of the

PERICARDIAL HEART VALVE

1971-2021

BILAL KIRMANI

50 Years of the Pericardial Heart Valve

Edited by Bilal Kirmani

Published in conjunction with the Society for Cardiothoracic Surgery in Great Britain and Ireland

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ISBN 978-0-9957260-3-1

First published in Great Britain in 2021 by Society for Cardiothoracic Surgery in Great Britain and Ireland, SCTS 5th Floor, Royal College of Surgeons of England, 35-43 Lincoln's Inn Fields, London WC2A 3PE.
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Designed, typeset and printed by CPL Associates, London, UK.

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Preface

April 2021 - 50th Anniversary of the first Pericardial Valve

An nescis, mi fili, quantila prudentia mundus regatur

It is thought humans began to exhibit behavioural modernity around 100,000 years ago, and it is only in the last 100 years that truly effective health care has been discovered, developed and adopted around much of world's population. A tiny fraction of our 'modern' existence.

In step with medicine, surgery proliferated in the 20th century enabled by the combined application of general anaesthesia and antisepsis. During much of this time it was considered impossible to operate on the heart due to its essential function supplying oxygenated blood to the body. How could a human 'interfere' with this vital organ, correct abnormalities and have a healthy patient at the end of the procedure?

Mankind's innovation accelerated in the second half of that century, exemplified by the development of reliable interventions on the heart, each one a story in itself: the ability to treat cyanosed babies and children; the development of the pacemaker; the defibrillator; cardiopulmonary bypass; valve replacements; coronary bypass surgery; heart transplantation; percutaneous coronary artery stents; percutaneous treatments for dysrhythmias and percutaneous valve insertion.

The introduction of safe cardiopulmonary bypass in the 1960's gave the patient safety to endure heart surgery and the surgeon time to operate with accuracy. No longer a precarious and rushed procedure using cold immersion or the use of a parent for living bypass. Serious thought could now be applied to strategies for diseased heart valves, especially the aortic and mitral valves so commonly affected by rheumatic fever.

This book recognises a very significant anniversary in the history of cardiology and cardiac surgery: 50 years, half a century, since the first pericardial valve was used to replace a patient's diseased valve. And subsequently around 10,000,000, 10 million, have been implanted worldwide.

At the time it was an innovation in a rapidly evolving field. There were mechanical valves, animal valves, prosthetic valves, each one carefully considered and tested. But it is the pericardium that has endured the test of time. This is the material that most implanted valves are made of: the material that is readily available; the material that is more predictable in its durability; the material least likely to cause thrombosis and embolus. More and more patients are choosing a biological valve to avoid the risks and inconvenience of anticoagulation, essential for a mechanical valve. And in developing the percutaneous valve it is pericardium that has been chosen for all of the qualities listed above but now with the added quality that it can be compressed for insertion and then expanded safely into place.

Mr Marian Ionescu is blessed with many qualities and skills. He is many things including gentleman, surgeon, loving husband, inventor, scientist, mountaineer. He had, and still has, a determination to find the perfect valve replacement. He was the leader of his era in researching and trialling new materials for a non-mechanical valve. He saw the harm of thrombus and emboli, he saw the benefit of a large orifice area and the benefit of non-turbulent flow. He still has a strong desire that calcification in the pericardial valve can be prevented. When he implanted the first pericardial valve 50 years ago it was the start of an era but it was also the culmination of years of hard work, science, research, innovation and ground breaking surgery.

This book not only recognises the 50th anniversary of the Pericardial valve but also the worldwide legacy Mr Ionescu has left to cardiology and cardiac surgery.

Simon Kendall

President SCTS

Foreword

Bilal Kirmani

Dignus vindice nodus

This book is published to celebrate fifty years of the clinical use of the Pericardial Valve. It celebrates, in fact, more than five decades; it describes briefly the 14 years during which this remarkable valve travelled through unending trials, failures, small successes and complex experimental models until it reached its zenith. The road from a dream to the heart valve which became the most used valve in the world became another difficult but beautiful dream. This book also extols the novel concept of man-made valves, the principle, the design and through its longevity, its success.

Formed, as it is, of eleven chapters, this book was planned in such a way that although each chapter alone reads as a succinct summary of the topic with which it was written to describe, no part should exist independently. Rather, the aggregate works of these familiar clinician-scientists come together as a whole that is much more than the sum of any of its parts. The chapters fit and follow each other in a unified manner, combining the knowledge of experts from many different fields, and form a volume that will be cherished by all those who seek to learn. In addition to the contributions from the most eminent minds of our time, this book also benefits from the rare advantage of having as its custodian, the same founding father who conceived the Pericardial Valve in the first instance.

Accordingly, the book also recounts the coincidences, challenges and curiosities which occurred during the valve's nascency. While Marian and Christina Ionescu waited in Paris for their American visas, the British Council decided to invite them to come to Britain to help establish an open heart centre in Leeds. They dispatched Mr. Geoffrey Wooler to Paris twice to convince them finally to abandon the plans, already organised at the Cleveland Clinic, and come to Leeds and start the great adventure. For this reason alone, the first porcine valves for mitral replacement, the Fascia Lata valves and finally the Pericardial Valve were created in Britain and not in America. The pioneering work carried out during the Leeds years by the Ionescus at the Leeds General Infirmary are a source of immeasurable pride for British Design. In the realms of invention, dominated by our cousins in the United States and neighbours in Europe, to know that this small corner of the world was the birthplace of antisepsis and vaccinations, hip replacements and in vitro fertilisation, and so, too, the Pericardial Valve, is inspirational.

It is, therefore, no accident that the experts upon whom we have called to contribute to this book are British physicians, surgeons, scientists and industrialists. Each leads in their field, and their names will be known to you already for prestigious works that have brought many contemporary advances to medical science. It is likely that all embarked upon their professional careers well after pericardial valves had been incorporated into cardiac surgical practice. Some may remember that during the first 16 years of use of the Pericardial Valve the clinical and laboratory investigations continued (cardiac catheterisation, pulse duplicator ciné studies and life testing of large numbers of valves). Echocardiography was in its infancy in those days. When Industry became aware and satisfied with the solidity of the concept and the results of multitudinous investigations, it became interested in manufacturing of the pericardial valve. Some eleven laboratories started copying the original valve. Progressively the attrition left behind only three manufacturing firms which used slight changes to the mounting of the pericardium on the stent; the inside placing of the pericardium slightly reduces the total surface area of the valve opening. The outside mounting does not differ at all from the original valve. It is interesting to note that those small changes were made by the manufacturers and not by the surgeons.

In researching the fifty years of pericardial heart valves, I happened upon the remarkable story of John Gibbon Jr. When we think of him, we think of the father of modern cardiac surgery: the man who built the first functional heart lung machine. His invention transformed the very bounds of what was possible – indeed, of what was conceivable – and enabled modern cardiac surgeons to save millions of lives. Although he became uncertain of the value of his own invention, the considerable importance and the potential of Gibbon's work sparked a flame in others who continued to develop his invention (the Mayo Clinic) or create other systems to obtain the same result (De Wall - Lilllehei bubble oxygenator) and to disseminate the heart lung

machine and the value he had once believed it had. The lives of pioneers are certainly fraught with the scrutiny of the watching world. When you read the complex story of the beginnings of the Pericardial Heart Valve it is all the more gripping to realise that the fate of this unique device was changed by the crucial discovery that calcification of the pericardium is age related and consequently this valve should be used preferably in older patients only.

So it is that this unique, epochal tome condenses more than half a century of dreams, passions and realisations, inspiration and innovation and the main subject the invention of the Pericardial Heart Valve which radically changed the treatment of aortic valve disease. The content encompasses the aggregate knowledge of the last fifty years and looks forward to the next fifty. Perhaps the invention and discoveries retold in this volume will spark an epiphany in young researchers who may find the solution to prevent or abolish tissue calcification. As we celebrate how much has already been achieved with this remarkable, unique invention we should also celebrate the coming on the distant horizon upon which we might, eventually find the perfect heart valve replacement.

Chapter 1

Introduction

The last three Mohicans from the LGI

Felix qui potuit cognoscere causas rerum

The Book

The Book, the soul and the heart of our civilisation, the Guardian of our past, the Ledger of our present deeds and the Last Judgement of our foot prints of a too short passage on this earth.

When Johannes Gutenberg started the printing revolution it was like a candle in the dark winds of an otherwise highly spiritual Medieval world.

There must be nowadays in the world several hundreds of millions of books; not enough for some readers or perhaps too many for the Internet users. There are innumerable varieties of types, of genres, of categories of publications in the form of a book. Among the maze of publications there are old and sacred texts and books, beautifully presented and preserved. They are bursting with wisdom and advise. Quite useful at times but none of them answers our questions.

From the abstract, philosophical ideas of Kant, Spinoza, Nietzsche and Hegel to the technical manuals of winding up clocks, everything on earth had passed through the typographers hands. There are also the giants among the great classics ; Dante Alighieri, Miguel de Cervantes Saavedra and William Shakespeare who unified languages, created words and expressions and enriched vocabularies and gave us enormous pleasure to read their oeuvres.

Passing centuries and decades of literary activity we come to the golden era of heart valve surgery, the period from 1961 to 1971 when a plethora of ideas, trials, experimenting and publishing, concentrated on artificial heart valves took place. The number of publications on this topic defy imagination. That activity resembled the 1848 - 1855 California Gold Rush. Marian Ionescu in Leeds, during this decade published and edited eleven books and 242 articles.

Most books have a finite active life due to many varied reasons. This present book, which is going to open its wings to you following this Introduction, could be placed in a different category ‘ Uniqueness ‘ and, possibly it may carry a greater longevity. This book is unique because it presents the life of an original heart valve which is still in use world wide 50 years following its invention.

This book was built on a structured plan with every chapter having its own life but when placed together they become a whole which is the story of the Pericardial Valve from its hazy beginnings in 1957 to its apotheosis in 1971 and its continuous clinical use world wide for 50 years.

The Valve

The valve which is the center piece of this book has a rare and singular origin. It was created by a surgeon and not by engineers as the other two ‘revolutionary’ creations (the mechanical Starr-Edwards and the Björk-Shiley valves). The pericardial valve was created out of a dream of Marian Ionescu and the whole process of developing it followed a biological not a mechanical approach.

Ionescu first established what a heart valve would do, especially when functioning in a complex medium like the blood. The two essential characteristics of the imaginary artificial heart valve were non-thrombogenicity and near normal haemodynamic function. During the study of the clotting mechanism and especially following the advent of the first mechanical valve, he made an important observation. One of the causes of embolism is the interface between rough and smooth surfaces as described in one of the Chapters in this book.

It must have been around this time, during his continuous search for the Holy Grail, that Ionescu created for himself an imaginary coat of arms on which it was inscribed: *I do not lose, either I win or I learn.* Probably the Herculean task that he ensconced in his secret being had to have an honorable exit, knowing the perseverance and the tenacity of his engagements.

The existence of the Pericardial Valve engendered the creation of a very ingenious system for inserting the pericardial valve in the aortic position by a special catheter (TAVI). This novel technique is being used in a progressively larger numbers of patients, mainly of an older age, with great success. The slight modifications

made to the pericardium to adapt to the catheter (crimping) as well as the small improvements in the valves used through thoracotomy, have not altered the essential characteristics, function and long term results of their use.

From the more than a dozen artificial heart valves used during the years, three were revolutionary inventions and the rest were modifications or plagiarism. All disappeared In a short time except the real inventions. Of these, the Starr-Edwards mechanical valve was very useful, in spite of its high risk of thrombosis and embolism. It sunk progressively into oblivion and is rarely used today, except in countries with limited financial means. The Björk-Shiley valve fell on its sword and had to discontinue its manufacture. In a manner of speaking natural selection operates everywhere.

The Pericardial Valve reached a dominant position in the world with more than 90% of all valves implanted.

The Man

There will be a journey of surprises to attempt to understand the soul, the heart and the mind of the man of many faceted and several reincarnations in time. He drew his roots from Scotland, Greece and Romania where he grew up in the shadow of the Carpathian Mountains, which adopted him early in life.

We met when we were in the Medical School. A mysterious chemistry attracted us to this elegant surgeon who finished his operations earlier than many but without rushing and always in a clean, orderly surgical field. We watched him using new techniques on complex congenital heart defects and often when he was using the surgical instruments he had himself devised.

Progressively we learned that he spoke four languages and that he read most of the classics in the original language and that he would recite, with pleasure, the melodious verses of Catullus as well as the recent poems of Pablo Neruda. A classic Scholar.

With time he became our Mentor. He taught us how to create our own parallel paradise at the back of our minds. A library and a garden, as Cicero suggested, would be enough. When we asked about a door for friends to enter, to visit, he answered dryly *be very careful, impressions are deceiving.*

When he walked on the Dales around West Burton or on the streets of San Francisco, he admitted that his heart was in fact beating in Florence.

In the 60s he was invited by the British Council to come to Leeds to help create an open heart surgical unit. He came with his life partner, his wife a cardiologist, and for the next 21 years they created not only a unit, but a World recognised Centre, a 'Mecca' for innovation and valve creation in particular. He created 3 types of heart valves used throughout the World. The last one is the Pericardial Valve which is celebrated now following 50 years of clinical use.

Out of the many souvenirs, we remember that before leaving for his mountains he told us that the only great gift which he received from Britain was the exceptional, unique friendship which he established with Geoffrey Wooler, his alter ego, his older associate at work and in life, one of the few true érudites and an impeccable gentleman. Their friendship continued over land and sea to the very end when our hero closed the eyes of his great friend.

He told us also about the other aspect of life. To be prepared to encounter pain and hurt and deceit and to bleed and to be vanquished, but in the great battle of life, to remember that the supreme defeat is only when you renounce your dreams.

When he thought that he had done his duty like the Moor of Venice in Othello, and attracted by the call of his forebears, the Mountains, he discontinued the surgical activity to start a new life, climbing at high altitudes. His gardens became the Mont Blanc massif, the Pennines Alps, Himalayas and Alaska where he scaled numerous peaks, most of them between 6 and 7 thousand meters high and of challenging technical difficulties.

Here is the best place to summarise his life.

His first incarnation was spent by learning and understanding; The second one in the operating theatre and the laboratory; The third one high above

the clouds in the realm of silence and beauty. During the last one he is using his knowledge and wealth to help others, people, animals and ideas.

Before leaving the LGI he admitted us in the select Club of the Mohicans (to continue to search and research for evermore). For us he was and remains a hero and we continue to call him *The Man from the Mountains.* His real name is Marian (Macu) Ion Ionescu-Mandresti.

Chapter 2

Such a Long Way
(The Period 1957 – 1971)

Marian Ion Ionescu

Non desistas, non exieris

In 1957 at the Cleveland Clinic, Donald Effler was trying to improve the surgical results of open heart operations on children with complex congenital heart abnormalities. On another floor, in the laboratory for Artificial Organs, Willem Kolff, the inventor of the artificial kidney, was involved with his main project, to create an artificial heart. I arrived at the Cleveland Clinic at the most exciting, beautifully ebullient time. Enthusiasm dominated everybody involved in cardiac work. I was instantly contaminated by that spirit.

In the morning I worked in the clinical service and assisted Effler in most of the complex open heart procedures. During the afternoons I worked in the laboratory for Artificial Organs until dusk or the night fall. I was awe stricken to see unfolding before my eyes, events which were to contribute to the creation of the great edifice of open heart surgery. I am grateful and proud to have been given the chance to participate, even in a very small way, to such events.

The first of Kolff's artificial hearts was a hexagonal, steel and lucite case containing two ventricles and five solenoids to drive the system. Today, in comparison with the recent devices, the hexagonal box looks primitive, cumbersome, ungainly but the idea and the daring behind it were magnificent. In the laboratory, one of my tasks was to construct from polyurethane the corrugated tubing for the connection of the device to the great blood vessels of the recipient dog and to build the flap valves at the ejection side of the artificial ventricles. Kolff suggested that in my little free time, I should try to create another type of valve for the box, as we called it. I started small with the single leaflet aortic valve made out of polyurethane and Ivalon (Figure 1).

Figure 1: Original photograph of a single leaflet aortic valve

The experiment had to be discontinued because the valves clotted often. From this failed experiment I learned something very important. The interface between smooth and rough materials might induce clotting. I did not understand then the mechanism of this event and I decided to make a great mental note to come back to this phenomenon later to find an explanation. *Felix qui potuit cognoscere causas rerum.*

My next attempt was to build a three cusp valve out of Dacron mesh and this time it functioned correctly and, with some improvements (Figure 2), it was used in a small number of patients until the Starr-Edwards prosthesis appeared for clinical use in 1961.

The idea of heart valves became an obsession. The need for a heart valve substitute took a disproportionate significance in my mind. It became the mystical object which did not exist and had to be created. The seed was sown. The dream took over my thoughts.

At that time I knew very little about artificial heart valves from some publications of unsuccessful attempts to build them. My 'project' was hollow but I knew the destination of my ambition and the determination to start on that road as Kolff used to say often 'No hope is needed to work'. But logically there was no sense to start anything before making a plan and several back up programmes. Because my apprehension for this enormous and uncertain undertaking, I kept the idea hidden in the folders in my own dreamland for a very long time, probably until 1971. To pacify my psyche I created for myself an imaginary coat of arms. At the bottom I placed a sibylline inscription: I will not lose; either I win or I learn.

Progressively a plan was established and the characteristics of my ideal valve formulated. The fundamental element in my equation was to never forget the fact that heart valves function in a complex, fluid environment THE BLOOD and this is a great problem. A valve, in order to become my life partner has to become progressively, a living being, to carry a soul like mine. I considered initially only two essential

prerequisites and a few secondary conditions. A valve must be non thrombogenic and it should possess hydrodynamic properties equal to those of a normally functioning heart. These two are the '*sine qua non*' essential conditions. There are some other smaller qualities to be discussed later. The durability property of the valve did not even cross my mind at that time simply because in those years one could not afford the luxury of looking beyond the day's horizon, *'primum vivere deinde philosophari'*. Beginning to look into the thrombosis and embolism pathology was as complex and complicated as it remains today. Even now one is flabbergasted by the magnitude and the complexity of the subject. Studying it in detail made me feel that I was sleeping every night with a ghost. A generally accepted apophthegm was that the presence of mitral valve disease and atrial fibrillation are the most common causes of cerebral embolism.

Figure 2: Original photograph of a three cusp valve made of Dacron mesh

Questioning the wisdom of this assertion later, following new developments like closed mitral valvotomy and the introduction in clinical use of artificial heart valves threw me into a deeper confusion. It would seem that the question of thrombus formation and embolism in patients with mitral valve disease is still shrouded in mystery now as it was a few decades ago. More recently, the medico-surgical scientific publications are packed with the term thromboembolism mixing an in-situ pathological event with a travelling particle of sometime unknown origin especially in patients with mechanical heart valves. All this reminds me of the story of the archaeological digs at Pompeium: because no copper wires were found there, one might conclude that the Romans used wireless transmitters. In reality the detailed knowledge on this subject has little interest when aiming to build an artificial, non thrombogenic valve.

The time to return to Bucharest approached. I acquired some materials which I would not find in Romania and I built on the lathe several types of moulds for my future experiences on valves (Figure 3).

I arrived home full of enthusiasm, great expectations and a little more knowledge. The task ahead was enormous. I organised the Department and a simple intensive care unit with a small laboratory attached, all for open heart surgery. I took advantage of space available in a new building and I created a modern laboratory for experimental heart surgery. I called it, like at the Cleveland Clinic, the laboratory for Artificial Organs. For a good start I was allowed to order and I received a lot of special surgical material mainly from USA. The main pieces were two heart lung machines with disk oxygenators made by Pemco in Cleveland. One for the operating theatre and a simpler one for the experimental laboratory.

Figure 3: Moulds for Valves.

In March 1960 we began work in the laboratory for testing mainly the heart lung machine and the heat exchanger efficacy (a special one made by Usifroid in France). We began almost simultaneously work in the operating theatre, every

morning and in the laboratory in the afternoon. During my stay in the USA the main questions about the extracorporeal circulation were: what should be the pump flow in relation to the surface area of the patient; what is the best degree of the mild hypothermia during by-pass and which is the best way to stop the heart during the surgical procedure? Cardiac surgeons today may smile when reading these lines. The Azygos flow principle, haemodilution, bilateral thoracotomy and many other historical relics are in the mothballs of history.

When I had my own laboratory and a good team of young surgeons and even younger technical assistants, all full of enthusiasm and curiosity I dared to start searching for answers to some of the questions raised. The most important work was the induction of progressively deeper hypothermia descending usually to 12 - 15 degrees Celsius and exceptionally as low as 7 and 8 degrees and with a total circulatory arrest of maximum 57 minutes. The recovery of both dogs and humans was impeccable without any impairment of physical, neurological, behavioural and of course electrical neuronal activity. The details of the entire work were published in a small book in 1964 in Romanian. Later on I realised that our experimental and clinical work of 1963 became the basis of today's techniques used in the surgical procedures involving the aortic arch and the carotid arteries. Towards the end of the day, late afternoon and often in the evening I continued in my '*Dream Land*', the laboratory and the work shop to try to correct the failures and botched 'sculptures' of the day before. A Japanese saying is simple and clear- seven times down and eight standing. My work, my imagination, led me unmistakably towards that empty space, the idea of that thing which was not there and I had to imagine it. Using a dentist's drill and bars of Lucite; or at the lathe, I could let my thoughts wander. At other times I made various forms by hand. It is surprising how easy it is to create shapes with '*papier mâché*'.

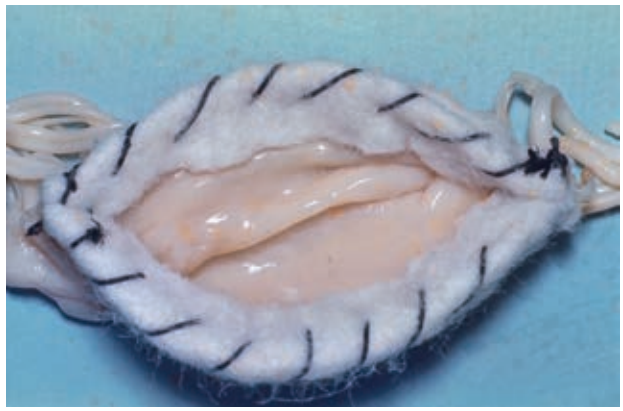

Figure 4: Original photograph showing a mitral valve made of Dacron and pericardium.

The second experimental and clinical study was performed on large numbers of subjects mainly animal and a few verifying tests on humans, concerning the best way to stop the heart beating during the surgical procedure. The conclusion of this evaluation of various techniques was clearly in favour of local ice cooling the heart throughout the surgical procedure. Ventricular fibrillation, ischaemic arrest, potassium arrest and ante or retrograde coronary perfusion were found to be either cumbersome or less efficacious. Among other experiments, I tried, unsuccessfully to replace the mitral valve in dogs with two cusps made of Dacron mesh encased in a pouch of autologous pericardium (Figure 4).

Adjusting the length of the chordae was extremely difficult.

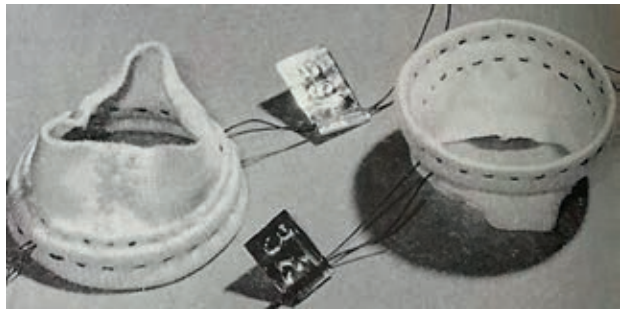

Figure 5: Teflon reinforced Dacron collars.

The first three years were very exciting and productive, both in the clinical department and operating theatre as well as in the experimental laboratory. It was a period of great activity, an atmosphere of great excitement, a continuous effervescence, that sense

of exhilaration which springs from self-confidence and achievements. I had not experienced such a happy time until my arrival in Leeds and the beginning of another feverish period of intense activity. It must have happened around that time of continuous excitement and intense work, that we choose our motto for our fighting little team. It was the battle cry of the Highland clans inspired from a sentence of Publius Vergilius Maro in the Aeneid: '*If I cannot move Heaven, I shall raise Hell*'.

Figure. 6: *Porcine aortic valve attached inside a Dacron collar.*

With the advent in 1961 of the cage and ball mechanical valve and its use in several centres, there might have been a chance to verify my hypothesis of the interface presence as one of the causes of embolism. But the time to obtain specimens from post-mortems to examine would have been very long indeed. In a few words, the connective tissue grows into and over the Dacron collar of the prosthesis and creates a thin neo-endothelium. When this neo-endothelium continues to grow over the smooth metal ring of the prosthesis, not knowing where to stop, and not being able to adhere to the smooth metal, it gets occasionally detached becoming an embolus.

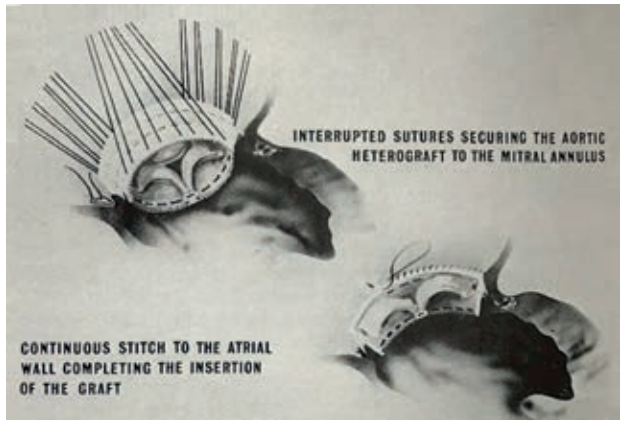

Figure 7: *Implantation technique for porcine aortic valve into mitral annulus.*

The long time necessary to verify my assertion, convinced me that it would be better to create a specific experimental model as a way to try to demonstrate the contrary, when there is no smooth-rough interface, a much lower number of emboli should occur. This could be done by inserting in the mitral position a valve made of animal tissue and Dacron. That tissue, logically should be a ready-made, by Mother Nature, the aortic valve of a large sow or from a small calf. By dissecting the aortic root of these two animals, both could be used but for a practical reason like availability, I had to choose the pig. The next step was to create a simple way to attach the pig valve to the mitral annulus and for this purpose I built a collar, like a short cylinder to encase the aortic root and its valve, within the Dacron support (Figure 5).

The original hybrid device would be sterilised with formaldehyde for clinical use, but it should first be constructed. I began with the Dacron collar but fate decided otherwise.

Beginning in 1963, my small loyal group and I started receiving, more often, the visit of the old companion of the medical profession called: INVIDIA MEDICORUM PESSIMA. It became persistent to the point of pushing us, Christina and I, to make the great decision to leave illegally the communist country, to cross dangerously the Iron Curtain and try to reach the United States and Cleveland where our good friends organised everything for us at the Cleveland Clinic if we would succeed in our perilous adventure. They did not know that failure meant prison for us. We prepared as much as we could but everything came to two small suitcases, two books, tinned food for several days, half a dozen Dacron collars for my valves and Great Expectations, all in the space available in our little Fiat 600. Taking the mountain small country lanes for safety, after 2350 kilometres we reached Paris where we waited for the American visas.

This time spent in Paris changed the course of our lives. The British Council (Mr. William Cleland and Professor

John Godwin both from Brompton Hospital in London) having visited my Unit in Bucharest two years previously heard of our escape from Romania. They wanted to invite us to come to Britain and asked Mr. Geoffrey Wooler from Leeds to go to Paris to convince us to come to Leeds to help his fledgling unit (he had a clever senior house officer, half of a senior registrar interested mainly in thoracic surgery and an archaic Melrose heart-lung machine). We were not tempted to change our American plan. Mr. Wooler returned shortly to Paris with the final argument, he needs support. We made the fateful decision to abandon the security of the Cleveland Clinic for the adventure of starting to build something new and challenging in Leeds with the gentleman with whom we established a unique, wonderful, life-long friendship which perdured to the end of the end.

We arrived in Leeds in October 1966. I started work next day. I found a small slaughter house for big sows. I obtained a few pig hearts and started to build my hybrid device with which I believed to be able to prove that my theory on the interface is one of the causes of the genesis of embolism (Figure 6). By the following January 1967 I already had a few valves ready and I started implanting them in a series of eleven patients requiring mitral valve replacement (Figures 7 and 8).

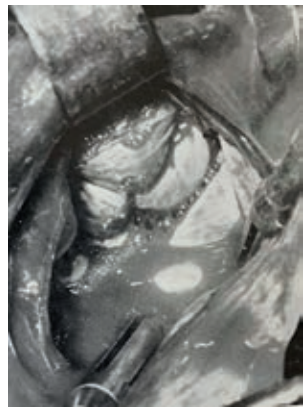

Figure 8: Atrial view of the porcine aortic valve in the mitral position

Six months later and without anticoagulant treatment (except the first six weeks after the operation) there were no signs of embolism in any of these patients[1]. By the end of the year we followed-up 26 patients with my hybrid device in the mitral position and only one episode of short-lived right arm paresis was noted. EUREKA! This demonstrated that my theory of the interface should be considered in the diagnosis and the interpretation of the origin of embolism, especially in the use of mechanical prostheses made of polished, lustrous metal. *Quod erat demonstrandum!* The success of the porcine valve mounted onto a collar gave me the impetus to try to mount the porcine valve on another support to enable its use for aortic valve replacement also.

Figure 9: Outflow view of the porcine valve.

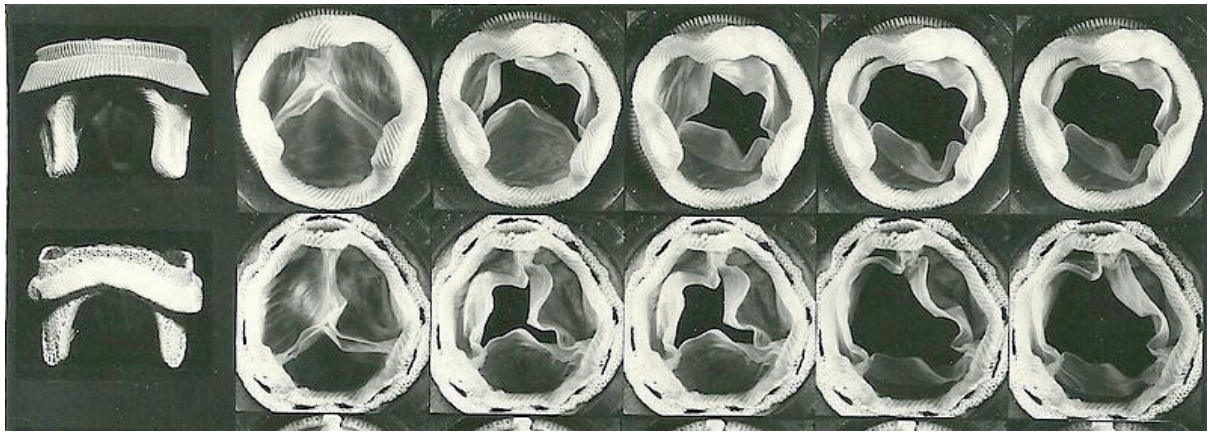

Figure 10: Systolic and diastolic photographs of the porcine valve..

After trying two other shapes of support, the classical coronet or the three pronged frame was chosen and successfully used (Figure 9).

This hybrid device has two shortcomings: the septal cusp of the pig valve is supported by muscle and this creates technical problems for mounting it on a round frame, the other one was the size of the opening of the chemically treated valve cusps. They never opened completely and regularly. The opening of the pig valve was much smaller than the implantation diameter (Figure 10).

Figure 11: Three cusp fascia lata valve.

Nevertheless, this hybrid valve was used over several years because of its lower propensity for embolisation, but always in competition with the mechanical valves. Because the haemodynamic performance of the porcine valve was far from what I wished for my ideal valve, the search had to continue.

It appeared to me that the best support for such a function is the three pronged stent for a three cusp valve. Occasionally, I used strips of the patient's own fascia lata for mitral chordae repair or for patching up an aortic valve cusp. That triggered the idea to use fascia lata for valve construction; first for in-vitro testing the hydrodynamic performance of a three cusp valve[2] (Figure 11).

All the parameters obtained from exhaustive pulse duplicator testing and from cinemato-graphic visualisation showed synchronous and rapid movement of all three cusps, a large central opening and extremely low gradients of pressure across this valve (Figure 12).

All these convinced me to start a clinical series of both mitral and aortic valve replacement. For the in vitro testing I built a special tool to produce rapidly a series of such valves. In the clinical setting the valve was constructed in the operating theatre using the patient's own fascia lata, while the surgical team was opening the chest and doing the cannulation ready for by-pass. Everything went well, clinical follow up and cardiac catheterisation showed excellent results.

This valve was created mainly as a means of testing and evaluating the performance of a three cusp valve and possibly to bring it into general usage.

Unwittingly and surreptitiously this valve became a world-wide success and after a few years of its use Frank Gerbode, from San Francisco, one of the pioneers of open heart surgery, organised an International Meeting in Silverado California, all around the use and long term results with fascia lata valves. In addition of the successes presented, it became evident that the shape and the general quality of fascia lata valves varied , sometimes significantly from one surgeon to the next. It became like a many men construction. However, the follow-up showed that this valve functioned well for about 8 to 12 years and with a very small number of embolic events. For me it was not a failure. I learned that autologous fascia lata was not the material to be used for my 'ideal' valve (*nil satis nisi optimum* - nothing but the best is good enough). Thomas Alva Edison once tested ten thousand types

Fig 12: Systolic and diastolic photographs of the fascia lata valve.

of filaments for his electric bulb, none acceptable. He was satisfied that he just found ten thousand filaments which were not doing what he was needing, almost like my Motto: I do not lose, either I win or I learn.

