Stentless bioprostheses improve postoperative coronary flow more than stented prostheses after valve replacement for aortic stenosis

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Objective: In some randomized studies, stentless aortic valves have demonstrated hemodynamic advantages in comparison with stented prostheses. The effect of more physiologic flow dynamics on coronary artery flow has not been investigated yet. This study compares coronary perfusion after aortic valve replacement with stented or stentless porcine bioprostheses in a prospective randomized study.

Methods: A total of 24 patients (73 ± 6 years) referred for treatment of aortic stenosis were randomized to aortic valve replacement with stented (Medtronic Mosaic; (Medtronic Inc, Minneapolis, Minn) or stentless (Medtronic Freestyle; Medtronic Inc) prostheses. Coronary flow was measured by means of magnetic resonance imaging preoperatively, 5 days after the operation, and 6 months postoperatively, then with evaluation of coronary flow reserve. Echocardiography was performed to quantify transvalvular gradients and left ventricular mass regression.

Results: Coronary flow increased in both groups significantly ($P < .001$) after aortic valve replacement. This increase was higher in the stentless group compared with that seen in the stented group (343 ± 137 vs 221 ± 66 mL/min). Also, coronary flow reserve was higher for stentless valves (3.4 ± 0.3 for stentless valves and 2.3 ± 0.1 for stented valves). Mean pressure gradients for Freestyle valves were lower (10 ± 4 and 8 ± 3 mm Hg, respectively, vs 19 ± 6 postoperatively and 15 ± 4 mm Hg at follow-up for Mosaic valves, $P < .05$). Left ventricular mass regression was similar in both groups.

Conclusions: Normalization of coronary artery flow after aortic valve replacement for aortic stenosis was more pronounced for stentless valves compared with stented valves. The fact that the stentless design also demonstrated a superior hemodynamic performance with lower pressure gradients might be explained by the design being closer to physiologic anatomy and thus the presence of lower turbulence levels in the sinuses of Valsalva.

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Long-term mortality is increased in patients after aortic valve replacement (AVR) compared with that in the normal population.¹⁻³ Findings from trials conducted in the 1970s and 1980s seemed to demonstrate that valve design did not influence long-term outcome, but recent studies observed varying mortalities between different stented biologic valve substitutes, which could not be explained by differences in structural deterioration and hemodynamic performance alone.^{4,5} Therefore other factors might contribute to the increased long-term mortality in patients undergoing AVR, which have not been investigated in detail thus far. With respect to valve-related complications, chronic coronary hypoperfusion or reduced coronary reserve might be one of the causes of sudden cardiac death or arrhythmia. Furthermore, deteriorating left ventricular function is common after AVR⁶ and might be related to insufficient coronary flow. Previous experimental studies

Abbreviations and Acronyms

AVR	= aortic valve replacement
LVM	= left ventricular mass
MRI	= magnetic resonance imaging
NYHA	= New York Heart Association
RPP	= rate pressure product

showed that postoperative coronary flow and coronary reserve is dependent on valve design and orientation. None of the tested aortic valve prostheses allowed for physiologic coronary flow rates.⁷⁻¹⁰

The aim of this prospective randomized study was to compare the hemodynamic performance of 2 biologic valves in patients undergoing AVR for aortic stenosis. We compared the stented Medtronic Mosaic and the stentless Medtronic Freestyle (Medtronic Inc, Minneapolis, Minn) prostheses and evaluated the acute and chronic changes in coronary artery flow, coronary flow reserve, hemodynamic outcome, and regression of left ventricular mass (LVM).

Noninvasive measurement of coronary perfusion rates in vivo can be performed either by using echocardiography or magnetic resonance imaging (MRI) scanning. Echocardiography is frequently limited by impaired postoperative conditions of analysis. Therefore we chose MRI scanning, which provides a more objective measurement of right and left coronary artery flow rates without additional exposure to x-rays.¹¹

Methods

From March 2003 through April 2004, 24 consecutive patients (mean age, 73 ± 6 years) undergoing AVR were included in this prospective randomized study. Patients had severe aortic stenosis (maximum gradient of >50 mm Hg or aortic valve area of <1.0 cm²), no patient had more than minimal aortic regurgitation, and all patients had angiographically normal coronary arteries. Exclusion criteria included active endocarditis, emergency operation, and a history of coronary artery disease, as well as myocardial infarction.

