

Prospective Evaluation of Aortic Valve Replacement in Young Adults and Middle-aged Patients: Mechanical Prosthesis versus Pulmonary Autograft

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Background and aim of the study: The best option for aortic valve replacement (AVR) in young adults and middle-aged patients remains controversial. A longitudinal comparison between the Ross procedure (RP) and mechanical prosthesis (MP) was conducted in this group of patients.

Methods: Between January 1997 and January 2003, 125 consecutive patients (age range: 20-50 years) were submitted for AVR; 62 patients (mean age 37.73 ± 7.28 years) were included in the MP group, and 63 (mean age 35.33 ± 7.63 years) in the RP group. Gender, etiology, NYHA functional class and other preoperative data were comparable between the two groups.

Results: The operative mortality was four (6.5%) in the MP group, and one (1.6%) in the RP group ($p = \text{NS}$). The postoperative complication rate was similar in both groups. Two RO patients required early autograft replacement due to severe regurgitation. There were no late deaths during the follow up period. In the MP group, three patients (4.8%) suffered major bleeding, three (4.8%) were diagnosed with prosthet-

ic endocarditis (one required reoperation), and three (4.8%) suffered valve- or coumarin-related thromboembolic complications. All RP patients were free from bleeding, thromboembolic, or infectious complications, but three suffered severe pulmonary homograft stenosis (one re-replacement, one Palmaz stent, and one under clinical surveillance). The combined freedom from death or major complications was $64.72 \pm 4.3\%$ in the MP group, and $87.92 \pm 9.65\%$ in the RP group ($p = 0.068$).

Conclusion: Intraoperative and early postoperative morbidity and mortality rates were similar among RP and MP patients, despite a steep learning curve during the early RP cases. Although the follow up was limited, and homograft-related morbidity was seen in the RP group, the overall five-year major complication rate supported use of the pulmonary autograft for AVR in patients aged between 20 and 50 years.

The Journal of Heart Valve Disease 2005;14:40-46

Although the Ross procedure (RP) is considered to be the most suited intervention for aortic valve replacement (AVR) in children (1), and in women who wish to bear a child after the operation (2), the recommendation for young adults and other age groups is not uniformly accepted (3).

Since its first description by Donald Ross in 1967 (4), the pulmonary autograft has been shown to provide several advantages, including the avoidance of anticoagulation, resistance to infection, outstanding hemodynamics, and silent performance (5-7). These

characteristics make the pulmonary autograft a good candidate for what has been called the 'ideal valve' (8). However, although the pulmonary autograft conforms well with accepted standards for prosthetic heart valves (9), it is not the perfect solution, for several reasons. First, the Ross procedure converts a single-valve disease into two-valve surgery; second, it is technically complex; and third, concerns have been expressed about the long-term performance of the pulmonary autograft and pulmonary homograft, mainly with regard to dilatation and regurgitation for the former, and stenosis of the latter.

Mechanical prostheses have been used for many years, and have evolved technically to become the most widely used valve substitute in younger patients. Consequently, there is a widespread experience with many thousands of implants having been made worldwide, the prostheses are less thrombogenic than in the past, their hemodynamics - though not perfect - have

Presented as a poster at the Second Biennial Meeting of the Society for Heart Valve Disease, 28th June-1st July 2003, Palais des Congrès, Paris, France

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improved substantially, and their implantation is both simple and reproducible. However, as anticoagulation is necessary after mechanical prosthesis implantation, young patients with a long life expectancy will be exposed to a high cumulative risk of bleeding and thromboembolic complications. Moreover, the hemodynamics of mechanical prostheses are not perfect, and their resistance to infection has been questioned.

Although many clinical series have reported the results of both options separately, to the present authors' knowledge only one formal comparison between the Ross procedure and mechanical prosthesis use has been published previously (10). The present clinical study was initiated to compare the mortality and morbidity of AVR performed at the authors' institution in patients aged between 20 and 50 years during the past five years, using both surgical approaches.

Clinical material and methods

Patients

Between 1997 and January 2003, young adults submitted for isolated AVR were included into either a Ross procedure (RP) or a mechanical prosthesis (MP) group in non-randomized fashion. Before performing the statistical analysis, the groups were matched for age, gender and duration of follow up; consequently, the total study group comprised 125 patients.