The next, probably the final act in the long search for a better artificial heart valve occurred one Friday morning or thereabouts, when that sliver of silvery, silken veil of light finally lifted and the tissue which I handled occasionally at the time of searching and choosing between the pig and the calf, jumped out of the blind spot and presented itself to me as the calf/bovine pericardium. I thought continually about the best, most appropriate material for this valve in the sense of a need. It was always there (Figure 13).

I started building a series of new valves, similar to the three cusp fascia lata but using the glutaraldehyde treated bovine pericardium and a different suture attachment

Fig 13: The Pericardial Heart Valve.

Fig 14: Heart Valve durability testers.

to the Dacron covered stent. Testing in the pulse duplicator showed a slight improvement on the previous fascia lata valve. The pericardium is thinner and more pliable, the opening of all three cusps was complete and synchronous, producing a central opening almost equal to the inflow surface area (Figure 15).

A series of valves were placed in four accelerating valve testers to estimate the potential longevity (Figure 14).

The first human implant of a Pericardial Valve, in the mitral position was performed on the 4 April 1971. One single essential conclusion emanates from these pages and the 14 years of work. When you become involved in research of things or ideas of any magnitude, you never give up, you never surrender.

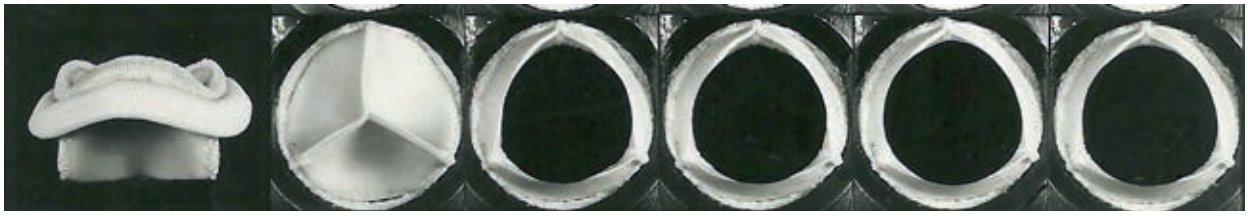

Fig 15: Systolic and diastolic photographs of the Pericardial Heart Valve.

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Chapter 3

In the Beginning...

Conception, Construction and Clinical Use of the First Pericardial Valve

Marian Ion Ionescu

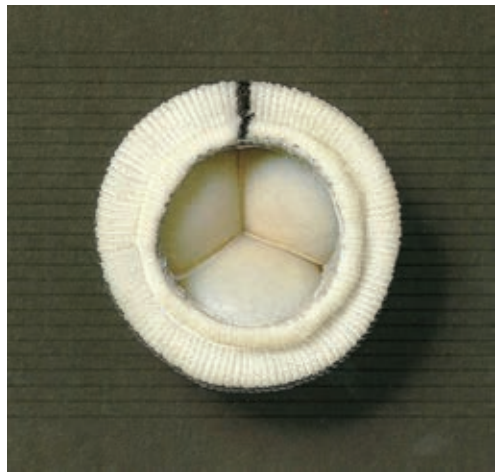
Nihil quod tetigit non ornavit

Describing here the story of the pericardial heart valve can not start at the 'beginning'. Its beginning followed other beginnings as it happened with many other events before.

Most advances in surgery - as in all fields of human endeavour - in discovery and invention took place by progressive, stepwise achievements and only rarely in a chaotic burst of intense activity around a dream or an idea.

Open heart surgery was not an exception in this respect although during its continuous progress it had been the only surgical speciality to have paid the heaviest price on the way to success.

It is hard to single out one investigator or one discovery which has made this brave new world of heart valve surgery possible because the seemingly sudden eruption of brilliant exploits is due to decades of smouldering intellectual curiosity and the dormant torment of disinterested fools who died forgotten to save their successors the trouble of thinking.



Pericardial Valve, Inflow View.

However we can mention several recent landmark developments in the evolution of heart valve surgery.

It should be remembered that the stone age finished, not because they ran out of stones, but because they discovered something better, and this was later called 'evolution'.

1957 **Geoffrey Wooler** at the General Infirmary in Leeds was the first to devise a surgical technique for repairing incompetent mitral valves by annuloplasty[1]. He used it successfully in a series of patients despite the rather primitive conditions of extracorporeal circulation and the absence of intensive care facilities. His original method for mitral valve repair spread rapidly to other centres and other countries. This concept was adapted, improved, refined and popularised by others. In its present form it is used world-wide with great success.

1961 **Albert Starr and Lowell Edwards** in the U.S.A created and introduced in clinical practice the first mechanical valve[2] which was subjected, in time, to multiple modifications and was followed by the invention and use of a multitude of various types and models of mechanical valves. Their benefits, drawbacks and significant risks are well known and thoroughly documented.

1962 **Donald Ross** in London introduced the use of aortic homografts into clinical practice[3] and, in 1967, the use of pulmonary autografts[4]. Following the use of free-hand insertion of these valves, it became apparent that stent-mounted animal tissue would represent a better solution for large volume manufacturing and easier insertion.

1965 **Carlos Duran and Alf Gunning** in Oxford published the results of their experimental work of implanting porcine aortic valves in dogs[5]. The previous year they had already performed the first successful porcine aortic valve replacement in one human patient[6].

1965 **Jean Paul Binet** in Paris, France, began the use of porcine aortic valves for aortic valve replacement in humans[7].

1967 **Marian Ion Ionescu** in Leeds used, for the first time, in the mitral position in humans, porcine aortic valves mounted onto a Dacron cloth support and began a series of such valve replacements[8].

1967 **Hancock Laboratory** in Irvine, California, introduced the first commercially available stented porcine aortic valves for use in patients[9]. This was followed shortly thereafter

by other American laboratories beginning to manufacture and commercialize such valves: Medtronic, Edwards and Shiley. Many surgeons and scientists contributed to the creation and improvement of the porcine valve.

1969 **Marian Ion Ionescu** in Leeds created and started the clinical use of the stented autologous Fascia Lata heart valve[10].

1969 **Alain Carpentier** and co-workers in Paris, France, advocated the use of glutaraldehyde for the chemical treatment of porcine aortic valves[11].

1971 **Marian Ion Ionescu** in Leeds created a completely novel concept for constructing a new and different type of heart valve made of chemically treated bovine pericardium attached onto a support frame. He began the clinical use of this valve in April 1971[12].

In 1976 Shiley Laboratory in Irvine, California, based on initial results obtained with the use of this new valve, began manufacturing and distributing this valve under the name "Ionescu-Shiley Pericardial Xenograft.''

The various progressive modifications made in the construction of this valve will be described later.

The essence of this novel concept is summarized as follows:

- The use of glutaraldehyde- treated bovine pericardium;
- The attachment of the pericardium onto a flexible Delrin stent;
- The technique of valve construction assured complete and synchronous movement of all three cusps allowing for a full orifice opening of the valve;
- The crucial and unique characteristic of this concept is that the valve being man-made, lends itself to a multitude of possible permutations of shape and configuration in order to progressively optimize its function. Due to this distinct and unique characteristic, the concept of the pericardial valve continues to persist and to be useful in various forms over a period of nearly five decades of clinical use.

During the first 6 years of clinical use of the pericardial valve manufactured by Shiley, its advantages and negative aspects became apparent and had been documented, studied, evaluated and in part explained and remedied through the efforts of many research workers who found vital information in the experience with the 'first generation' of pericardial valves.

This led to the development and manufacture in the early 1980s of the 'second generation' of pericardial valves by several specialised laboratories. All these valves benefited, firstly, from the existence of, and the experience with, the Ionescu valves, and secondly, by using the principles of the initial Ionescu concept of pericardial valves which allows for a variety of modifications retaining the essentials: glutaraldehyde treated bovine pericardium attached onto a flexible stent. These improved 'second generation' valves, used almost exclusively in older patients (aged more than seventy years), and mainly for aortic valve replacement, have already shown their clinical benefit.

Since the first balloon-expandable transcatheter aortic valve implantation (TAVI) in 2002 by Cribier and colleagues[13] and the first self-expanding TAVI by Grube and his associates in 2004[14] this technique for aortic valve replacement using the principle of the pericardial valve concept has grown rapidly to more than 80,000 implants world-wide.[15]

Realisation of the concept - Construction of the first valves

> *The success of most things depends upon knowing how long it will take to succeed*
>
> *Charles Montesquieu de Secondat (1689-1755)*

The leit-motif of Ionescu's continuous work on valve development was the dream, the idea to create a tissue heart valve which will perdure and will not require long-term anticoagulation.

The creation of a prototype for the pericardial valve to be built began, in 1970, with a rod of lucite (plexiglass) which was sculpted with a dental drill into a mould for a 3-cusp valve (Figure 1). Simple empirical visual estimations were used to create, out of imagination, some shape that looked like an aortic valve (a man-made one) should look.

Papier-mache was used to mould a valve over the lucite form. (Probably Ionescu used the Guardian newspaper which explains the lack of conformity with the God-made valve). The next step was to make metal moulds which could be covered first with a water-soluble silicone over which a solution of polyurethane was applied. When this was set and dry some simple trimming was necessary to free the polyurethane 3-cusp valve from its mould. In a simple, primitive laboratory-built pulse duplicator several such valves were tested and proved to be competent. The apposition of the cusps was empirically established by simple adjustments to the top of the mould.

Figure 1: Moulds for building the first experimental pericardial valves.

The movements of all three cusps was synchronous, their excursion complete and brisk, provided the thickness of the polyurethane for valve fabrication was correct. This thickness was obtained empirically depending on the cusps' movement and also by preventing air bubbles from developing inside the polyurethane solution. Ideal conditions for this were found by working in a cold chamber. This happened to be the butcher's refrigerator - the same butcher who also provided the bovine pericardial sacs.

Mr John Aylwin, a senior surgeon at the hospital in Leeds, who supported Ionescu in his unending experiments might have said that he saw some great things coming out of scruffy places!

From here the next step was to start the construction of the valve. Supporting stents were made in a small workshop in a village near Leeds, using a titanium alloy because of the lack of a more suitable material at that time. The prongs of the stent had, however, a certain amount of flexibility. These stents were covered with Dacron velour and the same material was used for the flange (the sewing rim) by Mrs Ionescu. The pericardial pieces, cut to size after treatment with glutaraldehyde, were attached on the outside of the stent and sutured at the base of the stent and to the top of the posts, initially around a small pledglet of Dacron.

During 1970, simple pulse duplicator tests were carried out during conditions of continuous and pulsatile flow, with measurements of pressure gradients and speed of flow across the valves. These measurements, together with high-speed cinematography, showed excellent hydrodynamic function of these valves.

From the very beginning of this project of building a 'man-made' valve the material selected to be used was bovine pericardium. The main reasoning was that looking forward beyond the pig aortic valves seemed to be futile, therefore looking sideways was the answer - the bovine pericardium. This material possessed, grosso-modo, what at that time were considered some of the requirements of thickness, pliability, abundance and availability. The histological structure seemed acceptable as far as general architecture of the tissue is concerned.

With so little knowledge about this whole project, and few ways of finding out more, it was the moment to repeat Winston Churchill's saying: *'It is difficult to look further ahead than you can see'.*

Between 1971 and 1976 the valves had been made in Ionescu's own hospital laboratory. Throughout these five years of usage in 212 patients, the performance of the pericardial valve in all three cardiac positions, was thoroughly evaluated. The results showed that

this original valve exhibited the best haemodynamic performance, at rest and during exercise[16] when compared with the reported results of all other artificial valves in existence. It demonstrated a very low risk of embolisation even in the absence of long term anticoagulation treatment of the patients. There were no cases of valve thrombosis, intra-vascular haemolysis or sudden, unexpected valve failure. The durability of the valve was good at 5 years of follow-up[17].

Based on these results, the Shiley Laboratory in Irvine, California, began to manufacture this valve and to distribute it worldwide under the name of the 'Ionescu - Shiley Pericardial Xenograft.' (Figure 2)

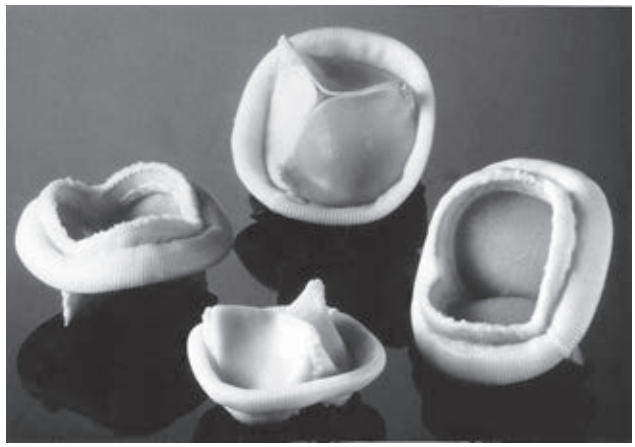


Figure 2: Family of Ionescu-Shiley Pericardial Valves.

From 1976 onwards a series of modifications were made in order to improve the qualities and the performance of the pericardial xenograft. The selection and preparation of the bovine pericardium were standardised and rigorously controlled. For tissue fixation a solution of 0.5% purified glutaraldehyde was used. It contained an optimal proportion of monomers and polymers and an ideal cross-link density was obtained by controlling the concentration and the pH of the solution as well as its temperature and exposure time of the tissue to its action.

The highest quality of commercially available glutaraldehyde was purified at Shiley Scientific Inc. using a selective technique to control the glutaraldehyde monomer-polymer composition.

No single glutaraldehyde solution could either optimize the durability and flexibility of the tissue treated, or reduce its antigenicity and also provide the most effective degree of sterility. The importance and priority of each of the following parameters must be established and the most appropriate balance reached in order to obtain the optimum quality of pericardium for valve construction:

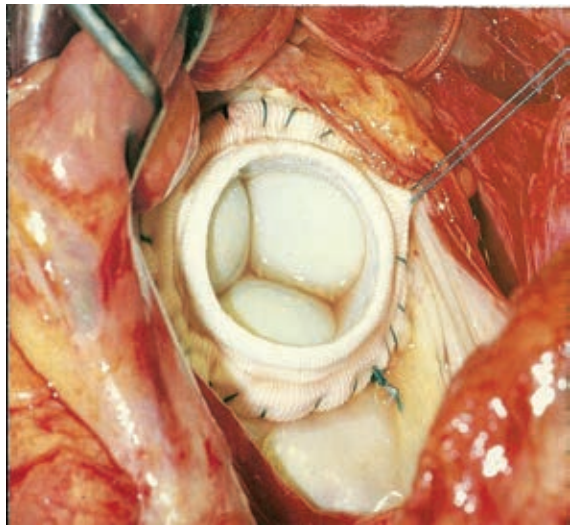
- Glutaraldehyde concentration and composition
- pH and ionic strength
- Time and temperature of tissue exposure to glutaraldehyde
- The tissue configuration during the initial fixation.

All other procedures of tissue preservation claiming increased valve durability and patient survival are illusory unless scientifically documented.

The thickness and pliability of the pericardium were standardized and the direction of the macroscopically visible fibres matched for each three cusps of a particular valve. The supporting stent was changed. The titanium was replaced with machined Delrin which is an acetyl homopolymer with low 'creep' properties due to a stable molecular memory. It is flexible and shock absorbent, essential qualities for a tissue heart valve support. This new stent contained a radio-opaque marker at its base for easy identification. The contour of the scalloped posts was modified and the height of the stent reduced. The entire Delrin structure was covered with seamless Dacron velour and at a later stage, the margins of the scalloped edges were covered with a thin layer of pericardium in an attempt to prevent or reduce the abrasion of the leaflets when in contact with this margin during valve closure. The sewing rim was bolstered for better and safer attachment to the heart annuli and its shape was anatomically contoured into two different configurations to better fit in the aortic and the atrio-ventricular positions. Two other additions were made: an integral valve holder which prevented the touching of the valve's cusps, and a

'freeze-watch' indicator, attached to the outside of the containers of the valves, as a safe-guard against exposing the valves during transportation or storage at temperatures below 4 degrees Celsius.

The geometry of the valve was slightly modified due to changes in the shape of the stent and by removing the outside pledglets around the posts. This gave a more streamlined shape of the whole structure. These modifications had been progressively introduced and all of them were incorporated in the 'Ionescu - Shiley Low Profile Pericardial Xenograft' valve, which became available in 1983.



In order to remove any risk of pericardial leaflet abrasion Ionescu devised, in 1986, a new and completely different technique for attaching the pericardial leaflets to the stent. Shiley began implementing this idea by redesigning the stent. The new one was made of two wafer-thin, unequal, flexible Delrin components: an outside, standard shaped frame and an inner, smaller structure. The pericardial cusps were mounted inside the outer frame and were kept in position by the inner frame which was smaller and much thinner than the outer one. Through this arrangement, the lower parts of the pericardial cusps exit from the supporting frame at its bottom, and therefore the pericardium does not bend over the upper margin of the stent, eliminating the possibility of abrasion during the closure phase of the valve. As it was learned from clinical and from in-vitro studies, abrasion of the pericardium was a cause of valve failure when the tissue was attached on the outside of the stent[18,19]. The in-vitro testing of this modified pericardial valve showed almost identical hydrodynamic performance when compared with the existing pericardial valve.[20] Accelerated life-testing showed that failure of this new valve occurred some 3 to 4 times later than that of existing valves. When valve failure occurred it was not due to abrasion but through progressive fraying of the pericardium. Encouraged by these results, Shiley decided to start manufacturing this modified, improved valve called the 'Ionescu-Shiley Pericardial Optimograft'.[21]

At about that time grave problems were encountered by Shiley Laboratory with an increasing number of sudden failures of the Bjork-Shiley mechanical disc valve.[22] As a consequence of this unacceptable situation Pfizer, the giant drug manufacturer and owner of Shiley, stopped all manufacturing activities at Shiley Laboratory, with a view to liquidate the company. Consequently, not only the Bjork-Shiley valve (the culprit) was affected by this action, but all other products - valves, oxygenators, catheters, etc. - went out of production and the company was wound down.

At that crucial time for valve development, that decision was a blow to further work already under way for the final testing and evaluation of the new Ionescu-Shiley Pericardial Optimograft.

Approximately 200,000 pericardial valves manufactured by Shiley Laboratories were distributed around the world between 1976 and 1987 and it is presumed that most of them were implanted in patients.[23] The use of this valve generated a lot of interest expressed in several specialist symposia, academic meetings, and numerous scientific articles published over the years.

The appropriation and organisation of this enormous material and the classification and interpretation of data has been a very difficult and complex task, especially because, contrary to what it is claimed, there remains a great deal of variation in standards of reporting in all essential chapters of a scientific work. In some cases it is quite impossible to follow such standards, as it will be described later. Despite

all these difficulties and impediments, a general view of the performance of the pericardial valve as close to reality as possible could be obtained.

One should however keep in mind that any single investigator should resist the temptation to write a review of such a complex matter as tissue heart valves, and to cover the subject completely and fairly. One should also remember that when we study complex and variable conditions, averages must be rejected because they confuse while aiming to unify, and distort while aiming to simplify.

From the material available it is evident that the reported hospital mortality and, up to a certain point, late mortality are similar among the various publications of different authors, and do not directly reflect on the quality of the valve used.

Haemodynamic Investigations and In-Vitro Testing of Valves

> *Truth is a torch which shines in the mist without dissipating it*
>
> *Claude Adrien Helvetius (1715-1771)*

The Ionescu pericardial valve had a large central opening almost equal with the inner surface area of the supporting stent. This, plus the pliability of the pericardial tissue, confer this valve exceptional

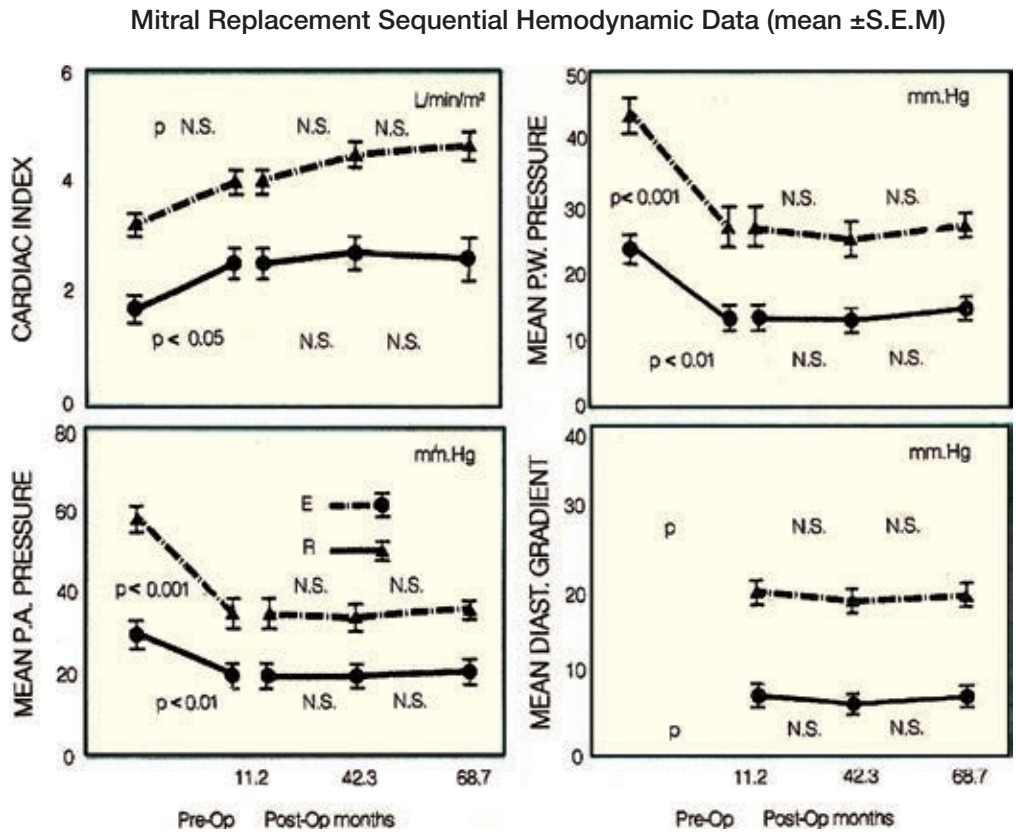


Figure 3A: Graphic presentation of mean values at rest (R) and during exercise (E) of results from sequential haemodynamic investigations performed on six patients with mitral pericardial valve replacement.

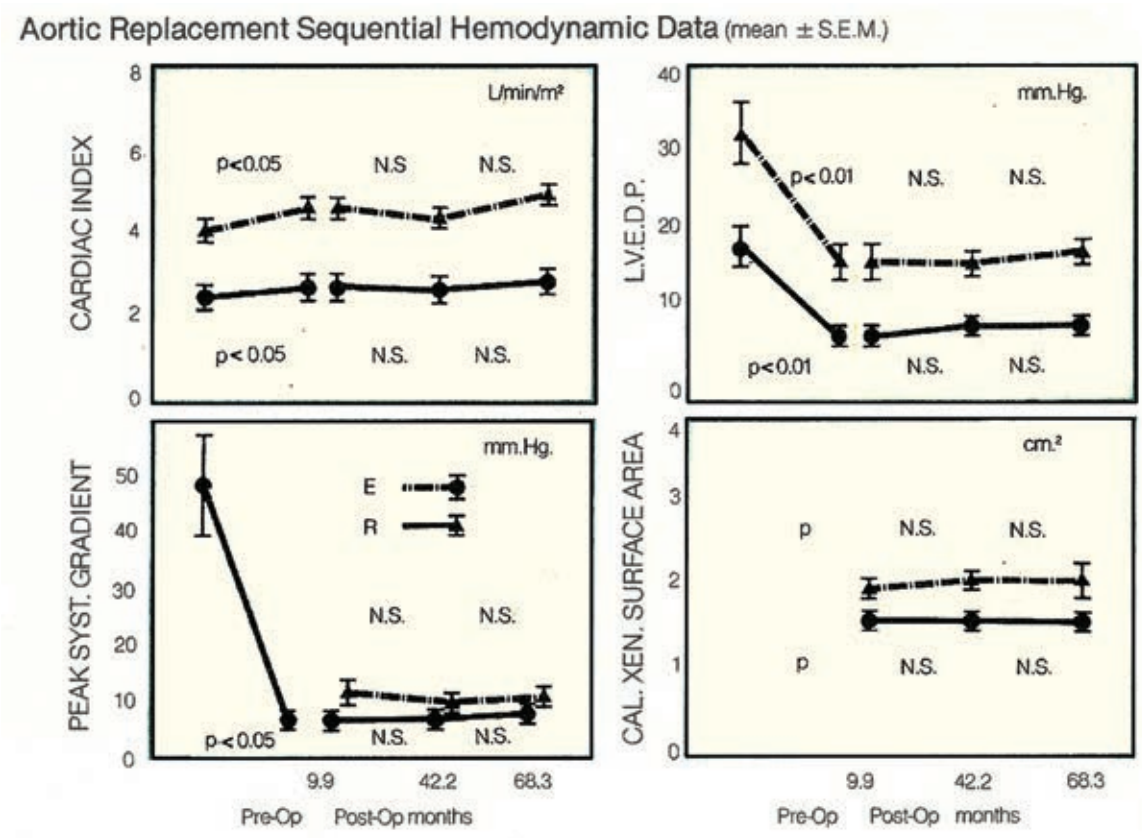


Figure 3B: Graphic presentation of mean values at rest (R) and during exercise (E) of results from sequential haemodynamic investigations performed on thirteen patients with aortic pericardial valve replacement.

hydraulic qualities. Haemodynamic studies by several authors[16,24,25,26,27,28,29,30;] investigating patients with pericardial valves, in both mitral and aortic positions, demonstrated that in all respects the haemodynamic function of this valve is superior to that reported for the porcine valves and, generally speaking, equal to that of the best mechanical prostheses. The haemodynamic results reported by other investigators are very similar to those by Tandon's group. Some authors stressed the advantage of very low pressure gradients across small pericardial valves (viz: 17, 19 and 21mm diameter) for implantation in small aortic roots without the need of complex surgical techniques for root enlargement.[25,26,27]

Tandon and associates[28,29] performed pre- and postoperative haemodynamic investigations at rest and during exercise in 110 patients. There were 51 with aortic valve replacement, 44 with mitral replacement, 3 with tricuspid and 12 who received multiple valve replacement. Following a technique and protocol developed at Leeds General Infirmary, from the group of 110 patients investigated, 13 patients with aortic and 6 with mitral valve replacement were subjected to multiple, sequential haemodynamic studies at rest and during exercise at the following intervals: aortic, preoperatively and at 9.9, 42.2 and 68.3 months postoperatively; mitral: preoperatively and at 11.2, 42.3 and 68.7 months postoperatively. The results obtained showed that the considerable improvement recorded at the first postoperative investigation was maintained up to 68 months following valve replacement[16] (Figs 3A & B).

In order to demonstrate visually the reasons for the great haemodynamic difference between the pericardial and porcine valves, Ionescu recorded in a 'pulse duplicator' the opening characteristics of two porcine valves (Hancock Modified Orifice and the recently modified Edwards valve) and two pericardial valves (the Standard and the Low-Profile Shiley valves).

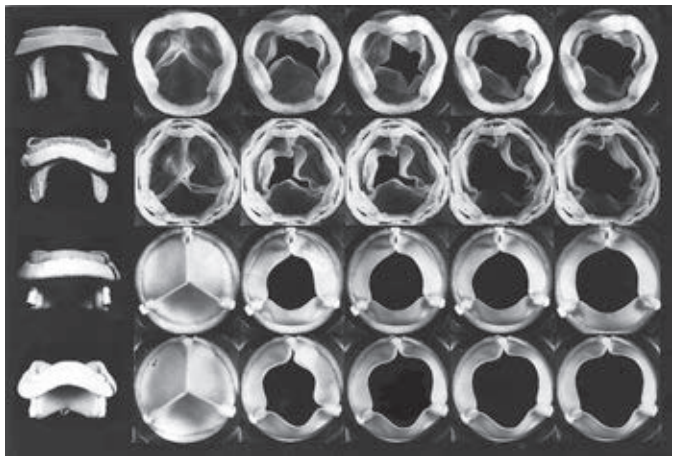


Figure 4: Opening characteristics of porcine aortic and Shiley pericardial valves.

All four valves were manufactured for clinical use and all had an implantation diameter of 25mm. The valves were tested under identical conditions in the mitral compartment of the pulse duplicator and photographs were taken at the peak of diastole. The flow rates were for each frame, from left to right: 0, 100, 200, 300 and 400 ml per second. The opening of the cusps of both types of pericardial valves is synchronous and regular, without three-dimensional flexure and the low-profile pericardial valve shows an even larger opening when compared with the standard pericardial valve. There are no crevices or dead spaces behind the open cusps of the pericardial valves. The difference between the porcine and the pericardial valves is clear in all respects (Figure 4).

Many authors had studied, in-vitro, the hydrodynamic performance of the pericardial valve and found that it possesses better functional characteristics than the porcine valves and similar to those of the best mechanical prostheses.[31,32,33] In summary, the excellent haemodynamic function of the pericardial valve is one of its' great advantages and sets it aside from all other stented tissue valves.

An interesting observation was made by Rainer[34] during in vitro testing of tissue valves. At a flow rate of between 4.4 and 5.2 l/min, in a pulse duplicator set at 72-80 beats per minute, high-speed photographs were obtained. The valves tested were Hancock and Edwards porcine aortic valves and Ionescu-Shiley pericardial xenografts. Both porcine valves developed flutter and vibration in one of the three cusps, while the pericardial valve did not exhibit this anomaly. The author considers that tissue vibration is more destructive than any other mechanisms.

In addition to the usual description of hydrodynamic function of tissue valves, several investigators[35,36] tried to find answers to other aspects of valve function. It is almost universally mentioned in the specialised literature and in the publicity of manufacturers descriptions, the notion that tissue valves have to be mounted on a flexible stent. Wright[37] questions this assertion by explaining that making the inlet or the annulus section of the stent too flexible leads to valve distortion and insufficiency. Also it has not been scientifically demonstrated that annulus flexibility improves the clinical function or durability of valves.

Figure 5: Valve frames made of titanium alloy with slightly flexible struts as originally used by Ionescu for the pericardial valves.

The reason for the use of a flexible stent stems from an article by Reis and Hancock from 1971[38]. They reported

a 90% decrease in mechanical stress on the porcine aortic valve cusps if the commissures have no rigid attachment.

Thomson and Barratt-Boyes[39] have stated that this figure is too high since the tip of each frame-post deflects by only 0 - 0.21mm at a pressure of 100mmHg. Brewer et al[40] measured 1.2mm mean radial change of the aortic root wall in a pulse duplicator at a pressure of 120/80 mmHg.

Drury et al[41] demonstrated that: 'There is a three dimensional movement of the commisural points within the natural aortic root and that at the present time there is insufficient data on which to make definitive recommendations regarding the ideal frame material and geometry. The resilient, flexible, creep and fatigue-resistant titanium alloy, together with the symmetrical design of the stent seems to present a logical step forward, but only long term clinical experience will confirm its significance.''

It is interesting to remember that Ionescu chose, for the first pericardial valves, to use titanium for stent construction for its lightweight and its flexibility characteristic. (Figure 5)

Clinical experience with bioprosthetic valves in many ways, exceeds design experience if true engineering, rather than empirical design procedures are considered.

The relevant information is scant in many respects and, as a consequence, valve construction has been empirical in nature with little understanding of the complex relationship between tissue properties, (following chemical treatment), the valve geometry (based on tri-leaflet design) and frame structure and flexibility and the flexibility distribution around the frame[41]

The creation by Ionescu of the first pericardial valve, in an empirical way, is certainly a good example of empirical design. It is worth mentioning that at the beginning of the use of flexible stents, the Hancock porcine valves suffered a series of failures due to the creep phenomenon until the qualities of plastic materials for stent fabrication became know.

Excessive flexibility of the Carpentier-Edwards mitral pericardial valve stent obliged the company to withdraw this valve from the market. It was reintroduced four years later following redesign of the support stent[42].

Finally to paraphrase Thubrikar[43] one may say: Pericardial valves continue to emerge in a variety of designs with the aim that their performance will be improved. Since they have proven to be the preferred substitute for replacement of diseased heart valves in humans, the evolution of their design will continue until the ideal valve is found. This proves the veracity and the strength of the Ionescu Pericardial Valve Concept.

Valve Related Complications

> *Valves are like clocks, the worst is better than nothing, and the best …… one could not expect them to function for ever*

Embolism, Thrombosis and Anticoagulation-related Haemorrhage

> *It is what we believe we already know that prevents us from learning*
>
> *Claude Bernard (1813-1878)*

While dealing with a very large number of reports from different hospitals with various numbers of patients who received pericardial valves and were followed-up for differing durations of time, from 5 to 10 years, and especially because the reporting did not follow an 'established' albeit loose 'standard' of identification, description and grading of the events, it was decided to enumerate the results from some of the more representative series reported and draw only general conclusions - Table 1.

The following data shows the results as given in actuarial percentages of freedom from embolism.

Table I. Freedom from Embolism

Main Author	*No of Patients*	*Duration Follow-up*	*Actuarial freedom from embolisation*
DA Cooley[44]	2701	5 years	93.2% for all patients. 96.1% for aortic, 89.7% for mitral and 94% for mitral and aortic replacement
A Pavie[24]	675	5 years	95.8% for all patients
M Holden[45]	290	6 years	5 Emboli (1 certain, 4 doubtful). 0.70% per patient year
JM Revuelta[26]	80	8 years	93.6% for all patients
Gonzales-Lavin[46]	224	8 years	95.3% for aortic, 97.4% for mitral replacement 4(46 (43)
JB Garcia-Bengochea[25]	248	8 years	97.5% for all patients
NP Silverton[47,48]	492	6-10 years	96.8% for mitral, 97.2% for multiple replacements
XD Zhu[49]	520	9 years	95.8% for all patients
MI Ionescu[17]	1171	10 years	96.4% for aortic, 96.8% for mitral, 97.2% for multiple replacements

It is interesting to note that the actuarially presented results of freedom from embolism improve in a direct proportion with the length of the follow-up.

