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DOCTORAL SCHOOL
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**CARDIAC SURGERY AT THE CROSSROADS:
STATE-OF-THE-ART, CHALLENGES AND FUTURE
ENDEAVORS**

ABSTRACT

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ABSTRACT

Cardiac surgery is a relatively new branch of surgery. While cardiac operations have been performed almost by accident and necessity prior to the development of the heart-lung machine, it was the device imagined and built by J.H.Gibbon from the Jefferson Medical School of Philadelphia that opened the possibility to open inside the heart [1]. Indeed, although Ludwig Rehn in Germany sutured a stab wound in the right ventricle in 1896 (and the patient survived) it was not until the second half of the 20th century that surgeons were able to arrest the heart, operate and restart the heart. Since then, cardiac surgery has dramatically evolved to the point of treating the whole spectrum of cardiac pathology from valve and coronary diseases, acute and chronic aortic syndromes, congenital cardiac malformations, rhythm disturbances up to mechanical VAD, TAH, cardiac transplantation and, very recently, xenotransplantation [2,3].

The current habilitation thesis presents the personal research I've conducted in this domain over the last 20 years.

1. SCIENTIFIC ACHIEVEMENTS

1.1. IN VIVO EXPERIMENTS ON LARGE ANIMALS

1.1.1. The effect of sevoflurane on RV function [4]

Although the effects of halogenated agents on both normal and diseased left ventricles have been widely studied, the influence of these anesthetic agents on right ventricular (RV) performance remains less well characterized. This study was undertaken to examine the effects of 2 different concentrations of sevoflurane on RV function, and coronary and pulmonary hemodynamics in acutely instrumented anesthetized pigs. **Conclusions:** Sevoflurane causes significant depression of global RV function associated with a qualitatively different effect on inflow and outflow tracts, without any modification of PVR.

1.1.2. The development of a novel LVAD [5]

The paper presents the first in vivo experiments with a new type of valveless ventricular assist device, a wave-generating pump. Our goal was to evaluate the

hemodynamic performance of the pump by comparing it with the Biomedicus BP-80 centrifugal pump and by sustaining a 3h long left ventricular assistance. **Conclusions:** Although promising, this novel pumping device needs further prototypes to be clinically applicable.

1.2. CLINICAL STUDIES

1.2.1. Alternative LVAD implantation technique [6]

The implant of a ventricular assist device is a standardized procedure. However, it carries a high-risk in reoperations, especially if there are patent by-pass grafts. In the following, we describe an alternative, off-pump technique that combines a median sternotomy with limited dissection of the right-heart with a left anterolateral thoracotomy. In our experience, it proves to be a safe way for the LVAD insertion in these high-risk patients.

1.2.2. Short term results of ECMO in pediatric patients [7]

We retrospectively reviewed the files of 19 extracorporeal life support (ECLS) applications performed after cardiac surgery in 15 patients from January 2002 to December 2004. **Conclusions:** These results support early placement of ECLS in children whenever a severe postoperative hemodynamic or respiratory failure, refractory to medical treatment, is present.

1.2.3. The fate of the homograft in the Ross operation [8,9]

The purpose of this study was to find homograft-related factors that might be associated with the development of stenosis after the Ross procedure, as well as to identify the natural dynamics of stenosis and find echographic cutoff values after one year of follow-up that might predict such an outcome. We followed up 71 patients (mean age, 24.27 +/- 16.57 years) who had such a procedure prospectively by transthoracic echocardiography, between 1993 and 2002. **Conclusions:** Homograft size is the most important homograft-related factor for stenosis. Most of the increase in transhomograft gradient occurs in the first 24 months. A gradient of 9 mm Hg or more after 1 year predicts the late occurrence of stenosis.