Valve implantation

All patients in the RP group (n = 63) were operated on according to the free-standing root technique (the so-called modified RP) which was described previously (11). Among the MP group (n = 62), six patients received a valved conduit (Carbo-Seal; CarboMedics, Inc., Austin, TX, USA); 32 received a CarboMedics valve (Sulzer Carbomedics, Inc., Austin, TX, USA), and 24 received a St. Jude Medical Regent valve (St. Jude Medical, Inc., St. Paul, MN, USA).

Both preoperative and perioperative data were

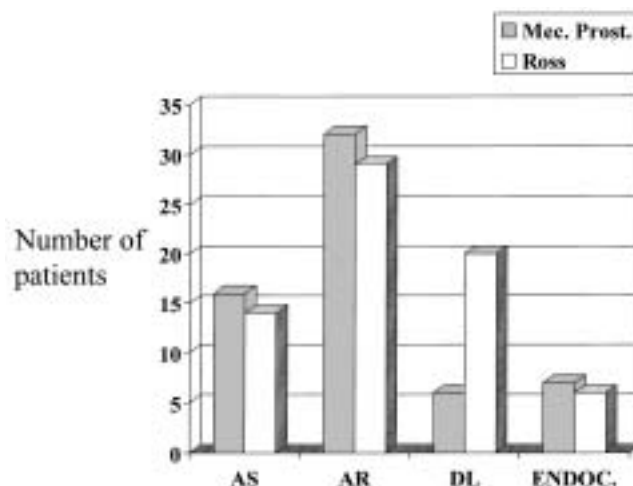


Figure 1: Incidence of the primary aortic lesion in the Ross procedure (Ross) and mechanical prosthesis (Mec. Prost.) groups. DL: Double lesion; ENDOC: Acute endocarditis; AR: Aortic regurgitation; AS: Aortic stenosis.

included in the database, and the patients were followed clinically at six and 12 months, and yearly thereafter.

Statistical analysis

Comparisons were made using the chi-square test and Student's *t*-test. Time-related events were analyzed using the Kaplan-Meier method and the log-rank test.

Results

The preoperative data were comparable between groups with regard to age, gender, etiology, ejection fraction, and type of aortic lesion (Table I; Figure 1). Three patients were operated on within 24 h of hospital admission in the MP group, compared with none in the RP group (p = NS). In the RP group, 15 patients had suffered at least one previous intervention (percutaneous valvuloplasty in six patients, open valvuloplas-

Table I: Preoperative characteristics of patients undergoing mechanical prosthesis implantation or the Ross procedure.

Variable	Mechanical prosthesis	Ross procedure	p-value
Age (years)*	37.73 ± 7.28	35.33 ± 7.63	NS
Gender ratio (M:F)	47:15	49:14	NS
NYHA class*	2.16 ± 0.81	2.53 ± 0.64	NS
EF (%)*	58.2 ± 1.3	63.2 ± 7.1	NS
Emergency surgery	3	0	NS
Endocarditis	7	9	NS

*Values are mean ± SD.

EF: Ejection fraction; NS: Not significant.

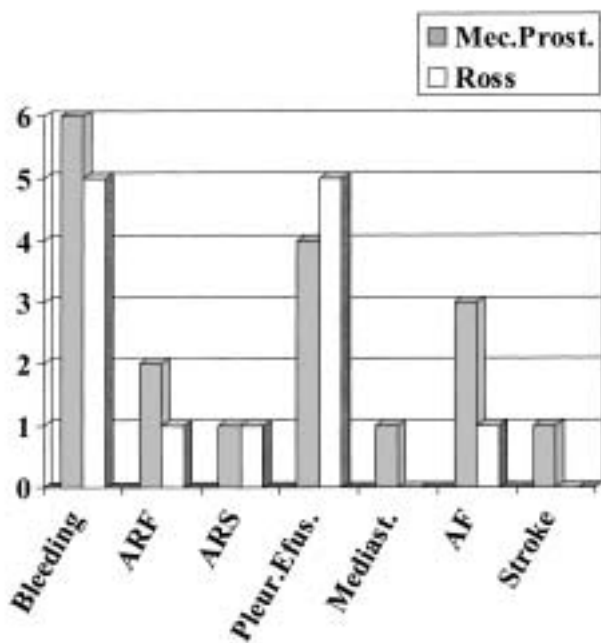


Figure 2: Numbers of postoperative complications in the two patient groups. AF: Atrial fibrillation; ARF: Acute renal failure; Bleeding: Re-exploration for bleeding; Mediast.: Mediastinitis; Pleur.Efus.: Pleural effusion; RDS: Respiratory distress syndrome; Stroke: postoperative neurological deficit.