From perusing innumerable publications on the results of heart valve replacement with pericardial valves, concerning the rate of embolic complications, one may formulate several conclusions.

A clear picture concerning the exactitude of thrombotic and embolic complications of artificial heart valves, and especially of pericardial valves, seems to be very difficult. Our knowledge at present is superficial and incomplete concerning the real causes and the risk and contributing factors to this complex phenomenon. Consequently, it has never been practical to try to standardise definitions, and even more complicated to establish lines of treatment. Everyone talks of 'causes' and 'risk factors' but no-one possesses any scientific evidence to this effect.

The so-called 'risk factors' for embolisation, with the exception of atrial fibrillation, can be called, at best, 'scientific illusions'. Consequently, any scientific, logical way of establishing a therapeutic means for preventing such phenomena due to unknown or incompletely understood causes is doomed to remain empirical, and the end results uncertain.[25,46,48,50] There are myriad reports for and against anticoagulant treatment for patients with tissue heart valve replacement. In addition, heart valve replacement patients are followed-up by a 'committee' made up successively by the surgeon, the cardiologist, the general practitioner in this or another town, etc., etc. The impression of knowledge or our acceptance of ignorance compound this matter further. Our only salvation - the patients and our own - would be an artificial heart valve which carries a very low risk of embolism, and therefore would not require, in the majority of cases, anticoagulant treatment.

One main draw-back in the recent 'scientific' literature on pericardial valves is the fact that the essential data for arriving at an intelligent interpretation of results is missing. There is no description of the pre-operative

condition of the patients concerning cardiac rhythm, various arrhythmias, atrial fibrillation, anticoagulant treatment, previous systemic emboli, etc. etc., and scant information about the post-operative condition: cardiac rhythm, the nature and duration of anticoagulation, the time of occurrence of embolic phenomena and the magnitude and sequelae, if any. All this is already in the past now, for practical purposes, one can conclude that the pericardial valve carries a very small risk of embolisation, much smaller than that of the porcine valves even in the absence of anticoagulant treatment. The risk of pericardial valve thrombosis is exceedingly remote. The extremely few cases reported have not been thoroughly investigated as far as the timing of occurrence, the cause or the contributing factors, related or not to the valve, are concerned. Anticoagulant related haemorrhage was very rarely reported because few patients received prothrombin depressants for long periods of time (*Sublata Causa Tollitur Effectus*).

There are a few reports about patients with tissue valves in the mitral position and with atrial fibrillation. Half of the patients were anticoagulated and the other half were not. However there was no difference in the embolic rate between patients with anticoagulants and those who were not anticoagulated[51,52]. In addition, it was observed that the rate of embolisation appears to be decreasing with the passage of time with the pericardial valves, unlike the experience with porcine valves in the mitral position where the risk remained constant during the whole period of follow-up in spite of different schemes of long-term anticoagulation.[48]

The favourable embolic rate and virtual lack of valve thrombosis of the pericardial valve appear to be due to the quality of the tissue, and especially to the design of the valve with a smooth and synchronous movement of all three cusps and the streamlined structure conferring the valve optimal haemodynamic characteristics even at low flow rates.[32,46,48]

Following the description of embolic complications surrounding the use of pericardial valves, it is important to discuss two essential points of this phenomenon.

The first one is the persisting but erroneous usage of the term 'thrombo-embolism' repeated ad nauseam in most publications and oral presentations.

Table 2: Embolic complications in Medically Treated Patients with Rheumatic Mitral Valve Disease[47]

Sources	*Patients*	*No of Follow-up years max mean*	*Emboli % per Annum*
	Without Anticoagulation		
Rowe et al	250	10 --	2.0
Szekely	754	22 7.7	1.5
Coulshed et al	166	16 3.9	3.7
	With Formal Anticoagulation		
Flemming	217	up to 9	0.8

Many investigators describing the clinical performance of artificial heart valves use the term 'thrombo-embolism' for what in reality are two distinct phenomena: thrombotic obstruction of the valve and systemic emboli or embolism. Thrombosis is a clotting event which occurs 'in situ', while emboli, of various sizes and differing composition and origins, are circulating particles which almost always reach the end of their journey in a branch of the arterial tree.

Nashef and his associates[53] consider that in the context of heart valve replacement, systemic embolism may appear to be unrelated to the type of artificial valve in situ, while thrombotic obstruction is directly related to the valve type. He also demonstrated that patients who develop thrombotic valve obstruction were not at a higher risk of systemic embolism than others. The analysis of Nashef shows that these two complications have markedly different incidence patterns.

This matter of nomenclature had been raised several times in the past by different authors but, surprisingly, unsuccessfully.[53,54] The second aspect of this matter is to try to clarify the complex phenomena of thrombosis and embolism in the context of heart valve replacement, especially with tissue valves.

At present it is impossible to determine with certainty whether all episodes considered to be embolic events are due to the migration of particles from an intracardiac thrombus. There is however some evidence that this may not be the case.

In a progressively aging population undergoing open-heart surgery such events could result from other causes than heart valve replacement. The commonly described causal factors are: atheromatous disease, sometimes calcification of the ascending aorta, the carotid arteries and the cerebral branches of the carotid and vertebral arteries. In addition, hyperlipidaemia, blood hyper-coagulability and polycythemia vera had been implicated, mainly in the context of strokes.

During open-heart procedures other causes for embolism may exist, such as: various particles of foreign material from the removal of calcified cardiac valves, flakes of dried blood from surgical instruments and even microscopic loose particles of cut sutures. Rare causes could also be considered like the paradoxical embolus through a patent foramen ovalae or an atrial septal defect.

It is surprising that when describing embolic episodes following tissue heart valve - or any other type of valve replacement for that matter, the factor 'stroke' has not been considered, especially when dealing with patients aged beyond 70 years.

Table 3: Factors Considered to be Related to Systemic Embolism in Patients with Mitral Valve Disease

Authors and treatment	*No of patients*	*History of embolism*	*Age*	*AF*	*NYHA Class*	*CTR (LA size)*	*Clot in LA/LAA*	*Calcified valve*
Coulshed et al Medical treatment	839	N/A	+	+	+	--	--	--
Flemming Medical treatment	500	N/A	+	+	--	--	--	--
Ellis and Harken CMV	1500	?	--	+	--	--	--	--
Vega et al OMC	159	?	--	+	--	--	?	--
Borkon et al MVR (Hancock)	62	--	--	+	--	--	--	--
Hill et al MVR(Hancock)	124	--	--	+	--	--	--	--
Lakier et al MVR (Hancock)	125	--	--	+	--	?	--	--
Cohn et al MVR (Hancock)	80	--	--	+	--	?	--	--
Silverton et al MVR (Pericardium)	400	--	--	+	--	--	--	--

AF - atrial fibrillation, NYHA - New York Heart Association, CTR - Cardiothoracic ratio, LA - left atrium, LAA - left atrial appendage, N/A - not-applicable, MVR - mitral valve replacement, OMC - Open mitral commissurotomy, Hancock - Hancock porcine valve, Pericardium - pericardial xenograft valve, ? - not clarified.

There is a very significant incidence of 'naturally occurring' strokes in the population.

Barratt-Boyes[55] drew attention to this situation explaining that the older the patients become for valve replacement, the more important this factor is. Because of this background of stroke in the population operated upon, he refuses to list as embolism such events in his publications on homograft aortic valve replacement although the incidence is recorded.

In the United Kingdom during the last three years there were approximately 150,000 strokes per annum (one every five minutes), causing, in 2010, about 50,000 deaths. In England the incidence is between 2.2 to 2.4% per 100,000 of population per annum, with similar figures for Northern Ireland and Wales, while in Scotland the rate was higher at 2.5 - 3.3%. It is also know that 85% of strokes are ischaemic in origin. In this group the cause is atherosclerosis in 50% of cases, lacunar strokes in 25%, cardiac in 20% and the rest are produced by conditions of rare or obscure origin. Of course there is considerable variation according to age with heavier prevalence in the 65 - 95 years old age group. World-wide there are 15million strokes every year[56].

The fact that the age of the population requiring aortic valve replacement advances progressively, the 'factor stroke' becomes more important in the interpretation and reporting of the cause and the nature of embolic complications. The known incidence of stroke in the elderly population represents a certain part of the reported embolic rate following aortic valve replacement with tissue valves.

Another element to be taken into account when describing the survival and the embolic rate of patients older than 70 years is the life-span of this population.

Leguerier and his colleagues[57] compared the survival rate of patients having aortic valve replacement with the death rate of the general population of the same age (as established by the French National Institute of Statistics - INSE) and found them quite similar. The actuarial survival curves showed at 5 years 84.3% for the general population and 67.2% for patients with aortic valve replacement (operative death of 10.1% included). At 8 years the figures were 65% and 56% respectively.

Ignoring this reality, several definitions for symptoms of systemic embolism were artificially created and published over the years, some of them touching the absurd and some others built on imagination. They did a lot of damage to the reporting of these complex and poorly understood phenomena. As an extreme example, one may quote: the person who experienced dizzy spells or had not remembered in time the name of the seventh king of ancient Rome remained a peaceful law-abiding citizen unless he had an aortic valve replacement, then these events will be classified

Table 4: Embolic Complications Following Conservative Rheumatic Mitral Valve Operations[47]

Source	*No of patients*	*Atrial Fibrillation %*	*Follow up max yrs*	*Follow up mean yrs*	*Operation*	*Anti -coagulation treatment*	*Emboli% per annum*
Ellis and Harken	1590	51.6	11.0	6.0	CMV	None	0.46
Ellis et al	913	?	15-20	-	CMV	?	1.1
Haseth et al	191	28.8	10.0	4.5	OMC	14	0.56
Gross et al	197	common	10.1	3.5	OMC	20.3	0.34
Vega et al	159	40.0	5.3	3.0	OMC and or MR	?	0.61
Tandon et al	115	72.5	19.0	9.0	MR	20	0.61

CMV - Closed mitral valvotomy, OMC - Open mitral commissurotomy, MR - Mitral repair

Table 5: Embolism in patients having Mitral Valve Replacements with Hancock Porcine Valves[47]

Institution	*Years of Valve range*	*No. of patients*	*Emboli % per annum*	*Long term anticoagulation*
Kansas University	1970-75	104	4.8	If LA thrombus
Henry Ford Hospital	1971-75	228	4.7	54% of patients
Henry Ford Hospital	1971-75	125	2.9	75% of patients
Stanford University	1971-75	243	5.2	15% of patients
Stanford University	1971-78	561	3.1	31% of patients
Brigham Hospital	1972-77	131	3.8	If AF or large LA

LA - left atriem, AF - atrial fibrillation

Table 6: Embolism in patients having Mitral Valve Replacement with tissue valves[47]

Institution	*Valve*	*Years of valve usage*	*No. of patients*	*Emboli % per annum*	*Long term anticoagulation*
Pacific Medical Center	Hancock	1974-77	126	5.3	50% of patients
Pacific Medical Center	Hancock	1974-79	124	3.12	62% of patients
Pacific Medical C enter	Hancock	1974-78	72	3.16	100% of patients
British Columbia University	Carpentier Edwards	1975-78	261	3.5	45% of patients
N.I.H Bethesda	Hancock	1970-75	62	3.3	6.5% of patients
Good Samaritan Hospital	Angell-Shiley	1975-80	103	3.4	If AF, history of T/E, LA thrombus, giant LA, intimal disruption
Leeds University	Ionescu-Shiley	1971-82	400	0.67*	NONE

AF - atrial fibrillation, T/E - thromboembolism, LA - left atrium, N.I.H - National Institutes of Health
**Similar low incidences of embolic events in patients with pericardial valve replacements were reported and presented in actuarial form by numerous authors*[17,24,25,26,44,45,46,47,48,49]

Table 7: Serious and Fatal Bleeding Complications in Patients with Mitral Valve Disease Treated with Anticoagulants[47]

Sources	*Year of publication*	*No of patients*	*Follow-up max years*	*Follow-up mean years*	*Treatment*	*Bleeding % per annum*
Flemming and Bailey	1971	217	9	--	Medical	2.3
Gross et al	1981	40	10.1	3.5	Open mitral valvotomy	0.79
Hill et al	1982	72	--	2.2	Mitral Hancock	6.32
Angell et al	1982	103	5	--	Mitral Angell-Shiley	2.1
Borkon et al	1981	32	10	5.4	Mitral Hancock. Aortic Starr	4.9
Bjork and Henze	1979	413	10	4.8	Mitral Bjork-Shiley	6.3
Edmunds (collective review)	1982	21	550 patient years from 9 reports		Various mitral prostheses	0.5-6.3 (2.19)
Oelert et al	1982	42	4	19.6 mths	Mitral and aortic Pericardial	8 episodes (2 severe)

as embolic episodes! This example calls for a clear differentiation between 'soft' and 'hard' symptoms of cerebral vascular accidents.

The exact incidence of systemic embolism generated by heart valve replacement in general, and by each type of tissue valve in particular, when considered in the context of the 'stroke factor' which itself is responsible for about 2.3% per annum (in England) of cerebral vascular accidents in the general population, is extremely difficult to ascertain. This probably is the cause of different figures of embolic rates published by various authors about series of patients of differing age groups.

In patients requiring medical or surgical treatment for mitral valve disease the problem is, in principle, the same as for those with aortic valve replacement, although it becomes more complicated because mitral valves - diseased or repaired / replaced - function in a different environment between two heart chambers and therefore are exposed to considerably different pressure regimes when compared to the aortic valve environment. In addition, the age of the patients in this situation is much lower than that of patients with aortic valve replacement.

In order to better understand the complex nature of embolism in patients with mitral valve disease a retrospective analysis of data published over the years on this subject may shed some light on the pathophysiology on this complication. The association of systemic embolism with chronic rheumatic mitral valve disease has been recognised for many years.

Table 2[47] lists the approximate incidence of systemic emboli in several large and well reported series of medically treated patients with chronic rheumatic mitral valve disease. The incidence of systemic embolism of 1.5 to 3.7 episodes per 100 patient years seems to have been reduced by the use of anticoagulation. It must be stressed that the enthusiasm for anticoagulant prophylaxis derived from a study in Norway initially in only 17 patients all of whom had

previously experienced recurrent documented emboli and who acted as their own control. A second study comprised 15 patients anticoagulated after their first embolic episode, for a mean period of 6 years, with 17 control patients. The particularly strong association of embolic phenomena with chronic atrial fibrillation is apparent in almost every reported series, but as shown in Table 3[47], there is no significant correlation between embolism and any other factor previously considered to be associated with an increased embolic risk. With the advent of closed mitral valvotomy it became apparent that amongst the benefits derived from the relief of mitral stenosis was a reduction in the incidence of systemic emboli following this operation.

Table 4[47] shows data from six reported series: two following closed mitral valvotomy, three more recent series describing the survivors of open mitral commissurotomy and one series following mitral annuloplasty. Although there is a variation in the number of patients receiving long-term anticoagulation there is a striking similarity in the low rates of systemic embolism following such conservative procedures. One may speculate that the slightly higher embolic rate in the series followed up for a longer duration, (15 - 20 years) may be due to the progressively less efficient mitral valve caused by restenosis and also, presumably, with the increasing incidence of atrial fibrillation.

It is against the background of this data that we should consider the embolic risk of tissue heart valve substitutes.

Tables 5 and 6[47] present in a similar manner to previous tables, the reported incidence of embolism in patients with tissue valves in the mitral position. With the exception of the Leeds series at the foot of Table 6, all these series used porcine xenografts for mitral valve replacement. Different groups have used differing criteria for long-term anticoagulation, but despite these therapeutic differences, there is an uncanny similarity in the reported incidence of embolism. The incidence of approximately 3 episodes per 100 patient years was considerably greater than that seen after conservative mitral valve operations and than that reported in the Leeds series and seems unaffected by the different proportions of patients anticoagulated. Whilst patients receiving tissue valves substitute have a similar surgical approach and a similar profile of diseases and of disease severity, the only difference lies in the nature of valve substitute. The construction and haemodynamic performance of the pericardial xenograft is known to be much different from the porcine aortic valves[16,31,32,33]. The incomplete and sequential opening of the leaflets of porcine valves may have some bearing on their propensity for embolisation and valve thrombosis.

The final element of risk in the equation lies in the use of long-term anti coagulation, mainly warfarin sodium. Table 7[47] summarises the reported incidence of severe and fatal haemorrhage associated with this therapeutic regimen.

In view of this risk of bleeding and also encouraged by the low incidence of embolism in patients undergoing mitral and multiple valve replacement, several authors have decided not to routinely use long term anticoagulation in patients with pericardial valve replacement[25,45,46,47,58]. It is also reported that most of the small number of embolic episodes following mitral valve replacement with pericardial xenografts occurred during the first six postoperative weeks[48,58].

The very low risk of embolisation, the virtual absence of thrombotic obstruction of the pericardial valve and the published evidence that systemic embolisation still occurred in patients treated with anticoagulants[59,60], justifies the decision, not to use prothrombin depressants beyond the six postoperative weeks in these patients.

Infective Endocarditis

> *Ignorance is the curse of God, knowledge the wing wherewith we fly to heaven*
>
> *Shakespeare (1564-1616) Henry VI Part 2, Act IV*

Infective endocarditis is a severe condition which occurs on native as well as on artificial valves. Both mechanical prosthetic devices and tissue heart valves are affected. The incidence of endocarditis, in western

Table 8. Freedom from Invective Endocarditis

Main Author	*No of patients*	*Duration of follow-up yrs*	*Linearized rate of infection*	*Actuarial freedom from Infective Endocarditis*
Pavie[24]	675	5		98.2% for all patients, 97.8% for aortic, 99% for mitral, 100% for multiple valve replacements
Duncan[62] (A)	2720	6		97.3% for all patients, 97.4% for aortic, 97.6% for mitral, 96.3% for multiple valve replacements
Ionescu[17] (B)	1171	10		93.7% for all Patients,94.7% for aortic, 97.1% for mitral, 89.3% for multiple valve replacements
Zhu[49]	520	10		98% for all patients
Revuelta[26]	239	8	0.67% per patient year	
Garcia-[25] Bengochea	248	8	0.78% per patient year	
Holden[45] (C)	290	6	1.1% per patient year	
Bachet[59] (D)	224	6	1.6% per patient year	

(A): The authors make an interesting remark. Prior to heart valve replacement 86 patients suffered from infective endocarditis but only 9 of these patients developed recurrent infection following pericardial valve replacement.

(B): It is of interest to note that of the 17 cases of infection, 15 occurred between 1976 and 1981 and only 2 cases between 1981 and 1985. Ionescu's group took draconian measures in trying to suppress post-operative infections which they considered to be, in great part, nosocomial in origin. Those measures were directed at systematic pre-operative dental examination and treatment, search for any hidden, potential foci of infection - urological, upper and lower respiratory tract, judicious selection of antibiotic cover of the patient before, during and following heart valve replacement operations and strict monitoring of all signs of infection in the post-operative period. It appears that these measures were successful.

(C): On two occasions Holden implanted, successfully, pericardial valves in patients with infective endocarditis and he even advocated the use of such valves in similar situations because some considered the pericardial valves to be more resistant to infection than other devices.[45]

(D): This group considered that in their hands the pericardial valves were more prone to infection than the porcine valves, and also when compared to the results with pericardial valves published by other surgeons.

countries, ranges from 1.5 to 6.2 cases per 100,000 people per annum. The cumulative rate of prosthetic valve endocarditis is 1.5 to 3.0% at one year following valve replacement and 3 to 6% at 5 years, the risk being the greatest during the first six months after valve replacement.

Prosthetic valve endocarditis arising within 2 months of valve surgery is generally the result of intra-operative contamination of the prosthesis or a bacteraemic post operative complication. The nosocomial nature of these infections is reflected in their primary microbial causes: coagulase-negative

staphylococci, S. Aureus, facultative gram negative bacilli, diphteroids and fungi. Epidemiologic evidence suggests that prosthetic valve endocarditis due to coagulase negative staphylococci that presents between 2 and 12 months after surgery is often nosocomial in origin but with a delayed onset.[61]

This short introduction may help to reflect on the various and sometimes opposing view-points concerning the 'origin' of prosthetic valve endocarditis. As in most recent scientific reports, some descriptions of tissue valve endocarditis suffer from the same lack of clarity and standardization in the presentation of facts and do not give all relevant details for a better understanding of events and their causes. From eight published articles of large series of patients with Ionescu-Shiley Pericardial valves, only one report presents a higher than average incidence of valvular bacterial infections.[59] The other seven publications describe the rate of infection with figures of similar magnitude, as shown in Table 8.

In conclusion, it is obvious that the risk of infective endocarditis in pericardial valves is not dissimilar from that encountered in porcine valves at least up to 10 years after valve insertion. It can also be considered that the minor variations occurring in the published reports are due to local hospital differences, surgical technique, general handling of the valves and other factors.

One rarely finds a patient who was treated medically for proven endocarditis on his own valve who does not require valve replacement sooner or later.

There is no fundamental reason why any pericardial valve should become infected more frequently than another one except if the patient becomes septicaemic and the infecting organisms will reach the valve area. It appears illogical to claim that because one surgeon reported a higher incidence of infective endocarditis with one type of valve, that there could be any significant differences between 'his' valves and those implanted by other surgeons. The difference is in the number of patients with circulating infecting micro-organisms capable of infecting the valve area.

Most authors do not consider infective endocarditis as a valve related failure and do not include cases of infection in such statistics. The pericardial valve does not behave in a different way from other tissue valves as far as infection is concerned, with probably one exception. In the impression of some surgeons, the pericardium itself may be more resistant to infection than the porcine valve.

Structural Valve Dysfunction

> *In the incense burner, smoke and perfume are inseparable*
>
> *Hindu saying*

The durability of the pericardial valve, like that of all other artificial heart valves, depends on multiple factors, one of the most important being the environment in which the artificial valves function. Structural valve dysfunction (SVD) occurred with pericardial valves and it has been reported in several publications. Unfortunately, many reports do not contain some of the essential data and details necessary for building a clear image of this crucial aspect of valve performance. Table 9 tabulates some of the available data on primary tissue failure.

This table is only an attempt to give a general impression and to provide a basis for a more detailed interpretation of results. However, several conclusions can be formulated on the complex, varied, and in some cases controversial results published. As very often, a good amount of significant data is missing and this complicates the task of being precise and fair in interpreting the results.

It appears that the great majority of pericardial valves function correctly until about 6 to 7 years post-implantation. Beyond 7 years of follow-up the actuarial figures for freedom from valve failure start to decrease. In the table, the risk of valve failure seems to be greater in the aortic position as reported by some authors. In reality, the general consensus among surgeons, in various presentations and formal discussions and the evolution in time shows the contrary. The durability of these pericardial valves varied, in general, from 5 to 27 years.

Table 9 Structural Valve Dysfunction

Main Author	*No of patients*	*Follow-up years*	*No of valves with structural dysfunction*	*Free from SVD Actuarial*
Pavie[24] (A)	675	5	2 Aortic, Calcified and Fibrosed	99.1% All patients
Revuelta[26]	90 Aortic	8	2 valves Calcified(0.71% per patient year	89.9%
Gonzales-Lavin[58]	240 Aortic	8	12 Valves, 11 Calcified	88.4% Aortics only
Garcia-[25] Bengochea	248	8	2 Valves (0.22% per patient year)	
Duncan[62] (B)	2720	6	77 Valves, 52 Calcified, 25 Tears	91.5% Mitral, 86.2% Mitral and Aortic, 84.5% Aortic
Bachet[59]	224	6	5 Valves, 4 Tears, 1 Calcifies (0.80% per patient year)	
Van Sweiter [(63)]	444	6	2 Valves, Tears, (0.20% per patient year)	
Zhu[49] (C)	520	9	5 Valves	92.1% mitral, 89.9% Aortic
Ionescu[17]	1171	9-10	25 Valves,15 Tears, 9 Calcified, 1 fibrosed (Mitral 0.72%, Aortic 0.94% per patient year)	88.7% Mitral, 86.9% Aortic
Keon[64]	637	8	19 Valves, 15 Tears, 4 Calcified	89% Mitral, 87% Aortic
Kawazoe[65]	319	7	4 Valves, 3 Mitral, 1 Mitral and Aortic (all cusp tears)	93.4% mitral, 90.5% Aortic
Nistal[66] (D)	133 Aortic	7	8 valves All calcified, 2 with additional tears	80% All Valves
Moran[67]	400	5	9 Valves (8 Mitral,1 Aortic) 4 Calcified - mean age 37.5, Tears - mean age 50.2 (0.87% per patient year)	

Remarks for structural valve dysfunction

(A): The age of the patients ranges from 8 to 90 years (mean 57). 74% were over 70 years of age. The age of the 2 patients with valve failure (calcification) was not mentioned.

(B): The most important element in this large series is the demonstration that one of the most important factors in valve calcification is the age of the patient at the time of valve implantation.

(C): In this series, the authors mention, in addition, 4 cases of entanglement of sutures around the struts. These 4 patients were re-operated upon at between one week and 50 months following the first valve operation.

(D): The authors stated that all 8 failures were due to valve calcification and that 2 of them had additional tears. They find that their results with 'calcification' in all failed valves are contrary to Gabbay's results[18] where failures occurred mainly through cusp tears.

The great majority of valves in the mitral position began to deteriorate from 5 years post-implantation and this process increased even faster after 10 years.

The valves in the aortic position fared much better. At 10 years and beyond, the valves did function well, as reported by various authors[69,70]. The deterioration through calcification and cusp tears advanced progressively from 12 years post-implantation.

There were, however, many valves that functioned correctly between 12 and 17 years. Ravichandran[69] reported a series of 34 patients (with 41 valves) which were operated upon for removal of Ionescu-Shiley pericardial valves. The failure of these valves occurred at a mean post-operative duration of 11.3 years (range 5 to 17 years). There were 30 mitral and 11 aortic valves involved and the majority were heavily calcified.

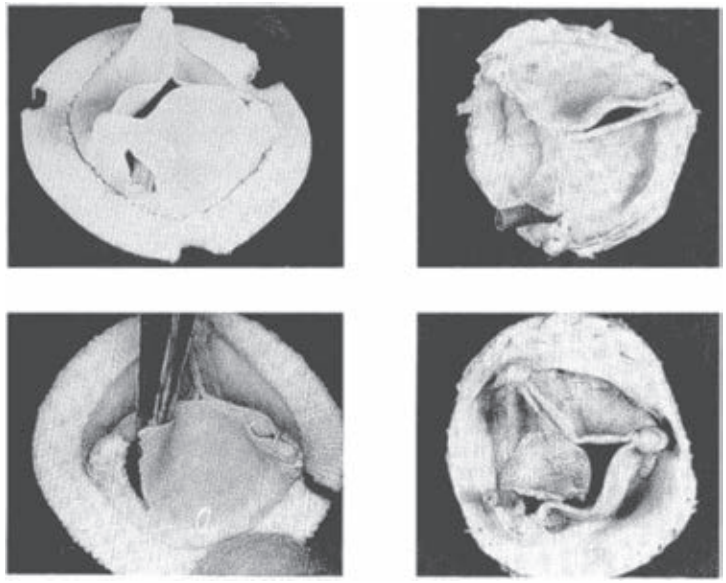


Figure 6: Comparison of abrasion lesions in pericardial valves in the 'life tester' (left side) and valves removed from patients (right side). The upper row shows an abrasion lesion which occured at around 8 o'clock (left) and a similar lesion around 4 o'clock in a valve explanted from the aortic position at 76 months after implantation (right). The lower row shows the abrasion tear which extended to the free margin of the cusp (left) and a similar lesion in a valve explanted from the mitral position at 89 months after implantation (right).

Exceptionally, 7 Ionescu-Shiley pericardial valves were reported to have been removed between 21 and 27 years post implantation[71,72,73,74,75,76]. Whether more such late events occurred and went unreported remains purely speculative.

There were 4 valves from the aortic position, 2 from the mitral and one each from a patient with mitral and tricuspid replacement. Only two reports mentioned the age of the patients at the time of implantation (37 and 49 years).

The pathology findings, very similar for all these seven valves, showed general stiffening due to diffuse calcification of the cusps but none of them had cusp tears. The most striking finding in all these valves was the presence of pannus formation by connective tissue growing over the upper margin of the stent - without any doubt - preventing the abrasion of the pericardial tissue and allowing, therefore, the valves to function for durations beyond any expectations.[76] The pannus grew exactly over the useful area of the Dacron covered stent, but only on that part without encroaching on the cusp tissue. It padded in a 'natural' way the abrasive part of the stent.

This finding may have great significance concerning valve durability. It may help to understand the causes of pannus formation in this particular situation and also the causes and mechanisms which help to delay or even to prevent early calcification of pericardial valves. Knowing that all the pericardial valves described here came from the same manufacturer, it seems logical to question the participation of the host in this phenomenon.

The known modes of tissue valve failure are: tearing of the pericardium, calcification of the valve and, exceptionally, fibrosis of the cusps. Tears represent approximately 25% and calcification 75% of primary failure. In some cases both pathologies could be encountered in the same valve. This proportion varies

considerably and could be seen reversed in some series of patients.

The causes for pericardial tears were described in detail[18,19] and can be summarised as an abrasive mechanism produced by the rubbing of the pericardium over the Dacron covered margin of the supporting stent. Such tears progress slowly until a part of one of the cusps becomes flail and the amount of regurgitation increases Figure 6. This explains the fact that there is no sudden catastrophic failure with the pericardial valve, except when the initial, obvious clinical signs and symptoms of incipient malfunction have been missed or disregarded by the treating physician or the patient. There may be, in a minority of cases, some slightly different mechanisms of pericardial damage at points of three-dimensional flexure or perforation caused by the excessively long ends of sutures used in aortic valve replacement.

The pericardial valves in the mitral position develop mechanical dysfunction, abrasion and possible rupture earlier than in the aortic position. In the mitral position the left ventricular contraction develops, abruptly, a much higher pressure than the systemic diastolic pressure applied on closure of valves in the aortic position. In addition, the unnecessary use of the largest possible valve size increases the risk of mechanical damage through abrasion. This practice is the relic of using, by necessity of its nature, the largest possible porcine valve.

Concerning the tearing of the cusps due to abrasion, it was considered that this happened more often in the Low-Profile Shiley valve compared with the Standard valve because of the reduction of the height of the stent. This is not the case as it was demonstrated by Christie and colleagues that the profile of the valve is not, per se, the important factor of stress. The important one was found to be the angle, inclination, that the tissue forms with the commissure at the stent post, and this angle varies considerably from one type of pericardial valve to another. Reducing the inclination increases the stress, and vice versa[77].

The coaptation stitch, as believed by some, does not seem to be responsible for initiating cusp tears. In fact, it is involved only later when the abrasion lesion advanced from its origin (at around 4 or 8 o'clock) at the bottom of the cusp to the top of the post, when the tear is completed and that part of the valve becomes flail. (Figure 5).

Within the limitation of the intrinsic durability of the chemically-treated bovine pericardium, various modifications, physical and chemical, could be employed to eliminate this type of failure and considerably extend the functioning life of this valve.

Several techniques have already been used in order to reduce or abolish 'abrasion', as described in this article. One of them being the modifications made under the name of the projected Ionescu-Shiley Optimograft.[21]

Calcification

> *Cromwell was about to ravage Christianity, when a grain of sand became stuck in his ureter*

Valve calcification is a local representation of a general biologic phenomenon which occurs under specific conditions in various parts of the body, especially in younger individuals. Valve calcification is known to have taken place in all types of tissue valves. Because some important details are not given in the reported series (age of patients, timing of occurrence, position of the valve, etc.) it is difficult to form a clear--cut conclusion in all situations.

One report on a large series of patients followed for 6 years, presented at a symposium in 1986[62], gave clear and complete information regarding the relationship between valve calcification and the age of the patients at the time of valve implantation. The authors showed that in the groups of patients aged between 10 and 59 years, the incidence of valve calcification ranged from 31.8% (in the age group of 10 to 20 years) to 1.8% (in the group aged 50 to 59 years) to reach zero calcification in patients older than 70 years. Similar conclusion about the relationship between age and valve related complications were published about porcine valves.[78,79]

The clear demonstration of this inverse relationship between the age of the patient and the rate of valve calcification 'sounded an alarm bell' and started to change the way in which tissue valves (porcine aortic and bovine pericardium) should be used in the future, and indicated the direction in which potential future research should be concentrated in order to make tissue valves universally acceptable by young and old patients. At this moment in time, tissue valves are almost exclusively used in patients older than 65 years because in old age the process of calcification is considerably slowed down and also because the life of the valves may outlast the life of those patients who reach a 'respectable' age.

