Early Structural Valve Deterioration of Mitroflow Aortic Bioprosthesis

Running title: Kaneko et al.; Early SVD of Mitroflow Bioprosthesis

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Journal Subject Code: Cardiovascular (CV) surgery:[35] CV surgery: aortic and vascular disease

Key words: Editorial, aortic valve, bioprosthesis, valve replacement
There has been a trend toward more frequent use of bioprosthetic valve, especially in the young generations, over the last decade.\textsuperscript{1,2} From the Society of Thoracic Surgeons database, the use of bioprosthetic valve has increased from 44\% in 1996 to 78\% in 2006 in North America.\textsuperscript{1} Freedom from warfarin, restrictions on diet and activities makes bioprosthetic valves more attractive and popular, and multiple reports have shown that choosing bioprosthetic valve does not decrease survival despite the increased rate of reoperation.\textsuperscript{3,4}

Mitroflow aortic prosthesis (Sorin Group Inc) is one of the most frequently used bioprosthesis, with over 100,000 implanted worldwide.\textsuperscript{5} The bovine pericardium is mounted externally around the stent, which maximizes the flow relative to the stent size. The valve is placed in supraannular position compared to intraannular position in some of the other bioprostheses. These characteristics allows superior valve hemodynamics in Mitroflow aortic valve especially in small aortic annulus (19mm and 21mm)\textsuperscript{6}, therefore considered an ideal valve for the small aortic root patients.

The Achilles heel of bioprosthetic valve is structural valve deterioration (SVD). Cusp tears and thickening, calcification, pannus formation and thrombus lead to deterioration of the valve\textsuperscript{7} which is the leading cause for reoperation in bioprosthetic valves. The rate of SVD differs among ages; valves implanted in younger patients degenerate faster. For patients over age 65, the 10-year freedom from SVD in new pericardial valves is typically over 90\%.\textsuperscript{8}

In this issue of \textit{Circulation}, Sénage et al.\textsuperscript{9} strikes a note of warning against the Mitroflow aortic valve. Some of the previous reports have shown 99\% 5-year freedom from SVD in Mitroflow valve\textsuperscript{6,10}, but in this report 5-year freedom from SVD was 91.6\% and 79.8\% when 19mm Mitroflow was used. The follow up time was short (3.8±2.0 years), but the first SVD was observed only 14 months after the implantation. The cumulative provability of SVD increased.
significantly from 0.8% in 2-years to 8.4% in 5-years. Most of this early SVD was caused by calcified prosthetic stenosis (92%) rather than tear of the leaflet or regurgitation. Small diameter prosthesis (19mm and 21mm) was used in 64.2% of patients, and was a significant risk factor for SVD in both univariate and multivariate analysis. This raises a high concern since Mitroflow has been considered ideal valve in the small root patients as mentioned earlier.

This is not the first report which questioned Mitroflow aortic valve’s durability. Alvarez reported their series of 491 patients over age of 70 who received Mitroflow aortic bioprosthesis.11 Freedom from SVD was 95% in 5 years but acutely dropped to 55.8% in 10 years. The median time from operation to SVD was 48 months. Joshi et al reported 3.6% incidence of early SVD within 6-years requiring reoperation in patients under age 60 that had Mitroflow aortic valve implanted.12 These numbers are high compared to the historical numbers for other pericardial valves. One study showed higher incidence of SVD in Mitroflow group compared to Carpentier-Edwards Perimount valve (Edwards life science, Irvine, CA) at 10-years (44% vs 13%).13 Interestingly, age, which typically is one of the most important factor for SVD, did not have any significance in this report. The high incidence of early SVD of Mitroflow was seen in both young and the elderly population.