ty in four, subvalvular resection in two, previous AVR in one patient and prior mitral valve replacement in one). In the MP group, nine patients had undergone a previous intervention (five with previous AVR, one percutaneous valvuloplasty, one mitral plasty and two open aortic valvuloplasties).

With regard to perioperative data, four patients died postoperatively in the MP group. One of these patients suffered a fatal stroke on the day before discharge, two patients died due to sepsis (one pneumonia, one mediastinitis), and one patient who required subaortic myectomy could not be weaned from cardiopulmonary bypass (CPB). In the RP group, one patient (a 43-year-old with acute endocarditis) died as a result of sepsis on the seventh postoperative day in the intensive care unit.

The extracorporeal circulation times (99.2 ± 25.6 versus 156.6 ± 35 min; $p < 0.001$) and cross-clamp times (60.2 ± 10.1 versus 110.4 ± 12.2 min; $p < 0.001$) were significantly longer in the RP group than in the MP group. Nine patients required associated procedures in the MP group compared with 15 in the RP group ($p < 0.05$), the most common being annuloplasty, aortoplasty and Dacron extension of the autograft.

As expected, due to the longer extracorporeal circulation times and the presence of up to seven arterial anastomoses, postoperative bleeding was less in the

MP group (709.0 ± 76.2 ml) than in the RP group (857.5 ± 112.1 ml) ($p < 0.05$). However, this did not result in more re-explorations for bleeding in the MP group ($n = 6$; 9.7%) than in the RP group ($n = 5$; 8.6%) ($p = \text{NS}$).

In terms of other perioperative complications, one RP patient required one aortocoronary bypass to the descending anterior artery in order to be weaned from CPB, and one MP patient suffered a postoperative myocardial infarction but recovered without significant ventricular damage. Other perioperative morbid events are depicted in Figure 2.

Follow up

The mean follow up was 30.46 ± 19.19 months, and 100% complete in both groups. There were no late mortalities in either group.

Two patients required autograft replacement with a mechanical prosthesis in the RP group at nine and 13 months, respectively. Perioperatively, both patients had mild to moderate aortic regurgitation that progressed to severe status after discharge. However, these patients were among the first six cases of the series, and the problems were attributed to technical problems encountered during the learning curve of the study. One 40-year-old male developed significant autograft dilatation (43 mm) at the neo-sinus level, and had associated moderate to severe aortic regurgitation. It is probable that this patient will require reoperation in the near future.

With regard to homograft function, the mean transvalvular gradient during follow up was 18.3 ± 7.2 mmHg. Three patients (4.7%) developed severe homograft stenosis (>50 mmHg by echo-gradient). One of these required percutaneous homograft dilatation and Palmaz stent placement, and one required homograft replacement due to progressive dyspnea (NYHA class II). The explanted homograft was not calcified, but was very retracted; microscopic evaluation showed intense fibrosis and an absent endothelium. Echo re-exploration of these two patients six months later showed residual gradients of 25 and 31 mmHg, respectively. The third patient had a 65 mmHg trans-homograft gradient and is currently under close clinical surveillance.

There were no cases of endocarditis in the RP group, but three MP patients (4.8%) developed postoperative endocarditis. One of these infections was early (<1 month), and two were late, and due to *Streptococcus viridans*. One of these patients developed an aortic root abscess after a Bono-Bentall operation, and required root re-replacement with a cryopreserved aortic homograft.

