In vitro assessment of heart valve bioprostheses by cardiovascular magnetic resonance: four-dimensional mapping of flow patterns and orifice area planimetry

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Abstract

Objective: The hemodynamics in proximity to stented aortic bioprostheses still differ from that under physiological conditions. This may prevent desired cardiac remodeling and promote aortic diseases. Further improvements in prosthetic technology require an accurate survey of the flow conditions on the prosthetic level and in the ascending aorta. Cardiovascular magnetic resonance (CMR) may have the potential to provide more information by determining the prosthetic orifice area and visualizing the intravascular flow dynamics. We tested the feasibility to better characterize the hemodynamics of various stented bioprosthesis in a pulsatile flow phantom by using CMR. Methods: The custom-made model consisting of a commercially available pump generating pulsatile flow, a tube system filled with a glycerin–water mixture, and a handcrafted bulbar-shaped cylinder holding the bioprostheses and simulating the aortic root, was located in a clinical 1.5 T CMR system. In this study, 10 stented aortic bioprostheses were investigated (Perimount® 21, 23; Mitroflow® 19, 25; Hancock® 21, 23, 25; Mosaic® 21; Epic Supra® 21, 23). The prosthetic orifice area was visualized using steady-state free-precession cine imaging (spatial/temporal resolution 1.3 × 1.3 × 5 mm3/29 ms), quantified by manual planimetry and compared with published transthoracic echocardiographic data. Time-resolved three-dimensional phase-contrast flow mapping (1.8 × 1.8 × 3 mm3/45 ms) was applied to analyze the transprosthetic flow pattern. Results: Visualization of the prosthetic orifice area and the transprosthetic flow pattern was feasible in all prostheses. All orifice areas obtained by CMR in vitro were within one standard deviation of the mean of the published reference values obtained by echocardiography in vivo. Turbulent flow with vortex formation occurred both in proximity to the prosthesis and on the ‘ascending aortic’ level. Larger prosthetic sizes led to decreased flow velocities, but not mandatorily to less turbulences. Conclusions: CMR allowed for a detailed interrogation of the fluid dynamics of various heart valve bioprostheses in a pulsatile flow model. It is an attractive tool to define proprietary reference values of the orifice area under standardized conditions and provides novel information regarding the flow pattern in proximity to the prosthesis.

Keywords: Heart valves; Heart valve prosthesis; Magnetic resonance imaging; Blood flow velocity; Hemodynamics

1. Introduction

Despite recent progresses in bioprosthetic heart valve technology, the achieved hemodynamics still differ from that under physiological conditions, particularly if stented devices are implanted [1]. The accurate survey of the blood flow on the prosthetic level and in the ascending aorta is supposed to be an important prerequisite to analyze prosthetic function and its impact on the adjacent vasculature, compare novel prosthetic designs and surgical techniques with older ones, and guide future developments in prosthetic technology and surgery. Cardiovascular magnetic resonance (CMR), with its versatility and inherent capabilities to assess both morphology and function with high spatial and temporal resolution, is supposed to have the potential to realize that survey, thereby providing additional important information regarding the hemodynamics of bioprosthetic heart valves. On the one hand, CMR using cine imaging has already been established as an accurate technique to assess the orifice area of bioprostheses implanted...
in aortic and mitral positions [2,3]. On the other hand, CMR with time-resolved three-dimensional flow measurements has been introduced to visualize the intravascular blood flow dynamics [4,5].

In the present study, we tested the feasibility to combine these CMR techniques in order to better characterize the hemodynamics of various stented bioprostheses in a pulsatile flow phantom. The experiment is intended to both define proprietary CMR reference values of the prosthetic orifice area of the tested devices and elucidate whether the flow pattern in proximity to the prosthesis differs between various prosthetic types.

