HABILITATIONSSCHRIFT

Titel:

“New Strategies & Surgical Techniques in Mitral Valve Disease, Atrial Fibrillation and Heart Failure”

Zur Erlangung der Venia Legendi der Universität Zürich
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Introduction

The growth of the metaphoric tree of cardiac surgery began a century ago with the landmark management of cardiac trauma and the initial description of a reliable method of pulmonary ventilation permitting open chest procedures. These accomplishments were followed by early surgical attempts to correct or palliate “approachable” lesions such as mitral valve stenosis and patent ductus. These efforts, in turn, were followed by the seminal investigation of hypothermia and the landmark development of cardiopulmonary bypass, the two “golden keys” that opened the door to the remarkable breadth of contemporary cardiac surgery [1].

Innovation has always been the trademark of cardiac surgery. The aim of this work is to illustrate the postdoctoral path innovation can take. Three major domains of interest are covered in this work.

First, deeper understanding of mitral valve disease and better repair strategies which offer improved long-term results.

Second, more insight into the mechanism of atrial fibrillation and the role surgery can play in restoring sinus rhythm in addition to device related stroke prevention.

Third and finally, heart failure with both medical and surgical strategies combined which yield improved outcomes.
1. **Mitral Valve Disease**

Current techniques of cardiac valve replacement are excellent and offer outstanding long-term results for many cardiac pathologies [2]. It is aortic valve stenosis which is the most common disease for aging population. In this scenario valve replacement is the treatment of choice in symptomatic patients. However for the mitral and tricuspid valves the situation is very different. Mitral and Tricuspid Valve regurgitation is a common problem and may have many causes. Mitral valve regurgitation is present when the valve does not close completely, causing blood to leak back into the left atrium. Mitral valve stenosis is present when the valve does not open completely, causing a relative obstruction to blood flow. Both of these conditions increase the workload on the heart and are very serious conditions. If left untreated, they can lead to debilitating symptoms including cardiac arrhythmia, congestive heart failure, and irreversible heart damage.

**a. Carpentier’s Technique of Valve Repair**

It is the seminal contribution of Alain Carpentier, who in 1968 first described the functional classification of mitral valve disease, in particular mitral valve insufficiency, which paved the way for this new approach. Carpentier refers to the confusion surrounding classification and description of mitral valve disease as “the Babel Syndrome,” in reference to the Biblical story of what happens when workers do not speak the same language. He went on to describing the explicit link between lesions encountered when analysing valve movement, understanding the aetiology of the underlying disease and finally deciding which treatment will offer the best possible outcome, characterised by the durability of repair. Many studies have since demonstrated the survival benefit of this technique when compared to valve
replacement. The philosophy of valve sparing techniques can be applied to all other valves, experience however with valve repair is mainly limited to the mitral and tricuspid. For surgeons, it is segmental valve analysis which is used to assess valve pathology and leaflet motion which has lead to novel approaches being developed for valve repair [3].

Figure 1: Carpentier’s Classification of Mitral Valve Regurgitation
With the creation of the remodelling annuloplasty ring, also know as the Carpentier – Edwards Physio Ring, an established therapy for patients with mitral and tricuspid valve disease was created. With the ever changing and aging of population addressed for cardiac surgery the prevalence of ischemic heart disease is on the rise. Functional mitral regurgitation, seen in this setting and subsequent tricuspid regurgitation leads to increased morbidity and mortality over time. Therefore it is crucial to offer an effective therapy for these patients. It is with functional regurgitation that the new annuloplasty rings were further developed in the 1990’s yielding new products addressing functional mitral and tricuspid regurgitation.

The etilogix™ IMR ring addresses mitral regurgitation in the setting of ischemic cardiomyopathy [4]. The MC3™ ring is made for patients with functional tricuspid regurgitation [5]. By rigorously applying these new devices to our surgical population better results are sought after [6]. To precisely analyze the effect this therapy we conducted retrospective chart reviews and echocardiographic follow-up of all patients having undergone implantation of either or both studied devices.
Figure 2: Etlogix Ring (A), D1 distance is normal, D2 undersized one size and D3 undersized twice to accommodate the asymmetrical tethering seen in type IIIb ischemic MR. Echocardiographic representation of Ischemic mitral valve (B).