All patients provided written informed consent before inclusion in the study. The study and consent form were approved by the local ethics committee.

All patients underwent transthoracic echocardiography and MRI scanning on the day of admission, before discharge, and at a 6-month follow-up. The MRI scan was used to measure coronary flow rates and dynamics. Additional measurement of adenosine-induced coronary flow reserve ($140 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ adenosine over 7 minutes) was performed at the follow-up MRI. Rate pressure product (RPP) as the product of heart rate multiplied by left ventricular pressure (systolic blood pressure plus systolic transvalvular gradient) was calculated as an indicator of myocardial oxygen demand. The intention was to exclude increased cardiac work load as the cause of increased coronary flow rates.

Echocardiography was used to evaluate the hemodynamics of the valves and LVM regression. At the follow-up visits, additional clinical evaluation was performed.

Echocardiography

Echocardiography was performed according to American Society of Echocardiography guidelines with a Vingmed Vivid 5 cardiac ultrasound scanner (GE Medicals, Fairfield, Conn). Continuous-wave Doppler scanning was used to derive peak transvalvular pressure gradients across the aortic valve (peak AVG). Aortic valve area was calculated according to the American College of Cardiology/American Heart Association guidelines to determine severity of aortic stenosis. Left ventricular ejection time was measured on the continuous-wave Doppler trace from opening to closing of the aortic valve. The mean of 3 separate readings was used for each parameter. All data collected were entered in a central database.

Cardiovascular Magnetic Resonance (MRI Scan)

Patients were examined in a 1.5-Tesla system (Magnetom Sonata, Maestro Class; Siemens, Erlangen, Germany) in supine position by using thoracic surface coils. The examination started with a set of transverse and double oblique scout images to localize the coronary arteries. Subsequently, a retrospectively electrocardiography-gated, breath-hold, phase-contrast flash sequence with high temporal and spatial resolution was used to acquire flow data. These sequences were oriented perpendicularly to the left (segment 5) and right (segment 1) coronary artery main stems. Resulting cine Magnetic Resonance Imaging flow data sets included rephased, magnitude, and phase images and were segmented manually by using the ARGUS flow analysis software (Siemens AG, Erlangen, Germany). According to the measured velocities at every time frame, velocity and flow curves were generated and analyzed. The preoperative measured values of coronary flow for each individual patient were set as 100% values. The postoperative values were then related to these preoperative flow rates. Coronary flow reserve was calculated as the ratio between maximum and rest coronary flow rates.

Additionally, the distance of the coronary flow velocity peak to the R-wave was measured, representing the time of maximal coronary flow in relation to systole and diastole.

Patients were randomized to receive a porcine bioprosthesis, either a stented Medtronic Mosaic or a stentless Medtronic Freestyle prosthesis. Both valves undergo identical processing with zero-pressure cusp fixation and amino-oleic-acid anticalcification treatment, and therefore the only difference between the 2 valves is the use of a stent in Mosaic valves.

Intraoperatively, patients were excluded from the study if the aortic root wall had severe calcifications that could not be removed surgically, thus making implantation of a stentless valve impossible, or if the aortic root was dilated.

Surgical Technique

A total of 9 surgeons performed the operations. All patients had retrograde cold blood cardioplegia and carbon dioxide insufflation of the open chest for organ protection. Access to the aortic valve was gained through a transverse aortotomy. After complete resection of the native aortic valve and debridement of the aortic annulus,

TABLE 1. Preoperative patient characteristics

	Mosaic	Freestyle	P value
Male sex	5	5	.89
Female sex	7	7	.89
Age (y)	76 ± 6	71 ± 7	.52
BSA	1.90 ± 0.1	1.85 ± 0.2	.54
Angina pectoris	6	7	.97
Hypertension	7	7	.90
Atrial fibrillation	3	2	.72
Preoperative mean gradient (mm Hg)	69 ± 22	73 ± 14	.31
NYHA class	3.5 ± 0.5	3.5 ± 0.4	.91
Coronary flow, RCA (mL/min)	65 ± 21	60 ± 30	.52
Coronary flow, LCA (mL/min)	90 ± 33	94 ± 31	.32
Preoperative ejection fraction (%)	60 ± 10	52 ± 5	.94