2. Materials and methods

2.1. Artificial circulation system

The circulation system consisted of a pump (Cardioflow®, 1000 MR, Shelley Medical Imaging Technologies, Ontario, Canada) generating pulsatile flow, a rigid u-shaped pipe (length 4.5 m; diameter 25 mm) and a fluid reservoir (Fig. 1). A customized Perspex® cylinder was integrated at the end of the antegrade part within the isocenter of the CMR scanner. Its inner form was accurately ground to resemble shape and dimensions of the native aortic root. At its basis, various bioprostheses could be fixed. The system was filled with a mixture of glycerol (40%) and distilled water (60%) to approximate blood viscosity and to fulfill technical requirements of the pump. The pump generated pulsatile flow with a cycle length of 860 ms, an antegrade flow of 300 ms (35% of cycle length), a maximum flow of 300 ml/s, a stroke volume of 50 ml and a total flow volume of 3.5 l/min with a stroke rate of 70 beats per minute. The settings were adapted to international standards for the hydrodynamic testing of heart valve substitutes (ISO 5840;2005) [6].

2.2. Bioprostheses

We tested 10 stented bioprostheses of various types and sizes: The Hancock® (Medtronic Inc., Minneapolis, MN, USA) was available for our studies in sizes 21, 23 and 25. It is a trileaflet porcine device fabricated using an acetal homopolymer stent [7,8]. The Mosaic® (Medtronic Inc., Minneapolis, MN, USA), tested in size 21, is similarly fabricated, but its stent design allows for supraannular implantation [9,10].

Fig. 1. Artificial circulation system for the in vitro assessment of heart valve bioprostheses using CMR. Left: Scheme of the complete circle. Right: Scheme of the bulbar Perspex® holder for the bioprostheses.

The Epic Supra® (St. Jude Medical Inc., St. Paul, MN, USA) is a stented porcine tissue valve based on the design of the Epic® and Biocor® valves, however allowing for a complete supraannular implantation. We tested sizes 21 and 23 [11,12]. The Perimount® (Edwards Lifesciences, Irvine, CA, USA), which we tested in sizes 21 and 23, is a stented bovine pericardial bioprosthesis. The valve stent frames are composed of Eligiloy, a corrosion-resistant cobalt-chromium spring alloy [13,14]. The Mitroflow® (Sorin Group, Milano, Italy) is composed of a polymer stent covered with a polyester cloth, while the leaflets are made from a single sheet of bovine pericardium mounted on the outside of the stent [15,16]. We studied sizes 19 and 25. All the prostheses used exclusively for our studies were provided by the manufacturer in original packaging. All the investigated prosthetic types are in clinical use for aortic valve replacement and are regarded as MRI-safe. Their hemodynamic characteristics derived from published echocardiographic studies are shown in Table 1 [8,10–12,15–18].

2.3. Cardiovascular magnetic resonance

All bioprostheses were investigated in a clinical 1.5 T CMR scanner with a 6-element phased-array matrix receiver coil

Table 1. Hemodynamic results of the studied bioprostheses determined by echocardiography derived from the literature.

<table>
<thead>
<tr>
<th>Prosthetic type</th>
<th>Peak pressure gradient (mmHg)</th>
<th>Mean pressure gradient (mmHg)</th>
<th>Effective orifice area (cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perimount® 21</td>
<td>25.7 ± 9.9 [17]</td>
<td>20.3 ± 9.1 [17]</td>
<td>1.5 ± 0.4 [17]</td>
</tr>
<tr>
<td>Perimount® 23</td>
<td>21.7 ± 8.6 [17]</td>
<td>13.0 ± 5.3 [17]</td>
<td>1.8 ± 0.3 [17]</td>
</tr>
<tr>
<td>Mitroflow® 19</td>
<td>29.7 ± 10.1 [16]</td>
<td>19.7 ± 3.3 [15]</td>
<td>1.1 ± 0.2 [17]</td>
</tr>
<tr>
<td>Mitroflow® 25</td>
<td>20.7 ± 7.2 [16]</td>
<td>11.0 ± 4.2 [15]</td>
<td>2.0 ± 0.3 [15]</td>
</tr>
<tr>
<td>Epic Supra® 23</td>
<td>30.0 ± 10.7 [17]a</td>
<td>20.0 ± 6.6 [17]a</td>
<td>1.3 ± 0.3 [17]a</td>
</tr>
<tr>
<td>Hancock® 21</td>
<td>20.0 ± 4.0 [18]</td>
<td>14.8 ± 4.1 [18]</td>
<td>1.2 ± 0.1 [8]</td>
</tr>
<tr>
<td>Hancock® 23</td>
<td>24.7 ± 5.7 [18]</td>
<td>16.6 ± 6.9 [18]</td>
<td>1.3 ± 0.4 [17]</td>
</tr>
<tr>
<td>Hancock® 25</td>
<td>20.0 ± 2.0 [18]</td>
<td>10.7 ± 3.0 [18]</td>
<td>1.6 ± 0.4 [17]</td>
</tr>
<tr>
<td>Mosaic® 21</td>
<td>Not available</td>
<td>15.2 ± 6.7 [10]</td>
<td>1.4 ± 0.4 [10,17]</td>
</tr>
</tbody>
</table>