1.2.4. Valvular surgery contributions

In the last decade, cardiac surgery in octogenarians is becoming a routinely performed procedure in our Western countries. The functional benefit of this surgery had already been proved. The aim of this study was to evaluate operative mortality, to identify pre- and post-operative risk factors of early and late mortality, to assess the Euroscore count in this high-risk group of patient and to evaluate late results of this surgery. We reviewed 215 consecutive patients with a mean age of 83+/-2 years having undergone valvular surgery. **Conclusions:** Valvular surgery in octogenarians is a safe and low risk procedure compared to functional benefit and long-term survival. Our data show that logistic Euroscore I overestimates the mortality in this high-risk group of patients [10]

The long-term performance of prostheses in the small aortic root is still unclear. Patients who received a 21 mm or smaller aortic valve between 2000-2018 were retrospectively analyzed. Propensity matching was used in order to account for baseline differences in 19 mm vs. 21 mm valve subgroups. **Conclusions:** There is no survival penalty in using 19 mm prostheses in the small aortic root in the current era. Although PPM is more prevalent in smaller sized valve recipients, this does not translate into reduced survival at 10 years of follow-up [11]

The effect of patient-prosthesis mismatch (PPM) in mechanical prostheses on long-term survival is not well-established. Patients who received a 21 mm or smaller aortic valve between 2000 and 2011 were retrospectively analyzed ($n = 416$). Propensity matching was used in order to account for baseline differences in patient subgroups (PPM vs. no PPM; severe PPM vs. no severe PPM). **Conclusions:** PPM or severe PPM does not impact long-term survival up to 10 years in mechanical valve recipients when matching for preoperative variables [12]

1.2.5. Aortic surgery contributions [13,14]

Malperfusion is a central limiting factor in the setting of acute Type A aortic dissections (TAAAD). We sought to find preoperative metabolic acidosis thresholds that might influence decision-making in this setting. We retrospectively reviewed consecutive patients operated on with TAAAD between January 2002 and December 2017. **Conclusions:** Patients with a prebypass pH ≤ 7.25 have an unacceptably high early mortality after TAAAD repair. Those patients might benefit from a two-stage approach [13].

At the same time, we investigated a modified cannulation technique for TAAAD which allowed us to dramatically lower early mortality from 40% to 8%. While the occasional use of innominate artery cannulation in TAAAD has been previously reported, our paper presented the systematic use of this artery as an arterial inflow, whether it was dissected or not [14].

1.2.6. The development of a robotic exoskeleton [15,16]

We presented the development of an improved home-based cardiac telerehabilitation system enhanced by a robotic and Virtual Reality module for cardiac patients to be used in their rehabilitation program. **Conclusions:** Implementing these novel features of the CardioVR-ReTone system, addressability, and efficacy of CR, so problematic in certain situations and especially in cardiac surgery, will be greatly facilitated, being independent of the skills and availability of the rehabilitation therapist.

1.2.7. Surgical case reports

The simultaneous existence of double orifice right and left atrioventricular valves in the absence of ostium primum defects is rare and scarcely reported. We presented the case of a 20-month old boy diagnosed with tetralogy of Fallot with pulmonary atresia who was found to have associated double-orifice mitral and tricuspid valves. Double-orifice atrioventricular valves (DOAVV) are incidental findings. While a left sided DOAVV is found with non-negligible frequency, there are to date few reported cases of a right sided DOAVV. Furthermore, most reported cases of right DOAVV appeared in the setting of atrio-ventricular canal defects and there is to date, to the best of our knowledge, only one report of their association with left-sided defects [17]

We also published in Circulation the rare case of a patient with coronary ostial stenoses due to tertiary syphilis. Untreated syphilis can reach the tertiary phase with cardiovascular and neurological manifestations. Progression may lead to erosion of the sternum, pseudoaneurysm formation, or outright dissection. Tertiary syphilis remains a diagnosis to be considered in patients with aortic pathology, especially if it is associated with coronary ostial stenosis with a normal coronary bed [18]

Hypertrophic obstructive cardiomyopathy (HOCM) is one of the most common hereditary heart diseases. The severely hypertrophied interventricular septum combined with the systolic anterior movement (SAM) of the mitral valve (MV) frequently cause a significant pressure gradient in the left ventricular outflow tract

associated with varying degrees of mitral regurgitation (MR). We present the case of a 64-year-old female patient who was diagnosed with HOCM two years ago and was admitted to the Institute of Cardiovascular Disease with exertion dyspnea and fatigue. In conclusion, MAO isoforms are expressed at the level of severely impaired mitral valve in the setting of HOCM and can be induced in conditions that mimic the activation of renin-angiotensin-aldosterone system. The observation that the enzyme can be modulated by MAO inhibitors warrants further investigation in a patient cohort [19]