Among thromboembolic complications, one MP patient suffered a stroke (INR of 1.7), one a transient ischemic attack, and another two patients had episodes of amaurosis fugax which were considered to

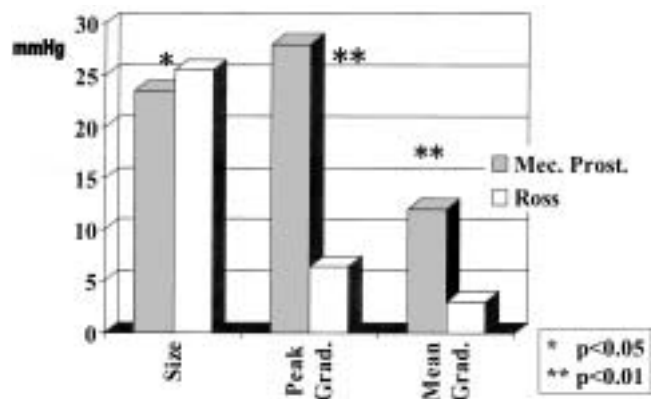


Figure 3: Left columns: Intraoperative size of the Ross autograft and mechanical prosthesis. Right columns: Echocardiographic peak and mean transvalvular gradients at the last follow up.

be of embolic origin. All three cases required hospital admission. Although not valve-related, one MP patient suffered a subclavian vein thrombosis. No thromboembolic complications were registered in the RP group.

Bleeding complications were reported in several MP patients. One patient suffered recurrent upper gastrointestinal bleeding that required multiple transfusions; another suffered intractable bleeding which required cystic artery coil embolization. One patient had a macroscopic hematuria, and one female patient suffered severe metrorrhagia. Three of the last four patients had an INR >3.5. In addition, two patients required emergency room evaluation due to minor complications of epistaxis and subconjunctival hemorrhage.

In the RP group, all patients were free from bleeding complications, though one 35-year-old male required hospital admission due to an active gastric ulcer that healed without bleeding.

In total, 59 patients (93.6%) in the RP group underwent an echocardiographic examination during the previous three months, compared with only 40 patients (64.5%) in the MP group; this difference was due to logistic problems.

Although at present the data are incomplete, there were significant inter-group differences with regard to transvalvular gradients (Fig. 3). Among the 40 postoperative echocardiograms reviewed (at between 3 and 49 months after surgery), three patients (4.8%; two females, one male) had transvalvular peak gradients >50 mmHg, and two of them had undergone reoperations. The prosthesis sizes of these patients were 19, 21 and 23 mm.

It is important to note that the autograft diameter was greater than the MP size at the time of implanta-

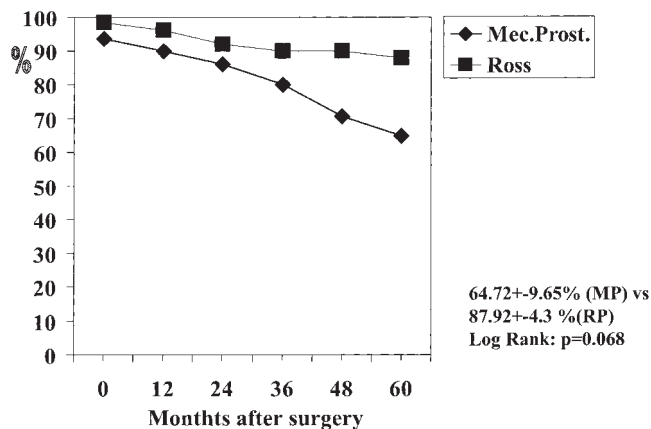


Figure 4: Freedom from major adverse events (%) after implantation of the mechanical prosthesis (Mec.Prost.) or autograft (Ross).

tion (25.45 ± 2.29 mm in the RP group versus 23.49 ± 2.33 mm in MP group; $p < 0.01$). Considering that the effective orifice area of the autograft was likely to be greater than that of any annular-matched stented prosthesis, the possibility of patient-prosthesis mismatch was minimal in RP patients.

By considering all major adverse events, including death, reoperation or reintervention, major hemorrhage, endocarditis, major thromboembolism and severe valvular dysfunction, it was possible to compare the freedom from a negative outcome after AVR. In the present study, $64.72 \pm 9.6\%$ of MP patients and $87.92 \pm 4.3\%$ of RP patients were free from valve-related mortality or morbidity ($p = 0.068$; Log rank test).

