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**CONTEMPORARY METHODS FOR DIAGNOSIS AND SURGICAL  
TREATMENT OF SIGNIFICANT CHRONIC ISCHEMIC MITRAL  
REGURGITATION**  
(study of influence of mitral repair on left heart chambers reverse  
remodeling)

ABSTRACT

of a thesis for granting an educational and scientific degree  
“Doctor of Medicine”

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The scientific thesis consists of 175 pages and is illustrated with 12 color or black and white figures and 23 tables. One figure, 6 tables and 56 diagrams are included in this abstract. The study is based on materials of the Department of Cardiac Surgery in "St Marina" University Hospital during the period January 2007 – June 2011 and comprises 140 patients operated for ischemic heart disease. The candidate himself operated 126 of them.

The reference list consists of 277 papers – 16 in Bulgarian language and 261 foreign papers.

The scientific thesis is discussed in a broad meeting of the Department of Surgery of the Medical University - Varna, and is referred for a defense before a Scientific committee.

The defense materials are available at the Postgraduate qualification department of the "Prof. Dr. Paraskev Stoyanov" Medical University - Varna.

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## ABBREVIATIONS

B.S.A. – body surface area  
OPCAB – off-pump coronary artery bypass  
PCI – percutaneous coronary intervention  
CABG – coronary artery bypass grafting  
AP – angina pectoris  
MCVC – major cardiovascular complications  
ERO – effective regurgitant orifice area  
SIMR – significant ischemic mitral regurgitation  
PML – posterior mitral leaflet  
PPM – posterior papillary muscle  
IHD – ischemic heart disease  
IMR – ischemic mitral regurgitation  
LV – left ventricle  
LCA – left coronary artery  
LA – left atrium  
MI – myocardial infarction  
MV – mitral valve  
MR – mitral regurgitation  
UAP – unstable angina pectoris  
AMI – acute myocardial infarction  
MVRepair – mitral valve repair  
AML – anterior mitral leaflet  
APM – anterior papillary muscle  
RV – regurgitant volume  
RF – regurgitant fraction  
CVD – cardiovascular diseases  
LVEDV – left ventricular end-diastolic volume  
LVEDD – left ventricular end-diastolic dimension  
TOE – transesophageal echocardiography  
LVESV – left ventricular end-systolic volume  
LVESD – left ventricular end-systolic dimension  
TTE – transthoracic echocardiography  
EF – ejection fraction  
FMR – functional MR  
MRI – magnetic resonance imaging

## **I. INTRODUCTION**

A „cardiac team“ is a term that was established as a part of the cardiologic and cardiac surgical practice during the last years. This forces cardiologists and cardiac surgeons to use the same terms and guidelines for the treatment of acquired heart diseases. To a great extent this concerns the ischemic heart disease and its complications and significant chronic ischemic mitral regurgitation in particular. As long as the choice of type and volume of the surgical procedure is often the operator's responsibility, it is mandatory that contemporary methods for diagnosis and evaluation of the mechanisms of CIMR are available to the surgeon. He needs clearly defined, easily reproducible and informative echocardiographic criteria for grading the CIMR, which could form the basis of algorithms for its surgical treatment. Despite the interest of cardiac surgeons and cardiologists in the problem of IMR – in which cases and how should it be corrected simultaneously with the revascularization and when should it be left uncorrected, there is no uniform statement regarding both diagnostic criteria and the IMR grade to be corrected.

In virtue of these facts the current thesis draws the attention onto the criteria for evaluation of the preoperative state of patients with IHD complicated by significant chronic IMR and their postoperative results. Based on the collected data it aims at designing algorithms for diagnosis and surgical volume selection in these patients as well as at evaluating the relationship between the volume of surgical intervention and the extent of left heart chambers reverse remodeling in different patient subgroups. This information could help the operating surgeon to make a decision regarding the type and volume of surgical procedure based on clearly defined criteria and to forecast the early and late postoperative results for different patient categories.