Most scientists who studied the pathophysiologic mechanism of bioprosthetic heart valve calcification attribute the initial and predominant mineralisation of devitalised connective tissue cells of the bioprosthetic tissue matrix to the unique calcium-binding properties of cells and their components[80]. Intact living cells have intracellular free calcium concentration of approximately 0.1mM, whereas extracellular free calcium is 1,000mM (10,000 fold gradient across the plasma membrane). Although calcium entry into cells is passive, cellular calcium is held low by energy-requiring metabolic processes, such as the Ca^{++} ATPase pump and intracellular binding. In contrast, intracellular phosphorous levels are relatively high, especially in the membrane-bound organella, such as mitochondria, the nucleus, and within the plasma and organella membranes themselves, which contain phospholipids as well as enzymatic system metabolizing high energy phosphates. These are the sites of initial bioprosthetic heart valve mineralisation. In necrotic cells as well as in cells devitalised by aldehyde cross-linking, passive calcium entry occurs unimpeded, but the mechanisms for its removal are no longer active. It is presumed that the calcium influx leads to hydroxyapatite formation with the compartmentalised intracellular phosphorous, and that these early nuclei progressively accumulate additional mineral, becoming in time, macroscopic crystal formations[81]. Of related interest is the mitochondrial calcification, which has been extensively studied in myocardial infarction[82].

It is well established now that the calcification is modulated through a complex inter-play of host and implant factors[81]. The possible interventions for mitigating or eliminating valve calcification are measures directed to either one of these two elements. Any intervention on the host appears to be extremely remote at present. Serious scientific research will have to continue, beyond present knowledge, in the hope that a successful solution will be found to prevent - at tissue valve level - the occurrence and progression of calcification.

Because, at present, none of these two interventions mentioned above are effective, the surgical community had opted for a third avenue. Knowing that the calcification of glutaraldehyde-treated pericardium represents two-thirds of the rate of structural valve failure and that this pathological process develops progressively and much slower in older persons (above 65-70 years of age) it seemed logical and safer to restrict the use of pericardial valves to older persons, those above the age of 70 years.

It is also evident that aortic degenerative valve disease is far more often encountered in today's heart valve pathology than mitral valve disease. Therefore, the enormous majority of pericardial heart valves are implanted nowadays in the aortic position of males older than 70years of age. The past experience with the first generation of pericardial valves showed that, in general, long term results are better in patients with aortic than those with mitral valve implantation. There was no thrombotic obstruction reported in these patients and the embolic rates were extremely low. All these additional benefits, plus the excellent haemodynamic function, even in small size valves, tilted the balance towards the use of the second generation of pericardial valves almost exclusively in the aortic position, of older patients.

In simple terms, with the exception of some technical improvements in the reduction of tissue tears due to abrasion which accounted only for about one quarter of pericardial valve dysfunction, the main difference between the first and the second generation of pericardial valves was made by shifting the 'target' from the general use - in all patients of all ages - to the restricted utilisation as mentioned above.

Some experimental work by Johnson and associates[83] was carried out on potential, preventative strategies like binding calcification inhibitors to glutaraldehyde-fixed tissue, removal or modification of calcifiable components of the valve, modification of glutaraldehyde fixation process and the use of tissue cross-linking agents other than glutaraldehyde: one example of this would be the use of calcium diphosphonate pre-treatment of the glutaraldehyde-fixed valve tissue.

Webb and colleagues[84] demonstrated inhibition of bioprosthetic heart valve calcification by the use of aminodiphosphonate covalently bound to residual aldehyde groups in an experimental model. Anti-calcification treatments, such as surfactants, applied to the leaflet tissue before implantation were considered to be effective in mitigating intrinsic calcification from extrinsic sites of calcium nucleation such as insudating plasma proteins and lipids.

Several attempts have been made in order to abolish or at least to delay the occurrence of calcification. Two chemical processes were put forward: the T6 (Sodium dodecyl sulphate) by Hancock Laboratory and the PV2 (Tweed 80) by Edwards Laboratory. The two chemical interventions had been tested in animals and in humans with unconvincing results. Subcutaneous implants, in rats, of cusps of porcine valves and strips of pericardium showed some positive results for the porcine cusps only. However, care should be exercised in extrapolating such data obtained from subcutaneous implants in rats to intracardiac location and function of valves in humans.[85]

Jones[86] and associates using the well known sheep model, which is a rapidly, universally and highly calcifying model, implanted porcine and pericardial valves either 'standard' or pre-treated with the Hancock T6 or the Edwards PV2 processes. The results showed that these processes mitigated the calcification of porcine valves but did not have any effect on the pericardial valves. Gallo[87] conducted similar experiments using the same model as Jones and Ferrans and implanted Hancock porcine valves, with and without the T6 treatment, in the mitral and tricuspid positions of sheep. He found no significant difference in the amount of cusp calcification between the standard and the T6 treated valves, whether in the mitral or in the tricuspid position.

To our knowledge, up to the present time, there are no scientific publications on clinical series of patients with tissue valves, porcine aortic and bovine pericardium, treated with 'anti calcification' processes showing any reduction of valve calcification. Dimitri and colleagues[88] were unable to show any demonstrable advantage in their series of patients for the T6 process, a treatment purported to mitigate calcification.

The fact that tissue valves are used almost exclusively in patients older than 70 years, is evidence enough that these two chemical processes are ineffective.

It would be more rigorous scientifically and ethically if valve manufacturers, and also some cardiac surgeons, will refrain from presenting, among the qualities of a tissue valve the fact that, a particular valve is treated with an anti-calcification process implying its usefulness, unless verifiable, factual, published evidence is presented to support such a claim.

It will also be necessary to remember one of the rules of research: *'No miracles allowed!'*. This is indeed a fundamental law of science. Despite the lack of clinical evidence and despite the fact that we know very little about the exact causes of this extremely complex process of calcification, we try nevertheless to treat it!

When Gertrude Stein, the artist, was dying she kept repeating *"What is the answer? What is the answer?"*. Just before she died she suddenly sat up and said: *"But we don't even know the question yet!"*

So we can postulate that unless we find out why the human valve calcifies, we are not going to find out why prosthetic tissue valves calcify. Macro and microscopic pathology studies of failed porcine bioprostheses by Schoen and Cohn[89] showed in detail the process of tissue degeneration in valves with tears, calcification, or both. They consider that patients with porcine aortic bioprosthetic valves follow a clinical, satisfactory course for around 5 years after operation. Late deterioration of these valves frequently necessitates re-operation. They estimate the rate of failure at approximately 15 to 25%, 7 to 10 years after valve implantation. Gallo and his associates[79] describe in detail the rate of occurrence and timing of primary tissue failure with the Hancock porcine valve, and

show a similar percentage of failures. The actuarial freedom from valve failure in the mitral position at 10 years is 69%, and in the aortic position only 53%.

The rate of tissue valve failure accelerated from the 3rd post-operative year in the mitral position, and from the 5th year in the aortic position with a precipitous fall during the 8th and 9th years of follow-up. They believed that the patient can be told that he or she had a 30% chance of requiring re-operation because of the porcine valve degeneration within the next 10 years. This general calculation does not take into account the other causes of valve 'problems' which may lead to re-operation or some other morbidity during that period of time.

Goffin[90] showed in a comparative histological study of explanted porcine and pericardial valves that the microscopic pathologic changes were similar in these two types of tissue. Grabenwoger[91] found similar pathologic changes in the failed Sorin Pericarbon pericardial valve.

These long-term studies showed that both the porcine and the bovine material used for valve construction and their long-term behaviour is similar. In a simplified way, the main difference between these two types of valves is the haemodynamic superiority of the pericardial valve and its smaller risk for embolisation. But the overwhelming advantage of the pericardial valve remains the fact that, being a man-made device, it lends itself to a variety of changes in order to improve its performance.

In most published reports about tissue heart valve replacement there are differences in the presentation of data and of the results in all aspects of a particular topic between the various publications. In almost all chapters of valve function, with the exception of haemodynamic and hydraulic measurements - which are scientifically obtained and mathematically expressed - there are differences from author to author. Why in the hands of one surgeon, the same type of tissue valve from the same manufacturer fails in one patient at 24 months, and in another one it lasts over 320 months? Microscopic studies performed on porcine and pericardial valves, explanted for various reasons between 12 months and 6 years, all showed gross histological changes in the structure of tissue.[90,91]

In view of such changes in those valves, how did some of the porcine and pericardial valves continue to function well beyond 10 years and several valves well beyond 20 years? Why did the rate of occurrence of bacterial endocarditis differ from one hospital to another, and the embolic rate vary from surgeon to surgeon?

Certainly the host factor has not been seriously considered. Some common sense and practical observations in this field give us some tentative answers. There are, generally speaking, several potential factors which may affect variously the durability of tissue valves, and which may explain the discrepancy among published results. Carlos Duran[92] summarised some of them in the following way:

- Variations at manufacturing level: Selection of tissue according to age of animal, thickness of the material in relation to the size of the valve to be constructed. The handling of the tissue from harvesting to the finished product. The design, chemical treatment and technique of construction of the device.
- About the patient: Complete information about the age and biological condition of the patient, history of other pathologies, heart rhythm, previous embolic episodes, anticoagulant treatment, etc.
- Concerning the surgeon: Correct rinsing of the bioprosthesis prior to implantation, maintaining the moistness of the valve throughout the time of implantation, careful handling of the device, extra care for the sterility and against possible contamination, correct positioning of the valve within the heart, especially in the mitral position, to avoid 'asymmetrical opening of the cusps'[93] The avoidance of trying to implant the largest possible valve in the respective heart annulus. All pericardial valves are large enough for the corresponding orifice in which they are supposed to be fitted comfortably.

Great damage can be inflicted on a bioprosthesis at the time of implantation[94]. One of the not so rare causes is allowing the cusps of the valve to become dry - at times looking like parchment - during the time of placement of sutures. Some incredible errors occurred exceptionally: the plastic identification tag

remained attached to the valve and became stuck to the left ventricle wall; the sutures meant to secure the introducer were not removed and all three cusps of a valve were limited in their movement; entangling sutures around the stent struts, sometimes around two struts: one of the incidents was published under the title of 'Fatal bioprosthetic regurgitation immediately after mitral and tricuspid valve replacement with Ionescu-Shiley bioprosthesis'[95]. This type of valve failure should have been called simply 'surgical failure'.

The 'family feud' between the porcine Montagues and the pericardial Capulets has been almost solved, not by words, but by time. This impartial arbiter has looked at facts and results.

Conclusions

> *What is now proven was once only imagined*
>
> *William Blake (1757-1827)*

A careful appraisal of the results and the evolution of the two types of tissue valves created and used during the past four decades brings into focus the similarities but mainly the discrepancies which set them apart as structures and as functioning valves. The porcine valve was subjected to several modifications which reached the limits imposed by the fixed geometry of the pig's aortic valve. The pericardial valve, the embodiment of the concept of 'man-made' devices, lends itself to an infinite permutation of changes of shape and physico-chemical interventions in order to improve its function, and indeed this is what happened. Almost 10 years after the creation, by Ionescu, of the pericardial valve, the concept behind it attracted several specialised laboratories to study this valve, to modify and improve it and bring it anew into the clinical field of usage, under different shapes and names, but always following the same general concept: glutaraldahyde-treated bovine pericardium mounted on a flexible frame as a three-cusp valve.

The prediction made by Ionescu when he created the concept of the man-made valve has proved to be not only true but extremely useful.

He might not have attained his dream of creating a perduring tissue valve to be used without anticoagulants, but he came very close to it; and we hope that the dream will continue to inspire his successors.

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Examine your yesterday's ledger and you will find that you are still indebted to people and to life

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Chapter 4

Pericardial Valves Built by Other Firms

Marian Ion Ionescu in an interview with Paul Modi

Facile est inventis addere

When I decided to write about the second generation of pericardial valves, I had to consider many things primarily related to: why did it happen at that time, why was bovine pericardium chosen and especially how could one explain the great leap from porcine valves to the pericardial ones? I would not find these answers any other place than at the source.

I visited Mr Marian Ionescu at his home and what happened there was more than I expected. We talked, despite the years which separated us, like old colleagues about anything and everything. The enormous leap from the pig valve to the pericardial valve cannot be simply and logically explained. As Newton once explained how he had discovered the law of universal gravitation, he said: *"By thinking on it continually I keep the subject constantly before me and wait till the first dawnings open slowly, by little and little, into a full and clear light."* This pattern of consistent, almost relentless questioning, led to a depth of understanding and reconstruction of previous theories about the universe. But that, Mr Ionescu rightly considered, was for a man of genius. For us simple mortals any original thought must meet a prepared mind and even then one occasionally has to look beyond the horizon. You never know, he said, you may be surprised!

But an original idea is only a part of a concept which represents a complex intellectual entity. Concepts are imaginative glimpses, the authenticity of which must thereafter be tested against the truth of reality and their duration in time. But how to translate an idea into reality is something different. It is an instinctive process or simply the will of our curiosity to push it to the end, if that end exists.

Mr Ionescu was an inspirational character and one could tell he still possessed a passion for scientific discovery and cardiac surgery, as well as the dissemination of knowledge. He reminded me of a discussion between two giants of science: Niels Bohr and Wolfgang Pauli: *'You think I am crazy?'* Bohr: *'I am afraid you are not crazy enough!'.*

Mr Ionescu spent a quarter of a century at the General Infirmary in Leeds, the most exciting and productive years of his surgical life, where he created, among many other interesting things, the pericardial valve. The first home-made pericardial valves were implanted in patients from April 1971 onwards and for the first five years nothing was published, awaiting - like Bedouins in the desert - to see whether a storm may appear. During these five years it became clear that the haemodynamic performance of these valves was excellent, thrombotic obstruction of the valves did not occur and long-term anticoagulant treatment was not necessary because the embolic rate was very low.

He confessed that he did not fully understand the essentials about embolism. What is exactly their nature, their origin and how to design an experimental model to further study them? He recounted this wisdom to me, without remembering its origin: *'Only when we know little do we know anything, doubt grows with knowledge'.* In the end he said *'OK, let's consider that, for the time being, embolism is a solution in search of a problem'.*

Five years later the fact that a new and different type of valve had functioned well and without signs of structural valve deterioration was considered encouraging and the results from that experience were published. Neither Ionescu, nor any of his associates have ever made any predictions or foolish promises about the long-term durability of pericardial valves. In fact he told me that at the beginning of this venture he did not have a clear idea about the potential durability of the pericardial valve, he only hoped that it would not deteriorate too soon but certainly did not believe that it would last forever.

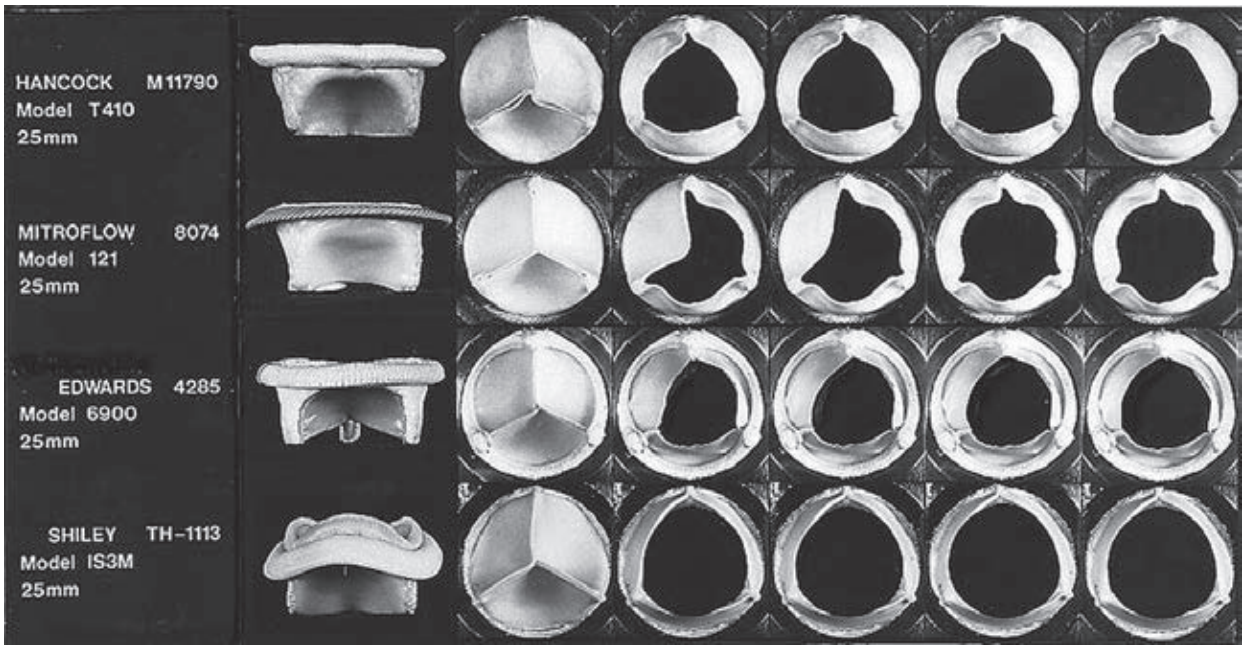

Figure 1: The opening characteristics of 4 pericardial valves - Hancock (no longer available), Mitroflow, Edwards and Shiley. All 4 valves were manufactured for clinical use and all were 25mm in diameter. The valves were photographed under identical conditions in the mitral side of a 'pulse duplicator' and the flow rates at peak diastole were: for each frame, from left to right: 0, 100, 200, 300, and 400mls/sec.

The surgical community received this valve with enthusiasm because of these good results and on the belief that it must therefore have a good durability, it became considered the panacea for heart valve replacement in all patients and at all ages. A further five years later, the haemodynamic performance and the reduced risk of embolism were maintained and the original results were reproduced and documented in many published series of patients. At about that time, structural valve deterioration began to progressively appear, more in the mitral than in the aortic position. This was a great disappointment for everybody and for some surgeons it was considered almost a betrayal of their own expectations based on nothing more than their own exaggerated desire or wishes.

During the ten years of worldwide use of the Shiley pericardial valves, five international symposia were organised in: Chamonix - France, Pebble Beach - California, Montreaux - Switzerland, and twice in London. These symposia were followed by the publication of their proceedings (five volumes). In addition, numerous scientific articles were published in specialised journals, all of them about the pericardial valve.

Towards the end of our discussions, Ionescu told me of yet another moment from the past, from the world of Giants. It was recognised by many that Otto Warburg's scientific writings were the clearest and the most precisely written articles. Only Szent Gyorgyi, who was of a similar standing in that world of Nobel Prize winners, dared to ask 'How do you do it?' The answer was prompt, simple and honest: 'I re-write them sixteen times!' I am sure that this was a veiled advice for my intention to write about the pericardial valves.

Most of the experienced, astute surgeons knew about Hermann's rule: 'Whatever you do, if you get it right the first time, you must have done something wrong', and they looked at the whole evolution of this valve as being the future of heart valve substitutes. The basis

Table 1. Mitroflow Pericardial Valve

Main Author/year	*No of patients Valve location*	*Patient mean Age (range)*	*No of SVD, position*	*Actuarial freedom from SVD-years*
Revuelta, 1990[9]	130-All, 90-A, 27-M, 10-D	55.4 (26-74)	1 Aortic, 4 Mitral	At 7 years, all valves *86%*
Loisance, 1993[10]	199-All, 107-A, 63-M, 28-D, 1-T	58		At 5 years *94.6%* At 10 years *63.7%*
Sjogren, 2006[11]	152 Aortic	79.5 (75-91)		At 5 years *99%* At 10 years *82%*
Benthamien, 2008[12]	161 Aortic	69.5 (60-94)	19 in group 60-69, 6 in group >70 years	At 15 years 60-70 *62%;* >70 *73%*
Yankah, 2008[13]	1513 Aortic	72.4	122. Stenosis *36.7%;* regurgitation *20.4%;* both *42.9%*	At 20 years <65 *71.8%;* >70 *84.8%*
Jamieson, 2009[14]	381 Aortic from 3 centres	76.4 (53-91)		At 10 years: <60 *85.2%;* >60 *85%;* 61-70 *95.7%;* >70 *83.2%*

A = Aortic, M = Mitral, D = Mitral and Aortic, T = Tricuspid, SVD = Structural Valve Deterioration

of Ionescu's pericardial valve concept carried with it from the beginning the possibility of design change to modify or improve it. Some people realised that the potential of this valve was therefore considerabl e and that changes could and should be made to improve its durability while maintaining the integrity of the basic structure.

The large amount of results documented during its clinical use over a period of fifteen years triggered two important fields of research. The first was in the field of structural valve deterioration (calcification and cusp tears) and by better understanding the process of tissue calcification it was hoped that this would lead to measures to prevent or retard the occurrence of calcification of chemically-treated (glutaraldehyde) pericardial tissue. The second line of research was directed at the physics, dynamics and mathematical calculations for a better, more scientific approach to the 'stent-valve complex' construction and tissue mounting.

A large number of scientists and dedicated researchers contributed to this effort and much important work was accomplished and published. Unfortunately, in spite of very interesting results, they have not succeeded in finding a solution for the prevention of calcification of pericardial valves. The complication of cusp tears due to abrasion of pericardium against the Dacron covering of the stent was remedied by various ingenious techniques of tissue mounting onto the stents, as will be described further in this text.

Another consequence of the usage of the Shiley pericardial valves was the realisation that tissue calcification was age-dependent with the calcification process progressing more slowly in patients older

Table 2. Edwards Pericardial Valve

Main Author/ year	*No of patients. Valve position*	*Patient mean age (range)*	*No of SVD, position*	*Actuarial freedom from SVD - years*
Pelletier, 1990[5]	284- All, 222-A, 77-M, 2-T	58[19-79]	3 valves, 1 M regurgitation at 26months, 2 A - thrombus at 20 months, tear at 68 months	Reoperation for all causes SBE, SVD, and perivalvular leak. Overall *92%* at 6 years
Jamieson, 1999 Multicentre report[15]	429 all Mitral, 318-M, 101-D	60.7	Calcification 70 .4%, leaflet tear 18.5%, both 11.1%	At 10 years: <40 *80%;* 41-50 *91%;* 51-60 *84%;* 61-70 *95%*
Marchand, 2001[16]	435 all Mitral, 333-M, 102-D	60.7(8-82)	56 episodes: calcification 73%, tears 20%, both 7%. Duration to explant 9.5 years (5-13.6)	At 14 years: all patients *66.3%*, <65 *62.8%;* >65 *85.9%*
Biglioli, 2004[17]	327 all Aortic, 298 study group	67.2 (19-83), 215 patients aged>65	Considerable increase on the risk of prostheses replacement after 10 years post-op	At 14 years: all patients *52.9%;* <65 *35.8%;* >65 *83.7%*
McClure, 2010[18]	1000 all Aortic	74.1	26 valves	At 15 years: age <65 *34.7%;* 65-75 *89.4%;* >75 *99.5%*
Welke, 2011[19]	2168 all Aortic	21 to over 75 years	Not mentioned	At 10 years: Age 21-49 *58%;* 50-64 *68%;* 65-74 *93%;* >75 *99%*

A = Aortic, M = Mitral, T = Tricuspid, SVD = Structural Valve Deterioration, SBE = Subacute Bacterial Endocarditis

than 65 years. Consequently it was decided to shift the goal of pericardial valve usage from all patients of all ages to only patients aged more than 65 years. In this way, the problem of valve calcification was considerably reduced, not by a chemical treatment but by transferring it to a different biological terrain.

The improvement in the techniques of mounting the pericardium onto the stent helped to reduce the rate of pericardial cusp tears. Based on these new premises, derived from the experience and knowledge gathered with the first pericardial valves, a second generation of such valves began to be manufactured and brought into clinical use. The originality of the concept, the successes and failures, the flaws and positive aspects of the original pericardial valve and the experience accumulated with its use over the first 10 to 15 years, together with the results obtained by scientific research, created the incentive and showed the way for changes, modifications and potential improvements in

Table 3. Sorin Pericardial Valve

Main Author/ year	*No of patients. Valve location*	*Patient mean age (range)*	*No of SVD, position*	*Actuarial freedom from SVD - years*
Folliguet, 2009[21]	277 all. 224 -A, 39 -M, 10 -D, 3-P	178 > 75 years (64.3%)	3 aortic, 2 at 7 years, 1 at 2 years	At 10 years: all patients *96.6%*; Aortic *96.1%*; Mitral *100%* (i)
Grabenwoger, 1994[22]	144 all.. 114 -A, 25 -M, 5 - D	69	9 valves, 3 mitral, 6 aortic, 7 stenotic, 2 regurgitant, 9 calcified. Valve failure at +/- 55 months post implant	See below (ii)
Caimmi, 1998[23]	78 all mitral	56.9	26 calcified-stenosis	At 12 years: All *56.8%* <60 *36.8%;* >60 *86.3%*
Seguin, 1998 Multicentre report[24]	321 aortic	75.8	6 valves - calcification	At 10 years *83.9%*

A = Aortic, M = Mitral, D = Mitral and Aortic, T = Tricuspid, P = Pulmonary, SVD = Structural Valve Deterioration.

(i) This figure should be interpreted with caution because the study was of only 39 patients with mitral replacement and only 2 patients were at risk at 10 years. The patients' ages were not shown with details.

(ii) This study describes only the pathology of failed valves in 9 patients (out of a series of 144), 51 to 79 years old (mean 69) followed-up for 6 to 8 years. The description of clinical use and results of the 144 patients who received Sorin Pericarbon Pericardial Valves would have been of great interest, but a search through the relevant medical literature has not found any such publication from the surgical team.

the manufacture of these second generation valves. There were too many to all mention here - tricuspid, bicuspid and even a monocusp pericardial valve were brought to the market by their protagonists shortly after some articles about the failings of the Shiley valve were published. It so happened that some of these inventions did not last more than several months until they had to be withdrawn from use.

Of the many pericardial valves developed since 1980, only three have stood the test of time. These three modified and improved pericardial valves were made by very gifted technicians at three laboratories: Mitral Medical Inc. (which later became part of the Sorin group), Edwards Laboratories (now Edwards Lifesciences)[1] and the Sorin Group[2]. All three laboratories have devised different techniques of valve construction with the aim of reducing or abolishing the risk of tissue abrasion. The specialists at Mitral Medical Inc. retained the technique of mounting the pericardium outside the stent as in the original Ionescu valve, but found later another and better way of reducing abrasion. The Edwards engineers used an ingenious way of mounting the pericardium inside the stent albeit with a minimal loss of useful opening to flow area. The Sorin technicians devised yet another way of mounting the pericardium in a double layer so as to have the stent margin padded with a pericardial sheet (similar to one of Ionescu's modifications, the Optimograft)[3].

The Mitroflow valve, as first manufactured by Mitral Medical in 1982, had to be redesigned because it showed a failure mode similar to the first generation

of pericardial valves. Since 1991 a modified version of this valve was introduced and has been used in a large number of patients[4]. The Edwards valve became available in 1980. The device made in the configuration for mitral replacement had to be withdrawn after implantation in a small number of patients because of excessive flexibility of the stent causing mitral incompetence. A new redesigned version of this valve was reintroduced in 1984[5]. The additional changes made in the configuration of these two valves demonstrate once again the advantage of the versatility of the 'man-made concept' of the pericardial valve.

The haemodynamic characteristics of these 3 types of valve[6,7] are similar to the excellent results found with the original Ionescu-Shiley valve as first described by Tandon's group[8]. The minor differences in gradients and calculated orifice area are not clinically significant. The images portrayed in Fig 1 show the opening characteristics of 4 pericardial valves - Hancock (no longer available), Mitroflow, Edwards and Shiley. The cusps of these valves open synchronously up to a very large surface area with only minimal difference from one valve to another.

Regarding other complications (embolic, anticoagulant-related haemorrhage and endocarditis), there is only scant data in the publications analysed for this article. It is presumed, and not without good reason, that the main emphasis was placed by the authors on structural valve deterioration (SVD). It can also be considered logical that complications of these three types of pericardial valves would occur at about the same rate as those of the original Ionescu valve due to their similar structure and dynamic function

The scientific publications on these three 2nd generation pericardial valves are not only few in number but they lack some of the necessary standardized data for a complete, clear and fair evaluation and comparison of results of the different publications. In order to avoid generalities and averages, the data reporting SVD are presented in the form of tables.

The lack of standardised data presented in these publications makes interpretation difficult. The discrepancy of the actuarially presented results between the various publications is evident. The inverse relationship between the age of the patients and the rate of SVD is obvious in most reports. There are very significant differences among the various publications concerning the figures of actuarial freedom from SVD. Data from Carpentier's group can be found in reference 20.

The symptoms of valvular stenosis due to calcification are insidious and often well tolerated by the patient. The reported actuarial figures of freedom from SVD may therefore, in fact, be different if the valves had been assessed by echocardiography. This pertains to the figures in all three tables. There are very few published reports containing sufficient data in order to be useful. One can only note, without much comment, the gross difference between the number and percentages of SVD shown in these three tables. However, in spite of some failings in reporting and the variability of the results in the different series, the considerable increase in valve durability of the second generation pericardial valves is quite evident. This is the best clinical evidence that over a long period of time, calcification, which was the main cause of pericardial valve failure (about 80% of SVD), could be controlled albeit with Nature's help.

Can a meaningful comparison be made between the Ionescu-Shiley and 2nd generation valves?

A scientific comparison among these 3 second generation valves, and between them and the Ionescu-Shiley valve is practically impossible. The number of patients in the published series varies considerably. In addition there had been an almost equal distribution of mitral and aortic replacements with the Shiley valves, while for the second generation valves the ratio was about 1:8 in favour of the aortic valve. The much smaller number of mitral valve replacements in the second generation series of patients is due, in part, to the reduction of rheumatic mitral valvular disease in the western world and at the same time because of the proportional increase in the number

Table 4. Actuarial values of freedom from structural valve deterioration (SVD) at 10 years or more of follow-up in patients younger than 65 years

Valve Manufacturer	*Author/ Year*	*Implant position*	*Duration of study - Freedom from SVD %*
Edwards	McClure 2010[18]	A	At 15 years: 34.7. CI: 6-67
Edwards	Biglioli 2004[17]	A	At 14 years 35.8 +/- 10.7
Edwards	Poirier 1998[25]	A	At 10 years . 84.7
Edwards	Welke 2011[19]	A	At 10 years 63
Edwards	Weber 2012[26]	A	At 10 years 59.5
Edwards	Banbury 2001[27]	A	At 10 years 48
Edwards	Jamieson 1999[15]	M	At 10 years 80
Mitroflow	Yankah 2008[13]	A	At 20 years 71.8
Mitroflow	Jamieson 2009[14]	A	At 10 years 85
Sorin	Caimmi 1998[23]	M	At 12 years 36.8

A = Aortic, M = Mitral, CI = Confidence Intervals

of patients with degenerative aortic valve disease in a progressively aging population. Another reason appears to be the knowledge that pericardial valves in the mitral position are more susceptible to SVD than in the aortic position, for reasons described in the first chapter.

Another confounding factor is that during the 1970s and 80s, Shiley pericardial valves had been used in patients of all ages, and particularly in patients under the age of 65 years. During the 1990s and into the following decade, the mean age of patients receiving the second generation of pericardial valves varied between 67.2 and 72 years, a very significant difference in age. Thus the inverse relationship between patient age and valve calcification confounds a meaningful comparison. To a certain extent this relationship was known beforehand from the porcine valve experience but it had not received sufficient emphasis until the use of pericardial valves.

Additionally, the time-frame of their usage also varied (1971 to 1986 for the Shiley valves and 1981 onwards for the second generation valves). Surgical techniques and experience in general have evolved over the past 40 years and the lessons from the past might have borne fruit.

The experience with the Shiley valves showed that 75-80% of valve failure was due to calcification and only 20-25% failed because of tissue abrasion and cusp tears. These figures are similar in percentages between the Shiley and the second generation valves (when the latter were used in younger patients and in all cardiac positions) as shown in Table 4. The technical improvements made in the second generation of valves has virtually eliminated cusp tear due to abrasion,

Despite claims that all 3 types of second generation valves were treated with 'so-called' anti-calcification processes, implying a clinical reduction of calcification, none of the published results have shown any benefits in patients whatsoever from such chemical treatments. The likely explanation for the reduced rate of calcification and therefore of structural valve deterioration in patients receiving these second generation valves was the advanced age of the patients who received them. The age of the patients

was shifted from a mean of around 50 years with Shiley valves, to a mean of more than 70 years with the second generation valves.

It is regrettable that pericardial valves, which are known to carry a very low risk of embolisation, could not be freely used in the mitral position where the need and benefit would have been greater. The main obstacle remains the risk of calcification. However, in general, the second generation pericardial valves represent a progress in the armoury of devices for the treatment of heart valve disease in older patients. If the process of valve calcification could be controlled through biochemical interventions, these pericardial valves would have the potential to come close to becoming the panacea for all patients in need of heart valve replacement. For the time being, however, we have to accept that the understanding of this phenomenon of 'calcification' and its prevention lies somewhere beyond the horizon.

It becomes obvious from this description that the two important creative stages in tissue heart valves (from 1964 to 1971) took place in a short space of seven years and that since 1971 when the concept of 'man-made pericardial valves' was created, the other great advance has been the transcatheter valve which follows the same concept: glutaraldehyde-treated pericardium supported by specially shaped frames and implanted transarterially or through the left ventricular apex, as will be described in a later chapter.

Conclusions

> *It was by trying and by persisting*
> *That the Greeks took Troy*

The bovine pericardial valve was created in 1971 in Leeds, UK, and over the ensuing four decades, with various modifications and improvements made by different laboratories, it became the tissue valve of choice for the great majority of surgical groups around the world.

The creation, within the pericardial valve concept, of the second generation of pericardial valves was a substantial improvement on the Ionescu valve by a considerable reduction in SVD, the main flaw of that original valve. This was achieved by two interventions: the changes made in the technique of tissue mounting onto the stent, thereby virtually eliminating abrasion and cusp tears (which represents approximately 20% of SVD); and by avoiding the risk of tissue calcification (approximately 80% of SVD) by implanting the second generation valves predominantly in patients over the age of 65 years in whom the natural calcification process is much slower.

