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**Outcomes of minimally invasive valve surgery in ischemic/nonischemic patients, and
their risk of arrhythmias.**

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General framework and introduction

Minimally invasive techniques are increasingly used in cardiac valve surgery, with satisfactory results to date. Although minimally invasive video-assisted techniques are proving to be more and more secure, however, few centres at European and global level are introducing such techniques, due to costs, learning curve, and lack of long-term studies.

Moreover, in today's guidelines, minimally invasive valve surgery still does not have a well-defined place. Especially if ischemic coronary artery disease is associated with indication of revascularization, indications of current guidelines do not include minimally invasive strategies, due to several factors. First, again, the lack of long-term, multicentre studies, only in 2017, 2018, was starting with the enrolment of patients in some European registries, which will follow about 8000 cases over 5 to 10 years. Secondly, there is the fear of haemorrhagic risk in patients with antiplatelet treatment, who will be subjected to valve interventions, thus continuing the preference for revascularization with aortocoronarian bypass, instead of the risk of haemorrhagic complications or early intrastent restenosis, when the use of double antiplatelet therapy is limited.

Currently, information is available in the literature only on unicentric series of cases, relatively heterogeneous, but which certainly shows the no inferiority of minimally invasive hybrid approaches, which include revascularization with stenting in the first phase, and subsequently the valve approach through minitoracotomies.

Also, the implications on the rhythm stability in these patients are less studied, the existing literature being given from limited series of cases, unicentric, heterogeneous. The incidence of atrial fibrillation, grade III atrioventricular block, newly installed branch blocks, other rhythm and conduction disorders, and their implications on patient evolution, hospitalization, costs, are problems that health systems and institutions are starting to approach, but there is still not enough data for a clear overall picture.

The present study is important because it is an attempt to address these problems at the level of a private centre, on a series of patients from 2018, who have benefited from the minimally invasive approach of the valve pathologies through techniques of last generation.

Structure of the thesis.

Part 1, general, is composed of four major chapters: A. Valvular, aortic and mitral pathology, with description of epidemiology, pathophysiology, and analysis of patient evaluation. Includes a chapter regarding the current stage in minimally invasive aortic and mitral surgery;

B. myocardial revascularization, with the evaluation of the patient and the current recommendations regarding the valve disease (with the updates from the current guides);

C. Atrial fibrillation, with epidemiology and patient evaluation, includes a chapter on the impact of evidence-based management on the evolution of AF patients, and a chapter on anatomic-imaging correlations and the role of echocardiography;

D. Anatomic imagistic correlations in the understanding of ventricular arteries.

Part II personal contributions, in which there are the results of the own research.

The first part summarizes the current data on the aortic and mitral valve pathology, the guides for surgery in the valve pathology, the indications of revascularization in ischemic coronary disease, the indications of revascularization in coronary ischemic disease concomitant with the valve or rhythm pathology. Also, in the general part, the minimally invasive surgical procedures from the mitral and aortic valve pathology are summarized, in a chapter regarding the current stage in the minimally invasive valve surgery.

The special part comprises three independent studies, each following the evolution of the valve patients with minimally invasive surgery at the level of the aortic or mitral valves, with ischemic pathology with or without revascularization, and the rhythm evolution of these patients.

Study A, determines the frequency of cardiac valve interventions and comorbidities, in a private centre, is a retrospective study, which for the period 2015-2016, in a private heart surgery centre, proposes the following objectives:

1. Check the frequency of valve surgery for a period of 2 years
2. Check the incidence of atherosclerotic coronary heart disease
3. Check the incidence of ventricular and supraventricular arrhythmias
4. Try to correlate with antiarrhythmic treatments.

Material and method

The study is an observational, retrospective, noninterventional one that included patients admitted to the Cardiovascular Surgery Section of the European Hospital Polisano Sibiu between 1.01.2015 and 31.12.2016.

After obtaining the approval of the Ethical Council of the Hospital, the data were collected from the internal computer system, from the outpatient records of patients, based on the codification of the surgical procedures, and of the associated pathologies.

The selection process consisted of identifying the outpatients with one of the procedure codes for aortic valve surgery (H02201, H02301, H02302, H02303, H02304, H02401, H02402, H02403, H0240, H2502, H2502, H0240, H2502, H2502 H02703, H02704, H02801, H02802, H02901, H02902, H02903, H03001, H03101, H03102).

Subsequently, in these cases, different diagnoses were sought from ischemic pathologies: unstable angina, atherosclerotic cardiovascular disease, atherosclerotic heart disease of unspecified vessels, atherosclerotic heart disease of the native coronary artery, and atherosclerotic heart disease of an autologous bypass graft; later in the cases with the valve interventions, the rhythmic disorders recorded in the outpatient diagnoses were sought: ventricular fibrillation, flutter and ventricular tachycardia; atrial fibrillation; ventricular and supraventricular extrasystole. Next, we tried to correlate the antiarrhythmic treatments by searching the patient's electronic file for the keywords (different antiarrhythmic drugs: bisoprolol, metoprolol and amiodarone).

