmonary arteries may be observed in all four Contegra grafts. This finding may have resulted from the more pronounced right pulmonary artery in the 2.5 l/min inflow rate.

The proximity of the low and moderate velocity regions inside of the graft and at the level of the proximal anastomosis may be sources of turbulent flow. The same could be said for the bifurcation and both ostia of the pulmonary arteries, as all three inflow rates in all Contegra diameters of the low velocity regions are conjoined to the moderate and high-pressure areas (Fig. 1).

**Pressure profiles**

Table 2 shows the pressure values and their repartition along the pulmonary trunk in all three velocity profiles for all four diameters. Figure 2 illustrates the local pressure conditions for all three velocity values of the four graft sizes. Inside of the Contegra graft (i.e. area between the distal and proximal anastomosis), the local pressure was augmented by increase of the inflow and diameter of the graft. In the 12 mm graft at an inflow of 1.5 l/min, the pressure was moderately elevated between 11.2 and 11.3 Pa, and by 11.6 at the 2.5 l/min inflow. With the larger graft size, the pressure was constantly augmented. At 2.0 l/min inflow in the 16, 18 and 20 mm graft sizes, the pressure ranged between 11.4 and 11.9 and at 2.5 l/min inflow in the 16, 18 and 20 mm graft sizes, the pressure ranged between 11.4 and 11.9 (Fig. 2). Note that the moderately-high-pressure areas at the distal anastomosis are conjoined to the low pressure areas at the pulmonary artery. This finding is especially prominent in high flow and the 16, 18 and 20 mm grafts. Additionally, high pressure was registered at bifurcation regions reaching 12.1 mmHg in the 2.5 l/min flow condition.

### Table 1: Computed fluid dynamics results, showing the reparation of the velocity profiles (mean values) for all three inflow profiles (1.5, 2.0 and 2.5 l/min) in all four geometries

<table>
<thead>
<tr>
<th>Flow Area</th>
<th>1.5 l/min</th>
<th>2.0 l/min</th>
<th>2.5 l/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflow</td>
<td>0.221</td>
<td>0.230</td>
<td>0.238</td>
</tr>
<tr>
<td>BF</td>
<td>0.225</td>
<td>0.225</td>
<td>0.226</td>
</tr>
<tr>
<td>RPA</td>
<td>0.228</td>
<td>0.229</td>
<td>0.230</td>
</tr>
<tr>
<td>LPA</td>
<td>0.231</td>
<td>0.232</td>
<td>0.233</td>
</tr>
</tbody>
</table>

RVOT: right ventricular outflow tract; Inf-Valv: infravalvular region; Sup-Valv: supravalvular region; PA: pulmonary artery; BF: bifurcation; RPA: right pulmonary artery; LPA: left pulmonary artery.
Low pressure areas were observed at the distal regions of the left and right pulmonary arteries, and ranged between 11.0 and 11.2 Pa in both pulmonary arteries. This unique finding occurred in all 12 CFD models (Fig. 2).

### Shear stress profile

The shear stress numerical repartition is detailed in Table 3. Local repartition of shear stress regions is presented in Fig. 3. In all four sample sizes, the low shear stress areas (range, 0–3.0 Pa) were present at the region of the Contegra graft between the distal and proximal anastomosis. Notably, low shear stress affected the conduit wall independent of the diameter and inflow velocity range (Fig. 3). The augmentation of the shear stress was noted between the distal anastomosis and free pulmonary artery. In this narrow area, shear stress ranged between 3 and 6.0 Pa depending on the flow rate and diameter implanted. In the 12 mm graft in the 1.5 l/min inflow range at this area, the shear stress was between 0 and 2.0 Pa. The same ranges were observed for the 16, 18 and 20 mm conduits at the same inflow. In the 2.0 l/min inflow range, the shear stress at this area was between 2.0 Pa.