The ETlogix IMR annuloplasty ring is the first remodelling ring specifically designed to treat asymmetric leaflet tethering and annular dilatation, as seen in ischemic heart disease. This ring was designed to address the geometrical issues found following the loss of the sphericity index in the left ventricle. It has been applied to patients with ischemic heart disease and severe mitral regurgitation. To precisely understand the specificity of this approach, and part of a multi-centre trial, we used quantitative 2-dimensional echo to examine early results of mitral valve repair with this new ring in patients with functional mitral regurgitation. Fifty-nine patients with significant functional mitral regurgitation underwent mitral valve repair with the new ring. Echocardiography was performed in a blinded core lab facility before, 3 and 10 days after surgery. After surgery, 97% patients had none or minimal mitral regurgitation, whereas 2 patients had mild (grade 2 out of 4) residual mitral regurgitation.
Surgical repair of functional mitral regurgitation with this new asymmetric ring provided excellent early results. This new aetiology specific strategy may result in improved outcomes in patient’s with functional mitral regurgitation in the setting of ischemic heart disease [7].

Functional tricuspid regurgitation occurs when the tricuspid valve is anatomically normal, but suffers from a backward failure. It is left sided heart disease, most often mitral and or aortic which can lead to functional tricuspid regurgitation. Moreover heart failure symptoms accompany this condition and make effective surgical treatment crucial. Moderate-to-severe functional tricuspid regurgitation (TR) should be corrected in patients undergoing surgery for left-sided valvular diseases, to improve long-term outcomes. Surgeons have many option to address this condition, however the most used are the least effective and a significant amount of patients are discharged after tricuspid valve repair with significant regurgitation. However, multiple clinical studies have shown the superiority of prosthetic remodelling annuloplasty over the other surgical approaches. With this in mind a new 3-dimensional remodelling prosthesis was developed to address the issue of residual tricuspid valve regurgitation.
We retrospectively reported a series of consecutive patients undergoing left sided valve surgery with aggressive tricuspid valve repair with the new ring. A total of 51 patients underwent concomitant to other cardiac valve procedures, tricuspid valve repair for functional tricuspid valve regurgitation due to annular dilatation, with the Edwards MC3 system. Echocardiography at discharge showed a significant decrease in tricuspid valve regurgitation. With an increase in left ventricular function. In addition follow-up echocardiography at 6 months after surgery demonstrated the stability of this new type of repair. Our experience showed that concomitant tricuspid valve repair for functional TR with left-sided valve surgery carries a low operative mortality, and that the Edwards MC3 annuloplasty system is relatively simple to implant and corrects TR effectively, while providing excellent short-term clinical results [6].
b. *New device for Mitral Valve Leaflet Prolapse*

Mitral valve repair remains an underutilized procedure. In the STS Database, it appears that only 50 to 75% of Patients with Mitral valve disease amenable to modern repair techniques, benefit from this therapy. Furthermore, minimally invasive and robotic applications remain challenging. A new device was developed and applied in an acute porcine model to evaluate feasibility of the approach. The device (patent pending) is intended for the treatment of leaflet prolapse, which is the most common form of mitral valve disease.

![Figure 4: PLI device. Normal Mitral Valve (A). Prolapsing Anterior leaflet (B). PLI device attached to the free margin of the anterior leaflet augmenting the surface of coaptation (C).](image)
It is composed of a semi-rigid titanium frame, covered with a biocompatible material, and is attached to the free margin of the prolapsed segment with a facilitated clip-fixation system. The device reduces excess leaflet motion of the prolapsing segment and provides an increased surface of coaptation with the opposing leaflet (Figure 1C). Through a left mini-thoracotomy, on cardiopulmonary bypass the mitral valve was exposed. Mitral regurgitation was created by transecting several marginal chordae (Figure 1B). Transesophageal echocardiogram and intraoperative saline-test confirmed mitral regurgitation. This was done in 10 domestic pigs using a new mini leaflet prosthesis, with very encouraging results. This new concept follows the principles of repair (preservation of leaflet mobility and creation of a large surface of coaptation). This study shows that the insertion of this new device is feasible and provides reproducible results by effectively correcting mitral prolapse. This may facilitate minimally invasive and robotic assisted mitral valve surgery and offer potential percutaneous applications. This device will be further developed at the University of Zurich in the future.
2. **Atrial Fibrillation**

Atrial fibrillation (AF) is a common cardiac arrhythmia and as such a significant risk factor for ischemic stroke originating from the left atrial appendage (LAA). The gold standard in the medical management of patients with AF remains oral anticoagulation. The prevalence of AF is on the constant rise, especially in patients addressed for cardiac surgery. It appears that up to 30% of these patients can be affected. Restoring sinus rhythm is the aim of the surgical procedure for AF – the Cox Maze procedure, which includes left atrial appendage occlusion for stroke prevention.