a Hemodynamic results of the Biocor® 23, as this information is not available for the Epic Supra® or the Epic® with size 23.

b Orifice area of the Epic Supra® 21 obtained in vitro in a pulsatile flow model with 50 ml stroke volume, as no in vivo orifice area is available for the Epic Supra®, Epic® or Biocor® with size 21.
in combination with a built-in spine array coil (MAGNETOM Avanto® and Espree®, Siemens Healthcare Sector, Erlangen, Germany). The control unit of the above described pulse generator simulated electrocardiographic gating with 70 beats per minute. Steady-state free-precession (SSFP) cine images were used to visualize the prosthetic orifice. Imaging parameters chosen were adjusted to the in vivo assessment of bioprostheses [2,3]: Slice thickness, 5 mm; repetition time (TR), 3.8 ms; echo time (TE), 1.6 ms; flip angle (FA), 80°; field of view (FOV), 340 × 276 mm²; matrix, 256 × 208; voxel size, 1.3 × 1.3 × 5 mm³; bandwidth, 930 Hz/px; and 30 phases per cycle (temporal resolution 29 ms).

Slice positioning for prosthetic orifice planimetry was achieved in a stepwise approach that ensured an accurate position of the imaging plane perpendicular to the transprosthetic jet (Fig. 2): (A) The jet was localized in sagittal and coronal planes. (B) A mid-systolic image was selected. (C) A stack of slices without interslice gap was planned perpendicular to the jet and parallel to its base covering the whole prosthesis and overlapping its margins about 1 cm in both directions.

For CMR reading and planimetry of the orifice area, the software CMRv2® (CIRCLE Cardiovascular Imaging, Calgary, Alberta, Canada) was used. Quantification of the orifice area was done in a stepwise fashion: (A) Selection of the optimally positioned slice, defined as showing cusp closure in diastole and flow within the prosthetic apparatus in systole, supported by the use of cross reference lines. (B) Manual contouring of the orifice area (Fig. 2).

In addition, fast gradient echo (FGRE) cine imaging was applied to assess whether this sequence, which is known to be less susceptible to flow turbulences, but at the cost of reduced blood/tissue contrast compared to SSFP, is also adequate to allow prosthetic orifice area assessment. Imaging parameters of the FGRE sequence were chosen as applied in vivo [2,3]: slice thickness, 5 mm; TR, 6.5 ms; TE, 3.6 ms; FA, 15°; FOV, 340 × 276 mm²; matrix, 256 × 208; bandwidth, 260 Hz/px; and 25 phases per R-R interval.

To assess the transprosthetic flow pattern, time-resolved three-dimensional phase-contrast imaging with three-directional flow encoding was performed. Imaging parameters were: 20 slices; slice thickness, 3 mm; TR, 41.6 ms, resulting in 19 temporal phases (temporal resolution 45.1 ms during 70 min⁻¹ stroke rate); TE, 2.7 ms; FA, 20°; FOV 127.5 × 340 mm²; matrix 72 × 192; voxel size, 1.8 × 1.8 × 3 mm³; bandwidth, 455 Hz/px. Visualization of the flow pattern was realized using a prototype software package for 4D flow visualization (Siemens Corporation, Corporate Research Princeton, USA).