Discussion

The search for the perfect valve substitute began with the history of cardiac surgery itself. Initially, the Ross procedure was considered to be only an experimental choice, and was not accepted by most cardiologists and surgeons until publication of the pioneer series in *Circulation* in 1997 (7).

However, in the American Heart Association Practice Guidelines, the pulmonary autograft is considered to be a valuable choice, especially in children and women of child-bearing age, because of its ability to grow, excellent durability, and avoidance of anticoagulation (2,12).

Although the pulmonary autograft copes with the FDA regulations for valve prostheses, the choice remains controversial, especially in adult males. Previous investigations have usually been small and non-comparative (13), the amount of experience in the long term has been limited (complete follow up has not been achieved in the International Registry) (3,14),

and some authors consider that adult patients with bicuspid aortic valves might have a greater risk of autograft dilatation, though this has not been proven (15). In fact, older patients fare better than their younger counterparts because rejection of the pulmonary homograft is less frequent (16).

The hemodynamic performance of the pulmonary autograft is expected to be superior to that of prosthetic valves, approaching a zero transvalvular gradient (17). Therefore, although no formal comparison has been made, exercise tolerance is expected to be better (18), making the pulmonary autograft the most suited procedure for patients who have an active lifestyle and/or are engaged in sports.

Resistance to infection is also expected to be superior because prosthetic material can be avoided in most cases. Technically, the versatility of the pulmonary autograft makes it a very interesting option in cases of complex aortic root abscess. Finally, the pulmonary autograft has shown to be cost-effective (19).

The pulmonary autograft is not the perfect solution, however. Although complexity of the procedure and longer pump and ischemic times are expected to increase periprocedural morbidity and mortality, this was shown not to be true in the present study, and the incidence and nature of perioperative complications were similar between groups. The long-term performance of the pulmonary autograft and the homograft remains a subject of concern. In the International Registry (14), the pulmonary autograft explant rate was 1.9%, while the rate of pulmonary homograft revision was between 2.8% and 1.3% in the latest period. Most studies have reported that the pulmonary autograft behaves well under systemic pressure and, although some dilatation occurs, few reach worrisome diameters and valve competence remains unaffected (20).

Early failures were most often related to the surgeons' learning curve, and indeed in the present authors' experience the two cases of reoperation occurred among the first six patients treated. Further confidence with the procedure and the incorporation of important technical modifications to prevent geometric mismatch between the aortic annulus, the autograft and the ascending aorta (21), have improved the present results. In fact, only two patients left the operating room with a mild aortic regurgitation, while others showed either perfect competence or trivial insufficiency.

Blood pressure should be controlled to levels below 135/85 mmHg, though no formal study has been made in this respect.

In the present study, homograft failure required re-intervention (surgical or interventional) in two cases, and proved to be severe in one more patient. The aver-

age size of the implanted homografts was 24.9 ± 2.8 mm (range: 22 to 35 mm). At implantation, the homografts were kept as short as possible (matched to the length of the explanted autograft). In these patients, right ventricular function was strictly normal, but cardiac magnetic resonance imaging (MRI) showed a mild to moderate right ventricular hypertrophy. As detailed in a recent report by Aranda et al. (24), these findings suggest that homograft stenosis is clinically and 'anatomically' very well tolerated unless a very high gradient develops (i.e. >100 mmHg). In order to evaluate if a sustained afterload might damage the right ventricle in the long term, and especially if gradients continue to rise, an annual cardiac MRI is performed in all patients who develop a gradient >30 mmHg. Risk factors for homograft stenosis have included, among others, younger age of the donor, shorter time of preservation and HLA mismatch (22,23). Current studies being conducted at the present authors' institution include an exploration of the role of blood transfusions as risk factors for homograft dysfunction (24).

