Proc. Indian natn. Sci. Acad., **B62**, No. 6, pp. 367-376 (1996)

THE ARYABHATA MEDAL AWARD LECTURE 1996 — The Chitra Valve : What does It Tell Us

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(Delivered on 7 October 1996)

In my college days, I had prided myself that Aryabhata was a Keralite because Aryabhatiya was a favourite, and had several commentaries, in Kerala. Moreover I had seen suggestions that the Asmaka Desha of Aryabhata was somewhere in Kerala. But I was soon disillusioned because Aryabhata clearly states that he 'sets forth in this country called Kusumapura, the knowledge honoured at Kusumapura'. Kusumapura was none other than Pataliputra of Magadha where Aryabhata was born in AD 476 as stated by him. He was acclaimed as a great scholar in his time and venerated by succeeding generations of students including Bhaskara as 'Sarva Sidhanta Guru'. He was probably an Acharya at Nalanda where he had outstanding pupils including Acharya Latadeva. In 121 stanzas divided into 4 padas, Aryabhatiya covers astronomical parameters, mathematics, units of time and planetary motion. For a non-expert like me, it is astonishing that so much authoritative, and often original, material could be compressed into such a short text. In brevity and high seriousness, Aryabhatiya ranks with Patanjali's yogasutras. In giving this lecture, I am conscious that Aryabhata's cosmic vision contrasts with my worm's view; that Aryabhatiya sits uncomfortably with a discussion on heart valve substitutes. I believe however that the universal need not abrogate the particular which may indeed reflect the universal. Instances are not wanting in human physiology when the body, or the heart for that matter, acts as a cosmic resonator!

Valves of the Heart

The earthworm is none the worse for a tubular heart sans valves. So long as the demand for oxygen was small and the pressure to part lung and body circulations light, ancient hearts could manage to pump without valves. The picture changed with the emergence of a four-chambered heart where a muscle wall separated the chambers on the right and left. This was imperative for survival because the demands on the heart had increased many fold over the millennia. The chamber on the right became obliged to pump against a resistance of 200

dynes/sec in the lung circuit when the chamber on the left pumped against 1150 dyne/sec of the body circulation, and the streams of blue blood to the lung and red blood to the rest of the body had to remain apart. Moreover the blood had to go forward constantly in the heart lest any reversal of flow should unbalance the right and left sided circulations and compromise cardiac function. Valves were the answer which evolution supplied to ensure the forward flow of blood in the heart: but they are more than one-way check valves.

Four in number, two inflow or atrio - ventricular valves regulate the filling of the ventricular pumps; two out-flow or semilunar valves guard the exits. Together they ensure the forward flow of blood; control openings whose dimensions change during the cardiac cycle; and open and close 100,000 times a day in the highly reactive medium of blood. But in structure and design the inflow and outflow valves could not be more different. Their forms are tailored to serve the specific functions of inflow and outflow; their designs are not interchangeable.

Replacement of Heart Valves

For all the masterly design, heart valves are prone to the ravages of disease, rheumatic fever in particular. Recurrent attacks of the disease devastate the valves which may consequently fail to open or close fully and impair the unidirectional flow of blood. Burdened by extra work, the heart will eventually fail when its functional reserves run out. The problem of rheumatic heart disease is enormous and five out of 1000 children in India are believed to be at risk. When the valves are damaged beyond repair, replacement alone is the answer. No one knows the exact number of patients who need heart valve replacement per year in India : a conservative estimate puts the figure at 20,000 with a cost of 450 million rupees for the same number of imported valves.

Replacement of the heart valve is not a new concept. (Hufnagel & Harvey 1953) opened the prosthetic valve era as early as 1952 when he placed a caged ball value of lucite in the descending arota and gave dramatic relief to a patient with aortic insufficiency. The following decades saw the rise and fall of many valve designs which came to litter the field of cardiac surgery. The Baxter museum lists over 300 models which appeared during those prolific years.