The pericardial valve is not simply another valve, it is the embodiment of a concept of tissue valve construction. At present bovine pericardium is being used, tomorrow perchance an even better material may be found. In this respect, Ionescu made, in one of his early papers, a significant and rather prophetic statement:

'The physico-chemical and biological properties of the natural porcine aortic valve have been profoundly altered by various interventions in order to adapt it for therapeutic means. In this way, the porcine valve has lost all its primordial characteristics except its shape which remains unchanged and unchangeable. The pericardial valve, on the other hand, has been conceived as an entirely 'man-made' valve and therefore its shape and general characteristics can be altered through a multitude of interventions in order to optimize its function'[28].

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CHAPTER 5

TAVI / TAVR

A Novel and Ingenious Technique to Insert Pericardial Valves in the Aortic Position

Apurva H Bharucha
Philip MacCarthy

Aequam memento rebus in arduis servare mentem

Introduction

Since its inception into clinical practice in 2002, transcatheter aortic valve implantation (TAVI) has revolutionised the management of patients with clinically significant severe aortic stenosis (AS). Indeed, TAVI has been shown to be a viable and efficacious alternative to surgical aortic valve replacement (SAVR) in those deemed to be of extremely high, high or intermediate surgical risk and as such, this practice has been incorporated into the European Society of Cardiology (ESC) and American Heart Association (AHA) guidelines for the management of heart valve disease[1,2]. The pericardial heart valve, the core of the TAVI catheter system, has played an integral role in the design of this device and continues to remain the mainstay in valve leaflet design.

The success of TAVI is owed largely to the seamless and synergistic collaboration between clinicians, engineers and industry which has been followed up with scientifically robust clinical trials. These key factors have culminated in the rapid, progressive and iterative evolution of valve system technology and the refinement of associated periprocedural practices with the ultimate aspiration of establishing a 'minimalist' intervention. This chapter provides an overview of the evolution of valve system technologies and periprocedural practice which have underpinned the performance, success and safety of TAVI and thereafter provides an outline of the outstanding challenges for the future.

Conceptualisation and early origins of TAVI

Severe symptomatic AS is associated with significant morbidity, mortality and healthcare costs[3,4]. Indeed, the estimated survival at onset of symptoms is 60% and 32% at one and five years respectively, with SAVR previously being the only effective intervention, offering low operative mortality (<5%), alleviation of symptoms and a return to normal life expectancy for patients deemed surgical candidates[5,6]. Unfortunately, operative risk increases markedly in patients with multiple co-morbidities and/or increasing age and as such, it is estimated that one-third of patients with symptomatic severe AS were not referred for SAVR[7]. In the 1980s, Alain Cribier pioneered transcatheter balloon aortic valvuloplasty (BAV) as an alternative intervention for those deemed unsuitable for SAVR. However, after showing initial promise it became apparent that BAV was liable to early valve restenosis hence providing only temporary relief of symptoms with no survival benefit[8,9]. Although disappointing, the experience with BAV enhanced the technical foundation towards a percutaneous transcatheter system facilitating the deployment of a stent frame containing a valvular structure (stented valve) within a calcified native aortic valve as an alternative to SAVR.

Nascent balloon-expandable transcatheter aortic valve technology and the first-in-human TAVI

The concept of intra-valvular stenting in the setting of severe calcific AS was further validated by Cribier et al through an autopsy study in 1994 which demonstrated the ability of balloon-expandable 23mm Palmaz peripheral artery stents to maintain a circular opening in aortic valves[10]. A paucity of commercial interest in the proposed technology prompted Cribier and colleagues to establish a start-up company (Percutaneous Valve Technologies (PVT) in 1999 which developed a prosthesis comprising a highly resistant steel frame containing a tri-leaflet valve structure (made initially of polyurethane but later changed to bovine pericardium) which could be crimped to 7-9mm over a balloon and then expanded to a diameter of 23mm without any resultant damage to the frame or valve structure. Adjuvant equipment, including a loading and delivery catheter system, was also conceived and developed[11].

Validation of the durability and biocompatibility of the first device was successfully undertaken in an ovine model in 2000 which set the stage for the first-in-

human TAVI in 2002, performed with an anterograde trans-septal approach on account of significant peripheral artery disease which precluded the proposed retrograde transfemoral approach[12,13].

Early clinical outcomes and technical challenges

Although limited, the REVIVE/RECAST Trial supported the feasibility of the anterograde trans-septal approach (85% procedural success rate). Note was made of a high incidence (25%) of significant paravalvular regurgitation, whilst revealing a thirty-day incidence of major adverse cardiac and cerebrovascular events (MACCE) and mortality of 26% and 20% respectively (14]. Despite its apparent feasibility, the anterograde trans-septal approach was associated with considerable technical complexity which limited its scope for widespread application. Extension of the technique to other centres revealed considerable rates of adverse outcome including acute procedural mortality[11,15,16].

Unlike the anterograde trans-septal approach, the transfemoral retrograde approach to TAVI is technically less complex, shares considerable commonality with other transcatheter cardiac interventions and is therefore naturally more amenable for widespread uptake and application. The early challenges to the transfemoral approach were not insignificant and included vascular complications arising from use of large bore femoral artery sheaths, difficulties navigating relatively bulky delivery systems through diseased, tortuous arterial vasculature and the challenges of crossing highly calcified native aortic valves retrogradely and obtaining optimal positioning of the prosthesis. These challenges resulted in a large proportion of patients being technically unsuitable for transfemoral retrograde TAVI (early rates of successful implantation were as low as 57%) and spurred the development of TAVI by left ventricular apical access which was viewed as a technically less challenging 'front door' alternative[14]. Transapical access has been all but superseded by the transfemoral route due to higher rates of adverse outcomes with the former and continued refinement of the transfemoral approach. Other 'non-transfemoral' (or so-called 'alternate access') techniques arose in these early years including subclavian/axillary access, carotid access and more recently trans-caval access.

The process of percutaneously implanting a pericardial valve within the native aortic valve

Prosthetic TAVI valves comprise pericardial valves suspended within a metallic frame, which can be crimped to a low profile and mounted on a delivery system, which is inserted via a sheath. This allows them to be navigated from the femoral artery to the native aortic position, where they are deployed within the stenosed native aortic valve. When the metallic stent frame is fully expanded, the pericardial prosthetic leaflets function to form the new valve. The early devices necessitated such large bore femoral access that a large proportion of TAVI valves had to be deployed using 'non-femoral' access (eg. trans-apical, trans-subclavian/axillary) but as systems have improved, the calibre of TAVI systems has decreased making femoral access possible in a vast majority of patients.

Balloon expandable transfemoral TAVI systems

In 2004 the Cribier valve system was substantively reconfigured for transfemoral retrograde TAVI by Edwards Lifesciences in conjunction with Dr John Webb. The new prosthesis – dubbed the Cribier-Edwards heart valve - featured a fabric skirt sewn around the lower third of the prosthesis to mitigate paravalvular leak (PVL) and valve leaflets derived from equine pericardium (changed to bovine pericardium in later iterations). To facilitate easier retrograde passage of the prosthesis through the arterial system and calcified native valve, a delivery system comprising of

a deflectable catheter and a balloon mounted crimped valve prosthesis was developed. The valve prosthesis was deployed by inflation of the delivery balloon under rapid pacing once optimal valve positioning was attained. The Cribier-Edwards heart valve system has since undergone substantial evidence-based iterative refinements (Figure 1) which have yielded significant dividends in technical performance, safety and procedural success (Figure 2)[17,18]. As such, the Edwards SAPIEN family of percutaneous heart valves form the mainstay of balloon expandable systems currently in clinical use.

Self-expanding transfemoral TAVI systems

In 2005, Grube et al successfully performed the first in-human implantation of a self-expanding aortic percutaneous heart valve- the CoreValve™-by the retrograde transfemoral approach thereby validating the technical feasibility and safety of such a concept[19]. The prosthesis featured a trileaflet valve composed of porcine pericardium, mounted and sutured within a self-expanding nitinol stent frame. The lower aspect of the stent frame featured a high radial force aimed at dilating and opening the calcified native aortic valve, the waist carries the valve and is constrained to avoid the coronary arteries whist, the upper segment of the stent-frame expands for fixation and stabilisation in the ascending aorta[20]. The CoreValve US pivotal trials and the Nordic Aortic Valve Intervention Trial (NOTION) were instrumental in characterising the safety and efficacy of the self-expanding TAVI systems and spurred their iterative evolution in the quest for optimal technical performance and procedural safety (Figs 3 and 4)[21-23]. Other self-expanding TAVI valves include the Portico (Abbott Vascular) and Symetis (Boston Scientific), with more recent devices currently undergoing clinical evaluation.

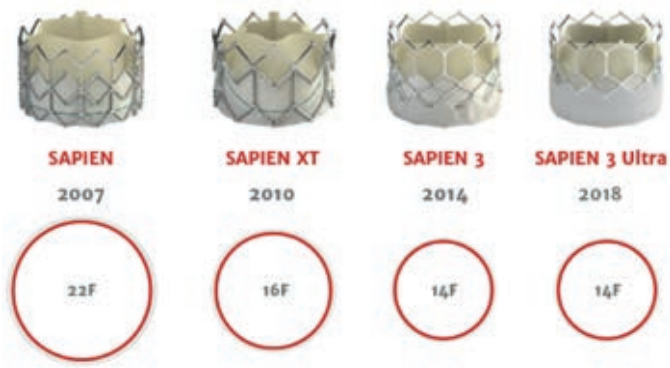

Figure 1: The iterative evolution of Edwards SAPIEN valve systems. Key adaptations to valve design include the use of an inner skirt and outer cuff to minimise PVL, adoption of a wide cell geometry to facilitate easy coronary access and reduction of strut thickness to enable tighter crimping of the valve thereby facilitating a lower profile delivery system. Morbidity and mortality from vascular complications have been reduced by refinements to delivery systems which have facilitated enhanced steerability and a reduction in sheath size as shown above. (Image courtesy of Edwards Lifesciences Corporation. Edwards, Edwards Lifesciences, SAPIEN, SAPIEN XT, SAPIEN 3, and SAPIEN 3 Ultra are trademarks of Edwards Lifesciences Corporation).

Other transfemoral TAVI technologies

The Lotus valve system features a mechanically expanding percutaneous heart valve which is fully recapturable, repositionable and retrievable. The prosthesis comprises of a braided nitinol frame containing a trileaflet valve derived from bovine pericardium. The valve frame expands radially and shortens axially during delivery and is locked into position using a 'post and buckle' mechanism with the prosthesis functioning early during deployment thereby mitigating the need for rapid pacing. Verification of the safety and efficacy of Lotus valve systems has been underpinned by the REPRISE trials and the RESPOND registry within which there appears to be a very low incidence of significant PVL (0.3%) which is traded off for high rates of PPM implantation for high degree atrioventricular block (34.6%)[24-25].

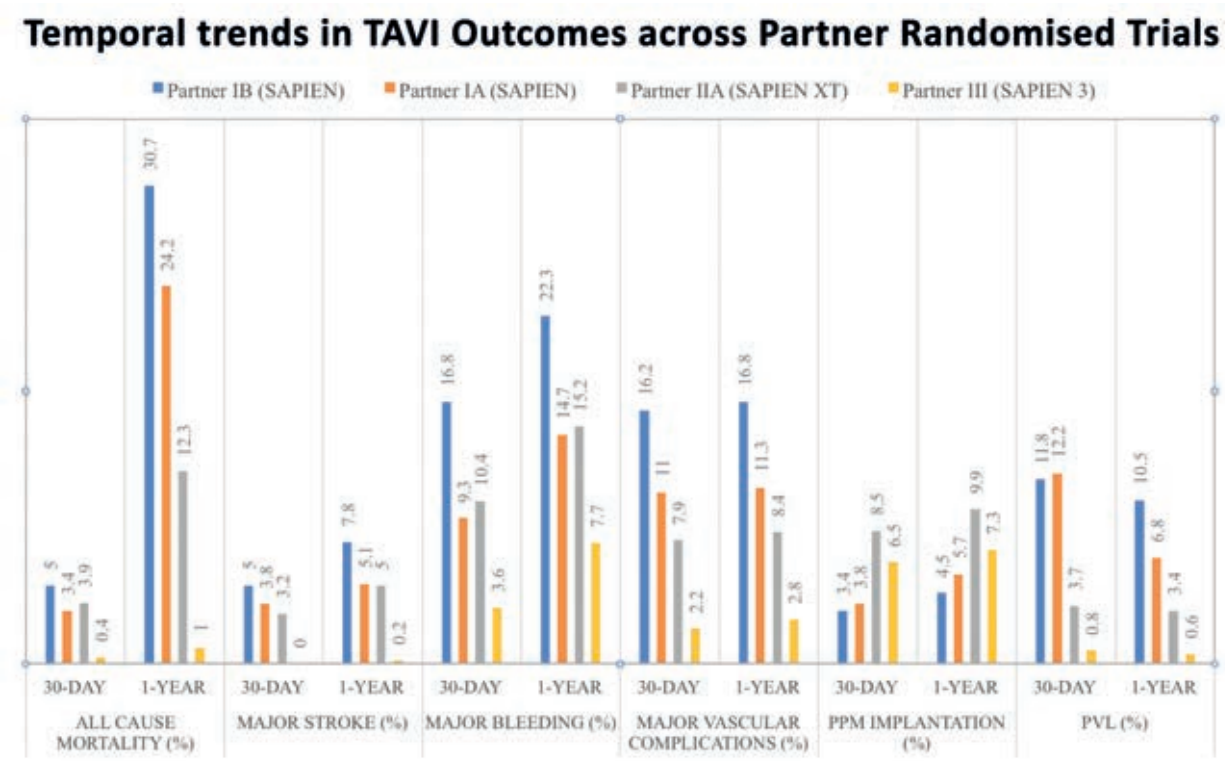

Figure 2: Temporal trends in key metrics of technical performance and safety of balloon expandable prostheses across the Placement of Transcatheter Aortic Valves (PARTNER) randomised control trials[48,72-74].

Evolution of peri-procedural practice in TAVI

The paradigm of 'minimalist' TAVI

The evolution of technology, increasing institutional experience and enhanced patient selection have all translated into substantial improvements in the safety of TAVI and in turn, paved the way for refinement of peri-procedural practice. The paradigm of 'minimalist' TAVI seeks to reduce perioperative morbidity, improve cost-effectiveness and enhance the patient experience. Fig 5 provides an overview of various minimalisation strategies available which are elaborated upon below.

The Heart team, pre-procedural planning and investigations

Multi-slice CT (MSCT) is instrumental in facilitating procedure planning and risk stratification by directing prosthesis choice and sizing, as well as guiding vascular access, anticipating potential procedural difficulties and screening for coronary artery disease (CAD). MSCT has played an instrumental role in this process by obviating the need for intraprocedural transoesophageal echo (TOE).

Pre-procedural screening for CAD should be undertaken by the transradial route to minimise vascular complications and preserve femoral access for the TAVI procedure. Recently, Barbanti et al have demonstrated the feasibility and safety of CAD

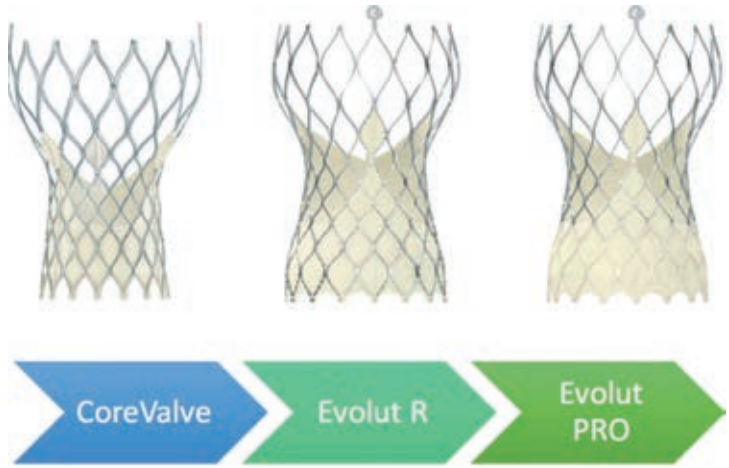

Figure 3: The iterative evolution of Medtronic self-expanding TAVI systems. Important design changes included a reduction in prosthesis height, adoption of a wide cell geometry and the addition of an external pericardial wrap to minimise PVL. Used with the permission of Medtronic © 2020 Medtronic.

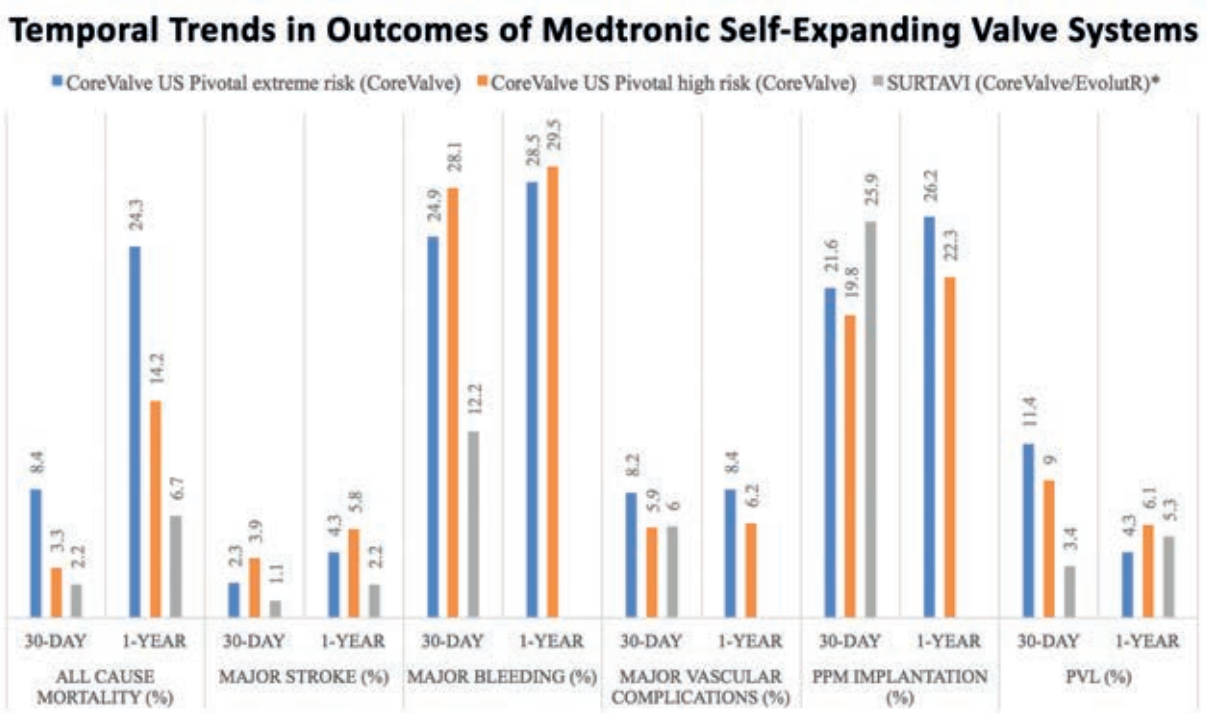

*Figure 4: Temporal trends in key performance and safety metrics of the Medtronic self-expanding valve system across key trials (21,22,75). *NB the depicted incidence of PVL depicted for the SURTAVI trial is at discharge as intervals used by investigators differed to the CoreValve US Pivotal trials.*

screening and ad hoc PCI during TAVI[26]. There is now a debate as to whether invasive coronary angiography is needed in all patients – many operators feel that major proximal coronary disease can be adequately identified by gated CT angiography.

The transition to conscious sedation

Although the first TAVI was performed under conscious sedation (CS), clinical practice largely shifted to the use of general anaesthesia (GA) between 2002 to 2008 in European centres but remains so in some North American centres. General anaesthesia offers the advantages of patient comfort, rapid conversion to surgery and the use of intraprocedural TOE. Conscious sedation has been shown to be feasible and safe with similar rates to GA of all-cause mortality, stroke, conversion to open-heart surgery, infection and major vascular complications[27-30]. The safety of CS is underpinned by appropriate patient selection through a Heart team approach and there must always be intraprocedural readiness for rapid conversion to GA if clinical circumstances dictate.

The 'fully percutaneous' approach

Early transfemoral TAVI procedures were performed via surgical cut-down which offered the benefit of direct control over haemostasis[31]. The refinement of delivery system profiles along with the availability of vascular closure devices and increased operator experience has resulted in the widespread transition to the fully percutaneous approach in TAVI. Indeed, the percutaneous approach has demonstrated comparable rates of mortality and major vascular complications to surgical cut down whilst offering early post-procedural ambulation and shorter hospital stays[32]. Importantly, approximately half of vascular complications associated with the percutaneous approach are due to percutaneous closure device failure, the incidence of

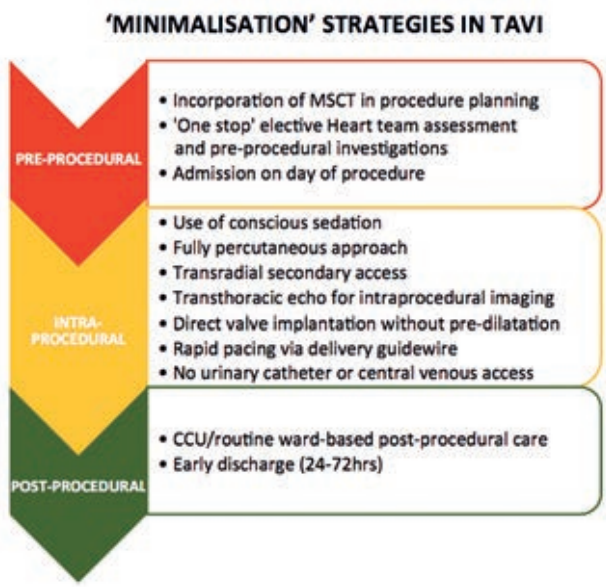

Figure 5: An overview of minimalization strategies in TAVI. The extent of minimalization should be guided by a Heart team approach and based on individual patient characteristics, institutional experience and available infrastructure.

which lies between 4% to 14%[33]. Key determinants of outcomes in fully percutaneous TAVI include operator experience, procedure planning directed by MSCT and ultrasound (US) guided arterial puncture. The advent of novel collagen based vascular closure devices such as MANTA™ have shown promise in reducing major vascular complications compared to conventional suture-based devices (e.g. Prostar XL Perclose-Proglide)[34].

Transradial as alternative secondary access

Contralateral transfemoral arterial access (TFA) has traditionally been used as secondary access in TAVI however, it has become apparent that this is responsible for up to one quarter of all major vascular complications[35]. There is therefore growing interest

in the use of transradial access (TRA) for secondary access. In addition to its relative safety, a recent multicentre study by Junquera et al suggested TRA conferred a relative reduction in 30-day mortality, stroke and renal injury[36].

Rapid pacing via valve delivery guidewire

Rapid pacing is a prerequisite for balloon expandable prostheses and for pre-/post-dilatation and has traditionally been performed using a temporary pacing wire (TPW) sited via femoral or jugular venous access. This technique invariably carries the risk of vascular access complications and right ventricular injury. Recent studies have confirmed the safety and feasibility of rapid pacing via the stiff left ventricular (LV) guidewire as an alternative to a right ventricular TPW. The EASY TAVI trial randomised patients undergoing balloon expandable TAVI to have left or right ventricular rapid pacing and found LV guidewire pacing was associated with a significant reduction in fluoroscopy time, procedural duration and cost with a similar safety and efficacy profile[37,38].

Direct valve implantation without balloon pre-dilatation

Improvements in new generation devices (namely the ability to reposition prostheses and addition of skirts to mitigate PVL) along with studies demonstrating no significant differences in outcomes associated with the omission of BAV and possible dividends in fluoroscopy time, contrast usage and procedural simplification have driven a trend towards direct implantation[39-41]. The recently published DIRECT-TAVI trial demonstrated non-inferiority of direct TAVI to BAV pre-dilatation with the Sapien 3 device with no significant differences between the two groups for PPM implantation, procedural time or contrast volume[42.]

Intraprocedural Imaging

Multi-slice CT-directed annular sizing along with the new generation of prosthesis has significantly reduced the incidence of PVL and heralded a transition away from intraprocedural TOE towards transthoracic echo (TTE). A number of observational studies have demonstrated no significant difference in the incidence of PVL between TTE and TOE guided TAVI which further support this transition in practice[43].

Post-procedural monitoring and early discharge

Meticulous haemodynamic and rhythm monitoring in the immediate post-TAVI period is essential in identifying early periprocedural complications and this has traditionally been undertaken in an intensive care unit (ICU) setting prior to transfer to the coronary care unit (CCU). With the increasing adoption of transfemoral TAVI and the use of conscious sedation, there has been a shift towards post-procedural monitoring on CCU or a lower-intensity ward particularly with patients triaged to be at low risk[44]. This has significant cost effectiveness implications as well the potential to greatly expand procedural volume. An evolving body of literature, most recently in the FAST-TAVI and 3MTAVR studies, has supported the safety and feasibility of early discharge (including next day discharge) in patients stratified as at low risk of procedural complications[45-47].

Remaining challenges in TAVI and future perspectives

Although the evolution of valve system technologies and the refinement of periprocedural practice has yielded significant advances in the safety profile and efficacy of TAVI, important limitations and challenges remain. These areas require further development

if TAVI is to become a viable treatment option for patients of low surgical risk, as suggested by the recent PARTNER 3 trial[48].

High-grade atrioventricular block in TAVI

Despite changes in valve technology and clinical practice, the incidence of PPM implantation for high-grade atrioventricular block (HAVB) remains high with the newer generations of some valve systems[49-50]. Evidence suggests an adverse impact of post-TAVI PPM implantation, with data suggesting longer lengths of hospital stay and cost[51-52]. Indeed, long term pacing has been associated with heart failure due to the introduction of desynchrony/RV pacing, negative LV remodelling and increased risk of atrial fibrillation (AF)[52]. The drive to reduce the incidence of post TAVI PPM implantation is particularly pertinent if TAVI is to become feasible for younger patient groups.

Periprocedural stroke and neuroprotection

Periprocedural cerebrovascular accident (CVA) remains one of the most catastrophic complications of all aortic valve interventions and is associated with significant morbidity and mortality. Indeed, 30-day mortality is shown to increase 6-fold in those with CVA post-TAVI, whilst 50% of patients are left with a permanent disability. Importantly, CVA has also been shown to be the most feared periprocedural complication amongst patients due to the prospect of permanent disability and loss of independence[53-54].

Mercifully, the incidence of periprocedural CVA has decreased from 2.8-5% in early pivotal studies to 0.6% and 1.2% at 30 days and one year respectively in the recent PARTNER 3 trial (new generation SAPIEN 3 valve) and 30-day and 2-year disabling stroke of 0.5% and 1.1% respectively in the Evolut Low Risk Trial (CoreValve, Evolut R or Evolut Pro valves). Importantly, the CVA incidence for TAVI in recent low risk trials has now been shown to be at least equivalent to SAVR[48,55].

Despite the reduction in clinically overt periprocedural CVA demonstrated by recent trials, diffusion weighted magnetic resonance imaging (MRI) studies have revealed up to 90% of patients have new clinically 'silent' cerebral lesions with an embolic distribution which occur independent of device type or access (56,57]. The clinical significance of these lesions post-TAVI remains unclear but some studies have suggested they predispose patients to late neurocognitive decline[58].

Cerebral embolic protection devices (CEPDs) are filter systems conceived as a means of mechanically reducing intraprocedural cerebral embolization. These are typically positioned across the origin of the supra-aortic vessels prior to the advancement of the TAVI system across the aortic valve and are retrievable at the end of the procedure. Devices can be broadly classified as deflector devices and filter type devices. The Sentinel device (Boston Scientific, CA, USA) features a dual filter providing coverage to the brachiocephalic and left common carotid arteries.

Although several studies have confirmed the safety and efficacy of CEPDs in reducing the burden of new sub-clinical lesions, they have been insufficiently powered to demonstrate a significant difference in incidence of periprocedural stroke. Indeed, the largest randomised trial evaluating CEPDs (n=363) (the SENTINEL study) revealed no statistical difference in subclinical lesion burden or rates of CVA with the use of a Sentinel filter [59]. Clearly, further work is required in this evolving area with larger adequately powered trials (such as the PROTECT TAVI trial which is currently recruiting[60] and further refinements in CEPD technology.

Valve Durability and Valve-in-Valve (ViV) TAVI

The increasing adoption of TAVI in patient groups of intermediate surgical risk and the prospect of extension to younger patients with low surgical risk has fuelled apprehension regarding the durability of

TAVI prostheses. Concerns relating to structural valve deterioration (SVD) stem not only from the experience with surgical bioprostheses, which demonstrate a sharp increase in SVD 10 years post implantation, but also from a limited understanding of the impact of altered flow dynamics in the neo-sinuses of Valsalva and crimping damage to prosthetic valve leaflets on long term durability.

However, mid-term 5-year durability data from the PARTNER 1 and the CoreValve US Pivotal High-Risk trial have been encouraging. Indeed, the PARTNER 1 study mid-term data recorded no patients with SVD requiring re-intervention and stable valvular haemodynamics[61]. Meanwhile, the CoreValve Pivotal study revealed incidences of severe SVD of 0.8% and 1.7% in TAVI and SAVR respectively demonstrating no statistical significance between the two groups[62]. The incidence of severe and moderate/severe SVD at 5 years in the FRANCE 2 registry was 2.5% and 13.3% respectively[63]. It seems from the current data that durability of TAVI valve prostheses is equivalent to surgical bioprostheses[64].

The practice of TAVI in failing SAVR (TAV in SAV) in high risk patients is gaining traction as an alternative to redo SAVR with favourable evidence from the Valve-in-Valve International Data (VIVID) and PARTNER 2 registries as well as the CoreValve US Expanded Use Study[65,66]. Indeed, surgical practice worldwide has moved away from metallic valves with increasing use of bioprostheses, perhaps with the intention to treat bioprosthetic failure with valve-in-valve TAVI in the future. Valve-in-valve TAVI requires careful preprocedural planning to avoid complications such as coronary obstruction and significant patient-prosthesis mismatch. Surgical AVR frame fracture has been shown to be an effective technique in reducing patient prosthesis mismatch in those with small surgical prosthesis sizes with low rates of procedural complications. For those at high risk of coronary obstruction, intentional splitting of the prosthetic heart valve leaflets with radiofrequency energy (Bioprosthetic Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary obstruction- BASILICA) directed by catheters and guidewires to facilitate coronary flow through the open cells of the TAVI prosthesis has shown promise[67]. The prospect of TAVI in younger patients raises the prospect of transcatheter ViV procedures in failing TAVI prostheses (TAV in TAV). Thus far, such procedures have only been described in case reports and are likely to be an area for future research.

Paravalvular Leak

In view of the adverse prognostic implications of moderate to severe PVL, significant effort has been expended towards its mitigation with considerable success, although perhaps at the expense of increased frequency of PPM implantation. The incidence of moderate-severe PVL has declined dramatically in the new generation of devices with a rate of 2%-3.4% with SAPIEN 3 whereas no significant PVL was detected with the CoreValve Evolut Pro. In low risk patients, the recent PARTNER 3 trial suggested the incidence of significant PVL to be 0.8% whilst an incidence of 3.5% was observed in the Evolut Low Risk Trial[48,55].

In addition to increased operator experience and a greater understanding of the significance of PVL, two keys factors have underpinned the reduction in incidence. First, the evolution of valve technologies with the introduction of cuffs and skirts and the ability to retrieve and reposition prostheses thereby enabling optimal device positioning. Second, the use of 3-dimensional imaging/MSCT for procedure planning in determining the size and type of prosthesis. Interventions available to correct significant PVL include further balloon post-dilatation, valve-in-valve intervention and for more focal lesions, closure with a vascular plug.

Future 'disruptive' technologies in TAVI

Evidence-based technological advancement of valve systems has formed the cornerstone of enhancing the performance and safety of TAVI and this continues apace with a number of potentially disruptive technologies on the horizon.

Dry tissue valve technology

Pre-mounted dry tissue valve technology mitigates the need for storage of TAVI prostheses within a preservative solution (e.g. glutaraldehyde) and therefore potentially the pre-implantation process of crimping and mounting the device on the delivery system. Residues of preservative solutions along with handling and crimping valve prostheses are thought to adversely impact durability. Furthermore, dry tissue technology offers the prospect of a pre-mounted and pre-crimped prosthesis requiring minimal preparation and thereby enhancing procedural simplicity and reducing procedure time[68].

Polymer based valve leaflet technology

Although pericardial xenografts currently form the mainstay of valve leaflet technology, concerns regarding SVD have driven the search for alternative leaflet materials. Polymers have the potential to enhance valve leaflet durability, reduce costs and offer greater design freedom. Attempts at developing viable polymeric aortic valves have yet to be successful; however, newer polymer technologies offer promise with a number of devices in development such as the PolyNova xSIBs TAVR valve (PolyNova Cardiovascular Inc, USA) and Triskele urethane (POSS-PCU) TAVR valve (UCL TAV, University College London, UK)[69].

Tissue engineered heart valves

The field of heart valve tissue engineering (HVTE) has made considerable advances towards translation with a landmark attained in 2010 with the first transcatheter implantation of a stented tissue engineered valve in adult sheep in the pulmonary position by Schmidt et al[70]. This was followed by implantation of a tissue engineered valve in the descending aorta of a sheep model as proof concept for this technique to withstand the pressures of the systemic circulation by Emmert et al[71].

Valve technologies for aortic regurgitation

TAVI in severe AR is inherently challenging due to distortions in aortic anatomy, minimal leaflet calcification and hypercontractility of the LV. These features introduce technical difficulties with prosthesis sizing, positioning and anchorage. A number of valve systems have been developed for the dual purpose of treating AS and AR and further work continues in this field.