*a. Surgical Management - The Maze procedure*

In patients with AF, restoration of sinus rhythm with a maze procedure after concomitant mitral valve (MV) surgery has been shown to reduce the rate of stroke and improve cardiac function and quality of life compared to MV surgery alone. The Cox Maze procedure was developed by James Cox. The operation was described as being the creation of a Maze to isolate all the macro and micro re-entry foci of AF. The operation is challenging and ads up to one hour of time of ischemia to an already long surgery. In addition, initially a high rate of reoperation for bleeding was seen. Unlike the classical Cox-Maze III operation, a simplified left-sided maze procedure can be performed without any significant increase in operative complexity and excellent outcomes.
Figure 5: Classical Cox Maze III cut and sew lesion set (A). Limited, modified Radio Frequency lesion set around both pulmonary veins, connecting the left atrial appendage, and down to the mitral annulus. The atriotomy is the only cut and sew lesion left from the historical Maze as described by James Cox (B).

A retrospective chart review was conducted to analyze current results in an academic tertiary setting, especially in regard to sinus rhythm restoration. The results of the study helped to establish RF- or cryothermy-simplified left-sided maze procedure as being efficacious and without associated complications in patients having MV surgery and a history of AF. We demonstrated that freedom from AF was 77% at discharge and 87% at one year mean follow-up. Predictors of failed Cryomaze in multivariate analysis were left atrial size >50 mm (OR=5.7), AF at surgery (OR=5.0) and cardiac reoperation (OR=3.4), whereas preoperative beta-blocker treatment was a predictor of success (OR=0.2). Our data suggest that a left-sided Cryomaze procedure effectively restores sinus rhythm in patients with AF undergoing MV surgery [8].
b. Left Atrial Appendage Occlusion and Stroke Prevention

Currently neither surgical nor percutaneous devices are available for safe and effective LAA occlusion. As part of any Maze procedure, already described by Cox et al in 1982, amputating the LAA is an integral part of this procedure. The causal relationship between the LAA and Stroke has become evident over the past years. A body of evidence now exists, so that the ACC/AHA/ESC guidelines now recommend amputation the LAA during Mitral Valve Surgery. To this effect several techniques are available for surgeons.

Figure 6: Current Approach for LAA occlusion. The rigid abdominal stapler known from abdominal surgery is often also used in thoracic surgery and can be applied in minimally invasive procedures for LAA occlusion. Reports state a high rate of LAA injury, and necessity of multiple shots needed to achieve effective LAA occlusion. Furthermore this device is cumbersome and rigid limiting the spectrum of its minimally invasive application.

In an open chest setting one can use a suture, loop or stapler to exclude the LAA. When the heart is arrested over sewing the opening of the LAA in the LA is often feasible. All these methods however have limitations, be it by there application in a minimally invasive setting, their efficacy in regard to the high rates of reperfused LAA after suture closure, or
there safety. This has led to the development of the new LAA Clip. The LAA Clip is a system consisting of a self-closing, sterile, implantable clip and a reusable deployment tool. When closed, the Clip applies uniform pressure over the length of the clip to ensure consistent, reproducible, and secure occlusion of the LAA. The Clip is available in 4 sizes (25mm, 30mm, 35 mm, 40 mm, 45 mm, and 50 mm). The system also includes a single use, sterile, disposable selection guide that assists the surgeon in choosing the appropriate size clip for the LAA being occluded.

Figure 7: LAA Clip applied to Papio Anubis on the beating heart (A). All materials are composed of a deflectable nitinol frame covered with a proprietary polyester mesh. The internal design of the clip consists of two polycarbonate elastomers, two nitinol springs, and two titanium elements. The nitinol springs provide the clamping force needed to approximate the LAA tissue thus providing immediate occlusion. The polyester mesh assists in the pressure distribution as well as serving as a matrix for epithelial tissue growth. The clip comes in different sizes, based on the length of the LAA base (from 25 mm to 45 mm in 10 mm steps). Incision of the LAA was done to confirm LAA Occlusion (B).