Chitra Valve

A serious effort to develop a valve began at the Chitra Tirunal Institute in the early nineteen eighties when it became apparent that foreign valves would be beyond the reach of most Indian patients (Valiathan & Bhuvaneshwar 1982) The Chitra group discovered like their western counterparts that valve development is bedevilled by problems in the choice of materials, fabrication of components and the development of test systems. The Chitra valve which successfully entered clinical trial in December 1990 was, in fact, the third in a series of candidate valves which were developed and tested according to the international protocol (figure 1). The protocol acknowledges that there is no ideal heart valve substitute. All it does is to specify types of tests, methods of testing, requirements of the test apparatus and the reporting of data. It covers, apart from tests for mechanical, chemical, physical and biocompatibility characteristics, hydraulic and fatigue behaviour of the valve. Confined to those areas which facilitate quality assurance, the international standards are still evolving. (ISO DIS 1988)

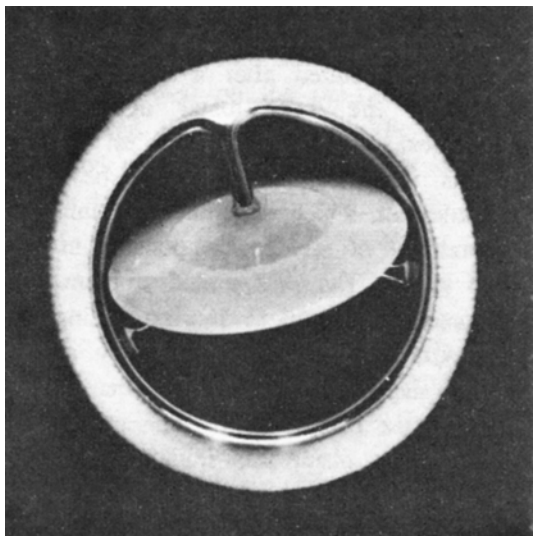

Figure 1. Chitra Valve

What Kind of Valve

Artificial valves can be homografts obtained from human cadavers, or bioprosthetic valves fashioned from porcine or bovine tissues. Alternately they can be mechanical valves. Tissue valves, in general, deteriorate and even calcify over time even though they have the merit of sparing the patient from anticoagulants. However the average Indian patient being in the 20-30 age group, the possibility of tissue valve degeneration and reoperation in ten years is a worrisome prospect. Secondly, it was clear that the logistics of collecting and processing homografts from autospy rooms and porcine valves from abattoirs would frustrate a commercially viable valve project in India. The global figures which showed that 75% of the valves produced were mechanical were also impressive. The Chitra group therefore chose the mechanical model which has the merit of durability, dependability, lower cost and commercial viability even though it does oblige the patient to take anticoagulants. Mechanical valves have different designs; but those which have stood the test of time are the caged ball and the tilting disc. Both types have three parts namely, the stationary housing and sewing ring and the moving occluder which may be a ball or disc. The tilting disc design was preferred because of its low profile and superior hemodynamic properties.

Materials and Construction

The three parts of a valve call for different mechanical properties which should preserve, in particular, the durability of the housing: occluder combination. The materials used in the Chitra valve as they graduated from Model 1 to 3, are listed in table 1.

In Model 1, the basic problem was the hygroscopic property of polyacetal which was used to fabricate the disc. Though the resultant change in dimension on autoclaving was small and reversible, polyacetal had to be dropped as indeed the western manufacturer had done earlier. Single crystal sapphire took its place in Model 2, thanks to a host of desirable properties including hardness, inertness, bio-compatibility and excellent surface smoothness. The change in the disc substrate dictated a change in the housing material which became Haynes alloy with a coating of titanium nitride to match

Table 1 *Materials used in various models of the Chitra artificial heart valve*

Model	Housing	Occluder	Sewing ring
1	Titanium	Polyacetal	Polyester
2	Haynes alloy with TiN coating	Sapphire	Polyester
3	Haynes alloy	UHMW-PE	Polyester

the hardness of sapphire. Though Model 2 passed the series of hydraulic and durability tests flawlessly its demise occurred when two sapphire discs fractured in sheep after several weeks of valve implantation. Model 3 featured a disc made of ultra-high-molecular weight polyethylene (UHMW-PE) and a housing of Haynes alloy sans the coating of titanium nitride. The unchanging material in all the models was polyester, a cloth of which was used to fabricate the sewing ring.

Even though the three materials in Model 3 are no strangers to surgical application, the use of UHMW-PE in a cardiac implant had no precedent. The characteristic and testing of materials used in Model 3 are reported in detail elsewhere (Bhuvaneshwar et al. 1983)

Fabrication Techniques

The techniques used in the fabrication of valve components paralleled the serial changes in the candidate materials (table 2). Electron beam welding, electric discharge machining, electro-chemical machining, thermal polishing, 3-D pantoagraphic milling and cryomachining, laser glazing were all tried, some to be retained and others to be discarded.