1.2.8. Various contributions

To assess drug optimization using systematic exercise tests (ET) in fusion CRT-P with preserved atrioventricular conduction (AVC), we studied the association of beta-blockers and ivabradine. Changes in drug management were assessed during systematic follow-ups in CRT-P patients without right ventricle lead. **Conclusions:** BBs/ivabradine titration and routine ET during follow-ups in patients with fusion CRT-P should be a standard approach to maximize resynchronization response. Fusion CRT-P showed a positive outcome with important LV reverse remodeling and significant LVEF improvement in carefully selected patients [23]

Mitochondria-related oxidative stress is a pathomechanism causally linked to coronary heart disease (CHD) and diabetes mellitus (DM). Recently, mitochondrial monoamine oxidases (MAOs) have emerged as novel sources of oxidative stress in the cardiovascular system and experimental diabetes. The present study was purported to assess the mitochondrial impairment and the contribution of MAOs-related oxidative stress to the cardiovascular dysfunction in coronary patients with/without DM. **Conclusions:** Abnormal mitochondrial respiration occurs in CHD and is more severe in DM and MAOs contribute to oxidative stress in human diseased hearts with/without DM [20]

Monoamine oxidases (MAOs), mitochondrial enzymes with two isoforms, A and B, have been recently recognized as significant contributors to oxidative stress in the cardiovascular system. The present study was purported to assess the effect of metformin and empagliflozin on MAO expression, oxidative stress and vascular reactivity in internal mammary arteries harvested from overweight patients with coronary heart disease subjected to bypass grafting. **Conclusions:** Endothelial dysfunction and oxidative stress were alleviated by either metformin or empagliflozin in both stimulated and non-stimulated vascular samples harvested from overweight cardiac patients [21]

2. ACADEMIC ACHIEVEMENTS

2.1. CAREER OVERVIEW

I graduated in 1998 upon presenting the dissertation paper titled “Lasers in Dermatology” from the University of Medicine and Pharmacy «Victor Babes», Timisoara. I then completed a practical year (1999) and passed the national residency exam having chosen cardiac surgery as my future specialty. I then started my residency in general surgery at the University General Hospital of Timisoara (2000).

My academic activity began in 2000 as part of the Department of Cardiology of the University of Medicine and Pharmacy «Victor Babes», Timisoara, Romania. My goal in my academic positions is to integrate clinical findings in real world patients as well as experimental studies in both teaching and research purposes.

I have completed a one-year research position at the Laboratory for Cardiovascular Mechanics and Hemodynamics at the University Aix-Marseille in 2001, during which I took part in experimental in-vivo studies on large animals on the cardiovascular effects of different drugs [4] as well as the first in-vivo studies of a novel left ventricular assist device (LVAD), the “Fishtail” pump [5]. After this, I enrolled in a 2-year formation as attached resident in cardiothoracic surgery in the Adults Cardiothoracic Surgery Department at the “La Timone” University Hospital, Marseille (2002-2003), a formation which was certified by passing the “Attestation de Formation Spécialisée” exam, in Narbonne, France. I returned to Timisoara, Romania where I engaged in a 6-month residency spell in adult cardiac surgery department of the Institute for Cardiovascular Diseases. I returned to Marseille, France, for a one-year training in pediatric cardiac surgery at the “La Timone Hospital for Sick Children” (2004), where I worked as resident in the Pediatric Cardiac Surgery Department. During this time, I enrolled in a 6-month course and completed my degree in the mechanical assistance of the failing heart («Diplôme Inter-Universitaire d’ Assistance Circulatoire») at the Faculté de Médecine Pierre et Marie Curie, Université Paris VI. I passed the “Attestation de Formation Spécialisée Approfondie” exam, in Narbonne, France in April 2005.

I entered clinical research during this period and initiated and took part in numerous studies, which completed my training in France [6–8,22].