This device was initially tested in animals [9]. The final stage of this research was composed of a long-term primate study to assess healing and in-growth properties of the LAA clip. Satisfactory conclusions on in-growth lead to the next step. A first in human trial was started at the university hospital of Zürich. Concomitant LAA Clip placement during routine cardiac surgery in patients with AF was started. A total of 32 Patients with 3 month Follow-
up will be necessary to obtain CE Mark approval. This data has been presented at the annual scientific session of the American heart association in New Orleans from Nov 9-14\textsuperscript{th}, 2008. The next steps will be to further develop the minimally invasive applications of this new device, an important second step will be to launch a multi centre trial to assess the precise role of isolated LAA occlusion in stroke prevention. Hence potentially creating a new indication in cardiac surgery. A thoracoscopic approach is being prepared as the main scope of interest will be thoracoscopic ablation procedures in patients with isolated AF not requiring any other cardiac surgery.
3. **Congestive Heart Failure**

   **a. BNP as a predictor?**

   B-type natriuretic peptide (BNP) is a key cardiovascular peptide hormone mainly secreted from ventricular cardiac myocytes in response to increased transmural wall tension due to ventricular stress, hypertrophy, or volume overload. While there is a wide individual variation in plasma BNP values, its level is frequently increased in patients with an impaired left ventricular function, and there is a body of information suggesting that the plasma BNP level is a sensitive predictor for the occurrence of future congestive heart failure events. Several studies have shown that BNP levels are also increased in patients with valvular heart disease, especially in patients with impaired left ventricular function.

![Neurohormonal activation in Congestive heart failure leading to cardiac cell death, apoptosis and myocyte necrosis.](image-url)
Little is known about the preoperative level of BNP in patients with mitral valve (MV) disease undergoing cardiac surgery and its potential relationship with early postoperative outcome. In this study, we sought to determine the pre- and postoperative values of BNP in a cohort of patients undergoing MV surgery and analyzed the potential impact of the preoperative value of this biological marker on surgical outcome. For this a prospective trial was undertaken to assess the predictive role of BNP prior to surgery [10].

Figure 8: Distribution of preoperative and postoperative BNP level. POD4 = postoperative day 4. The preoperative BNP level ranged from 9.7 to 995.0 pg/mL (median 108.0, IQR 59.1 to 240.3 pg/mL). Twenty two (52%) patients had a preoperative BNP level above 100 pg/mL.

Preoperative plasma BNP level presents with a high individual variability in patients with MV regurgitation. Atrial fibrillation was the only independent predictor of an increased preoperative BNP level. The preoperative BNP level was not a predictor of surgical outcome. Further studies will be necessary to confirm these findings and evaluate the potential role of this marker for patient selection.
Recombinant BNP – as therapy?

Recombinant BNP (Natrecor, Nesiritide, Scios Inc, Sunnyvale, CA) initially made its way into daily clinical practice for the treatment of congestive heart failure. More recently, BNP has also been used in postoperative cardiac surgical care as an adjunct in the management of low cardiac output and pulmonary hypertension, however, these have been small series with limited patient numbers. Encouraged by our initial experience with the use of this drug in the postoperative setting [11], we sought to explore whether this drug could also be usefully applied to preoperative hemodynamic optimization and postoperative use in high-risk mitral valve patients with pulmonary hypertension. Most of the previous work directed at reducing the mortality risk of pulmonary hypertension has been focused on postoperative management with pulmonary vasodilators. The limited use or preoperative interventions may in part be because potent pulmonary vasodilators have either been inhalational (nitric oxide and prostacyclin) or cause considerable systemic hypotension (phosphodiesterase inhibitors), making them impractical for use in the ambulatory patient before cardiac surgery.

For this purpose, we conducted a prospective non-controlled study of patients undergoing high-risk mitral valve surgery. Inclusion criteria for this study were severe mitral regurgitation (grade MR >3), impaired left ventricular function (EF < 50%), and pulmonary hypertension measured by cardiac catheterization (PA systolic > 45 mm Hg). The aim was to assess what effect a preoperative reduction of pulmonary artery pressures had on outcomes, especially when considering that the Euroscore risk stratification adds an extra point for Pulmonary Artery Hypertension (PA sys>45mmHg).
The treatment was administered preoperatively in all patients prior to mitral valve surgery. It was well tolerated in all. Our results, demonstrate that the perioperative use of Nesiritide was seen to be safe, and may contribute to improved early outcomes in high-risk patients undergoing MV surgery (especially when compared to the Euroscore). This may be due to improved ventricular loading conditions (decreased PA pressures, more effective diuresis) and/or a direct myocardial effect of BNP. In addition we have shown in a larger series that a Reno-protective effect in this high risk population may be found [12]. Further prospective evaluation of the role of BNP in cardiac surgery is warranted.
c. Treatment of terminal CHF – The DeBakey LVAD