Table 2 *Techniques of fabrication of materials used in the Chitra heart valve*

Model	Cage	Disc	Sewing ring
1	Electron-beam welded struts	Machining	Knitted
2	All-integral cage tin coating	Cut and polished with diamond coated tools	Knitted
3	All-integral cage	Cryomachining	Knitted

In Model 1, the struts of the titanium had been electron beam welded: but the inlet strut fractured after a mere 100,000 cycles in the wear tester against the requirement of 360 million cycles! Failure analysis identified the cause to be weld embrittlement, which underlined the inherent vulnerability of welded components in the blood stream. The weld-related problem was eliminated in Model 2 by introducing an all-integral housing of Haynes alloy and a disc of single crystal sapphire. This greatly increased the complexity of fabrication. The Haynes alloy blank was initially subjected to CNC wire cut and electric discharge machining followed by CNC machining, multi-stage operations for finishing and coating with titanium nitride. For the disc, coins of required thickness were sliced from boules of single crystal sapphire and then ground and polished using diamond coated tools by the manufacturer according to our specifications. When the unexpected fracture of the sapphire disc killed Model 2, the titanium nitride coating was dispensed with in Model 3 and the disc material changed to UHMW-PE. The machining of UHMW-PE was no easy task because the blanks had to be cut from rods under cryogenic conditions. Thermal polishing of the disc was accomplished in a three piece stainless steel die with controlled heating and cooling cycles even as a uniform compressive load was applied. The flash generated during thermal polishing was removed with a polished formed tool under cryogenic conditions again. The sewing ring was made from knitted polyester cloth in all the three models.

Design Features

The changes in materials and fabrication methods did not affect the design, which

remained unchanged throughout. The basic features included an opening angle of 70° for the disc, which was non-seating and had a taper and well on the out-flow side to accommodate the minor strut. The sewing ring fitted snugly into the concavity of the metallic housing (figure 2).

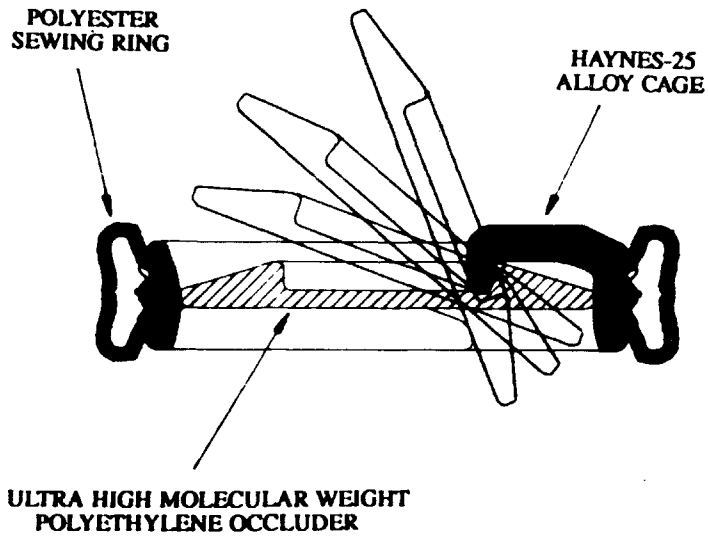

Figure 2. Chitra Valve design-features

Performance tests

The performance of a heart valve substitute is gauged in terms of hydraulics, durability and long term function in an animal model. The pulse duplicator to measure the hydraulics consists of a model of the left heart which enables the study of pressure drops and regurgitant volume as well as the recording of flow patterns. In all these measurements, the Chitra valve was found to be marginally superior to an imported model in wide use (Bhuvaneshwar et al. 1991). The durability was tested in an accelerated wear tester and the valve was shown to have no mechanical failure and negligible wear at 360 millions cycles. These special purpose test machines were built on the basis of sketchy information available in the literature. As experience grew innovations were introduced in the test systems such as the ultrasonic doppler for flow velocity measurements.

The successful engineering tests for performance were followed by the insertion of the valve in the mitral position of sheep under heart-lung bypass and the careful monitoring of the animals for a minimum of six months. The pressure drop across the valve, healing characteristics, status of viscera and evidence for blood damage were assessed at the elective termination of the animal trial. The Chitra valve showed smooth healing, good hydraulic function and no evidence of tissue damage in these extensive studies (Valiathan 1991).

Clinical Trial

The test data in terms of the ISO recommendations were considered by the

ethics committee of the Institute who approved its clinical trial subject to the informed consent of each patient. The trial began in December 1990 and entered the multicentric mode in five other major hospitals in India two years later. The results of the trial in over 300 patients have been reported elsewhere. (Bhuvaneshwar et al. 1996). They showed that in terms of operative mortality, over-all survival, event-free survival and thrombo-embolism rate, the indigenous valve compares favourably with the imported tilting-disc valves in current use-Medtronic-Hall, Bjork Shiley and Carbo-medic. Echocardiographic assessment of valve function in patients was found to be excellent, and the negligible noise on closure was particularly welcomed by the generally lean patients. A notable observation was made during pressure field and cavitation measurements at the Department of Biomedical Engineering, University of Iowa, which showed that the impact energy at closure is absorbed by the non-rigid UHMW-PE disc and the soft polyester sewing ring of the Chitra valve. This would necessarily imply reduced stresses on the sutures and the tissue annulus and an improvement on valve models employing rigid discs (Bhuvaneswar et al. 1996).

The multicentric trial Monitoring Committee cleared the valve for commercial production in February 1995 and the factory of TTK Pharma will begin manufacturing operations in Madras in early 1997.

What does Chitra Valve Tell Us?

General

Limited to a cardiac site, weighing no more than five grams, does the valve have a larger message? Does it have a significance beyond the heart, or medicine for that matter? In response to such questions, one can only make a series of observations based on the Chitra experiment. If nothing else, they have the merit of springing from the fire of direct experience. The Chitra valve is no more than one among the vast range of medical devices which sustain modern medical practice. Whether disposables or implants, devices are indispensable at every level-primary to the tertiary - and in every speciality. The demand for devices technology in India will in fact exceed Rs. 1000 crores by the turn of the century (Vijay Kumar 1985). So long as India is obliged to import 95% of its devices requirement at the present rate, there is little hope that average Indians will have access to even simple devices such as transfusion bags, let alone heart valves: nor will health care be safe. Take away devices technology, Indian health care system will limp into the twenty first century on imported crutches. While India cannot be self sufficient in medical devices, it is imperative that we choose a few critical technologies for development and commercialization in every field with no less than the global market in view. The choice must be guided mainly by the need of the technology for the largest number of Indian patients. This would meet particular needs but more important, it would give us the confidence and experience to develop other technologies, however complex, when the need arises. The valve and its companion devices - the blood bag, oxygenator, cardiotomy reservoir, hydrocephalus shunt, and vascular graft - have achieved this objective in a small sector of medicine. The Chitra model must however become the forerunner of a broad-based national initiative to realise its full potential.

Networking

The Chitra valve offers much of interest to the medical technologist. A US study revealed not long ago that even in a technology-driven, fast paced industry like electronics where a new product is launched every 90 days the actual effort of development spans many years. It is therefore a remarkable feat that the clinical model of a mechanical valve, fully conforming to international standards, could be developed in ten years from conception to clinical trials passing through three models on the way. This would hardly have been possible without a multidisciplinary team which included biomedical engineers, cardiac surgeons, materials scientists, toxicologists, pathologists and veterinary surgeons with Dr Bhuvaneshwar, a skilled biomedical engineer, bearing the brunt. This was not all. The valve project cast the net wide and drew upon the resources of top level institutions who were only too ready to assist. The NAL analysed the weld failure of the housing in Model 1; South India Textile Research Association provided the knitted polyester fabric for the sewing ring; Hindustan Aeronautics worked out a method of CNC - EDM wire cutting for the basic profile followed by EDM die sinking operation to shape the struts in the flow direction: Government Tool Room, Bangalore did the CNC machining of the valve housing and the NCL provided inputs for the choice of UHMW-PE as the disc material in Model 3. Chitra valve exemplifies the synthetic nature of medical technology and its dependence on a variety of disciplines. It is a costly folly for institutions to attempt the development of medical technology all on their own; cooperation must be sought on the basis of mou's, work orders, contracts or informal consultancy from organisations and individuals who have top level expertise in electronics, materials processing, non-destructive testing and other technologies which may be relevant to the experimental device on hand. Medical technology is no place for loners.