Conclusion

Iterative, evidence-based evolution of transcatheter technologies and refinement of periprocedural practice have underpinned remarkable advances in the success and safety of TAVI and its transformation into a 'PCI-like' procedure as first envisioned by Cribier. These strides notwithstanding, a number of challenges remain, particularly the incidence of PPM implantation, PVL, uncertainty about valve durability and periprocedural CVA. These concerns assume greater significance with the prospect of extending TAVI to younger patient cohorts at low surgical risk. The success of TAVI has also heralded the prospect of its wider use in valvular heart diseases such as AR and bicuspid aortic valve disease which will require further evaluation. The scale, rate and breadth of research and innovation in transcatheter technologies along with an evidence-based approach will ensure these challenges and questions can be safely addressed. This unique book celebrates the 50 years of use of the Pericardial Heart Valve. As the Pericardial valve is the core of TAVI insertion system, it is apposite to celebrate its success also through this Chapter.

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Chapter 6

The Pericardial Heart Valve, Fifty Years of Clinical Use

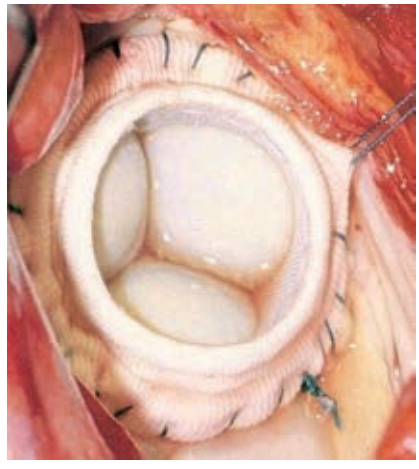
Anand P. Tandon

Vides ut alta stet nive candidum

On the 4th April 1971 the first Pericardial Valve was inserted in a patient in the mitral position. This was the beginning of a journey, indeed an Odyssey, which continues today as we approach 50 years of worldwide use of this enduring and remarkable prosthesis. That surgical operation was performed by Marian Ionescu, the pioneering surgeon who invented and constructed the first pericardial valves; and it happened at the General Infirmary in Leeds, UK.

As we approach half a century since the invention and the introduction of this original valve in surgical practice it is important to describe the evolution of its journey over the years. To understand the evolution of this unique invention, one needs to establish the historical framework of that period. The possibility to replace diseased heart valves remained for a long time just a dream. Sporadic attempts had been made to create an acceptable artificial heart valve without success. The real work of designing and constructing artificial heart valves took place during the decade 1961 to 1971.

During an interview in 2015 Marian Ionescu speaking on the history of open heart surgery said: 'It is hard to single out one investigator or one discovery which made this brave new world of heart valve surgery possible, but this seemingly sudden eruption of brilliant exploits was due to decades of smouldering intellectual curiosity compounded by the dormant torment of the forgotten predecessors, those gifted fools who by their work saved their successors the trouble of thinking'. In artificial heart valve work, as in all innovation there are two ways to advance: revolutionary creation and modifications on the same theme.



There were three personalities who created the main three events which brought heart valve replacement into the modern era.

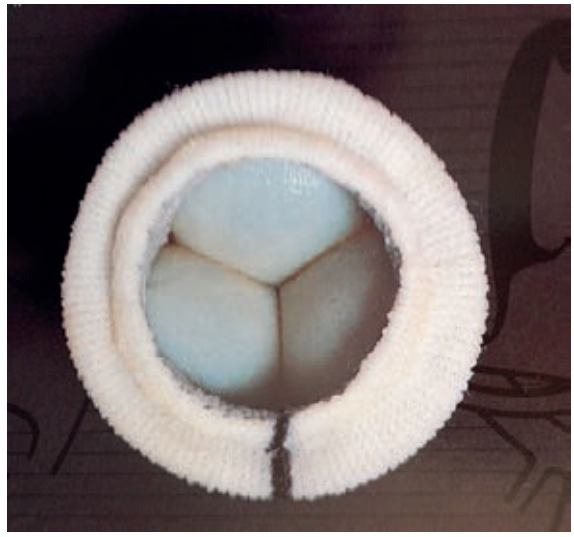
1. In 1961 Lowell Edwards, an American engineer imagined and built a cage and ball valve as well as a bi-leaflet valve. This second one was not pursued due to lack of adequate materials. He teamed up with a surgeon, Albert Starr, and the well-known Starr-Edwards ball valve was born and used, with occasional modifications, for decades. This was the beginning of the heart valve replacement era. This revolutionary invention was followed by a plethora of variations on the same principle, all interesting but ephemeral.

2. In 1971 another American engineer, Donald Shiley in his garage, created and built the floating, tilting disk valve. It was another revolutionary creation but Donald Shiley needed a surgeon to start using it. Viking Björk from Sweden accepted, with certain conditions, the offer. The new valve became the Björk-Shiley tilting disk valve. Like the Starr-Edwards valve this new and interesting device carried a high risk of valve thrombosis and embolism. In 1979, in order to help reduce these risks, the shape of the valve was slightly modified. This change reduced its strength and catastrophic valve failures occurred in a large number of patients. As a consequence of this, Pfizer, the giant pharmaceutical group and the parent company of Shiley Laboratories, decided in 1987 to close Shiley as a commercial entity and sell all the individual manufacturing units.

3. The third revolutionary creation, the Pericardial Valve, was born out of the dream of Marian Ionescu to create a tissue

heart valve which will perdure and will not require anticoagulation. From the very beginning of this project he stated that 'This is not only a valve but a concept of man - made devices. As such the embodiment of this concept, the Pericardial Valve lends itself to infinite permutations of shape and physico-chemical interventions in order to improve its function while maintaining the exceptional haemodynamic performance and the very low propensity for embolisation'. And this is exactly what happened over the years.

When asked how this major leap occurred, from where the concept of using bovine pericardium, such a different material from the porcine aortic valve, came from, he went a little deeper into the unspoken life of ideas. 'Out of the many dreams which burn softly inside the mind, occasionally one becomes prevalent, that triggers the dream to imagine, to look, to see with your inner eyes that which is not there, a sliver of silvery silken veil of light lifts.....and the rest is just toil, unending trials, repeated failures, more hard work and perseverance until the vision become reality. It takes what it takes in time. It is said that success depends on knowing how long it will take to succeed, but us, little creatures, we are not allowed to read the future. Sometimes the Goddess Fortuna may smile on you. You may reach the point where success will make you bask in the prize of critics and the envy of your colleagues and suffer when your work falls into the wrong hands. Do not despair, Invidia Medicorum Pessima has always been an old companion of our profession'.

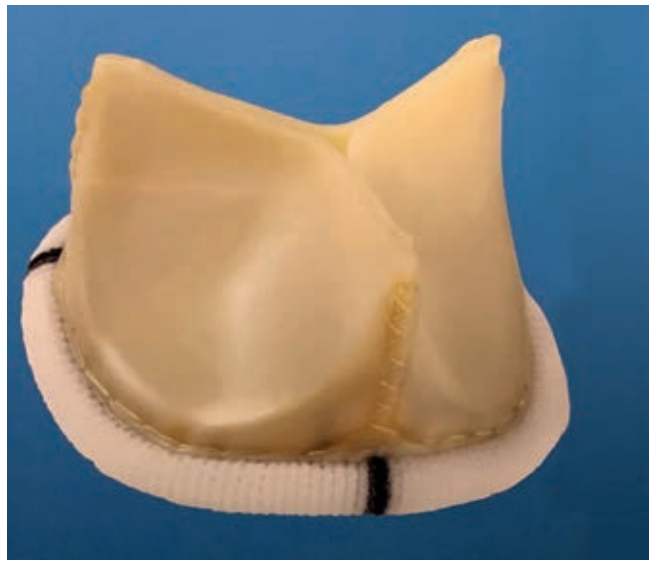


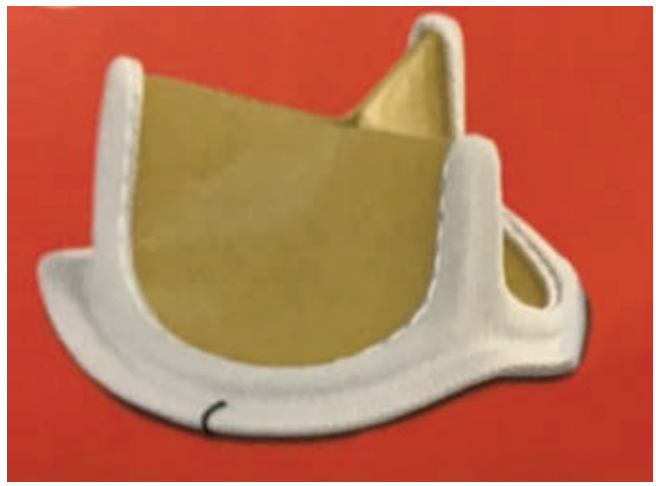
The evaluation of the pericardial heart valve went through several stages during the two years prior to its first clinical use. Initially the valves were made in Ionescu's hospital laboratory by Dr Christina Ionescu. Between 1971 and 1976, 212 patients received hospital made valves.

Away from the light of the ramp thorough investigations were carried out in these patients. In addition to the usual clinical and laboratory tests, haemodynamic investigations, at rest and during exercise, were performed on 110 patients (51 aortic; 44 mitral; 12 multiple and 3 tricuspid valve replacements). Nineteen of these (13 aortic and 6 mitral) were subjected to sequential haemodynamic studies at intervals of approximately 1, 3.5 and 5.7 years post-implantation. These studies demonstrated excellent function, better than with porcine valves and equal to the best mechanical valves. In the six years of usage the valves implanted retained their physical and functional integrity. In those days echocardiography was in its infancy.

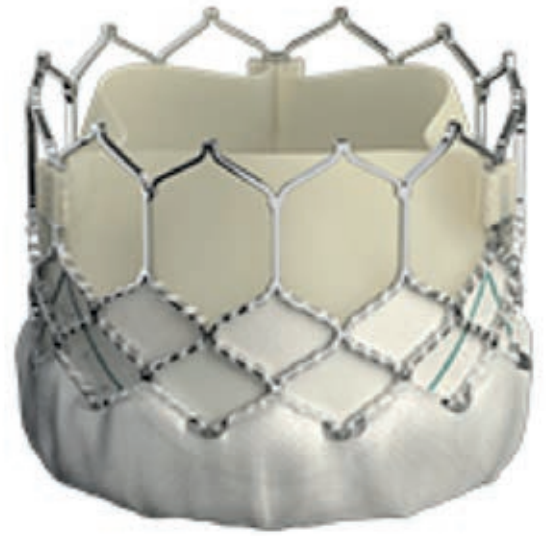
During these first 6 years anticoagulants were not used beyond the first six post-operative weeks in any patients with aortic or with mitral valve replacement. Valve thrombosis was not encountered and the rate of embolic events was as low as in patients with mitral valve disease treated medically. Due to the experience gained in these first six years of function, the

exceptional haemodynamic performance and a low propensity for embolism, the American company Shiley Inc. began in 1976, following some modifications, the manufacture and worldwide distribution of the Ionescu-Shiley Pericardial Xenograft. In 1983 more changes were made to create the Low Profile Pericardial Xenograft. In 1986 the Ionescu-Shiley Optimograft was created by a different mounting of the pericardium inside a double, thinner stent in order to avoid the abrasions of the pericardium on the Dacron cloth covering the Delrin support. Just before the start of manufacturing of the Optimograft some unfortunate evidence arose showing many failures in one of the modified models of Björk-Shiley mechanical valves. Pfizer decided to stop all production and end the Shiley Company as a commercial entity. The Porcine Aortic Valve was not included in this description because it is not an invention but a hybrid construction created by Marian Ionescu in 1967 for the first time for mitral valve replacement. The aortic valve of the pig created by Mother Nature, was chemically treated and attached to a supporting frame to allowing suturing into the mitral annulus. This is neither an invention nor a concept. Despite its many shortcomings the porcine valve was extensively used in preference to mechanical valves which have their own imperfections. Following the Pfizer decision, a few companies started, during the 1980s, to manufacture pericardial valves. Some of them with very poor results abandoned the project while two or three continued successfully to manufacture the pericardial valve with some changes but always maintaining all the characteristics and exceptional qualities of the original Ionescu Pericardial Valve. During the long term follow-up of the Ionescu-Shiley Pericardial Xenografts a crucial discovery was made in 1985. It was already known that calcification of the pericardium is by far the main cause of valve dysfunction and eventual failure. Statistical analysis of the two largest series of patients with the Ionescu-Shiley pericardial valves (Denton Cooley with 2720 and Marian Ionescu with 1171 patients) revealed that calcification of the pericardial valves occurred more often and advanced much quicker in younger patients than in those older than 70 years. In short, the process of calcification is age related. The consequence of this significant discovery was to restrict the use of pericardial valves solely for patients above the age of 70 years. In this way the pericardial valves of the second generation were protected from calcification, the main cause of valve failure and the results improved substantially. In a strange way, the difference in the results between the original and the second generation pericardial valves was made by a





statistical event which brought in evidence a biological phenomenon. The difference in long term results between two identical types of pericardial valves, the Ionescu-Shiley Pericardial Xenograft and the second generation pericardial valves is, simply explained by the following facts.



1 The Ionescu-Shiley valves were used, between 1971 and 1987, in patients of all ages from children to 70 years old (most of them were middle-aged people) and the valves were implanted in all three cardiac valvular positions (about half of them in the mitral position)

2 The second generation pericardial valves were used since 1987 almost exclusively in patients older than 70 years and only in the aortic position.

The comparison of results obtained in these two series of patients is illogical and whenever published it would be in mala fide. *Dixit et anima mea salvavit*.

Now the real, serious solution to the calcification of tissue heart valves ought to be a scientific approach to the study of the causes of tissue calcification in man in general and in heart valves in particular. Solving this problem would make the Pericardial Heart Valve the ideal valve replacement for a long time to come, or until the white bell of progress will ring three times. *Sublata causa tollitur effectus*.

Some of the manufacturers of the second generation pericardial valves assert that a special solution or treatment of the valves possesses anti-calcification properties. There is not a shred of scientific evidence to support this assertion. At the same time they advise surgeons not to use such valves in patients younger than 70 years. *Quod erat demonstrandum.*

It is strange that the manufacturers of pericardial valves, of all types including those used in TAVI, whose essential material for constructing the valves is pericardium, systematically omit this word 'pericardium' from their advertisements. All of them have opted for bizarre names which have no relationship with heart valves or the material from which they are made (Trifecta, Intuity, Perceval, Sapien, etc. etc.). Has the heart ceased to be the noble symbol of our existence? Some valve manufacturers and even surgeons had the temptation to appropriate the paternity of Ionescu's whole pericardial valve concept. To claim to have discovered the 'philosopher's stone' 10 years after its creation is ridiculous, but to consider to arrogate someone else's intellectual property is always reprobative. In general the second generation of pericardial valves are well made. Following changes in the mounting of the pericardium onto the supporting frame, all the exceptional characteristics of the original Ionescu valve were maintained intact. They function well and many published accounts on the long term results of their use demonstrate good performance of these valves up to 20 years in the aortic position of older patients.

Progressively the utilisation of pericardial valves has increased to reach a now dominant position of approximately 80% of all heart valves used worldwide and this is without taking into account the very large number of pericardial valves inserted through TAVI. One of the most fascinating examples of the use of the pericardial valve concept is the trans- catheter aortic valve implantation (TAVI or TAVR) imagined and created by Alain Cribier in Rouen while acknowledging the patent of Dr. Henning Rud Anderson, a cardiologist from Denmark who first arrived at the valve-by-wire idea to treat his father. Following several years of

research and trials Cribier succeeded in 2002 to use the technique of inserting pericardial valves through a catheter. This technique obtained FDA approval in 2012 and since then some 300,000 procedures have been performed in 65 countries. This figure is increasing by 40% year on year. It is considered that by 2025 there will be 280,000 such procedures performed yearly. The medium and long term follow-up demonstrated very good results.

It is gratifying that now we have the privilege to extol the Pericardial adventure, which through all the meanders of its evolution, is still here and in a strong position nearly 50 years after its creation here in the UK and it serves loyally its purpose for the treatment of patients.

None of this would have been possible save for the ingenuity and perseverance of Marian Ionescu who is undoubtedly the 'Father' of the Pericardial Heart Valve. When a scientific remedy to prevent calcification will be found, the initial dream of Marian Ionescu for an artificial heart valve which will perdure and not require anticoagulation would have been fully realised.

Grateful thanks are extended to Mr Marian Ionescu for his insight and help with details and photographs.

Chapter 7

The Role of Echocardiography in Evaluation of Pericardial Valve Function

Vishal Sharma
John Chambers

Faber est quisque fortunae suae

Introduction

Transthoracic echocardiography (TTE) is the key imaging technique for the assessment of pericardial as well as all other replacement heart valves. Transoesophageal echocardiography (TOE) may be needed if pathology is suspected, although less frequently than for mechanical valves in which shielding and blooming artefact are more prominent. Computed Tomography (CT) may occasionally be necessary for detecting pannus or elucidating aortic abscesses in infective endocarditis.

This chapter discusses the minimum standard TTE, the normal appearance of stented, stentless and transcatheter pericardial valves, the differentiation of patient prosthesis mismatch from obstruction, pathological regurgitation, the diagnosis of early structural valve deterioration and the timing of echocardiography after surgery.

The minimum standard TTE in the normal valve

A comprehensive TTE should be undertaken according to established guidelines[1,2]. The clinical data needed to interpret a study are shown in Table 1. It is essential that all components of the pericardial valve and sub-valvular structures are carefully assessed.

The sewing ring or stent is easily imaged and particularly for TAVI may partially obscure the leaflets. In normal valves in the aortic position the sewing ring is stable and any movement or rocking of the sewing result may indicate partial dehiscence of the valve with a significant paravalvar leak. In the mitral position rocking or a piston-like motion of the sewing ring can be normal if the surgeon has retained the posterior leaflet. It is, however, important to check the region particularly carefully using colour mapping.

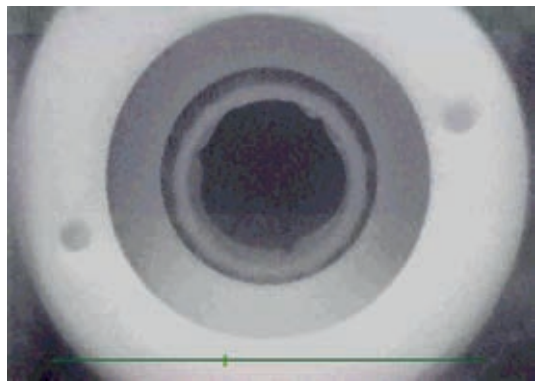


Figure 1: Still frame of a Mitroflow valve in systole filmed in a pulse-duplicator.

A normally functioning pericardial valve of any design has thin and mobile leaflets opening symmetrically (Figure 1). These are particularly easy to image for the mitral position, but imaging is usually feasible in all standard views for stented or stentless surgical pericardial valves (Figure 2). TAVI may be harder to image because the leaflets are thinner than in a surgical valve and there may be significant shielding from the stent. However, the leaflets can often be imaged in the apical views if this is not feasible parasternally.

Colour Doppler should be used in all views. Additional and sometimes multiple, off-axis views may be required to detect and assess paravalvar leaks which can occur at any point around the suture ring. The jet may often be eccentric and it is important to follow it carefully back to its base to find its origin. Only if the base is found is it possible to differentiate with confidence whether a leak is paravalvar or through the valve. For example, an eccentric jet originating at a commissure can be hard to differentiate from a paraprosthetic jet. The parasternal short axis views are particularly useful and can localise even minor regurgitation for valves in the aortic position. For the mitral position it is possible to miss minor regurgitation on TTE.

Trivial or mild transvalvular regurgitation is noted in up to 10% of cases[3] and may be slightly more common in stentless pericardial valves in the aortic position usually at the point of apposition of the cusps. If regurgitation is seen in the context of thickened leaflets this is more likely to be suggestive of structural valve deterioration (SVD). For TAVI, minor leaks through the valve or in a paraprosthetic position are much more common. There may be multiple small jets due to a failure of apposition of the stent to the tissue annulus.

Table 1. Clinical parameters required to interpret an echocardiogram

Clinical Parameter	*Rationale*
Type and size of valve	Acceptable velocities and gradients across a valve vary significantly depending on type. Knowing the size of valve can help distinguish valve dysfunction from patient-prosthesis mismatch.
Date of implantation and implanting centre	Useful to determine cause of any potential valve dysfunction. It may be necessary to discuss abnormal findings with the implanting centre and/or compare against initial post-operative baseline echo
Blood Pressure	The blood pressure at the time of the echocardiogram can impact the haemodynamic parameters. In particular regurgitant lesions such as mitral regurgitation can appear more severe in the context of increased LV systolic pressure
Heart Rate	Transvalvar gradients, particularly across prosthetic mitral valves are increased in the context of tachycardia.
Height and Weight	Calculation of Body Surface Area in order to allow indexing of the effective orifice area. This is important particularly if the patient is symptomatic despite an absolute effective orifice area that is in the non-severe range.
The presence or absence of symptoms	It is important to document any symptoms or change so that any new findings can be interpreted correctly. In addition, a comprehensive echocardiogram should be undertaken to exclude any non-prosthetic valve related findings that may be responsible for symptoms.

This is more common if the LVOT is elliptical rather than circular.

A comprehensive spectral Doppler examination should be undertaken with appropriate optimisation of the Doppler traces. This includes obtaining a Doppler profile of forward flow through the valve and where relevant a profile of any trans or paravalvar regurgitation. The key Doppler parameters are outlined in Table 2. These vary by design and label size. However, in general pericardial valves have relatively low resistance to forward flow and in meta-analyses, perform better haemodynamically than porcine replacement valves in meta-analyses or descriptive studies[4,5]. Labelling conventions differ between valve designs which limits comparisons. However even randomised controlled trials show small but statistically significant differences in favour of pericardial valves[6,8]. TAVI valves are less obstructive than surgical valves and the avoidance of severe patient prosthesis mismatch is sometimes a secondary criterion for recommending a TAVI procedure. If the V max is >3.0 m/s, patient or prosthesis mismatch should be considered. These are discussed in the next section.

Finally, it is important to assess other cardiac structures and function. In particular a full assessment should be undertaken of any co-existing valve lesions, left and right ventricular function and atrial size including left atrial volume. An assessment of the probability of pulmonary hypertension being present should be made as per current guidelines[9].

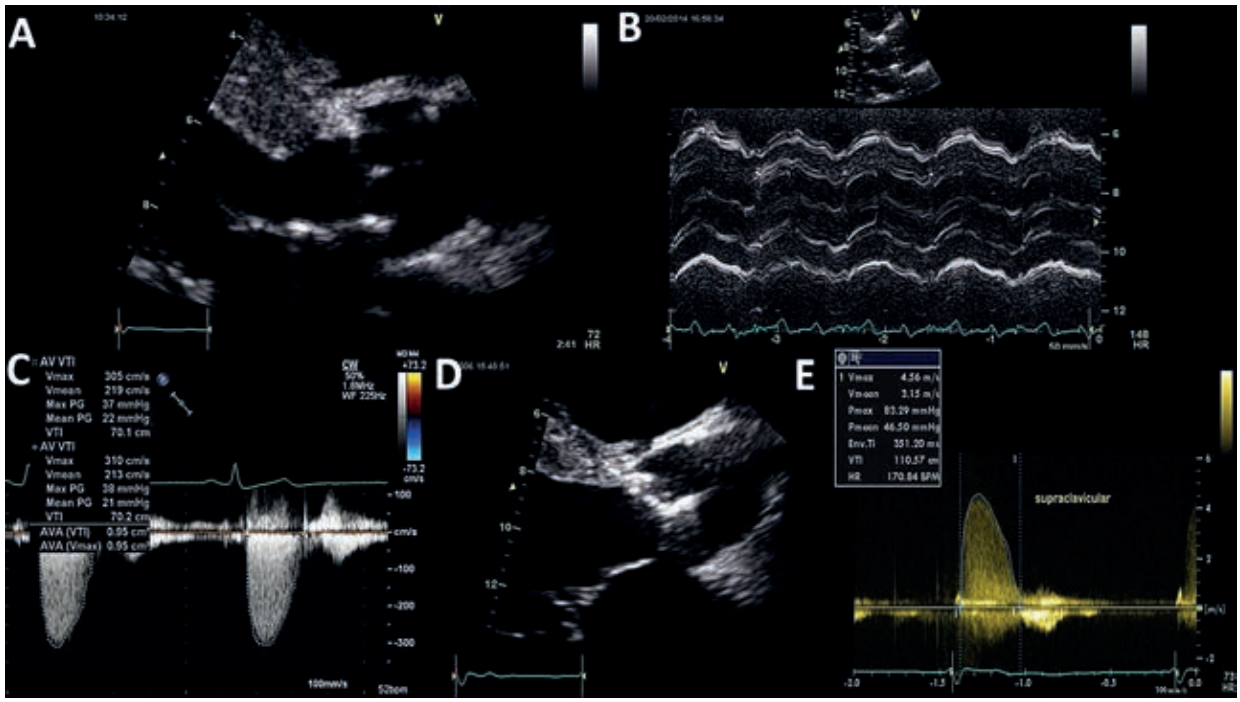


Figure 2: Echocardiography of normal and failing Perimount aortic valves. Note: 2A-C are baseline scans. 2A is a parasternal long-axis view and 2B an M-mode both showing thin leaflets. 2C is the continuous wave trace through the valve showing velocities within the normal range. 2D and E are recorded in a patient late after implantation who presented with breathlessness. 2D is a parasternal long-axis view in systole showing thickened and immobile leaflets. 2E is the continuous wave trace showing severely elevated velocities.

Table 2. Key Doppler parameters to record when assessing pericardial valves

Doppler Parameter - Aortic Position	*Doppler Parameter - Mitral and tricuspid position*
Peak Velocity and VTI – (CW Doppler)	Peak Velocity - (CW Doppler)
Mean Pressure Drop - (CW Doppler)	Mean Pressure Drop - (CW Doppler)
Acceleration Time – (CW Doppler)	Pressure Half-Time
LVOT velocity VTI – (PW Doppler in LVOT)	
Doppler velocity Index - (LVOT VTI/Peak VTI)	
Effective Orifice Area (continuity equation)	
Pressure Half time (regurgitant lesion)	

CW, colour wave; LVOT, left ventricular outflow tract; PW, pulse wave; VTI, velocity time integral.

Patient-prosthesis mismatch vs pathological obstruction

It is common to find a high velocity across a replacement heart valve in the aortic position. This can be caused by pathological obstruction or patient-prosthesis mismatch.

Patient-prosthesis mismatch (PPM) means that the valve orifice area is too small for the size of the patient. All replacement valves have a smaller area available for flow than a normal native valve because of the presence of the stents or sewing ring and reduced compliance of the leaflets. However, below an EOAi 0.85cm^2/m^2 the transaortic velocities at rest rise exponentially and this is taken as the cut-point for moderate PPM. Severe PPM is taken as an EOAi less than 0.65cm^2/m^2 which is accompanied by higher event rates perioperatively and in the longer-term[14-16]. Lower cut-point values should be used in obese patients (body mass index ≥ 30 kg/m^2)[10]. Partition values for mild, moderate and severe PPM for the aortic and mitral positions are shown in Table 3.

By contrast structural valve deterioration (SVD) occurs as a result of limited durability leading to failure of the valve. It is therefore characterised by the development of abnormal morphology or movement of the leaflets with initially normal haemodynamic function. As it progresses it is associated with a change in haemodynamic function (Figure 3). A proposed definition of moderate SVD in aortic replacement valves is:

Thickening of the leaflets and an increase in mean gradient by >10 mmHg from the baseline study or new or worsening transvalvar regurgitation

Table 3. Thresholds for patient-prosthesis mismatch in replacement aortic and mitral valves[11]

	*Mild**	*Moderate*	*Severe*
Aortic (cm^2/m^2)	>0.85 (>0.70)†	0.65-0.85 (0.6-0.70)†	<0.65 (<0.6)†
Mitral (cm^2/m^2)	>1.2 (>1.0) †	0.9-1.2 (0.8-1.0)†	≤0.9 (≤0.8)†

† Values between parentheses are for obese patients, i.e. body mass index ≥ 30 kg/m^2

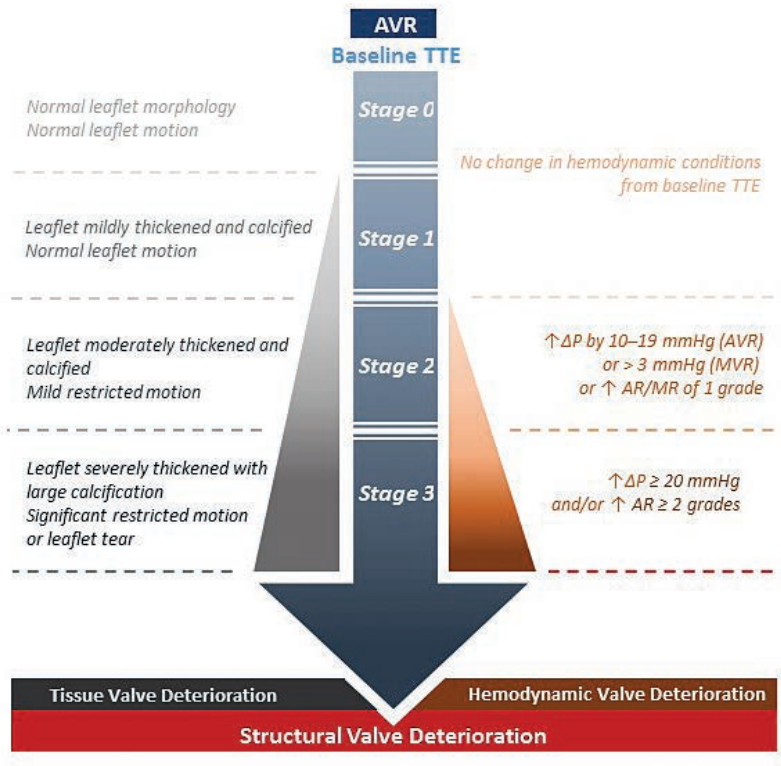


Figure 3: Schematic showing the development of structural valve deterioration. Initially there are morphological changes then a rise in mean gradient or transvalvar regurgitation subsequently develop.

Table 4. Features to distinguish Patient-Prosthesis mismatch from valve dysfunction (for patients with reduced EOAi)

Finding	Favours PPM	Favours valve dysfunction
Valve Velocity	Normal or mildly increased velocities. Finding present on initial post-operative echocardiogram and unchanged	New finding of high velocities or a significant increase in velocity compared to baseline echocardiogram
Leaflet Appearance	Thin leaflets with no/minimal calcification	Thickened and calcified leaflets
Leaflet mobility	Relatively normal mobility	Reduced opening
Transvalve regurgitation	None/minimal	Increasing from earlier studies

The key echocardiographic features suggesting PPM versus a pathological problem with the valve are shown in Table 4. Comparison with the early post-operative baseline echocardiogram is essential as in cases of PPM, these patients will typically have high velocities from the outset. In particular a new finding of a high velocity or a significant increase in velocity suggests that this is more likely to be due to valve dysfunction. Careful assessment of the valve leaflets is also essential as in cases of pathological obstruction, the leaflets of pericardial valves may be thickened and calcified with reduced mobility. Conversely in PPM, the leaflets may look relatively normal with good opening.

High velocities through a valve may also be due to significant transvalve or para-valvar regurgitation. A careful sweep of the valve with colour Doppler as described above is essential to ensure no off-axis jets are missed. If image quality is sub-optimal or it remains difficult to distinguish between PPM and valve dysfunction, TOE may be helpful in order to visualise the valve better and exclude any regurgitant lesions.

A statement released in 2017 by European Association of Percutaneous Cardiovascular Interventions which was endorsed by the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery inappropriately allowed SVD to be defined solely by an absolute mean gradient ≥20 mmHg[12,13]. In fact, a mean gradient of ≥20 mmHg is often found immediately after implantation and represents patient prosthesis mismatch and not SVD. In studies comparing TAVI with surgical valves SVD was apparently less common for TAVI but apparent failure rates were dominated by absolute mean gradients ≥20 mmHg representing patient prosthesis mismatch[14-15] (Fig 4). However new transprosthetic regurgitation, a robust sign of SVD, was less common in surgical bioprostheses than TAVI.

Trans-prosthetic and paravalvular regurgitation

It is an increasingly common to detect mild regurgitation in normally functioning pericardial valve replacements. This is part due to the fact that echocardiography machines have developed significantly with superior imaging quality. The finding of valvular regurgitation is more common in stentless valves.

When quantifying trans-prosthetic regurgitation, the same techniques are used as those for native valve regurgitation[16]. However, the grading of para-prosthetic regurgitation is more challenging particularly due to their eccentric nature and the fact that particularly in trans-catheter valves there may be multiple jets. For para-prosthetic jets, the proportion of the circumference of the sewing ring occupied by the jet gives an approximate guide to severity of para-prosthetic regurgitation: mild (<10%), moderate (10–30%), severe (>30%)[17]. However, the width of the para-prosthetic jet(s) at origin assessed in multiple views is also helpful to assess severity[11].

Subclinical leaflet thrombosis

Leaflet thrombosis (LT) may cause thromboembolism, symptomatic obstruction and reduced durability[18,19]. It may present as 'silent' thickening of the valve on computed tomography (CT) with or without mild restriction of leaflet motion. It occurs in about 10-18% TAVI compared with 4-7% of surgical replacement valves (SAVR)[19]. SVD occurs in 15-20% with LT[19-20] (Figure 5).