The incidence of chronic heart failure (CHF) is increasing due to the aging population and its improved medical management. With disease progression to terminal heart failure, therapeutic options become fewer and cardiac transplantation (HTx) presents itself as the last option. HTx is also one of the most limited therapies, not only in regard to the lack of donor hearts (<3000 HTx performed each year worldwide) but also due to the surgical limitations inherent to the clinical aspects of this severely ill patient population. Mechanical circulatory support systems have been developed as effective adjuvant therapeutic options in these terminally ill patients [13]. Since the creation of the artificial heart program by the national institute of health (NIH) in 1964, numerous different mechanical circulatory support systems have been elaborated upon. Copeland and associates performed the first bridging to HTx by mechanical support in 1985. Mortality of terminal heart failure being very high as disease progresses, HTx candidates die while waiting on long lists. According to the recently published REMATCH study, the use of left ventricular assist devices (LVAD) resulted in more than twice the survival rate and an improved quality of life, in comparison to optimal medical management. Researchers from the Baylor College of Medicine (Houston, TX) with engineers from NASA have been developing the DeBakey LVAD produced by MicroMed Inc. since 1988.
Figure 10: The DeBakey LVAD, was developed by researchers from the Baylor College of Medicine (Houston, TX) with engineers from NASA since 1988. This implantable continuous axial flow pump creates a maximal flow in excess 10 l/min, hence providing relief to the sick heart by taking over part of the pumping action.

As the DeBakey LVAD has been available at our centre since October 1999, we evaluated this new device in 15 consecutive patients and report our results in regard to overall outcome in HTx candidates. In our experience [14], The MicroMed DeBakey LVAD is simple to implant. Patients were able to be discharged. An outpatient treatment program was established, allowing for safe and social integrative treatment. Patients' condition improve, they develop a positive, anabolic metabolism. Subsequent HTx can be performed in low-risk situation, allowing better donor-recipient matching and improving overall outcome.
d. Right Ventricular Function on LVAD support

A subset analysis on pulmonary resistances in these patients yielded interesting results. PVR seem to normalize within 6 weeks, making previously considered inoperable patients amenable for HTx. The problem of increased pulmonary resistances is attributable to Disease progression bringing backward failure, which in turn alters the pulmonary circulation ultimately leading to decreased right ventricular function. The remodelling occurs quickly, leading to changes of the pulmonary vasculature, which at first seems to be reversible, but over time becomes irreversible. On a capillary level, increased vascular remodelling, in situ thrombosis and vasoconstriction are all perpetuating mechanisms, leading to fixed pulmonary hypertension (PH). Fixed PH and high PVR are both tributaries of advancing heart failure and lead to poor outcome after heart transplantation due to the postoperative failure of the non-conditioned right ventricle increasing early morbidity and mortality. However after heart transplantation, 80% of survivors will normalize their PVR at 1 year, highlighting the fact that even with fixed PH, reversal of pulmonary disease is achieved with through normalized blood flow, as seen in patients under LVAD support.
Figure 11: Reduction of PVR in LVAD patients. Serial right heart catheters were done on these six study patients. After a period of 6 weeks, the mean PVR decreased from 398 (501–305) to 167 (74–216) dyne s cm$^{-5}$, systolic pulmonary artery pressure from a mean of 47 (29–67) to 29 (12–49) mmHg, $P<0.05$ in all.

The role of LVAD support, especially with the new continuous flow devices, as provided by new generation LVAD's, was evaluated in a series of clinical implants. We studied the role of LVAD support as bridge to heart transplantation, but more specifically we identified a subset of patients with pulmonary hypertension (PH) and high pulmonary vascular resistance (PVR) [15]. Elevated PVR and severe PH were both previously considered as contraindication for heart transplantation. A period of LVAD pumping, as seen in our series, leads to a progressive decrease of PVR and normalization of pulmonary pressures, making these patients amenable for heart transplantation. LVAD as bridge to heart transplantation is safe and highly beneficial for terminal heart failure patients with severe PH.
Summary

In this overview of postdoctoral activity, the emphasis on implementing innovation and improving outcomes was set. This is crucial in a young specialty like Cardiac Surgery. Our profession is ever moving, technologies are changing, and innovative strategies play a crucial role. This work illustrates the clinical path innovation can take. When applying the critical scientific mind to modern problems or when attempting to offer new solutions to optimize treatment strategies in modern medicine, finally it is the application and acceptance from clinicians which will lead to new innovative evidence based treatments.
References: