

Session 1:

Searching for a Correct Method of Evaluation for Valve Prosthesis Performance

Laboratory Assessment

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Valve replacement is established as a definitive treatment for valvular lesions. Nevertheless, heart valve substitutes are not entirely safe, and therefore the prosthesis-related intrinsic risks must be outweighed by patient benefits. Market release of new heart valve substitutes is authorized after the completion, with positive results, of extensive in-vitro and in-vivo testing to confirm the suitability for clinical application in patients.

Nowadays, although careful regulatory in-vitro evaluation is performed on most heart valve substitutes, including both tissue and mechanical prostheses, two important categories of heart valve substitutes - autografts and homografts - do not undergo pre-market evaluation.

Since the first clinical report of the Ross procedure, the technique has been applied worldwide, particularly during the past three decades. Today, the procedure is performed in more than 120 heart surgery Institutions. The rationale for use of autologous pulmonary valve for aortic valve replacement is its similarity to the aortic valve, as well as its viability and absence of antigenic properties, with the possibility of remodeling following implantation. The only chance of pre-implantation evaluation of the pulmonary autograft that is used to replace the diseased aortic valve is

limited to an echocardiographic functional assessment.

As far as pre-market quality assessment of homografts is concerned, quality control of harvesting, sterilization and preservation techniques are currently performed by the individual homografts banks. Therefore, there is lack of uniformity regarding mechanical characteristics of individual valves. Studies performed by single institutions on the mechanical behavior of cryopreserved aortic and pulmonary homografts are not reproducible (1).

Both biological and mechanical prostheses are subjected to an extensive pre-market in-vitro evaluation, which is regulated by different International Standards: ISO 5840, CEN and FDA guidance. ISO (International Standards Organization) 5840 (Cardiovascular Implants) prescribes guidelines for specific fatigue test methods for heart valve substitutes. The European Community (CE) marketing approval, defined in CE medical devices directive developed in 1993, is testified by CE marking of conformity or 'CE mark'. The FDA guidance document for the submission of marketing approval request was issued in 1993, and revised in 1994 by the Division of Cardiovascular, Respiratory and Neurological Devices.

Two laboratory testing levels are currently used. Basic material testing is intended to test the mechanical, physical and chemical properties of the heart valve device, as well as its biocompatibility. The 'gold standard' of laboratory testing is represented by the steady flow test, pulsatile flow test and wear test. The steady flow is the simplest test which can provide information on valve performance, but does not allow the testing of

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prostheses at different heart rates or cardiac outputs. The pulse duplicator is a system for pulsatile hemodynamic testing of heart valve prostheses, in which a pump generates a flow that, through the mitral valve, enters the model ventricle and is directed toward the aortic valve. A compliance chamber and downstream restriction act as systemic resistance (fixed component). Heart rate, cardiac output and the additional variable component of systemic resistance can be regulated by the user (2). During wear testing, at the peak transvalvular pressure required by the Standards, valves are cycled (the cycle number corresponds to a determined real time) in a distilled water test fluid at room temperature. Surface lesions such as scratching and cracking are visually investigated at regular million-cycle intervals. At longer million-cycle intervals, valves can be studied by using scanning electron microscopy and laser surface scanning, after removal from the apparatus (3).

Ideally, the in-vitro testing should obtain the following results: (i) the site of fatigue as shown in vitro should correspond to the wear site in vivo; (ii) the valve components showing failure in vitro should be responsible for in-vivo failure; and (iii) valve durability in vitro should be similar to durability in vivo. This is not true for currently performed laboratory tests, that show many limitations. First, there is no uniformity in the guidelines required by the three major Standards. According to accelerated wear tests, both test conditions - such as pressure difference across the closed valve and cycle numbers - differ widely; for example, a 75 mmHg pressure difference across the valve is prescribed by ISO 5840, while the FDA guidance recommends a maximal pressure difference of 110 mmHg for the aortic valve and 140 mmHg for the mitral valve. Reul and associates showed that tests performed with two different devices on a single 29-mm Björk-Shiley concave-convex valve at the same given standard conditions produced different loading conditions in vitro. Furthermore, the impact of valve loading could not be reproduced in vivo in a sheep model. The results of this experimental study suggested that in-vitro testing has no absolute value, and that valve loading conditions should be evaluated either in vivo or in a system mimicking physiological conditions, such as a mock circulatory loop (4).

The ability, by the use of bench testing, to predict structural failure in the clinical setting is questionable. Iwasaki and associates (5) tested a polymer valve usually employed in artificial hearts (Jellifish valve), in attempting to identify an ideal methodology to test heart valve prosthesis durability. Fracture patterns documented in vitro were compared with those demonstrated in vivo in an animal experiment, showing different outcomes in the two models (membrane

fractures localized at the spoke edge, and between adjacent spokes, respectively). The discrepancy in results questions the clinical relevance of in-vitro failure (5).

King et al. (6) performed laboratory real-time wear testing on three types of mechanical heart valve prostheses (St. Jude Medical, CarboMedics and Sorin Bicarbon) in order to document surface and wear damage within the pivots. After one million cycles (corresponding to a real time of less than two weeks), the pyrolytic coating was worn away in the pivots of all the Sorin Bicarbon valves examined. On the other hand, the St. Jude Medical and CarboMedics valves showed areas of surface roughness only at the hinge recess level. Even if the test documented evident loss of pyrolytic coating within Sorin Bicarbon pivots, the impact of such abnormalities is practically nil in vivo (6).

The Medtronic Parallel valve is sadly known for post-market failure due to thromboembolism. Ellis and colleagues studied the retrograde flow fields of this bileaflet mechanical valve: in comparison with the St. Jude Medical valve, the turbulent fluid stresses generated by retrograde flow were twice as elevated in the Medtronic Parallel valve, suggesting a possible correlation with the in-vivo failure, due to damage to formed blood cells. These results in this case provide predictive significance to the test (still not available at Medtronic Parallel pre-marketing testing) (7).

The unsuitability of laboratory testing emerged clearly with the reported cases of post-market failure consisting of thromboembolism (Medtronic Parallel) or in leaflet escape due to strut fracture, which has been reported for both monoleaflet valves (Omnicarbon, Björk-Shiley convexo-concave) (8,9) and bileaflet valves (Edward-Duromedics, TRI technologies) (10,11). On the other hand, this lesson from the past was useful to generate awareness in both the manufacturers and users of potential catastrophic complications related to prosthetic valve implantation. This awareness led to increased timely identification and efficient management of catastrophic valve-related events. During the early 1980s, 100 Björk-Shiley valves could fail before an adequate action of market removal. In the 1990s, after the documentation of three thromboembolic events, Medtronic interrupted the experimental clinical evaluation of the Parallel valve. In 2002, the death of a single patient who had received a TRI Technology prosthesis led to the immediate discontinuation of TRI technologies valves in clinical use (11).

Among several proposals, we believe that the following should become essential guidelines for good practice when facing the release of new heart valve substitutes, though several different options are available:

- Standards of pre-market testing guidelines need to be uniform.
- Any positive and negative information must be shared by valve manufacturers, independent research laboratories and clinical users.
- Patient follow up and data collection are mandatory by the individual Institutions, National/International Scientific Societies and Manufacturers.

The immediate notification of catastrophic events to the scientific community is mandatory; at the same time, the scientific community itself has a unique responsibility in spreading early information. The same priority has been recognized in our report on the occurrence of leaflet escape of TRI Technology valves that has been promptly published by the journal *Circulation* as rapid track. Finally, manufacturers should guarantee the ability to handle catastrophic events such as structural failure, in terms of prosthesis tracking, patient recall, and internal processing control.

References

1. Vesely I, Casarotto D, Gerosa G. Mechanics of cryopreserved aortic and pulmonary homografts. *J Heart Valve Dis* 2000;9:27-37
2. Razzolini R, Gerosa G, Leoni L, Casarotto D, Chioin R, Dalla Volta S. Transaortic gradient pressure-dependent in a pulsatile model of circulation. *J Heart Valve Dis* 1999;8:279-283
3. Elizondo D, Boland ED, Ambrus J, Kurk JL. Mechanical characteristics valve prostheses: Wear characteristics and magnitudes in three bileaflet valves. *J Heart Valve Dis* 1996;5(Suppl.I):S115-S123
4. Reul H, Eichler M, Potthast K, Schmitz C, Gunther R. In vitro testing of heart valve wear outside of the manufactures laboratory-requirements controversies. *J Heart Valve Dis* 1996;5(Suppl.I):S97-S104
5. Iwasaki K, Umezu M, Iijima K, Imachi K. Implications for the establishment of accelerated fatigue test protocols for prosthetic heart valves. *Artif Org* 2002;26:420-429
6. King MJ, Olin L, Fisher J. An initial investigation into wear and damage within the pivots of three types of bileaflet mechanical heart valves. *J Heart Valve Dis* 1996;5(Suppl.I):S111-S114
7. Ellis JE, Fontaine Weston W, Jarret CA, Saxena R, Yoganathan AP. An in vitro investigation of the retrograde flow fields of two bileaflet mechanical heart valves. *J Heart Valve Dis* 1996;5:600-606
8. Kornberg A, Wildhirt SM, Schulze C, et al. Leaflet escape in Omnicarbon monoleaflet valve. *Eur J Cardiothorac Surg* 1999;15:867-869
9. Ericson A, Lindblom D, Semb G, et al. Strut fracture with Björk-Shiley 70 degrees convexo-concave valve: An international multi-institutional follow-up study. *Eur J Cardiothorac Surg* 1992;6:339-346
10. Hemmer WB, Doss M, Hannekum A, Kapfer X. Leaflet escape in a TEKNA and an original Duromedics bileaflet valve. *Ann Thorac Surg* 2000;69:942-944
11. Bottio T, Casarotto D, Thiene G, Caprili L, Angelini A, Gerosa G. Leaflet escape in a new bileaflet mechanical valve TRI technologies. *Circulation* 2003;107:2303-2306