The data was completed in the Excel file. Descriptive calculations were numerical and percentage.

140 valvular surgeries were identified, and ischemic status, documented arrhythmias and some antiarrhythmic treatments were correlated.

Conclusions in study A

1. The frequency of valve pathology with operative indication is significant, and at the level of the respective centre there are sufficient cases for a more detailed descriptive study.

2. Ischemic heart disease is common among valve patients, with valve surgery indication, and this has important implications in the clinical setting.

3. Supraventricular arrhythmias, especially AF, are very common in valve patients, especially in ischemic patients.

4. Treatment with amiodarone and beta-blockers is important in patients with operative valve pathology, to reduce comorbidities, and hospitalization times.

Study B, Evolution of minimally invasive, ischemic and non-ischemic valvular patients, analyses the evolution of 93 minimally invasive patients at the level of aortic and mitral valves in 2018, whether they were with PCI or not, in the same private centre, in terms of the following problems:

1. To determine the mortality at 30 days, in patients with minimally invasive valve surgery, with or without stenting in the history.
2. To determine the frequency of thoracotomy reinterventions / reopening due to significant bleeding or coronary obstruction.
3. Determine the frequency of major events such as stroke, renal failure, and prolonged ventilation.
4. To compare the cross- clamp times and extracorporeal circulation, in the two categories of patients (PCI/ no PCI) operated minimally invasively.
5. To determine if there are significant variations of LV ejection fraction between the two categories of patients and if there are cases of acute heart failure.
6. Determine the frequency of pulmonary complications.
7. Check whether hospitalization times differ in ischemic / non-ischemic patients.

Material and method

In the European Hospital Polissano Sibiu, after obtaining the acceptance of the Ethical Council, for gathering the data of patients, in compliance with the rules in force, for an observational study, in which data are collected from the observation sheets.

Retrospective data were collected, in 2018 and 2019, in an observational, noninterventive study, for patients with minimally invasive cardiac valve surgery in 2018 and the parameters under discussion, but these were completed in the computer systems prospectively.

The types of procedures are: biological or mechanical mitral valve replacement; mitral valve repair; biological or mechanical aortic valve replacement.

The characteristics of the study population were collected as follows: gender (M / F), age (years), presence / absence of HTA diagnosis, presence / absence of DZ diagnosis, presence / absence of a history of cerebrovascular disease; presence / absence of BAMI diagnosis; IRC, or IM in the background.

An Excel format database was built, which included the following: type of procedure, cross-clamping times and CEC (minutes), need for prolonged ventilation (> 24h), type of associated procedures (including implantation of pacemakers), ischemic status was completed as PCI / nonPCI, but initially each procedure was defined with the location and type of stents; the number of days of hospitalization was completed, the preoperative and postoperative ejection fraction at 5 and 30 days; cases with thoracic haemorrhagic complications, or digestive bleeding, or postoperative stroke have been identified; cases with postoperative IM were sought; chest infections were recorded; pulmonary complications

defined as pneumonia, pneumothorax, pleural collection without drainage were noted; cases of death, and the need for coronary reintervention were recorded.

The evolution of these patients is recorded during the perioperative period, and at the evaluation after 30 days. With a series 93 cases, of which 16 were preoperatively stented, for statistical calculations, the following subgroups were formed: MIAS (minimally invasive aortic surgery), MIMS (minimally invasive mitral surgery), and PCI (percutaneous coronary intervention) - stenting procedure before valve surgery, and NON-PCI.

Statistical analysis was performed using SPSS v.20 and Microsoft Excel programs from the Microsoft Office 2016 package. Fisher's Exact Test 2-sided was used to compare dichotomous variables, with the definition of statistically significant correlation if $p < 0.05$, and for the study and correlation of mean times. (in minutes for the duration of aortic cross-clamping and CEC; and in days for the average length of hospitalization), the ANOVA test was used, with $p < 0.05$ defined as statistically significant.

The conclusions of this study are:

In this series of patients:

1. There is no increase in postoperative mortality in those with prior stenting, and minimally invasive surgical approach.
2. There is no statistically significant different haemorrhagic risk in patients with prior stenting, nor STEMI, or minimally invasive post-surgery ACS
3. Digestive bleeding is not observed; does not statistically significantly increase the frequency of stroke, IRC or mechanical ventilation time.
4. There is no statistically significant difference between crossclamping times and extracorporeal circulation, in PCI patients, compared with those without stenting, after minimally invasive valve surgery.
5. There were no significant differences in LV ejection fraction in the two categories of patients.
6. Pulmonary complications in cases with MIMS are statistically significantly more frequent.
7. There is no difference in hospitalization times between patients with PCI and those without, in this series of minimally invasive valve surgery patients.

Study C, Rhythmic stability of minimally invasive, ischemic and nonischemic patients, has the following objectives:

1. To determine the frequency of pre and postoperative atrial fibrillation, to compare between the categories of patients.