In contrast, MPs are under continuous evolution, require less anticoagulation, and their hemodynamic performance - though not perfect - is improving even in the small-sized valves. The most important experience acquired with thousands of patients and long follow up indicates that MPs are easy to implant, and that the technique is reproducible. Indeed, today the structural failure of MPs can be considered as zero. Unfortunately, the need for chronic anticoagulation involves a significant hazard, and in patients with a long life expectancy the risk of bleeding (2.2-2.7% per patient-year) and thromboembolic complications (1.8-4.1% per patient-year) (25,26) may represent a considerable cumulative risk. In addition, when a prosthetic device is inserted there is a greater risk of infection in the setting of bacteremia ($\sim 0.42\%$ per patient-year in all age groups) (27). However, a recent report in the *Journal of Heart Valve Disease* by Aagaard et al. (28) in 55 patients aged 15-50 years with the CarboMedics prosthesis showed excellent results at 14 years, with an actuarial freedom from all valve-related events of 92.37%.

The need for regular check-ups, a daily dependence on medication (with associated problems of patient compliance), and the audible valve sound reported by some patients have proven to provide a poorer quality of life in MP patients as compared to those with a pulmonary autograft (9,29).

The results of the present study reflected the authors' clinical experience. The incidence of endocarditis, thromboembolic and hemorrhagic complications was higher than expected. Patients take coumarin to maintain the INR at 2-3, with coagulation tests being per-

formed every three to four weeks. At discharge, all patients receive a standardized written protocol about self care with regard to endocarditis prophylaxis and anticoagulation management. In addition, the authors' hospital covers a large area with a wide spectrum of rural towns - a fact that might have influenced the results to some extent.

Although the differences did not reach statistical significance, it is important to note that in the RP group there were no cases of endocarditis, thromboembolic or hemorrhagic complications. Despite the previous assumption that the Ross procedure would yield more adverse events, the perioperative mortality and morbidity was similar between the groups.

Although incomplete, the echocardiographic results highlighted some important points. Two patients had autograft regurgitation and required autograft replacement; one showed dilatation of the autograft with moderate regurgitation; and the remainder showed either trivial or perfect competence. The trans-autograft peak gradient was 6.45 ± 3.5 mmHg, and the mean gradient 4.01 ± 2.0 mmHg. In the MP group, three patients showed mild perivalvular leakage, and four of the 40 patients studied had a moderate to severe residual stenotic gradient. Since the year 2000, the present authors have used cardiac MRI to follow up adult RP patients. It is believed that this new technology will provide additional information from which predictions can be made as to which patients would benefit more from a pulmonary autograft (30).

Study limitations

Although prospective in its design, the present study was non-randomized and, by definition, not blinded. The study was intended initially to include patients aged between 14 and 55 years, but patients aged <20 years were treated consistently with the RP, and only one has received a mechanical prosthesis during the past five years. By contrast, patients aged >50 years were most likely to receive a MP, and very few received a pulmonary autograft. Thus, the groups were targeted at the 20- to 50-year-old patient segment. In this way, although the mean age in the MP group was slightly higher, the difference was not statistically different. The cumulative follow up was also slightly less in the MP group as surgeons became increasingly confident with the RP and treated more patients in this way during the second half of the study; this difference was not statistically significant, however. A further limitation was that the MP group included patients with three types of commercially available device, and this may have biased outcomes. Finally, it must be appreciated that the number of patients was limited and that the longest follow up was only five years. Consequently, future data obtained after 10 or 15 years

of experience will be more consistent, notably with regard to autograft and homograft performance in the long term.

In conclusion, the present study - despite its limitations - is one of the first to compare the two accepted options for AVR in this particular age group. Although non-randomized, the preoperative data were similar and follow up was comparable. The results of the study showed that despite longer operative times, postoperative morbidity and mortality was not higher in the RP group. In addition, the five-year incidence of endocarditis, thromboembolic and bleeding complications was probably higher in the MP group. Although the data were not 100% complete, the hemodynamic performance of the pulmonary autograft was superior to that of the mechanical prosthesis in general, and this was expected to enhance left ventricular recovery. The combined adverse event rate at five years was similar between groups, with a clear trend towards better results in the RP group. Based on these available data, patients aged 20 to 50 years should have the option to receive a pulmonary autograft. This must be stressed in the cases of contraindications for anticoagulation, endocarditis, patients with a high level of physical activity and, as previously established, in women who wish to bear a child in the future.

The future completion of this study will doubtless result in the acquisition of more reliable and consistent data. The quality of life assessment, complete echocardiographic follow up, and the 10-year results will most likely indicate, with a high level of confidence, which is the best option for AVR in this subset of patients.

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