The higher incidence of LT in TAVR compared with SAVR is likely to be explained by a number of factors. Firstly, there are important differences in leaflet morphology which are thinner, 0.25 mm in TAVR compared with 0.4 mm in SAVR[21], and which may be damaged from crimping [22] or balloon expansion. [23] Secondly, there are increased stresses on the leaflets caused by the non-expansile TAVR stent, and the potential for asymmetric deployment[21]. Thirdly, there can be increased stasis downstream because of the presence of native valve tissue[22].

Leaflet thrombosis is not usually detected on TTE but is seen on CT or TOE. There is no consensus on the routine use of these techniques after valve deployment. The hope is that a way of predicting a higher risk of leaflet thrombosis will be developed at the time of implantation, probably based on measures of incomplete stent expansion to allow targeted CT[19,24].

Timing of Echocardiography Follow up

Baseline

It is essential that an echocardiogram is performed once the patient has fully recovered from cardiac surgery and their haemodynamic parameters have returned to normal. This scan establishes a reference against which future surveillance echocardiograms can be compared. Ideally this is performed around 6-8 weeks months post implantation, assuming the patient has fully recovered by this stage[25]. However,

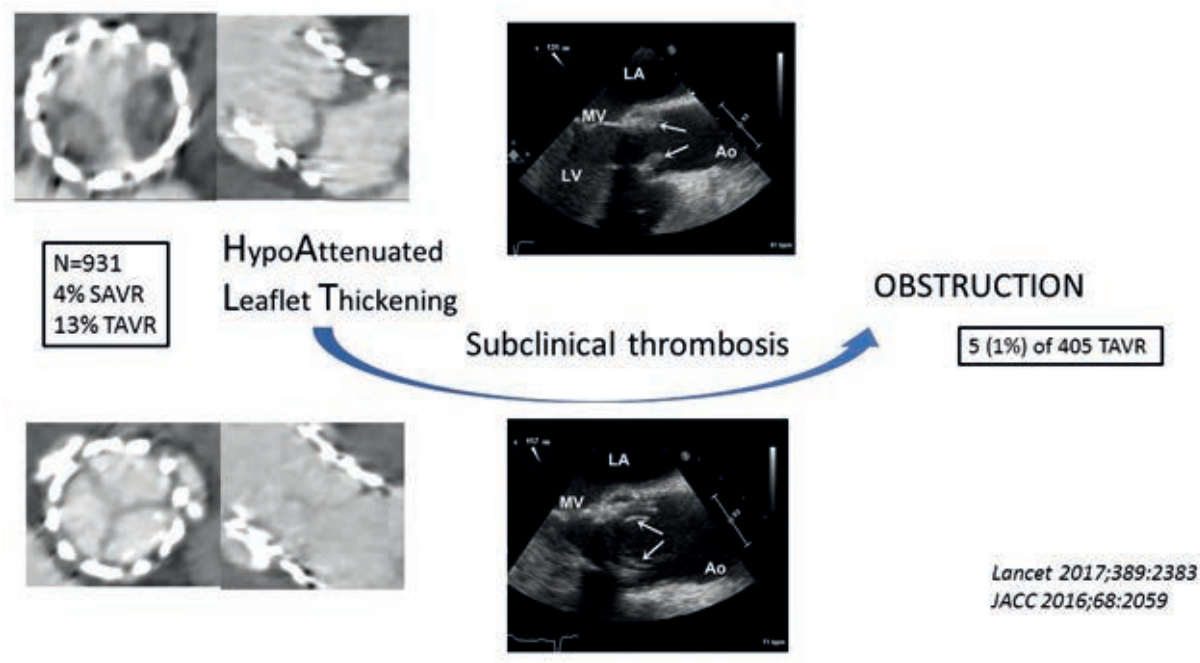


Figure 5: The development of subacute leaflet thrombosis.

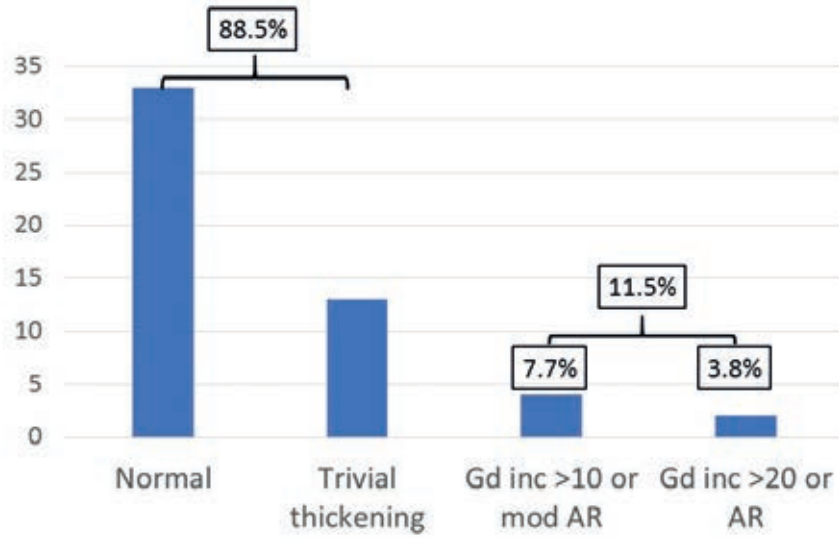


Figure 6: The incidence of structural valve deterioration at 10 years in 52 patients with Perimount aortic valves. These were part of a long-term follow-up study at Guy's and St Thomas' Hospital, London.

in the COVID-19 era it may be appropriate to perform the study predischarge to limit the number of visits required by the patient[26]. The predischarge study is also useful to exclude unexpected findings requiring further management e.g. impaired LV systolic function or a pericardial effusion. If the study is done pre-discharge due to COVID-19 this must be clearly documented on the report.

Routine

The purpose of routine echocardiography is to detect early SVD in order to observe the patient more frequently both clinically and with echocardiography and plan a redo procedure if appropriate.

All people with replacement valves require regular clinical follow-up usually annually. However routine echocardiography may not be needed immediately. The rate of SVD in Perimount valves implanted in people aged > 60 is very low (Fig 6) before 10 years. British Heart Valve Society/ British Society of Echocardiography guidelines suggest the following schedule (Fig 7):

- Annual echocardiography - TAVI or new designs
- From 5 years – Pericardial valves in the mitral or tricuspid positions or designs lacking long-term data or Perimount with more than 2 risk factors (age <60, systemic hypertension, renal failure, diabetes)[6]
- From 10 years - Valves in the aortic position with good durability in long-term data

Other indications for surveillance echocardiography

Other abnormalities may be detected on echocardiography either in the immediate post-operative period, at the time of the baseline echocardiogram or at any time during long term follow up. These findings include:

Pericardial effusion

Regular echocardiography should be undertaken until the effusion resolves

Coexistent valve disease

Echocardiography should be repeated annually for moderate valve lesions, or 6-monthly in the case of severe valve disease. A repeat echocardiogram is warranted if there is a change in the symptomatic status of the patient[27].

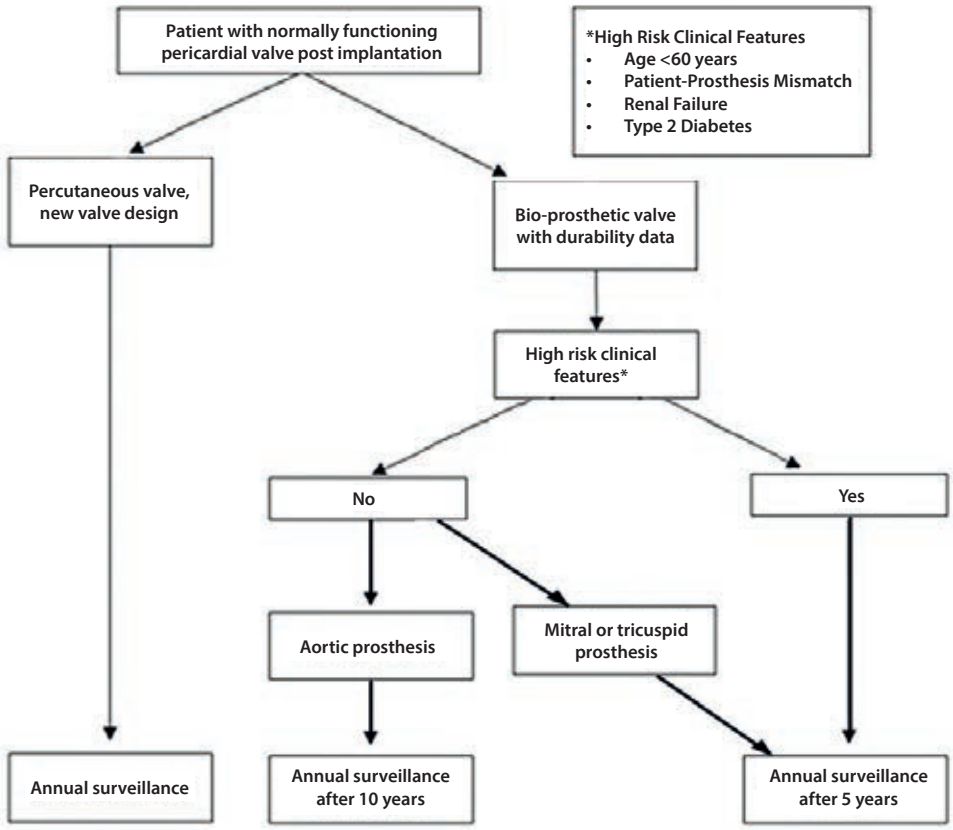


Figure 7: Flow chart for surveillance of pericardial valves with normal function on baseline post implantation echocardiogram.

Aortic dilatation

Annual surveillance echocardiograms are recommended if the aortic root or ascending aorta are dilated (>21mm/m^2). However, if the image quality is sub-optimal or the maximal dilation is in a region of the aorta that cannot be visualised on echo, surveillance with an alternative imaging modality such as CT or CMR may be required[28].

Trans-prosthetic or paravalvular regurgitation

Annual echo-cardiography is recommended if the regurgitation is mild or moderate, but this should be increased to 6-monthly if there is severe regurgitation.

Left ventricular or right ventricular systolic dysfunction

If there is severe left or right ventricular systolic dysfunction, echocardiographic surveillance could be considered initially to assess for improvement. However, if this remains unchanged and the patient is stable on appropriate heart failure treatment, in the absence of other indications for echocardiography, further scans are indicated if the patient develops new or worsening symptoms of heart failure.

Pulmonary hypertension

If there was pre-existing raised pulmonary artery pressure prior to surgery, it is reasonable to undertake annual surveillance echocardiograms to monitor this. This is particularly the case in patients with mitral valve replacements, particularly if there is patient prosthesis mismatch or where there was tricuspid regurgitation present with no concomitant surgical repair.

Advanced imaging techniques for pericardial valves

Trans-oesophageal echocardiography

Trans-oesophageal echocardiography (TOE) is extremely useful in assessing pericardial valves that are either not well visualised on TTE or where there is uncertainty regarding the presence of SVD. TOE is useful in assessing the location of and the severity of regurgitant lesions, particularly when this is uncertain on TTE. The use of 3D colour Doppler can allow the visualisation of trans-prosthetic and indeed para-prosthetic regurgitation allowing a regurgitant orifice area to be measured which can assist with grading of severity, particularly for valves in the mitral position. For trans-catheter valves, a deep trans-gastric view can be useful in distinguishing trans-prosthetic regurgitation from paravalvular regurgitation.

TOE is often recommended if there is a clinical suspicion of endocarditis or if there is a clinical history of thrombo-embolic events.

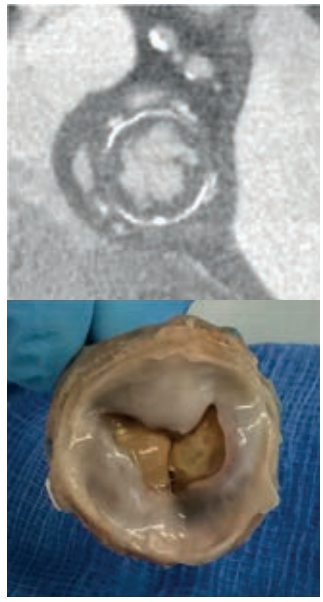


Figure 8: Pannus. 8A shows the pannus on Computed Tomography and 8B the appearance on the explanted valve.

Cardiac CT in pericardial valves

CT is the technique of choice for detecting subclinical leaflet thrombosis. It may also detect pannus[29] (Figure 8). A retrospectively gated, functional cardiac CT can assess mobility of valve leaflets and allow for an anatomical orifice area to be calculated. Cardiac CT is also useful for assessing the aorta if there are concerns regarding aortic dilatation, or aortic calcification, particularly if redo surgery is being considered.

Summary

Pericardial valve replacements have transformed the lives of patients with native valve disease and modern valves have good longevity. They have better haemodynamic profiles than porcine valves and avoid the need for anticoagulation required with mechanical prosthetic valves. However, eventually over time they will develop structural valve degeneration (SVD) and consequently regular clinical and echocardiographic follow up is mandatory. All patients should have at least annual clinical follow up, ideally in a specialist heart valve clinic.

It is essential that a baseline post implantation echocardiogram is done around 6-8 weeks post operatively once the patient has fully recovered and their haemodynamic status has returned to normal. Parameters obtained at this echocardiogram will be used for comparison in the future to help detect early SVD. For pericardial heart valves in the aortic position for which there is good long-term data available it is recommended that surveillance echocardiography is commenced at 10 years and annually thereafter unless there is a change in clinical status or alternative reason for echocardiography to be done more frequently. For patients with high risk features, e.g. those under the age of 60, patients with diabetes, renal failure of patient prosthesis mismatch and patients with pericardial valves in the mitral or tricuspid position, surveillance echocardiography should commence after 5 years. For trans-catheter valves and newer valves without long term data, annual echocardiography should be performed.

In the majority of cases trans-thoracic echocardiography is all that is required but in selected cases, TOE, Cardiac CT and Cardiac MRI may be useful in identifying SVD or other pathological findings.

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Chapter 8

Long term results of the Pericardial Valve in the Mitral Position

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Natura appetit perfectum

The advent of prosthetic heart valves

It was in 1960, seven years after John Gibbon first performed open-heart surgery using cardiopulmonary bypass, that a durable mitral replacement was first implanted in the human. Shortly after, Starr and Edwards wrote of their mechanical invention "considerably more information is required before the search for the ideal mitral prosthesis may be discontinued".

Indeed, from an early stage in the history of cardiac valve surgery, there has been an interest in non-mechanical prostheses – an agenda promoted by patients even before shared decision making became the norm[1]. The majority of valve implants worldwide currently are tissue valves. Even in patients younger than 50 years of age, a 2 in 5 preference for tissue valves showed that the risks of redo surgery in this group were offset by major bleeding risks[2]. A durable valve with excellent haemodynamic performance but without the rigours or risks of anticoagulation has always been the holy grail.

The search for the ideal prosthetic material

Porcine valves were the first to be trialled for their similarity to human tissue[10]. Issues of collagen breakdown, cusp calcification and fibrosis were partially addressed with glutaraldehyde fixation, but the valve geometry was fixed by the size and quality of the source leaflets, causing asymmetric valve opening and impaired haemodynamic performance[3].

To address the biological variability resulting from harvesting whole animal valve leaflets, the concept of an entirely engineered valve was invented by Marian Ionescu, a surgeon in Leeds, England in 1971, using abundantly available bovine pericardium. This was the primum moven of this global enterprise and one that would see a paradigm shift away from mechanical valve replacement to a preponderance for pericardial valves. The size, shape and thickness of the valve leaflets could be precisely modified and this allowed greater control over valve opening. Furthermore, as additional biological material could be obtained easily, contiguous with the leaflet tissue, the geometric restrictions on stent and commissure placement were not as problematic.

Responding to design challenges

As had been the case with mechanical valve technologies, once the concept had been released into the wild, its value was quickly understood and commercial entities sought to imitate. Industrial collaboration[4] and competition took different approaches on how to manage questions such as the ventricular systolic pressure load on the pericardium at the struts[5]. Five separate commercial entities manufacturing pericardial valves grappled with the issue of tissue abrasion and cusp tears with varying degrees of success. Eventually, the technicians at three laboratories developed their own solutions to the enigma with unique design modifications including double layer reinforcements around the struts and internally mounted commissures. The issue of calcification was, in part, addressed by avoidance of valve implantation in younger patients whose metabolism appeared to accelerate the process. Methods to address the issue of tissue calcification were explored, identifying the problem of free aldehyde and phospholipid binding sites, but providing limited solutions to negate these.

Long term outcomes

Definitions and data quality

The long term assessment of prosthetic heart valves over more than half a century is fraught with difficulty. Notwithstanding that data synthesis, especially in the

form of meta-analysis, is common in modern literature, this approach relies heavily on homogenous patient populations, surgical techniques, post-operative management and the reporting of clearly defined outcomes. Few of these have remained constant over the years and it is cognisant of this limitation that the long term outcomes below are presented.

Survival

The reported survival at 5- and 10-years following insertion of first-generation pericardial heart valves in the mitral position (72% and 54%, respectively) are similar to the actuarial survival rates for pericardial valves still in use today (76% and 57%)[6,7]. These series, however, were published over thirteen years apart and aside from the general advances in medicine, were also confounded by different populations. The original valves were implanted in patients with a mean age of 48y, nearly a quarter of whom were undergoing re-do cardiac surgery and 35.2% of whom had concomitant surgery. A decade later, the mean age of patients in the study was 63y and the rate of re-do surgery had fallen to under 20%.

The longest follow-up of any pericardial valve in the mitral position found an actuarial valve related survival rate at 20 years of 62.4% ± 9.0% in a cohort with a mean age at surgery of 68y[8]. The all-cause actuarial survival for the same time period was 16.9% ± 3.9%, indicating the multi-comorbid populations in whom mitral replacements are usually required. In the large series by Bourguignon et al, however, following up 450 pericardial valves implanted in the mitral position for 24.8yrs, the age- and gender-adjusted life expectancy of patients following surgery was the same as the general population[8].

Structural valve deterioration

A definition for structural valve deterioration (SVD) has been proposed recently[9], but assessment by these criteria is yet to be universally adopted. Rates of SVD between different studies, particularly historical works, should therefore be interpreted with caution. Nonetheless, Doenst et al provide a comprehensive assessment of the evidence on structural valve deterioration in pericardial mitral valves[5]. Five year freedom from structural valve deterioration was high for all pericardial heart valves, and this trend persisted regardless of age at insertion with 100% freedom from primary valve dysfunction at 5 years[7]. At ten years, the patient populations became too heterogenous to draw broad conclusions, but another study found that, compared to porcine bioprosthesis made by the same company, pericardial mitral valves had superior actuarial and actual freedom from structural valve deterioration at 10 years even in patients under 60y old (84.0% ± 3.7% vs 64.7% ± 3.3%)[10].

Doenst noted, however, that “patients over the age of 70 seldom, if ever, require reoperation for SVD”. Expected valve durability in all-comers for pericardial mitral valves has been estimated at 16.6 years, ranging from 11.4y in those <60y to 19.4 years for patients aged >70 years[8].

Endocarditis

The reported incidence of prosthetic valve endocarditis in general is 0.32 – 1.2% per patient per year[11], and the incidence even in early-design pericardial valves was 0.7% per patient per year[12]. Data comparing the incidence of endocarditis following prosthetic valve implantation are variable: some early studies indicated that bioprosthetic valves had a higher rate of endocarditis than mechanical valves[13]. A more recent review suggests that bioprosthetic heart valves are less susceptible to early endocarditis than mechanical valves and are more likely to be treatable with antibiotics as the infections tend to be restricted to the leaflets[11]. A thorough systematic review and meta-analysis by Flynn et al[14] indicated no difference between the two valve types in re-infection rates with antecedent endocarditis. At 20 years, the freedom from endocarditis for pericardial heart valves is 94.8% ± 1.4%[8].

Reoperation

Reoperation for pericardial heart valves is indicated for several reasons including endocarditis, prophylactic re-replacement during cardiac surgery for another cause and, predominantly, structural valve deterioration. No studies examined the rates of re-operation stratified by age, but this would likely be correlated to age as a function of SVD. The linearised rate of re-operation is 2.5%/valve-year and actuarial 20-year freedom from reoperation for all reasons is 37.1% ± 7.4%[8].

Thrombosis & Thromboembolism

Thrombosis of bioprosthetic valves themselves is rare, but complications of thromboembolic phenomena from pericardial mitral valves occurs with a frequency of 1.0 – 1.5% per patient per year. Such data is confounded, however, by the presence of risk factors frequently associated with mitral valve disease such as atrial fibrillation, left ventricular impairment and atrial dilatation[5]. The twenty-year freedom from thromboembolic complications for pericardial valves in the mitral position was 83.9% ± 7.6%[8], representing a linearised rate of 0.7% per valve-year.

Bleeding complications

Management of anticoagulation following insertion of mitral valve bioprostheses has evolved over the years. Current recommendations for mitral (and tricuspid) bioprosthetic valves are that oral anticoagulation with vitamin K antagonists should be considered for 3 months following implantation (Class IIa recommendation, Level C evidence)[15]. Only 28% of surgeons in the UK comply with these guidelines[16]. For patients with other indications for anticoagulation, such as atrial fibrillation or severe left ventricular impairment (both of which are more common in patients with mitral valve disease), the recommendation is Class I, Level C. It is surprising, therefore, that major haemorrhage occurs at a rate of only 0.26% per valve-year[17]. The twenty-year freedom from anticoagulant-related haemorrhage following pericardial mitral valve implantation is 80.2% ± 10.8%.

Challenges for the future

Pericardial valves in the mitral position have demonstrated superb haemodynamic properties with excellent long term outcomes in terms of survival, freedom from structural valve deterioration and low rates of other complications. Nonetheless, there remain several areas of potential development to further enhance their design.

- anti-calcification treatments that could retard the development of structural valve deterioration (several have been proposed, but none have demonstrated freedom from tissue calcification in vivo)
- preservation or fixation of the leaflet material (either pericardial tissue or some future, novel material) to prevent its degradation and enhance its longevity
- use of materials or adjuncts to prevent pannus formation onto the functional parts of the valve without affecting the endothelialisation of the sewing ring
- adjustments to the structure of the stent scaffold to further enhance the available orifice area and reduce tension in the frame

Conclusion

The force of the left ventricular systolic contraction exerted upon the closed mitral is the highest pressure tolerated by any of the cardiac valves. The gradient required to trip the valve, conversely, is much lower than that of the aortic valve. In order to emulate these functions, therefore, the mitral prosthesis is a delicate interplay of strength and flexibility. The pericardial valve in the mitral position has superb longevity and freedom from structural valve deterioration and other

complications, in all ages but particularly in patients over the age of 60y. As the risks of re-do surgery diminish with improving technology and medical advances, increasingly younger patients have opted for a bioprosthesis with a pericardial valve in lieu of anticoagulation, and data continues to grow to support that choice. The search for the perfect mitral prosthesis is not yet over, but it has come tantalisingly close since the dawn of the pericardial valve.

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Chapter 9

Long term results of the Pericardial Valve in the Aortic Position

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Aung Oo

Abundans cautela non nocet

The aortic valve is a refined essence of human tissue, it is the quintessence of shape and function, placed at the exit of a pump which sends, throughout the body the oxygenated fluid of life. Its pellucid, limpid, transparency belies its strength and resilience. Its geometric self symmetry of each cusp create their synchronous movement. The perfection of its shape inspired the giants of the Renaissance to draw and sketch this marvel and imagine its function. From Leonardo da Vinci and Domenico Ghirlandaio to the great Anatomists before Harvey's *de motu cordis* and afterwards into the modern world, described the aortic valve with awe and wonder. But we all know from the Little Prince that nothing on earth is perfect. The aortic valve ages in our company in different ways at differing times, but it ages nevertheless.

Aortic Valve Disease

Aortic valve disease is the most common valvular heart condition, with a worldwide prevalence of over 7 million. While rheumatic heart disease represents the majority of cases in low-income countries, congenital and degenerative disease is the predominant aetiology in high income countries, and this affects 1% of the total population in the United States. Prevalence increases exponentially with age such that 5% of those over 65 years of age show signs of calcific valve degeneration. Projections indicate that the incidence of degenerative aortic stenosis will more than double by 2050[1]. In patients with severe aortic stenosis, symptoms usually develop within five years and deterioration following that is rapid. Event-free survival may be as low as 21% at two years[2]. Aortic stenosis is typically a disease of the elderly, frequently concurrent with coronary artery disease, although younger patients with bicuspid valves also present with concomitant aortopathy. In younger patients, aortic regurgitation is more common both with and without aortopathy.

For these patients, aortic valve intervention confers both symptomatic and prognostic benefit that cannot be achieved by any other means. The risks of open, surgical aortic valve replacement have fallen precipitously since the procedure was first developed and now sit at less than 1%[3]. The options for aortic valve replacement are limited to mechanical versus bioprosthetic; the latter as pericardial or porcine. Pericardial valves may be bovine, occasionally equine or, latterly, autologous as an Ozaki repair. Further developments have also provided the option of transcatheter delivery of pericardial valves in select patients. The dilemma of choice between mechanical and bioprosthetic valves is a concern for patients, particularly the young and of childbearing age: the rigours of warfarin must be balanced against the risks of an expected re-do procedure. In some patients, the question of durability of a repair versus that of a bioprosthesis arises. In current practice, balancing these risks has led to the dominance of a tissue valve that provides optimal haemodynamic benefits with minimal thrombogenicity and acceptable durability: the pericardial heart valve.

Pericardial Valve Design and Characteristics

The concept of man-made valves and the invention of the pericardial valve by Marian Ionescu in 1971 followed many years of gestation and evaluation. Unlike the two other innovative valve designs of that time, the Starr-Edwards ball-in-cage and the Björk-Shiley tilting disc mechanical prostheses, the pericardial valve was invented by a surgeon and not by engineers. The first pericardial valves were comprised of glutaraldehyde-treated bovine pericardium, formed into three leaflets that were mounted onto the outside of a Dacron mesh-covered three-pronged Delrin frame (Figure 1). Although derived from animal tissue, unlike the porcine bioprostheses that came before it, the pericardial valve was not reliant on pre-existing valvular form or function from the donor animal. Each valve leaflet was cut to a precise specification from sheets of uniform and abundant pericardium, and therefore not subject to the anatomical variations, such as muscular bars, present in pig valves. As demand grew, there was also a significant advantage of yield of pericardium per individual host/donor animal compared to valve tissue. Pericardial valves therefore conferred

a host of benefits which persist in the multitude of pericardial valve descendants available now. Their essential characteristics, by design, are exceptional haemodynamic function, excellent freedom from thrombosis, a very low propensity for embolisation and a respectable durability[4-6].

These unique properties fundamentally changed the practice of aortic valve replacement when introduced fifty years ago. Various methods including sub-coronary aortic valve homografts, autografts, stentless valves and other techniques have been developed in the search for better haemodynamics and durability, as well as the avoidance of anticoagulation. Of all the available options, however, the pericardial valve has become the most used heart valve in the world, both in conventional surgical procedures and as the basis for all transcatheter valve technologies.

Initial Experience

Early reports of the use of pericardial valves were not just favourable, but effusive, with predictions from one five-year follow-up that the "pericardial valve will surpass (the durability) of previous bioprosthesis"[7]. Denton Cooley's case series of 326 patients in 1980 considered that the results from the initial experience were so remarkable that it was likely to be "the biologic valve of choice"[8]. After 6-7 years, however, signs of valve failure appeared and progressively increased so that by 9 years there were actuarially only 82% of patients free of valve failure, reducing to 51% at 15 years. Similar to the porcine aortic valve used in this period, the causes of valve failure were structural tissue degeneration and various pathological changes due to the calcification of pericardium. A retrospective review of the literature paints a clear picture of why this might have occurred: a case report of a 29 year old patient[9]; accelerated deterioration in an adolescent[10]; case series where the mean age of patients was 50.8 years (ranging from 15 – 78)[11]. The enthusiasm and inspiration ignited by the advent of the pericardial valve had led to wholesale adoption across the cardiac surgical community. From 1971 to 1985, the pericardial valve was being used by all surgeons, in all cardiac positions and in patients of all ages including children, but predominantly in the middle aged.

By 1985, a comprehensive and detailed statistical analysis of the two largest series of patients (Denton Cooley with 2680[12]and Marian Ionescu with 1171[13]) determined that the main cause of failure – calcification of the leaflets – was most often encountered in younger patients. These, and subsequent, studies confirmed that not only is calcification age dependant, but that patient age at implantation was the single most important factor determining longevity. Following this finding, the use of pericardial valves was necessarily reserved for patients above the age of 70 years and, although this threshold has been under constant attrition, adoption of this principle allowed the long term durability of the pericardial valve to be demonstrated.

Longevity of the Pericardial Valve in the Aortic Position

Metrics for long-term outcomes following aortic valve implantation include:

- Survival
- Symptom relief
- Freedom from major adverse cardiovascular or cerebral events (MACCE)
- Freedom from reintervention for bioprosthetic valve dysfunction, encompassing
  - structural valve deterioration (SVD – intrinsic permanent changes in the valve such as calcification, fibrosis or tears leading to haemodynamic dysfunction)
  - non-structural valve deterioration (e.g. paraprosthetic leak, malposition, mismatch etc)
  - thrombosis (including dysfunction with or without thromboembolism)
  - endocarditis

Attempts to standardise the reporting of these valve-related outcomes has been inconsistent, so aggregation

and comparison of valves, whether mechanical, bioprosthetic, porcine or pericardial is fraught with difficulties. Broadly, however, the pericardial valve has excellent outcomes using any of the above measures, demonstrated by its dominance as the prosthesis of choice for over 80% of the aortic valves implanted worldwide.

Symptom relief from aortic stenosis is conferred by the haemodynamic properties of the prosthesis, and pericardial valves benefit from symmetrical and wide opening (compared to porcine valves which might require aortic root enlargement[14]) and are far less complex than subcoronary implantation of stentless valves or homografts. The flow dynamics through the valve and the low thrombogenecity of pericardium also ensures that complications related to thrombotic valve dysfunction and thromboembolic phenomena are low, even without anticoagulation[15]. Additionally, as warfarinisation is not required following implantation of pericardial heart valves, patients are further spared the risks of bleeding on anticoagulation[16].

Structural valve deterioration is particularly susceptible to reporting bias, as many studies reporting long term data on prosthetic valves do not clarify their definition of SVD or the criteria for reintervention. What is clear is that structural valve deterioration in pericardial valves in the aortic position is virtually unheard of at 5 years and is uncommon at 10 years in most patients. After that time, SVD is especially age-dependent and in septuagenarian patients receiving aortic pericardial valves, freedom from SVD at 15 years may be up to 90%. Compelling evidence for a 50-85% freedom from SVD in pericardial aortic valves up to 20 years also exists[6,17]. While the actuarial outcomes might be enhanced to some degree by the life expectancy of older patients, the magnitude and persistence of this effect indicates additional factors also influence the age-related longevity of pericardial valves. Haemodynamic variability related to activity levels, metabolic differences in calcium handling, renal function or altered immune responses have all been theorised, but no strong evidence published.

Contemporary Use of the Pericardial Valve in the Aortic Position

Surgical aortic valve replacement remains the gold standard treatment for aortic valve disease, despite the developments in transcatheter technologies that also utilise the benefits of the pericardial valve. The overall number of aortic valve replacements performed has remained stable[18] but the proportion of bioprosthetic (predominantly pericardial) valves being implanted has increased over time, from a 37.7% share between 1998 – 2001 to 63.6% in the period 2007 – 2011. In particular, the use of pericardial valves increased most markedly in patients between 55 and 64 years of age, and especially in patients with multiple comorbidities. From the most current UK national data, 82% of aortic valve replacements were with a biological valve. In patients over 70 years of age, 98.2% had a biological valve, 81.7% of those in their 60s had a biological valve and even in those under 60 years, 39.9% had a biological valve implanted.

Expanding indications for pericardial valves

With constantly improving surgical techniques and the advent of valve-in-valve transcatheter technologies, the risks of re-intervention have also diminished, and this has enhanced survival in patients requiring treatment for structural valve deterioration or endocarditis. Such incremental improvements in the long term outcomes for patients has, however, created a second wave of interest in pericardial valve implantation in younger patients, not only for transcatheter aortic valve implantation (TAVI), but in open surgical cohorts, too. Despite early studies highlighting the lower durability for pericardial valves in younger patients, therefore, the appeal of bioprosthetic valves and avoidance of warfarin is particularly great for this cohort of patients.

The attrition of the 70 years age limit for use of these valves has even made its way into European guidelines. Current ESC/EACTS guidelines strongly recommend a mechanical valve in those under 40 years of age (Class I, Level C) but make only a moderate recommendation for mechanical valves in those under 60 years of age (Class IIa, Level C). They go on to provide a Class IIa, Level C recommendation for bioprosthetic valve in those over 65 years[19].

Future Research

Current trends in usage indicate that avoidance of mechanical valve prostheses, with their requirement for life-long anticoagulation, remains a high priority for patients and their surgeons. Transcatheter valve-in-valve options mitigate the risk to some degree and the diminishing risks of re-operative surgery have made this a less unattractive option to patients than it previously was. The gradual erosion of age boundaries for implantation of pericardial valves, however, ideally requires the invention of a functional anti-calcification treatment that might limit the structural valve deterioration that is accelerated in this group of patients. Apparent anti-calcific treatments have been much touted by valve manufacturers over the last five decades, but this panacea has yet to be realised and proven with scientific rigour. Alternatives to this approach would require the development of some synthetic material (e.g. long-lived polymers or mechanical valves without the need for anticoagulation) that possess the unique properties of pericardium – abundant, affordable, strong, flexible and antithrombotic – but with greater durability. Fifty years since Marian Ionescu explicated the properties of the ideal material, it seems likely that pericardium will remain the medium of choice for prosthetic valves for some time.