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**Table 2**: Computed fluid dynamics results, showing the repartition of the pressure (mean values) in all four geometries for three different inflow values (1.5, 2.0 and 2.5 l/min)

<table>
<thead>
<tr>
<th>Flow Area</th>
<th>1.5 l/min</th>
<th>2.0 l/min</th>
<th>2.5 l/min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pressure mmHg</td>
<td>Pressure mmHg</td>
<td>Pressure mmHg</td>
</tr>
<tr>
<td>Graft size</td>
<td>RVOT</td>
<td>Inf-Valv</td>
<td>Sup-Valv</td>
</tr>
</tbody>
</table>

RVOT: right ventricular outflow tract; Inf-Valv: infravalvular region; Sup-Valv: supravalvular region; PA: pulmonary artery; BF: bifurcation; RPA: right pulmonary artery; LPA: left pulmonary artery.
and 4.0 Pa for the 12, 16, 18 and 20 mm conduits. In contrast, in the 2.5 l/min flow rate, the shear stress ranged between 0 and 10 Pa in the area between the pulmonary artery and proximal anastomosis site.

Low shear stress areas were found at bifurcation in all three flow rates and in all four Contegra graft diameters (ranging between 0 and 4.0 Pa). Additionally, the anterior wall of both pulmonary arteries was affected by low shear stress (Fig. 3). The ostia of the pulmonary artery showed a different reparation. In the low flow model, independently from graft diameter, shear stress ranged between 0 and 3.0 Pa. In the model for 2.0 l/min, the range was between 0 and 5.0 Pa. At 2.5 l/min, the range was between 0 and 9.0 Pa.

**DISCUSSION**

In the present study, in an oversized RVOT 3D CFD model, a link between the appearance of intimal hyperplasia and local haemodynamical conditions is suggested. The experimental set-up simulated a paediatric cardio-surgical scenario with the reconstruction of a 12 mm RVOT. Corresponding to oversizing for a $Z$ score of 0, 4, 6 and 8, the RVOT tract was replaced using 12, 16, 18 and 20 mm valved grafts, respectively. Parameters determined during the experimental measurements in low, normal and high flow conditions were used for CFD modelling in all four geometries. Low shear stress and high pressure, as potential predictive factors for intimal hyperplasia, were identified at the pulmonary...
artery bifurcation and ostia of both pulmonary arteries and was more prominent in normal and high flow profiles, as in low flow conditions.

The pathophysiological mechanism responsible for the development of neointimal hyperplasia and degenerative plaques is currently not understood in detail. The interaction between the vascular wall shear stress and endothelial biology seems to be a key element in this process \[10\]. Shear stress is a dynamical interaction between the surface of the endothelium and the flowing blood expressed in unit of force per unit of surface \[6\], and can be assessed by 3D time-related computed fluid dynamics model \[10\]. It is an important mechanical signal that is transduced into a complex sequence of biochemical reactions in endothelium. At the regions of the laminar flow a laminar drag force on the endothelial surface activates atheroprotective genes and is considered as protective element for atherosclerosis \[10\]. In contrast, the regions of non-laminar flow, as at lateral wall of bifurcation, at inner areas of curvature and/or shoulders of stenosis are allied to a degenerative process and neointimal hyperplasia \[11\]. It became evident that proatherogenic genes are activated in regions with turbulent flow, low shear stress and elevated pressure \[5, 6, 8, 12\].

The restitution of the continuity between RVOT and pulmonary artery is challenging. Independently of age and initial reconstructive procedure, the valved RVOT conduit may become dysfunctional in the short term. This is regardless of the surgical technique and conduit used. Freedom from reintervention in the first 3 years is 65% \[2, 3\]. In order to find an ideal substitute with a long-term lifespan, and to avoid the relatively high reoperation rate with all its complications, different conduit types have been compared \[13, 14\]. To date, an ideal conduit for RVOT reconstruction has not been found. In the paediatric population, a small graft size, patient age and small body surface are predictive factors for conduit failure \[2, 15, 16\]. One could conclude that somatic growth and consequent prosthesis patient mismatch are the most striking reasons for reinterventions; consequently, graft oversizing for a Z factor of 1–3 was proposed as a solution \[1, 2\]. Soon, however, it became evident that somatic outgrowth was not the only reason for early graft replacement \[3\]. The fact is that following the RVOT conduit implantation, stenosis other than at distal anastomosis does exist. Stenotic areas were identified at the pulmonary artery bifurcation and at the initial segment of both pulmonary arteries. Interestingly, the freedom from reoperation at 3 years was 76% \[1\] for the mentioned pathology and is similar to the results reported for RVOT overgrowth \[2, 3\]. Intimal hyperplasia was proposed as one of the mechanisms for the degenerative process and development of sclerotic regions \[17, 18\], following RVOT reconstruction. Recently, however, is inconclusive in regard to intimal hyperplasia and RVOT degeneration. Several explanations were suggested for this phenomenon such as length of the conduit, implantation technique and immunological reactions. Unfortunately, to date, there is no clear explanation for this very frequent pathological phenomenon in the reconstructed RVOT.