I became assistant professor in 2005 and finally associated professor at the University of Medicine and Pharmacy “Victor Babes”, Timisoara, in 2019.

I worked as a staff surgeon, for a brief period of time (February - August 2015) in the University Klinik Saarland in Homburg, Germany under Professor Hans-Joachim Schäfers. I then rotated to a visiting fellowship position in the Rhön Klinik Bad Neustadt an der Saale, Germany, under Professor Anno Diegeler, where I worked with Dr. Patrick Perrier and Dr. Fitsum Lakew to acquire the thoracoscopic mitral valve repair techniques (August 2015).

During my activity as staff surgeon of the Department of Cardiovascular Surgery, Institute for Cardiovascular Diseases, Timisoara, I introduced many operations in the clinical practice, such as thoracoscopic mitral valve surgery (in 2018), minimal invasive aortic surgery (aortic valve, ascending aorta- in 2016), aortic arch aneurysm surgery using a hybrid prosthesis (2019), combined cardiac and urologic surgery for renal tumors that grow into the inferior vena cava and right atrium (2019) as well as introducing modified surgical techniques that allowed to significantly improve results in high-risk pathologies, such as Type A Aortic Dissection.

2.2. PHILOSOPHER’S DEGREE (PHD)

My interest in the surgical treatment of the failing heart led me to choose this area as the subject of my PhD thesis, which I enrolled in in 2004. The thesis had three parts:

1. An experimental in vivo part, in which I presented my research performed in the Laboratory of Cardiovascular Mechanics of the Aix-Marseille University
2. A clinical part in acute heart failure, in pediatric patients, in which the use of the Extracorporeal Membrane Oxygenation (ECMO) in patients with low-output syndrome after cardiac surgery was investigated.
3. A clinical part in acute heart failure, in adult patients, in which I researched the effect of the use of the Intraaortic Balloon Pump (IABP) in adult patients operated upon in the Institute of Cardiology Timisoara, was assessed.

The thesis was presented in a public lecture on 11.02.2011 and recognized by the Romanian Ministry of Education, confirmation order MECTS nr. 4387/06.06.2011.

2.3. ACADEMIC AND INTERNATIONAL RECOGNITION

I am a member of the Romanian Society for Cardiovascular Surgery as well as the European Association of Cardio-Thoracic Surgery (EACTS). I have been invited lecturer to the National Congress of the Romanian Society for Cardiovascular Surgery for many years, at the “East meets West” Congress of the International Society for Endovascular Surgery, as well as other congresses.

I've been chairman of the ECLS session of the 27th Annual Meeting of the EACTS, Vienna, 5-9 October 2013, as well as other national meetings, such as the Annual Meeting of the Heart Institute Cluj (2022) as well as the Annual Meeting of the Timisoara Institute for Cardiovascular Diseases.

I am residency supervisor since 2022 for resident doctors in the specialty of Cardiovascular Surgery, according to the training curricula, activity which is pursued in the Institute for Cardiovascular Diseases, Timisoara.

On a university level, I am currently coordinator of the Discipline of Cardiovascular Surgery, which is part of the VIth Department (Cardiology) of the University of Medicine and Pharmacy “Victor Babes”, Timisoara. As part of my university

With respect to the absorption of European funds, I've led as programme director the European crossborder cooperation project Romania - Hungary, Cross - Border Cooperation Programme 2018-2021, ROHU-401, *“Improving health-care standards in prevention, identification and treatment of cardiovascular and gynecological diseases in the crossborder area”*, acronym *“HEARTS& LIVES”*. The aim of the project was to improve the prevention, diagnosis and treatment of cardiovascular and gynecologic diseases in the crossborder area by increasing the awareness of cardiovascular modifiable risk factors in the general population, lower the threshold for primary diagnosis and increase the access to state-of-the-art treatment of cardiovascular diseases in our respective populations.

In the scientific field I am a reviewer for several journals in the MDPI consortium, such as *Journal of Clinical Medicine* (IF= 4.964), *Diagnostics* (IF= 3.992), *Materials* (IF=3.738) and *Life* (IF=3.253) and work with the editors to assess the scientific soundness of their manuscripts.

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