Conclusion

The pericardial heart valve has shown excellent long term outcomes in the aortic position: low thrombogenicity, excellent haemodynamics and superb longevity. Although pericardial valves demonstrate optimal durability in patients over 70 years of age, the host of other benefits associated with avoidance of anticoagulation continues to attract the interest of younger patient groups. With a lineage that includes both transcatheter valves and surgical prostheses, pericardial valves form the cornerstone of modern aortic valve intervention, and continue to grow exponentially.

The invention of the Pericardial Valve and its successful use over a period of 50 years reinforces the knowledge that this invention has completely changed the outlook and the technique of aortic valve treatment for a long time to come. Perfection does not exist as such but evolution, discovery and invention remain the instruments of the intrepid surgeon on his way towards the hidden face of the moon.

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Chapter 10

The Pericardial Valve seen from the Industry and Commerce Viewpoint

A novel Concept, a new Material, a new Design and a new Manufacturing Challenge for a new Industry

John McKenna

All men who have turned out worth anything have had the chief hand in their own education

(Sir Walter Scott (1771-1832)

Introduction

I am pleased and proud to be invited to contribute to this epochal volume, which celebrates 50 years of the use of the pericardial valve concept and to extol its advantages. I arrive from a very different but similar world - the heart valve industry. The pericardial valve as envisioned, created and initially hand crafted by Marian Ionescu was, and still is to this day, a challenge to produce for the medical device industry. However, imagine a time some 50 years ago when the medical device industry was embryonic, where visionary medical professionals had to enthuse, liaise and engage in unknown manufacturing terminology with highly trained engineers, material scientists and quality system designers. In turn many non-medical engineers had to learn about anatomy, physiology, biology, surgery and epidemiology. In the 1960s, mechanical heart valve prostheses were available and, on the whole, they worked well with a few glitches along the way. Even with the glitches, sadly involving sometimes the loss of human life, it was better than the 100% mortality of the earlier decades. In the early 70's, a new idea emerged, the pericardial valve concept.

Regulatory Control of Medical Devices – the Food and Drug Administration

It is perhaps germane to remind ourselves that the current regulatory controls we all take for granted were then not a matter of statute. Regulatory control over medical devices in the USA through the Food and Drug Administration (FDA) commenced in 1976 when the Medical Device Amendments bill passed to ensure safety and effectiveness of medical devices[1]. The amendments required manufacturers to register with the FDA and follow quality control procedures. Some products needed pre-market approval by the FDA; others had to meet performance standards before marketing. This was all new to the industry.

In 1990, the Safe Medical Devices Act was passed, requiring nursing homes, hospitals, and other facilities that use medical devices to report to the FDA incidents that suggested that a medical device probably caused or contributed to the death, serious illness, or serious injury of a patient[2]. Manufacturers were required to conduct post-market surveillance on permanently implanted devices whose failure might cause serious harm or death, and to establish methods for tracing and locating patients depending on such devices. The act authorized the FDA to order device product recalls and other actions.

In 1997, the Food and Drug Administration Modernization Act reauthorized the Prescription Drug User Fee Act of 1992 provisions including measures to accelerate the review of devices[3]. In 2002, under the Medical Device User Fee and Modernization Act, fees were assessed for sponsors of medical device applications for evaluation, provisions were established for device establishment inspections by accredited third-parties, and new requirements emerged for reprocessed single-use devices.

In 2012, the Medical Device User Fee and Modernization Act (MDUFMA III) allowed the FDA as part of FDA Safety and Innovation Act, to reauthorize user fees from industry to fund reviews of medical devices in exchange for the FDA to meet certain performance goals. Each of the above changes required industry to respond to ensure compliance. In many companies, the growth in internal quality management systems ensured the growing body of regulations were met fully.

Regulation in the Rest of the World

In the EU, the member states agreed to align their regulatory compliance systems under a Council Directive of 20th June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices (90/385/EEC). This has been amended many times since. However, there was an agreed International Standard agreed (ISO) for heart valves which has been updated and amended

many times[4]. Many governments also imposed strict controls and follow up requirements on medical devices.

It was once said by L.P Hartley that *"The past is a foreign country; they do things differently there"*. The original mechanical valves were for the most part designed by engineers with cleverly adapted designs from aero and automotive engines. Surgeons and physicians who learned the engineering discipline quickly and adeptly, far outside their base educational experience, rose to the challenge with breathtaking adeptness. At the outset of surgery, operating rooms were basically an empty room with instruments and an anaesthesia machine. These once bare rooms would be filled with the carefully designed, crafted mechanical and electronic wonders we know today. The making of such required technology is unseen, but thousands of people in a largely unseen industry enable modern surgery, diagnostics and aftercare to take place. The modern hospital would be a very different place without the private industries which innovate, supply and manufacture at scale the wonders therein.

The medical conferences of cardiac and thoracic surgeons were gradually attended more and more by industry engineers, executives and sales teams. Today this is seen as normal but then it was radical. Sales teams slowly became the conduit between the surgeon and cardiologist in departments, hospitals, cities, regions and countries all over the world. The closeness of this interchange of ideas, discussions in operating departments or the coffee room cannot be underestimated. This was the theatre of ideas for new designs, discussion of problems and feedback through the company hierarchy to drive the company's focus.

The Medical Device Industry Conundrum

This new industry then faced something most industries do not face - a disjointed and convoluted supply chain. Most industries can use or test their own products be it cars, computers or jellybeans. Most products are sold to the people who will use them, and they pay personally, or in the case of business to business, the purchaser's employers will pay and use them. Not in medical devices as the chain of supply is diverse.

The Patient

The recipient of the product is often ignorant of its method of construction, operation, design specifics or implantation. They do not strictly need to know all this, although informed consent is required, as they are anxious about the procedure they face. In most cases they will not know the price of the product or pay for it directly. It is against the law in most countries to promote medical devices such as heart valves directly to the general population.

The Surgeon

The implanting surgeon is the primary user of the device. He or she wants to know everything about the device and will often make multiple enquiries in the literature, from companies directly, colleagues and investigations at congresses to consider which devices to include in their armamentarium. They are very concerned with performance, durability, ease of use and if the device fits in well with their surgical practice, operating procedure and patient's lifestyle. In most cases they will not know or enquire about the price of the product or pay for it directly.

Operating Room Staff

They will want to know how to order the product, store the product and how to handle the product with any ancillary equipment in the surgical department. They want an easily handled product to be delivered and on the shelf when needed, plus emergency priority attention should it be required. Most deliveries are required within 24 hours of request with appropriate sizers and handles provided for single use or with the ability to be sterilised in-house.

The Purchaser

The purchaser (often a national purchaser but sometimes health maintenance organisation or buying group) rarely knows the specifics of the device they are ordering on behalf of the surgeon or department, but they want the lowest price. They will want a full range of stock on the shelf preferably on consignment (paid for only when used) at the lowest price and the longest terms. Often contracts will have provisos attached such as an obligation to provide education, a proctor visit, or educational visits to other hospitals or institutions to enhance or augment surgical training.

The Manufacturer

They cannot promote to the end user, i.e. the patient. They work in close cooperation with the surgical team but cannot use, implant or self-test their own product. All feedback is second or third hand.

Before Pericardial Valves – The Porcine Valve – A Production and Material Supply Challenge

From a manufacturing standpoint the porcine valve was relatively straightforward to produce but it was an extremely wasteful process. Often as many as 5000 to 15000 pigs per day were slaughtered at a 'bacon' weight of approximately 70Kg, but different sized animals either smaller or larger were often purchased at a premium. The median size of aortic valves for humans is 23mm (size range for biological valves is usually 19mm to 29mm in 2mm increments) but smaller means using pigs earlier before they reach 70kg. At this initial stage, about 1 in 10-20 valves is deemed worthy of transport for inspection. Some valve manufacturers can have as few as 50 to 75 valves go through to final product from a harvest of

5000 porcine valves inspected. An army of highly trained fabricators were employed in clean rooms to place up to 900 individual stitches in each valve. As a result of pioneering work by many, fixation of the leaflets and supporting tissue with gluteraldehyde prevented a profound immunological response and increased porcine and pericardial valve durability.

A Disruptive Approach to the Biological Valve for Industry – the Bovine Pericardial Valve

With the advent of porcine valves in the 1960s and 1970s, and with claim and counterclaim for mechanical versus biological product superiority, there started a real 'arms race' with new mechanical valve designs superseding previous designs seemingly every year. Following 14 years of research, with ups and downs and an unusual persistence, Marian Ionescu, as a consultant cardiac surgeon at Leeds General Infirmary, finally succeeded to create through the concept of manmade artificial valves, the first successful Pericardial Heart Valve.

The involvement of Shiley in 1976 in the manufacturing of the first ever Pericardial Valve represented a disruption in the technology of valve construction. In general, the Pericardial Valve in all its iterations is credited today with being the most implanted tissue heart valve in the world. The vision of Marian Ionescu was to be free from the limitations imposed by pre-existing shapes of animal aortic valves and to use the pericardium which allowed endless permutations of shape.

In the beginning, there was the task of translating the valves manufactured in Leeds into a commercial valve to be made at scale often in the hundreds of thousands in the sizes required. This is often the greatest challenge for manufacturers of any product. Between March 1971 and March 1976, Marian and Christina Ionescu had been carefully and diligently sewing valves in the hospital laboratory. This could not be the basis of production at scale. Prior to the first implantation, the

pericardial valves were subjected to various studies of hydrodynamic function as well as durability tests available at the time. It should also be remembered that the way to assess a valve's gradient (the pressure drop across the valve) was inserting a catheter into the patient's aorta with pressure measurements being taken on both sides of the valve. Echocardiography was in its infancy and doppler just not available in either transoesophageal or transthoracic scans.

The pericardial valve's innate advantage, that the pericardium was malleable, was a challenge for production, which commenced in Irvine, California, with the new valve being launched in April 1976. In 1984, there was a symposium in Pebble Beach, CA, on the then current results with the pericardial valve. The entire symposium's proceedings were published in a book printed by Shiley Inc. Reading this book today, the excitement was palpable for the future of pericardial valves. In the book, Marian Ionescu noted that many companies were now making their own pericardial valves:

"Several laboratories are actively involved in the design, construction or testing of pericardial valves either similar, different or identical to the one we have discussed here: Vascor, Edwards, Polystan, Bentley, Xenofic, Mitral Medical International, Mocchi to mention a few".

Some of these companies are still around today while others have been absorbed into larger entities. All tried to modify or improve the original Ionescu Pericardial Valve, in some cases to adapt the valve for its implantation through the TAVI system. Oscar Wilde once said: *"Imitation is the sincerest form of flattery".*

In 1987, the Shiley Company was divested of all manufacturing activity by its then owner, the Pfizer Corporation, following a large number of catastrophic failures of the modified Björk- Shiley mechanical valve. Questions were levelled at the competence of the manufacturing and testing of this mechanical valve. As a consequence of these events, all manufacturing at Shiley ceased. The Ionescu-Shiley Pericardial Xenograft became a casualty of Shiley's problems. This, unfortunately, occurred at a time when the Pericardial Valve was being used in progressively more centres and in larger numbers, and when the next iteration of this valve, the Pericardial Optimograft, was ready to enter production.

Other corporations now provide slightly modified versions of the same concept of man-made valves. The improved results obtained during the past 10-20 years is due to the fact that the majority of pericardial valves nowadays are being used in the aortic position of patients older than 70 years of age when calcification (the main enemy of pericardium) occurs late and advances slowly. In fact, Mother Nature rather than technical prowess has improved the results. The success of the Pericardial Valve has continued to increase not only due to its qualities but also backed by superb business practices, large R&D spend and enthusiastic clinical follow up. As a remedy for valve disease, it has come to conquer the planet.

Throughout the years, a varied and copious number of anticalcification treatments have been expounded and tried by all the companies involved in the production of pericardial valves. The claims have been many but to date no scientific proof of efficacy can be concluded as the literature of the companies themselves are required to note.

Transcatheter Aortic Valve Implantation / Replacement (TAVI / TAVR)

Transcatheter aortic valve implantation is exactly what it's acronym says, an original, ingenious, finely crafted and extremely useful mechanism created as a vehicle for delivering and implanting, in the great majority of cases, Pericardial Valves in the aortic position. This delivery mechanism is especially useful in elderly, fragile patients for whom the open-heart technique would be too hazardous. Transcatheter aortic valve implantation could not have happened if the surgical bovine pericardial valve, as created by Marian Ionescu in 1971, had not proven so successful. Day by day, its acceptance increases and continues to grow exponentially.

The Future

Having proved itself so ably in both surgical and transcatheter valves, is bovine pericardium ever going to be usurped as the material of choice in prosthetic heart valves? The steady careful progress in the performance and durability of the pericardial valve has been a process of evolution not revolution. The last revolution in biological heart valves was the adoption and use of bovine pericardium as a material for cusps. The next revolution will surely be, after 50 years of pericardial success, finding a new material which equals the gold standard of bovine pericardium. An artificial material, probably one of the new emerging medical grade polymers for TAVI, will allow preloading of the catheter with the valve in the factory thus eliminating operating room loading with all the risk of crimping in a non-industrial laboratory setting. The leaflets could also be thinner if an artificial material equal in strength, inertness, flexibility and resilience to bovine pericardium could be found. Perhaps valves will become bespoke, based on the latest imaging techniques to custom build a valve for each patient's individual anatomy and needs.

Over the years, five international symposia and meetings about the Pericardial Valve have been organised. These were in Chamonix (France), Pebble Beach (CA), Montreux (Switzerland), and two in London, and all have had their proceedings published. In the 1984 book of the proceedings of the Pebble Beach Symposium on the Pericardial Xenograft, Marian Ionescu said with considerable prescience – "It appears to me far more interesting to turn the kaleidoscope of the imagination towards possible new developments related to the pericardial xenograft than to attempt probable prophecies of its future behaviour". Today with surgical and transcatheter techniques and the great success of the pericardial valve concept, it would appear Marian Ionescu had Nostradamus-like foresight.

Many people worldwide have reason to be grateful to Marian Ionescu, who persevered through thick and thin, since the beginnings of his dream in 1957 to the realization in 1971 of the novel concept of the man-made pericardial valve. Perhaps also the many patients who have received such valves should give thanks to the many men and women in industry, with specialists in so many domains. They have taken up the Ionescu concept and through equal difficulties brought the pericardial valve to worldwide clinical use.

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1 www.fda.gov 2020

2 www.fda.gov 2020

3 www.fda.gov 2020

4 www.ema.europa.eu/en/human-regulatory/overview/medical-devices

Chapter 11

A View Through an Old Mirror

Another look at the Pericardial Valve

Marian Ion Ionescu

Vi Veri Veniversum Vivus Vici

From the diary of Aleister Crowley (1875-1945) from The Cry of the 4th Aethyr

The Alphabet

'It was many and many a year ago, in a Kingdom by the sea' where I happen to travel during one of my peregrinations. It must have been in the year 1546 BC exactly one century after the explosion of the volcano Thera, now Santorini. I was fascinated and enticed by Herodot of Halicarnassus and by Tucydides to go to that Phoenician Kingdom by the shores of the Mediterranean Sea. I was given to understand that the Phoenicians were established around Canaan from today's Turkey to Lebanon and beyond, on the Mediterranean shore. They were a group of Semitic Canaanite people with a King and with the capital at Byblos. Their empire existed from about 2500 to 300 BC. They had established ports around the Mediterranean for their commerce as far as Iberia.

I found myself in a dream on Phoenician soil in Byblos. A little castle, many houses and more shacks, dust and mud and an enormous well organised harbour. All that looked rather a nightmare than a dream. First impressions are not always a reflection of reality. In the central square, there was a dazzling fantasy of colours, sheiks and pashas, emirs and mandarins, friars of all faiths and orders, fortune tellers, sorcerers, healers, street barbers and assorted half-naked women selling what they knew best, all there for the great business at this crossroads of land and sea.

I found myself pleasantly lost in this hullabaloo of multiple tongues and variegated colours. A soft-spoken man who knew a little Greek approached me and offered to show me around. His preference was to look at all this from above. We started on a pass towards the nearest hill. His choice was right. Away from the clay and dirt that paved the thriving port town, reflected the lights against the looming fog which, thus, became a chimerical blaze. On both sides of our pass, oleanders spread the bittersweet scent of their flowers, cypresses darted toward the clouds and a profusion of flowers made a multicoloured tapestry around us. In the velvety shadow of the cedar trees, we rested and abandoned ourselves to the blue magic of the Mediterranean in the distance.

C. Brancusi – The Endless Column.

The low mist, left behind by a short shower, bled in all colours of the rainbow under the spears of slanted sun rays as did the shadows on leaves and petals. There was a volatile display of colours to seduce the eye - from heavy purple at sunset, to violet blue, to hoary transparencies in the long, slow crepuscular slide of the sun in the sea.

The time came to descend to the harbour. A flotilla of seven galley-like boats, which in Greek are called Galoi for the great, fat cargo ship and Hippoi for the smaller, narrow shape, rapid boats protecting and fighting if necessary. The departure was usually in the dark, just before or after midnight, depending on the winds. It was completely dark. The sky was stormy at this moment while the stars were muffled by the thick clouds, while the buildings around the harbour were shaken by blasts of wind, while the sea roared and bellowed horribly, our boats cast off on the long voyage. The round large boats were heavily laden with a huge quantity of cargo so that the great part of their hulk was hidden beneath the waves. They carried cedar timber and glassware, Tyrian purple and trinkets, a great fortune floating westward.

The morrow came with its pink tint, the sea was smooth and glossy like a shallow pool and fencing within her winding coastline the perfect reflection of the turquoise blue of the vault of heaven and the ivory clouds. We sailed through the Aegean Sea and the view changed again; now an affluence of colours, then a firework of sparks, now faded and flat, then alive and restless bustling and foaming towards the heaven whose daughter she

is. Finally, we felt the sharp winds of the open sea and the salubrious smell of algae. In a few days we reached the tip of Peloponnesus and stopped for a strange encounter. The Captain of our boat handed over a folder of papyrus to a person on the shore. I could not resist to ask a mariner who spoke Greek, what happened. I had a shock to learn that the papyruses were the Phoenician Alphabet, the first ever created, containing only 22 consonants. I should have read Herodotus in its entirety. I shall do it on my return.

Lovely Tuscany.

Soon, dark clouds arriving from the west announced the coming of a storm. The whole fleet changed direction and went north to find shelter in the port of Heraclea in the South of Italy. We had to sit out the storm. I had a couple of days to think, to ponder, to reason and to decide that I will disembark there and remain in Europa. Moving alone to a different world, on promises of a great future as a global merchant nation did not assure me at all. The safety of Europe, the safety in numbers and diversity, the cradle of our civilisation, the centuries of art and science were more than reassuring. I packed my meagre belongings and with the greatest treasure, the alphabet, under my arm I started walking Northward. During my journey, the thread of my voyage in the past-future started to fray and I only wanted to go home.

The dream melted and flowed around me. I found and brought to Europe the alphabet, which was later completed with vowels by the Greeks, brought in a final order and established its permanence of today by the Romans, THE LATIN ALPHABET.

The Printing Press

Johann Gensfleisch zur Laden zum Gutenberg, known by most by the name of Johannes Gutenberg was a goldsmith and inventor, mainly in metal and precious stones. Born around 1400 AD in Mainz Germany, departed from this world in 1468 AD.

It is difficult to produce as a dreamlike description his life and work because there were many undocumented periods of time, locations and activities in his life. There were temporary associations with various donors, court cases for misunderstandings and all the vagaries of a complex life spent between Mainz and Strasbourg due to political reasons. He dedicated his whole life to a formidable goal. He designed and built the first printing press to incorporate movable type and mechanised inking.

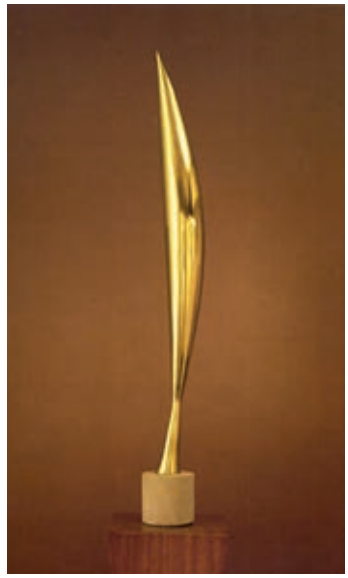
Although Gutenberg was financially unsuccessful in his lifetime, he introduced the printing technology in Europe, created the printing revolution, a milestone in the history of the second Millennium, ushering in the modern period of human history. Printing greatly contributed to the spread of literacy and education in Europe. It fed the growing Renaissance, it was a factor in the Reformation and it greatly facilitated the scientific revolution and its corollary the Industrial Revolution. It permanently altered the structure of society and beyond and above all, it gave us the Book. For me, the book is the essence of our soul, the Alpha and Omega of our intellectual existence, it became the heart and the soul of our progress in all domains of life and activity. It is as Stephen King called it: the uniquely portable magic, and in the words of Garrison Keillor, a gift you can open again and again. Literacy, for Kofi Annan, is the bridge from misery to hope. Books have the power to conquer despair in the midst of sorrow, to light the darkness in the valleys of life, to whisper ‘one more time’ in the face of failure. They bring hope which gives life to dreams, making the fairy tales reality.

It is not true that we have only one life to live. We can create our own repeated reincarnations, but with books we can also live many more lives, as many as

we wish. Please, believe me, I know, I was there. Now in the crepuscular light of a complex, arduous and adventurous life, I feel in security when surrounded by my thousands of books, much more than when surrounded by human beings, we are funny creatures, we have no roots, we are blown away by the winds of time.

It is surprising that Gutenberg, the father of the printing machine and all its universal consequences, is not sufficiently known in our present world. If one day I would be placed in a high, powerful position, instead of ceaselessly twittering illiterate inaccuracies, I would order to erect a statue to Gutenberg at all great crossroads of history.

The fascination and attraction to the contents of books starts early in life and continues incessantly to the very end of it. It was so overwhelming for me that it made me include in the training of young surgeons a small segment of literature starting as a 'suggestion'. Each Thursday morning, my whole team (some nine people and fellows) met, following rounds, down in the Bunker where we discussed the cases, the problems, the new publications and impressions of the weekly contact with one of the literary masterpieces of Dante Alighieri or Shakespeare, Miguel Cervantes or Dostojevski, William Wordsworth, Pablo Neruda, Charles Baudelaire, Edgar Alan Poe and many others. I was elated to sea that the miracle worked. Most of them, and even one or two of my secretaries, joined in occasionally. I prepared, in translation, some of the more representative segments from the masterpieces of six of the greatest writers and just as many from great poets. My younger colleagues and students discovered another facet of beauty and became attached to it, to my great delight. Students of diverse nationalities came closer to each other and the team got happier and stronger. But that was then, only half a century ago! Why must progress look like destruction asked John Steinbeck? And there is no answer. As far as surgery was concerned, they learned enough, I gave them all I knew to help eight of them over the years to become Professors or chiefs of departments at the great universities of the world from Palo Alto to Beijing. My simple pieces of advice might have helped: keep always a clean operating field, do not rush, precision in everything, will save you time and make each successful procedure an aesthetic pleasure too.



C. Brancusi – Gold Bird in Space.

The Book

This book, which celebrates 50 years of clinical use of the Pericardial Valve, is a significant event in the short history of heart valve replacement. Among the myriad publications amassed in medical libraries of the world, this book is but a pebble in the grand edifice of open-heart surgery. In the world literature, there are few books which transcended centuries, they are some of those which I mentioned in a previous paragraph. But with the exception of those few books, all publications have a finite lifespan which depends on the quality and the interest of their content. This, our present book, because it is a celebration, might gain a little more importance.

The book is structured around the Pericardial Valve and gives a general view of the origin and its evolution over many years. It extols, in a subtle way, the qualities and the reasons for its longevity. The book describes the Pericardial Valve irrespective of the little modification made over time by various manufacturers. It is a small hymn to human imagination, inventiveness and perseverance over 14 years of search and research to create it.

All the chapters, well researched and clearly presented, carry with them a different aspect of the main subject to create a coherent entity, which at 50 years of existence becomes a necessary publication. All the

various, strange names given by the manufacturers to this valve, all the small modifications real or virtual, all the means for transaortic implantation, deal with the same thing, the Pericardial Valve, as described in this volume.

But for those who know how to read in between the lines, this book contains, in a condensed way, a whole world of additional information from the field of heart valves. One would find those who dreamed about, attempted, failed or succeeded for various reasons; the birth and extinction of some important valves, mechanical like the Björk-Shiley and biological like the Ross-Barrat-Boyes. There is to be seen as from the back of a Venetian mirror the evolution in time of the commercial implications, rivalries and tribulations of the valve industry.

As the greater enemy of tissue valves is calcification, there are only two ways to address this problem - acting on the host which is scientific folly in the present stage of our knowledge or acting on the pericardium. This has been tried unsuccessfully despite unsubstantiated claims by some valve manufacturers. Persistence and determination might help to find a better, more successful answer to this knotty question. Little has been said in the preceding chapters about an essential element related to this Pericardial Valve. It is the most used medical device in the world but because of the process of body calcification, its use is restrained to patients older than 65-70 years. On the positive side, aortic valve replacement is required mostly in this group of elderly patients. As far as the mitral valve is concerned, various techniques of valve repair are available and valve replacement is nowadays less often required.

The future of the treatment of heart disease in general and of heart valve disease is located, at present, on the other side of the moon. We will all wait with enthusiasm and trepidation to see the younger generation creating a road, if one does not exist, to be able to reach there. Personally, I was blessed by the goddess Fortuna with the creation of the Pericardial Valve and I am grateful, but I shall be greatly satisfied if a better or a perfect heart valve is created, mainly for the benefit of patients.

Remember Percy Bysshe Shelley the great romantic poet.... *'Nought may endure but mutability'*

Postscriptum

Francis Wells

I will not lose; either I win or I learn

Marian Ionescu, circa 1971

'I will not lose: either I win or I learn' – thus, wrote Marian Ionescu beneath an imaginary coat of arms, that he created to inspire himself in the gargantuan task of creating a replacement non-thrombogenic heart valve with great durability. This sibylline prophesy came to define the life and work of this Rumanian born classics scholar, cardiac surgeon, pioneer of heart valve development and later, mountaineer.

It is with great pleasure that I write the postscript to this book celebrating half a century of the investigation and use of pericardium within the heart and in particular in the formulation of replacement heart valves. It is an exciting story with several of the great names in cardiac surgical history involved. One name stands out, however, that of our hero in this book, Marian Ionescu, the true pioneer in this field. Happenstance is an important component of any meaningful development and it is true in this story. As clinical and research assistant at the Cleveland clinic in 1957, Marian Ionescu had the great good fortune to be working with two of the pioneers of our specialty. Donald Effler and Willem Kolff (the inventors of the artificial kidney in 1944) were his mentors at the time of early work on the surgery for congenital heart disease and the first steps in the development of an artificial heart. Following a morning in the operating theatre with Don Effler, Marian would work with Kolff on his development of the artificial heart, being charged with the responsibility of making polyurethane connections and to build flap valves for the ejection side of the artificial ventricles. Kolff suggested that in his "free time" he create a different type of valve. His initial attempts using polyurethane and Ivalon were abandoned because of thrombosis of the valves. He observed that the junctional region between materials seemed to be the focus for thrombus formation. His next attempt used a Dacron mesh and was used in a few cases until the arrival of the Starr Edwards ball-in-cage mechanical prosthesis. At this point Marian became obsessed with the idea of creating a truly functional non-thrombogenic heart valve. He realised that the essential conditions for a heart valve to function long-term it had to be non-thrombogenic and possess hydrodynamic properties close to the natural valve. Interestingly, at that time durability was not perceived as a priority.

The early work using pericardium and Dacron for mitral prostheses confirmed and addressed the importance of overcoming thrombosis at the tissue material interface. Using a Dacron cuff a porcine aortic valve was encased within it for implantation in the left atrio-ventricular junction. The whole device was fixed in formaldehyde. However, before the work could really develop, Marian made the decision that he had to leave his homeland, driven significantly by inherent medical jealousies. His aim was to return to Cleveland. The journey promised to be perilous and uncertain. Failure would mean imprisonment for him and his family. Determined as ever to succeed they packed everything into two small suitcases and with food for a few days and great hope they departed in their Fiat 600. After 2,350 kilometres, through small country lanes and mountain passes, they reached Paris and waited for American visas.

Having heard of the Ionescu couple escape from Romania, William Cleland, cardiac surgeon and John Goodwin from Brompton Hospital, alerted the British Council which decided to invite them to Britain to help create a true Department of cardiac surgery in Leeds. Mr. Geoffrey Wooler, cardiothoracic surgeon, was sent twice to Paris to persuade Marian and Christina Ionescu to renounce their ready prepared jobs at the Cleveland Clinic and come to help his fledgling unit in Leeds. Following discussions at the British Embassy in Paris, the Ionescus finally decided for the challenge

and the adventure of creating something new In Leeds with Mr Wooler. In October of 1966 the course was set for the next exciting phase of the adventure. On his arrival in Leeds work on the hybrid device was commenced immediately. By January of 1967 human implants began. By the end of the first year twelve implants had been carried out with only one episode of short-lived arm paresis. This early success prompted development of an aortic prosthesis and a three-pronged stent was developed. The low propensity for thrombosis was encouraging but the use of the porcine aortic valve was hampered by the muscular bar underneath the septal leaflet. This compromised haemodynamic efficiency and prompted the search to continue for improved haemodynamic performance.

This led to the use of fascia lata as a leaflet material to allow equalisation of the leaflet size and length.[1] This homogenous material was already in successful use for patching inside the heart. Initial pulse-duplicator work revealed a valve with even opening of the leaflets with good central orifice diameter, leading to low pressure gradients across the valve. A mule was produced to allow construction of the valve during the operation whilst the rest of the team opened the chest and prepared for cardio-pulmonary bypass. Its use spread across the cardiac surgical world quite quickly with such luminaries as Frank Gerbode in San Francisco. An international meeting was arranged in Silverado California to discuss the results of the fascia lata valve, whose use had been quite quickly disseminated to several units around the world. Whilst results were promising, variability in quality of build was, not surprisingly, a big issue and durability was not consistent. The search continued.

The eureka moment was the observation that the ubiquitous tissue in the operative field was pericardium which was flexible and plentiful. The pericardium of the Ox was chosen and a new series of valves was developed using glutaraldehyde treated bovine pericardium. The thinner and more pliable pericardium showed great promise in the pulse-duplicator. The opening of the three cusps was seen to be synchronous with an opening that was almost equal to the inflow surface area. Longevity was tested in the high-speed pulse-duplicator. The first human implant of a pericardial valve in the mitral position was performed on the 4th April 1971.

All the valves performed very well until 6 - 7 years post implantation. There was virtually no valve thrombosis and a very low number of embolic phenomena. However, valve incompetence occurred in a number of cases starting around seven years later. During the first 15 years the pericardial valve was used by all surgeons in patients of all ages and mainly below 65 years old. Some 80% of valve failures were caused by calcification while in the remainder, regurgitation occurred due to abrasion by rubbing of the pericardium on the Dacron mesh covering the stent. This started around 4.30 and 7.30 on a clock dial and the tear progressed upwards toward the top of the stent post when the affected leaflet became detached and flail. It was here that I was able to add a small contribution to the story as Marian asked me to install several of his high speed testing machines at Papworth and for me to observe the valves independently from him. We were able to document the mechanism of abrasion and leaflet incompetence as a cause of valve failure. It is an attribute to the man that he would encourage an independent observer to examine the valves in accelerated testing and to report on it without fear or significant favour (although one favour was to be treated to an exciting ride in the blood red Ionescu Ferrari on the roads between Papworth and Huntingdon!)

In 1983 the geometry of the valve was slightly modified and the height of the posts reduced to mitigate the risk of abrasion. This Shiley valve became known as the Low Profile Pericardial valve. In 1986 a completely new technique for mounting the pericardium on a thin layered double stent, to eliminate abrasion, was successfully tested. The name of this novel valve was ‘Optimograft’. Sadly, the difficulties experienced by Shiley corporation over the failure of its mechanical valve led to the closure of the company, which was a severe but temporary blow to the future of the Pericardial Valve and a great disappointment for our hero. Whilst tissue failure was documented regularly in later years following implantation, a case report by Cooley and colleagues reporting 25 years of good function is testament to the true potential of the material pericardium in replacement heart valves.[2]

The closure of Shiley corporation and the end of production of the Ionescu-Shiley valve led to a new phase in the life of Marian Ionescu in the great mountain ranges of the world. Marian became an intrepid climber scaling many great peaks and experiencing wonderful adventures in the greatest garden on earth, the mountain ranges of the seven continents. His accomplishments in the world of climbing are of a legendary scale, especially so as he embarked on these at a late stage in his life. The inherent danger in this sport of extremes was witnessed by the deaths of some of his climbing colleagues during some of these expeditions. In these endeavours, Marian exhibited great courage and enormous resilience as he had in his earlier times developing one of the most important valve prostheses that still sets the standards for low thrombogenicity, excellent haemodynamics and longevity.

In conclusion it seems apposite to iterate the three rules of mountaineering, rules which can also be applied to meaningful clinical research:

"It's always further than it looks. It's always taller than it looks, and it's always harder than it looks."

1 Heart valve replacement with autologous fascia lata. Ionescu M, Ross D, Deac R, Wooler G et al. J Thoracic and Cardiovasc Surgery. Vol 60. No 3. Sept 1970 pp 331 - 354

2 Unusual 25-year durability of an Ionescu-Shiley pericarial bioprosthesis. Fiore A, Cooley D et al. Annals of Thoracic Surgery. Vol 91, issue 4, E52-E53 April 01, 2011.