Herein, a CFD model of RVOT oversizing was presented in order to evaluate the influence of the oversizing geometry on repartition of low shear stress and high pressure. A 12 mm RVOT was chosen to simulate paediatric RVOT circulation and to serve as a future reference for further investigations of RVOT haemodynamics following oversizing. Notably, the 12 mm graft has identical characteristics to that of a natural 12 pulmonary tract \[8\], and may thus serve as a reference to compare 16, 18 and 20 mm models. The results from the 16 mm CFD model graft were very similar to the 12 mm, and in the cases of the 18 and 20 mm grafts, repartition of the shear stress and pressure were different from those in the 12 mm graft. This finding was especially true for

![Figure 3: Shear stress repartition in pulmonary tract wall at three different non-pulsatile inflow rates, in four geometries. Low shear stress is marked in blue and ranges between 0 and 2.0 Pa. Moderate shear stress is marked in green and yellow colour and ranges between 3.0 and 7.0 Pa. High shear stress is marked in red, and ranges between 8.0 and 10 Pa. The solid line indicates the distal and proximal anastomosis site of the Contegra graft.](image)
normal and high flow conditions where the low shear stress areas and moderately high pressure covered larger areas at the distal anastomosis and opening of the pulmonary arteries when compared with the 12 and 16 mm geometries. The local distribution of the mentioned parameters may contribute to a better understanding of the mechanism of neointimal hyperplasia and of the degenerative changes in the reconstructed RVOT. Additionally, since the grade of local expression in low shear stress and high pressure in the four geometries show different distribution patterns, our results can suggest the size of the graft utilized in clinical practice for the well-accepted oversizing manoeuvre, while also keeping the haemodynamical parameters within acceptable ranges. According to our CFD real-time model, the maximal accepted oversize for a 12 mm RVOT is implantation of a 16 mm graft.

The CFD model developed in this study is based on real pressure, flow and natural geometry parameters; therefore, it may be considered as a tool for future investigations focusing on the influence of fluid dynamics on the development of intimal hyperplasia following RVOT repair with an oversized valved conduit. We are aware that mechanism of valved conduit failure is of a multifactorial nature and our results will hopefully contribute to a better understanding of this clinical phenomenon. To the best of our knowledge, there are no reports in the current literature dealing with haemodynamical conditions in oversized RVOT, and as such we are unable to derive any comparisons in observation. Further clinical and experimental trials are needed to fully explain the complex mechanism of valved conduit degeneration in the RVOT.

Study limitations

Although the haemodynamical conditions that may lead to early graft failure were identified and the maximal oversizing size was determined, this study does have some limitations. First, the flow investigated was a steady-state constant flow, and therefore, does not correspond to the pulsatile flow present in vivo, and local flow conditions such as turbulent flow may not be identified. Additionally, the valve was considered to be constantly open, which is also not representative of the situation in vivo. The effect of pulsatile flow in combination with a moving valve may lead to new insights into the haemodynamical nature of the RVOT pulmonary artery and its branches. Further, a pulsatile numerical model may give us insights not only of the repartition of the local shear stress distribution, but also insights into oscillatory shear stress. The role of oscillatory shear stress in development of intimal hyperplasia is inconclusive in the current literature [12].

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