Failures as Teachers

The glamorous technologies which hit the Indian market from abroad seldom reveal the setbacks in development. Failures are never made known except involuntarily. The reason for this is not entirely one of prestige. A more important reason is the wealth of information one gains from failure and its subsequent impact on technology development. This wealth is too much to be given away. The weld failure in Model 1 was more instructive than tragic and, in its absence, the all-integral housing would not have appeared in Model 2. Failures dictate major changes not only in materials and fabrication but also in the very protocol for development. We learnt this in a moment of crisis when the sapphire disc fractured in two sheep and wiped out, so it seemed to us, the effort of several years. An alternate material had to be found quickly to make the discs for Model 3. There were several candidates and if the discs were fashioned from each and as many valve models made, their testing and validation would have taken a further ten years. What was critical was the wear of the disc material on mating with Haynes alloy and Prof Ramaseshan and Mr Ramani suggested that we could screen the wear of each combination fairly quickly through locally designed sand-slurry and pin-on-wheel test instruments. The switch to the testing of subassemblies instead of the final product saved no little time and effort.

Only the ignorant will denounce failures which are neither to be mourned nor scoffed at.

Ethics

Patient safety overrides every other consideration in the development of medical devices. Adherence to ISO recommendations, repeat studies, accurate documentation, peer discussions and ethics committee approval are, in fact, aimed at ensuring patient safety. Institutional ethics committee includes a jurist as chair, an external expert and three or four other members who must be convinced that the device fulfills the ISO criteria beyond doubt before approval is given for the clinical trial in the host institution. Furthermore the committee will insist that the trial is carried out by the principal investigator personally on the basis of special informed consent from each patient: it may suggest additional tests or may limit the size of the initial trial: it will approve a multicentric trial only when the initial trial shows results which are comparable to those of FDA approved and similar devices in conventional use. Transfer for commercial production cannot begin until the multicentric trial confirms the results of the initial trial. It is a matter of pride that hundreds of patients including teachers and office workers in Trivandrum, Coimbatore, Pune, Bombay, Pondichery and Calcutta showed the confidence and readiness to take part in the multicentric trial of the Chitra valve, and senior cardiac surgeons in all these centres agreed to be co-investigators.

Technology Transfer

The toil and hardship of technology development pale before the hurdles in technology transfer in India. The Chitra Institute took three years to develop a blood bag, and longer to transfer it for production. This experience came in handy in transferring the valve technology a few years later. They discovered the need to involve industry in the penultimate stage of technology development if not in the beginning itself. The dialogue builds mutual confidence and smoothens the road to multicentric trial and pilot production. From the blood bag experience it was learnt that the R&D laboratory is poorly equipped to produce several hundreds or thousands of any device with uniform quality for multicentric trial. It was equally clear that industries would not set up pilot plant facilities for an indigenous technology. Risk taking or investing in knowledge are not the strong point of Indian industries who are long used to the soft option of licensed production. The Chitra Institute therefore created a facility-Technoprove-which offered GMP conditions for pilot production. This was available on suitable terms to any industry whose staff could produce the device on pilot scale under the supervision of the Institute's engineers. When the commercial plant was ready in a couple of years the staff trained in the Technoprove could be relocated and the devices from pilot production used to 'seed' the market. This strategy worked well for the oxygenator and hydracephalus shunt which are now produced commercially in Madras and Trivandrum. The same approach was adopted for the transfer of the valve technology which will enter commercial production in Madras early next year. In the absence of a Technoprove or its equivalent, the gap between the laboratory and industry will continue to handicap both. The blood bag is a success story today. The first licensee in the joint sector produces over 3 millions bags a year and exports one third to Europe; the second unit has

started production recently. But things were far from rosy in the early years when the fledgling Indian company faced the assault of a multinational who cut the price of the bag by half and launched a price war. Extraordinary measures were needed to overcome the crisis and salvage the Indian company. Therefore one must ensure that the industry which takes up an Indian technology is qualified not merely in terms of technical competence but also in financial and managerial terms.

Conclusion

The last barrier for the success of Indian technology is the Indian himself whose faith in the superiority of imported products is pathetic. The medical community has been reared for a century on imported technology, drugs and concepts and their distrust, if not dislike, of Indian technology will take much time and patience to erase. The scrupulous compliance with internationals standards, detailed engineering data and the results of multicentric trial will be lost on the medical fraternity who will be more impressed if the Indian product penetrates the foreign market or gets distributed under a foreign label! The rapid rise in the cost of imports, rising pressure from thousands of deprived patients and the power of skilful marketing by Indian companies will however break the last barrier. This was amply borne out by the blood bag story.

The development of medical technology of which the heart valve forms a tiny part, is a fine chapter in the saga of national reconstruction. But the chapter can be scarcely written unless the authors have faith in themselves. For the recovery of faith and for the liberation of the Indian mind there can be few Rasayanas as potent as the spirit of Aryabhata.

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