In the report by Sénage et al., one third of patients had experience SVD presented in a fashion which the authors describe as “accelerated SVD”. This was defined by increase of mean valvular gradient greater than 25mmHg/year. Recently, Saleeb et al has reported this accelerated degeneration of Mitroflow in young patient population under the age of 30.14 Freedom from valve failure was 53% in 2-years and 18% in 3-years in this series. Life threatening SVD was detected at a median of 6 months after normal or mild gradient on previous echocardiogram. Pathological examination showed that intrinsic calcification causing valve fixation was the main
cause for this accelerated degeneration. Sénége’s report gives us more insight to this phenomenon; accelerated SVD was seen more in small aortic prosthesis (76.9%) and patients with prosthesis gradient more than 30mmHg. This subgroup had 46.2% valve-related death after the occurrence of accelerated SVD. SVD had the strongest correlation of mortality with an increased risk of death of 7.7. This highlights the importance of frequent monitoring with echocardiogram in patients who has small prosthesis and gradient over 30mmHg across the bioprosthesis. Given these data, echocardiogram surveillance should be performed 6 months or less, for early detection.

Another important finding in this paper was the underreported incidence of SVD. In many reports, SVD is reported as rate of reoperation and explantation of the old prosthesis. This underestimates the incidence of SVD, since many patients may develop SVD but only few may receive surgical treatment. In this series, echocardiogram was used to follow these patients and increased gradient or valve insufficiency were used as criteria for SVD. Only 10.3% of patients with SVD underwent reoperative AVR. 11.4% died suddenly and another 11.4% died while they were on the waiting list. There is a question to why 51.4% did not get referred to surgery, but this shows the underreported incidence of SVD if reoperation alone was used as criteria.

The externally mounted pericardial valve poses problem for valve-in-valve transcatheter solutions. Because of the internal diameter of Mitroflow valve being only 15.4mm for 19mm valve and 17.3mm for 21mm valve, currently no transcatheter valve is recommended due to likelihood of postprocedural gradient.15 There is also a concern for coronary obstruction when valve-in-valve is performed due to the externally placed valve leaflet pushing into the ostium.16 For these reasons, reoperation for small Mitroflow SVD likely has to be done through traditional surgical approach. This report does not provide the presence of symptoms at the time of
diagnosis of SVD, however, given the poor outcome of these patients reoperative aortic valve surgery or transcatheter procedure for high-risk non-small annulus patients should be offered when diagnosis of SVD is made, even if the patient is asymptomatic.

This early SVD could be attributed to the absence of antimineralization treatment in older generation Mitroflow aortic valve. Flameng at al compared the incidence of SVD in valves with and without antimineral therapy. There was an increased incidence of SVD (70.1% vs 90.9% 10-year freedom from SVD) in valves without antimineralization therapy.17

Mitroflow A12 was introduced in 1992. This model was modified from the original Mitroflow A11, by reversing the external cloth so that the ribbed side was external. This valve was used widely in Europe and Canada, and was subsequently approved in the United States in 2007. The Mitroflow LX is a variation of A12 and had minor revisions such as use of automatic sewing machine, reduction of sewing ring seam to one and prefixation by glutaraldehyde rather than postfixation.18 Both Mitroflow A11/12 and Mitroflow LX does not undergo antimineralization treatment. Most recent modification, Mitroflow with phospholipid reduction therapy (PRT) added this step. This chemical process uses long-chain alcohol solution to remove phospholipids from the tissue. This new valve was approved for CE marking in 2011 in Europe, and just recently in April 2014, was approved by the Food Drug and Administration (FDA) in the United States.19

Although antimineralization treatment still is a hypothetical explanation for the accelerated degeneration seen in Mitroflow valve, this reports warns potential epidemic of SVD in patients who had Mitroflow A12 and LX implanted. It is unclear whether Mitroflow with PRT will be able to prevent this type of SVD, but this is a separate issue. Monitoring patients who received older generation Mitroflow with frequent echocardiography is mandatory to prevent
undesired complication, especially in a high risk patient. Aggressive treatment is needed even in asymptomatic patients once the gradient reaches severe.

**Conflict of Interest Disclosures:** None.

**References:**


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Circulation. published online October 29, 2014;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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