3. Results

3.1. Feasibility to visualize the prosthetic orifice area using CMR

Visualization of the prosthetic orifice area using SSFP was feasible in all prosthetic types and sizes and allowed for planimetry of the orifice area in all examinations (Fig. 2, Video files 1 and 2). The use of FGRE sequences to image the prosthesis led to non-diagnostic image quality in five of the studies. In the remaining five studies, prosthetic orifice planimetry was feasible. However, the delineation of prosthetic stent, cusp borders and blood became more difficult compared to SSFP (Fig. 3). Both in SSFP and FGRE, the Perimount™ prosthesis came with a circular stent artifact that did not render the image quality non-diagnostic (Fig. 3).

3.2. Quantification of the prosthetic orifice area using CMR

Fig. 4 shows the orifice areas obtained by CMR planimetry and illustrates that all CMR results lie within one standard deviation of the mean published echocardiographic result.

3.3. Visualization of the transprosthetic flow pattern using CMR

The visualization of the transprosthetic flow pattern was feasible in all prosthetic types and sizes. The time-resolved
technique allowed to follow the course of the fluid starting from the emitter plane, through the prosthesis and within the bulbar Perspex® cylinder resembling the ascending aorta (Fig. 5). In all cases, the blood flow velocity increased on the level of the prosthesis, with the maximum flow velocity within the flow center (Fig. 6). Turbulent flow with vortex formation was detected both very close to the prosthesis (Perimount® 21, Epic Supra® 21, Mosaic® 21, Hancock® 21), and in some distance (Epic Supra® 23, Hancock® 21/23, Mitroflow® 25) (Fig. 6). Vortex formation rarely involved the complete circumferential fluid volume, but predominantly occurred localized, as exemplarily shown for the Mitroflow® 25 in Fig. 7. When comparing smaller and larger sizes of the same prosthetic type, the increase in prosthetic sizes led to decreased flow velocities, but not mandatorily to less turbulences, as depicted in Fig. 6 (Epic Supra®, Hancock®, Mitroflow®).

4. Discussion

Aortic valve disease is the most common valve disease in adults, and aortic valve replacement, the most common heart valve surgery, with approximately 200,000 recipients each year worldwide [19]. Over the years, medical progress led to reduced perioperative mortality, technological improvements led to prolonged freedom rates from structural valve deterioration following biological aortic valve replacement, and strategies to omit patient–prosthesis mismatch are increasingly used to encounter its negative impact on cardiac remodeling and prognosis. Nevertheless,
4.1. Determination of the prosthetic orifice area using in vivo CMR

To determine whether an aortic bioprosthesis in a subject is working well or not, it is common practice in echocardiography analysis to compare the obtained orifice area with reference values published in the literature for each prosthetic type and size [17,18]. However, the accuracy of such reference values is not always as clear as it is supposed to be in clinical practice. For example, inaccurate measurements of the left ventricular outflow tract diameter in the presence of a prosthetic stent may complicate the use of the continuity equation. Furthermore, the individual patient’s hemodynamics (e.g., stroke volume, flow acceleration, aortic stiffness and early vs late postoperative state) in the interplay with the degree of cusp stiffness are complex confounding factors and lead to a high variability of the hemodynamic outcome of biological heart valve substitutes. Such limitations may lead to heterogeneous data for a single prosthetic type, with reference values containing large standard deviations, as indicated in Table 1. For example, according to the echocardiography-based literature, a normal-functioning Hancock® 23 prosthesis is supposed to have a mean orifice area of 1.3 cm², but with a range considering one standard deviation from 0.9 cm² to 1.7 cm² [17]. Hence, the decision whether the orifice area in a specific patient is normal or abnormal can become very problematic. On the other hand, in vitro measurements are mostly carried out by flow-measuring transducers or high-speed cameras [20,21]. These techniques are supposed to perform accurately, but have the obvious disadvantage that they cannot be translated directly to in vivo settings. Finally, the geometric orifice area, which is often provided by the manufacturer or can be simply assessed by Hegar dilators, is a geometric measure of the orifice area under static conditions. Hence, it does not reflect the true orifice area that is effectively used for blood flow and is also no adequate parameter for reference values.

Thus, a non-invasive tool that uses the same approach both for the in vivo assessment of a heart valve bioprosthesis and for the definition of normal values under standardized in vitro conditions would be very desirable. CMR seems to be a suitable technique for this purpose. In vivo, the accuracy of CMR to assess the prosthetic orifice area has already been proven [2,3]. In vitro, the principal feasibility to assess orifice areas using CMR and a phantom model has already been shown in 2001 by our group [22]. We now demonstrated for the first time the feasibility to visualize and determine the orifice area of bioprostheses by using a pulsatile flow model and CMR with the identical settings compared to in vivo.