BSA, Body surface area; NYHA, New York Heart Association; RCA, right coronary artery; LCA, left coronary artery.

accurate sizing was carried out with the original Medtronic sizers for the Freestyle stentless and Mosaic stented valves. Freestyle valves were implanted in the modified subcoronary position, leaving the noncoronary prosthetic sinus intact, by using single Ethibond 4-0 sutures for the proximal and a running Prolene 4-0 suture for the distal anastomoses. The Medtronic Mosaic stented valves were implanted in a supra-annular fashion by using pledget-armed U-

stitches with Ethibond 2-0 sutures. Bites were taken from the ventricular to the aortic side of the annulus.

Statistical Methods

As a first step of statistical analysis, Gaussian normal distributions of results obtained for hemodynamic parameters and coronary flow rates were tested by using the Dallal-Wilkinson corrected and Kolmogoroff-Smirnoff test. Data were compiled and analyzed with Microsoft Excel (Redmond, Wash) and Statview (Cary, NC) software. The baseline characteristics and hospital outcomes for the 2 groups were compared by using χ^2 or Fisher exact tests for categoric data and Mann-Whitney *U* tests for continuous variables. Results are reported as the mean ± standard deviation in text and tables.

Results

Preoperative coronary artery flow and also other clinical characteristics, including age, sex, body surface area, ejection fraction, New York Heart Association (NYHA) functional class, and cardiovascular risk factors, were comparable in the 2 groups (Table 1). Coronary flow rates varied distinctly between individuals, but mean and median values were similar in the stentless and stented groups. Evaluation of the coronary perfusion pattern demonstrated a pathologic early flow velocity peak and even partially reversed flow during systole (Figure 1). RPP was 20,031 ± 4855 beats/min · mmHg, again with no difference between groups.

Table 2 summarizes the operative data. Crossclamp times and cardiopulmonary bypass times were significantly longer in the Freestyle stentless valve group. The mean valve size was 23 ± 1.2 mm for the stented group and 23.5 ± 1.1 mm for the stentless group. Because only the stentless sizers were metric, Mosaic sizes had to be converted into their metric value,¹² which was 20.6 ± 1.0 mm. Severe patient-prosthesis mismatch was not observed in any patient, moderate mismatch occurred in 2 stented patients, and mild mismatch occurred in 6 Mosaic and 4 Freestyle patients. The remaining 12 patients did not demonstrate any patient-prosthesis mismatch, and

Figure 1. Coronary artery flow pattern in a patient with aortic stenosis preoperatively. During systole, reversed coronary flow was observed (arrow); during diastole, a double peak of flow velocities occurred; and distance of highest flow velocities from the R-wave (indicated by the ruler) was measured.

TABLE 2. Intraoperative data

	Mosaic	Freestyle	P value
CPB time (min)	84 ± 19	105 ± 13	.013
Crossclamp time (min)	58 ± 10	76 ± 9	.001
Implantation technique	Supra-annular	Modified subcoronary	
Valve size (mm)			
21	2	2	
23	6	4	
25	3	4	
27	1	1	
29	—	1	

CPB, Cardiopulmonary bypass.

Figure 2. Comparison of preoperative and postoperative coronary artery flow rates for stented (Mosaic) and stentless (Freestyle) valves in the left (LCA, A) and right coronary arteries (RCA, B). Preoperative flow rates were set as 100%, and a significant increase was observed for both valves postoperatively. Flow rates were significantly higher for stentless valves both in the left and right coronary arteries ($P < .01$).

mean indexed effective orifice area was 0.95 ± 0.2 for stentless and 0.77 ± 0.09 for stented valves.