2. To determine the frequency of total AV block, pre and post operatory, to compare between groups.
3. To determine the incidence of postoperative BBB, to compare.
4. Describe the typology of other arrhythmias in valve patients operated minimally.
5. To compare MIAS and MIMS groups from the point of view of the installation of rhythm and conduction disorders.
6. Compare PCI / NO PCI with minimally invasive valve surgery, from the point of view of the installation of AF and total AV block.
7. To check if there are significant differences between the hospitalization times in the cases that have post-operative AF; if there are significant differences in the length of hospitalization in those who have developed BBB or total AV block; if in terms of the length of hospitalization there are differences between those with revascularization and those without.

Material and method

In the European Hospital Polissano Sibiu, after obtaining the acceptance of the Ethical Council, for gathering the data of patients, in compliance with the rules in force, for an observational study, in which data are collected from the observation files.

Retrospective data were collected, in an observational, noninterventional study, for patients with minimally invasive cardiac valve surgery in 2018 and the parameters in question, but these were completed in the computer systems prospectively.

The types of procedures are: biological or mechanical mitral valve replacement; mitral valve repair; biological or mechanical aortic valve replacement.

The characteristics of the study population were collected as follows: gender (M / F), age (years), presence / absence of HTA diagnosis, presence / absence of DZ diagnosis, presence / absence of history of cerebrovascular disease; presence / absence of BAMI diagnosis; renal insufficiency, or MI in the background.

An Excel format database was built, which contained the following: type of associated procedures (including implantation of pacemakers), ischemic status as PCI / non PCI was completed, but initially each procedure was defined with the location and type of stents; the number of days of hospitalization was completed; those with pre and postoperative AF were identified, those with total AV block installation, of the left or right branch block, and all other postoperative rhythm and conduction disorders were recorded: AV block gr I, AVblock gr II, VT and NSVT, Atrial Flutter, paroxysmal supraventricular tachycardia, AF with slow ventricular rate, electromechanical dissociation. The evolution of these patients is

recorded during the perioperative period, and at the reassessment from 30 days. With a series of 93 cases, of which 16 were preoperatively stented, for statistical calculations, the subgroups were formed: MIAS (minimally invasive aortic surgery), MIMS (minimally invasive mitral surgery), and PCI (percutaneous coronary intervention).) – PCI before valve surgery, and NON-PCI.

Statistical analysis was performed using SPSS v.20 and Microsoft Excel programs from the Microsoft Office 2016 package. Fisher's Exact Test 2-sided was used to compare dichotomous variables, with the definition of statistically significant correlation if $p < 0.05$, and for the study and correlation of mean times. (in minutes for the duration of aortic clamping and CEC; and in days for the average length of hospitalization), the ANOVA test was used, with $p < 0.05$ defined as statistically significant.

It concludes that:

1. The frequency of preoperative and postoperative AF in patients with PCI / without PCI does not differ statistically. There is statistically significantly more frequent preoperative AF in patients with mitral surgical pathology, without significantly differing the incidence of postoperative AF depending on the type of valve operated.

2. Postoperative total AV block is not statistically significantly different in patients with aortic or mitral pathology, or in patients with PCI/ non PCI.

3. The BBB newly installed does not correlate statistically with the type of valve operated, or with the PCI/ non PCI status.

4. Other rhythm or conduction disorders are described, without statistically significant correlation with ischemic status or type of valve operated.

5. The prevalence of the postoperative AF does not cause a significant change in the length of hospitalization. The installation of complete AV block and the bundlebranch block does not significantly change the length of hospitalization. Patients with stenting prior to valve surgery did not have a longer duration of hospitalization.

Originality and innovative contributions of the thesis

Given that the data available in the literature on the minimally invasive hybrid approach with percutaneous myocardial revascularization, followed by minimally invasive valve surgery, through assisted video minitoracotomy, are limited, our study on the 93-case group joins the unicentric data from the present time, at European and global level.

Study A, although purely descriptive, shows that at the level of this private clinic, there are sufficient cases with valve pathology with last-generation interventions, with

significant comorbidities determined by ischemic pathology, and with rhythm disorders important for the evolution of these patients.

Study B, in which the 93 patients with minimally invasive valve surgery in this centre are observed, in 2018, brings significant information. There is no statistically significant difference between cross clamping times and extracorporeal circulation, in stented patients, compared to those without stenting, after minimally invasive valve surgery. The bleeding risk of these patients does not increase. The fact that minimally invasive valve surgery is performed in patients with prior stenting does not increase their risk of having an ACS, or longer hospitalizations. There is no significant difference in the risk of immediate or 30-day postoperative mortality.

Study C is important because it discusses the stability of these patients in terms of rhythm and conduction disorders, and the implications that these comorbidities have in the evolution of these cases. It is important to point out that postoperative AF, or complete AV block, or bundle branch block installation does not differ significantly depending on the ischemic status of the patient, or depending on the valve operated. Also, these comorbidities do not significantly extend hospitalization times.