In our setting, the sequence of choice was SSFP. It is also the standard sequence to evaluate heart valves in vivo, particularly due to its excellent blood/tissue contrast and its high robustness even in the presence of arrhythmia [3]. FGRE performed unsatisfactory and should not be used for in vitro assessments. Only in cases with strong flow artifacts, FGRE with less susceptibility to turbulent flow, may be an option. However, overestimation of the orifice area may occur [2,3,23].

Visualization of the orifice area was achieved with satisfactory image quality in all the 10 studied prostheses, even though the image quality seemed to be influenced by the type of device. In accordance with previous in vivo experiments [2,3], the Perimount® exhibited an artifact close to its stent, which consists of a cobalt–chromium spring alloy, while such a phenomenon did not occur in the other prostheses containing acetal homopolymer stents. Nevertheless, this observation should not exclude this prosthetic type from CMR assessment.

In all prostheses, the orifice areas obtained by CMR planimetry in vitro were within one standard deviation of the mean of the published in vivo reference values obtained by echocardiography. This finding indicates that CMR planimetry seems to be quite accurate and may allow the use of echocardiographic reference values when assessing bioprostheses by CMR in vivo as long as proprietary CMR reference values are not available. Nevertheless, both methods do not entirely agree, even though the discordance is small. This discordance may be attributed to method-based difficulties and differ-
ences between CMR and echocardiography as mentioned above, and different hemodynamic conditions during orifice area measurements by CMR in vitro and echocardiography in vivo. To address the first limitation, the preferable validation of our CMR in vitro data would consist in a direct comparison with orifice areas obtained by CMR planimetry in vivo in patients with recently implanted bioprostheses of the same types. Unfortunately, such data do not exist until now. A prospective solution to acquire them within reasonable time would be for the manufacturers of heart valves to integrate CMR in their approval studies in addition to echocardiography.

To address the second limitation, in vitro and in vivo CMR measurements should be performed under similar hemodynamic conditions, in particular regarding stroke volume. In fact, the stroke volume during our experiments, which represented the maximum achievable value within our setting, was lower than it is physiologically common. Hence, we cannot exclude that the orifice areas would differ during higher stroke volumes [11,20]. Thus, we propose that a more sophisticated setting than the experimental one should be used for further in vitro assessments, which allows hemodynamic tests during various stroke volumes, for example, 25–100 ml as proposed by international recommendations [6].

Finally, when looking at the absolute numbers for the orifice areas, the Mitroflow® with labeled size 25 exhibited a larger orifice area than the Hancock® 25, as well as the Mitroflow® 19 achieved results comparable to the Hancock® and Mosaic® prostheses with labeled size 21 under the same hemodynamic conditions. These findings may be indicators for the potential benefit of the valve design of the Mitroflow®, which differs from the other tested prostheses where the pericardial sheet is mounted on the outside of the stent, instead of placing the tissue within the stent. Hence, a larger orifice area can be achieved [15].

4.2. Determination of the transprosthetic flow pattern using CMR

Each stented bioprosthesis still constitutes a left ventricular outflow obstacle. Apart from the constant pressure burden of the left ventricle, this leads to turbulent flow in the ascending aorta, which is associated with decreased blood transport efficiency and damage of the prosthetic cusps and the aortic wall [24]. Hence, to further improve the hemodynamic performance of heart valve bioprostheses towards a physiological state, not only a large orifice area should be aspired, but also a widely laminar ascending aortic flow pattern achieved. However, to manage the latter objective, a tool to visualize the flow pattern is essential. Time-resolved three-dimensional phase-contrast CMR, which registers the blood flow velocity in three dimensions during the entire heart cycle and provides color-encoded blood flow maps after postprocessing, has the potential to close this gap [4].