The discharge MRI evaluation of coronary flow revealed a significant increase in coronary flow for the left and right coronary arteries for each individual patient ($P < .01$). The left coronary artery flow increased to $223\% \pm 43\%$ in the stentless group (related to the preoperative values) versus $143\% \pm 29\%$ in the stented group; the right coronary artery flow increased to $265\% \pm 33\%$ of preoperative levels for stentless versus $203\% \pm 34\%$ for stented valves (Figure 2). Thus the difference in favor of the stentless group was highly significant ($P < .01$). At the follow-up examination, coronary flow rates were lower compared with the discharge evaluation (mean, $144\% \pm 35\%$), with the difference between the valve groups being maintained. Coronary reserve

Figure 3. Relation between indexed effective orifice area and increase in coronary flow for the 2 valves. No correlation could be detected.

induced by adenosine was 3.4 ± 0.3 for stentless and 2.3 ± 0.1 for stented valves (normal, >2.5).

The coronary flow pattern changed in both groups postoperatively toward a more diastolic velocity peak of perfusion, with no more reversed systolic coronary flow. In the stented group the distance of the velocity peak of coronary flow to the R-Wave was 400 ms preoperatively and 550 ms postoperatively. In the stentless group the preoperative value of 500 ms preoperatively increased to 570 ms postoperatively. There was no significance between the 2 valve groups. No correlation was seen between indexed effective orifice area (effective orifice area/body surface area) and increase in coronary flow (Figure 3).

All echocardiographic results are summarized in Table 3. Mean gradients for Freestyle valves were significantly lower at discharge and at 6-month follow-up ($P < .05$). LVM index regressed significantly in both groups over time. However, there were no significant differences in LVM regression between the groups at either discharge or 6 months postoperatively, although a trend toward more pronounced LVM regression was seen for Freestyle valves.

RPP decreased for all patients toward normal values (Freestyle, 9124 ± 1002 beats/min $\cdot$ mmHg; Mosaic, $10,489 \pm 1120$ beats/min $\cdot$ mmHg).

The overall rate of perioperative complications was low in both groups. In the stentless group we observed a case of atrioventricular block of grade III with the need for implantation of a DDD pacemaker. In the stented group there was a case of pericardial effusion, which was treated with medication alone. There was no case of severe clinical events or death in either group either perioperatively or until the 6-month follow-up.

TABLE 3. Postoperative echocardiographic data

	Mosaic	Freestyle	P value
Mean gradient (mm Hg) at discharge	17 ± 5	9 ± 4	.001
Mean gradient (mm Hg) at follow-up	14.8 ± 5.2	8.0 ± 2.5	.001
LVM (g/m ²) preoperatively	265 ± 56	276 ± 65	.723
LVM (g/m ²) at discharge	260 ± 54	265 ± 70	.72
LVM (g/m ²) at follow-up	191 ± 54	159 ± 70	.060

LVM, Left ventricular mass.

NYHA classification improved in all patients (mean of 1.5 ± 0.5 for stentless and 1.7 ± 0.4 for stented valves at follow-up), and no patient was in NYHA class IV.

Discussion

AVR with a biologic prosthesis is the treatment of choice in patients over the age of 65 years with a significant aortic valve stenosis. Despite excellent early postoperative outcome, long-term survival is not satisfactory, with survival rates as low as 36% after 12 years.⁵ In several studies the long-term mortality after AVR was higher compared with that seen in a matched patient population.^{13,14}

Patients with severe aortic stenosis present with a high incidence of angina pectoris as a clinical symptom.^{15,16} Many hemodynamically unfavorable changes in this disease contribute to dysfunction of the coronary macrocirculation and microcirculation, such as left ventricular hypertrophy, including high left ventricular cavity pressure, low coronary artery pressure, increased extravascular compression, reduced diastolic perfusion time, and vascular remodeling. Furthermore, the coronary endothelium regulates coronary blood flow of the epicardial and intramyocardial microcirculation.¹⁷ This myocardial blood flow impairment has been identified as a strong independent predictor for the progression of heart failure.¹⁸

AVR leads to improvement of coronary artery flow immediately but not to a complete normalization.¹⁹ In a previous animal study, we demonstrated that no mechanical valve prosthesis could restore the physiologic values of coronary perfusion measured in a control group with a native aortic valve.¹⁰ Coronary flow rates depended on valve design and orientation. The optimal orientation with respect to hemodynamics also resulted in coronary perfusion rates closest to normal physiology. This correlation between systolic performance and coronary perfusion was explained by low levels of turbulence downstream during systole, which also affects diastolic backflow. Thus the optimally oriented valve allowing normal diastolic regurgitation into the sinuses of Valsalva also provided the highest coronary artery flow rates.

The current prospective randomized study was designed to investigate the clinical effect of the findings in our

previous animal setting for bioprosthetic valves. The 2 groups were comparable with respect to their preoperative clinical characteristics. The preoperative MRI scan demonstrated a disturbed coronary flow pattern, with even reversed flow seen during end systole. This observation can be related on the one hand to a pathologic pressure relation between the left ventricle and the ascending aorta and on the other hand to Venturi-type suction in the aortic root caused by highly turbulent flow in aortic stenosis.²⁰

Regarding the operative data, larger stentless valve prostheses could be implanted with respect to their metric values, and as expected, longer bypass and crossclamp times were observed for the Freestyle valves. This, however, did not lead to an increased need for inotropic medication or to any perioperative morbidity. The subcoronary implantation technique for the Freestyle stentless valve was chosen to retain the normal patient sinus geometry with the stent in Mosaic prostheses, being the only variable remaining between the 2 valves. A full root replacement would have changed not only the geometry of the sinuses of Valsalva and the coronary artery origin but also aortic wall compliance.

Postoperatively, we observed low morbidity and also a comparable postoperative course in both groups, with lower transvalvular pressure gradients in the stentless group, as described in previous studies. For both groups, pressure gradients further decreased during the follow-up period of 6 months, with the superiority of stentless valves remaining significant. At follow-up, we also documented a significant regression of LVM index in all patients, with a nonsignificant trend for better LVM regression in the stentless group, RPP as a marker for myocardial oxygen demand, and lower cardiac work load for the patients receiving Freestyle valves.

Coronary flow rates increased significantly after AVR in each individual patient, and a pathologic reversed flow pattern could not be observed postoperatively. Stentless valves demonstrated significantly higher perfusion rates at discharge and follow-up. The decrease of coronary perfusion rates 6 months postoperatively can be explained by the LVM regression and normalization of cardiac output compared with the hyperdynamic phase immediately after the operation. Patients receiving stentless valves now showed a normal flow reserve, whereas those receiving stented valves demonstrated slightly reduced flow reserve. Thus the valve correcting the pressure difference between the left ventricle and the aortic root best provided the most physiologic coronary flow as well. The low resistance to transvalvular flow reducing the intraventricular pressure might be the most important contributor to this result.

No correlation was seen between valve size and coronary perfusion rates, and therefore the fact that larger stentless valves were implanted (especially with respect to the metric size) could not account for the more physiologic flow dy-

namics postoperatively. Also, severity of patient-prosthesis mismatch did not correlate with postoperative flow rates.

The effect of flow dynamics in the sinuses of Valsalva on coronary flow was recently demonstrated by Miller and colleagues²¹ for patients who had undergone aortic valve repair with different techniques of T. David⁴ operations. Therefore not only the quantity of the pressure gradient but also the quality of transvalvular flow is important for coronary artery flow. Preserved annular flexibility was the main difference between our 2 study groups; this design feature allows active dilatation of the annulus, at least to an extent closer to normal physiology compared with a stented valve. Active annulus motion and its effect on flow dynamics has recently been demonstrated by Duran's group.²²

A superior hemodynamic performance in combination with increased coronary artery flow and a normal flow reserve might contribute to the observed lower midterm mortality that has been reported for stentless valve designs.²³

As a major result, this study draws attention on the influence of the type of aortic valve prosthesis on coronary perfusion. This property should be included in investigations regarding the hemodynamic performance of mechanical and biologic valve prostheses in the future and its effect on late myocardial morbidity and survival rates.

There are some limitations in this study. In this pilot project we have included a small number of patients. Other limitations are the relatively short duration of follow-up and, in part, the negative effect of postoperative arrhythmia on MRI quality postoperatively. Atrial fibrillation at the time of MRI scanning was present in 3 patients in the stentless group and 2 patients in the stented group, and rate control was achieved in all patients before the MRI scan by using antiarrhythmic medication. Fortunately, these patients did not demonstrate arrhythmias at the follow-up examination.

From the surgical perspective, longer follow-up periods and a larger number of patients are necessary to purport any long-term advantage of better flow pattern and higher flow velocity in different valve substitutes.

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