Our studies demonstrated for the first time in a pulsatile flow model that the time-resolved visualization of the transprosthetic flow is feasible in a variety of prosthetic types and sizes. This holds true even at the prosthetic level, despite the presence of stent material and the associated risk of signal void. Turbulent flow with vortex formation was detected both very close downstream to the prosthesis, in vivo corresponding to the level of the aortic sinus, and with some distance to the prosthesis on the level corresponding to the ascending aorta. Although eccentric flow has been observed close to the aortic valve even in natural human anatomy, the turbulences observed here close to the prosthesis exceeded that normal degree. The smaller prostheses tended to exhibit vortex formation closer to the prostheses than the larger counterpart. At present, it can only be speculated whether this may explain differences in the speed of prosthetic cusp deterioration and aortic remodeling between smaller and larger prostheses.

Furthermore, even though the increase of the prosthetic size led to a decrease of the flow velocity, this change was not mandatorily accompanied by less turbulences. This finding underlines that it is important to consider the prosthesis as a whole, including the design of the stent, instead of solely focusing on the orifice area, when evaluating its hemodynamic performance.

Vortex formation rarely involved the complete circumferential fluid volume, but predominantly occurred localized. This observation may explain the sometimes more eccentric ectasia formation of the ascending aorta following aortic valve replacement compared to subjects with an inherent aortic wall disease, who generally show a more concentric loss of the normal aortic silhouette. Furthermore, the focal distribution of turbulences underlines the need for three-dimensional techniques when analyzing the transprosthetic flow pattern, as they were used in the present study, because two-dimensional techniques could miss the decisive segments.

Up to now, only few studies exist, which used CMR phase-contrast imaging to analyze the flow pattern adjacent to a bioprosthetic valve [24,25], and are suitable for a comparative debate. Kvitting et al. recently reported on differences in the degree of turbulence intensity between mechanical, stented biological and stentless biological prostheses using three-dimensional phase-contrast CMR in an in vitro model. Interestingly, they also detected small vortices immediately downstream from the stentless xenograft in this case, which is comparable to the findings in our series. However, these experiments were performed under steady inflow, which limits their observations [24]. Dyverfeldt et al. from the same group reported on the application of CMR in one patient with a Perimount® 25 aortic heart valve prosthesis. They found the highest values of flow velocity and turbulent kinetic energy immediately downstream from the valve, corresponding to the flow profiles in our series. Furthermore, they detected complex flow patterns in the ascending aorta and elevated values of turbulent kinetic energy also at the wall of the ascending aorta [25]. This finding also resembles our observations that complex vortices occur at the surface of the liquid stream. It can be assumed that such flow dynamics are important influencing factors regarding the strength of wall shear stress and the extent of aortic remodeling following aortic valve replacement.

However, the present flow pattern results have to be interpreted considering two main limitations. First, as aforementioned, the characteristics of the applied hemodynamic cycle (e.g., stroke volume, acceleration) may differ from those in the in vivo states. As acceleration has a stabilizing effect on flow, the flow pattern may be different under physiological conditions [24]. Second, even though the geometry of the Perspex® prosthesis holder resembles the
human aortic root and the diameter of the tubes resembles the aortic lumen, both structures do not behave as being compliant, which is in contrast to the human aortic wall. Thus, transprosthetic flow encountering a compliant ascending aorta may exhibit different flow patterns than shown in the present experiments.

In conclusion, cardiovascular magnetic resonance imaging allowed for a detailed interrogation of the fluid dynamics of various heart valve bioprostheses in a pulsatile flow model. It is an attractive setting to define proprietary reference values of the bioprosthetic orifice area for each prosthetic type and size and to compare them under standardized conditions. The integration of time-resolved three-dimensional flow mapping provides additional novel information regarding the flow pattern in proximity of the prosthesis. This information may help to understand the impact of prosthetic function on diseases of the adjacent vasculature. In future studies, the quantification of the flow data and the analysis of the impact of different flow patterns on prosthetic and aortic morphology and function need to be addressed in humans.

Acknowledgement

We thank Michael Markl from the University of Freiburg (Germany) for providing the time-resolved three-dimensional phase-contrast sequence for measuring the flow patterns.

References


Appendix A. Supplementary data

Supplementary data associated with this article (Video 1 and 2) can be found, in the online version, at doi:10.1016/j.ejcts.2010.12.040.