The importance of this problem is also determined by the fact that 85.5% of all patients referred to the Department of Cardiac Surgery in “St Marina” University Hospital for surgical treatment of IHD have any grade of IMR. In 15.6% (186) of them the IMR is hemodynamically significant (data consistent with previous publications) and in the rest 84.4% IMR is minimal. Specialized literature prove that any grade of IMR adversely affects the prognosis of IHD patients – 5-year survival free from major cardiovascular complications is 20 – 50% lower compared to survival of IHD patients without IMR. The presence of IMR in patients subjected to isolated revascularization increases the risk of MCVV by 20% compared to patients without IMR.

## **II. AIM**

The aim of the study is to select and analyze a set of diagnostic criteria for the surgical treatment of patients with ischemic heart disease complicated by significant chronic ischemic mitral regurgitation. These criteria could be used for comparison of patient subgroups and evaluation of the extent of postoperative left heart chambers reverse remodeling.

### **III. GOALS**

1. Set up of a database of the Bulgarian patient population with ischemic heart disease complicated by significant chronic ischemic mitral regurgitation based on data of patients operated in the Department of Cardiac surgery in "St Marina" University Hospital, Varna.
2. Categorization of patients in groups, unifying their clinical course and facilitating the evaluation of the influence of mitral annuloplasty, defining inclusion and exclusion criteria for studied groups and defining typical clinical pictures.
3. Statistical analysis of the preoperative medical state of patients with ischemic heart disease complicated by significant chronic ischemic mitral regurgitation, who are included in the study of influence of the mitral annuloplasty.
4. Comparison of the diagnostic and prognostic performance of the parameter "EF" and its modification introduced in this study – "modified EF".
5. Evaluation of the influence of the mitral repair on the reverse remodeling of the left ventricle and left atrium in different patient groups by means of quantitative statistical analysis.
6. Designing a set of parameters to forecast the success of the surgery during the early postoperative period and aiming at optimization of treatment and prognosis of late results.

## IV. MATERIAL AND METHODS

### IV.1. Patient selection

The study is conducted on patients of the Department of Cardiac Surgery in “St Marina” University Hospital, Varna, who were subjected to surgical treatment of ischemic heart disease during the period from January 2007 till June 2011. These are a total of 1398 patients with IHD and 1196 of them had any grade of MR. The study of the current thesis is based on a group of 140 of these patients.

Study inclusion criteria:

1. Patients with IHD that was demonstrated by coronary angiography (interventional or computer-assisted) and having indications for surgical revascularization according to the guidelines of the European Association of Cardio-Thoracic Surgery;
2. Diagnosed LV ischemia in the zone of the postero-medial and/or antero-lateral papillary muscle (ECG-signs of postero-inferior and/or anterior and lateral myocardial infarction; from the angiography – lesions of epicardial arteries in a zone of LV dysfunction; segmental or diffuse hypokinesia or akinesia or dyskinesia signs at TTE);
3. At least 7 days after the onset of an acute myocardial infarction;
4. Echocardiographic evaluation of the morphology and function of the MV, demonstrating SIMR without any morphologic changes of the mitral apparatus;
5. Age between 18 and 80 years;
6. Subjectively judged life expectancy more than 3 years;
7. Signed informed consent regarding the surgical intervention.

Echocardiographic evaluation in criterion 4: it is assumed that the chronic MR has an ischemic genesis when there are no primary morphological changes of the mitral apparatus and the regurgitation develops as a consequence of dilatation of the mitral annulus, secondary to the LV remodeling, dislocation of one or both papillary muscles in lateral or dorsal direction, tethering of one or both mitral leaflets as well as any combination of these factors (types I and IIb of the Carpentier's functional classification of mitral regurgitation), in contrast to the cases combining degenerative MR and IHD. Regarding the same criterion the following grades of CIMR are assumed significant:

- mild to moderate IMR, or 1+ to 2+ grade;
- moderate IMR, including 2+ and 2+ to 3+ grade;
- moderate to severe IMR, or 3+ grade.

The term “significant IMR” puts an emphasis on the fact that according to previous publications any of these IMR grades affects the functional class, quality of life and survival of the patients. The severe IMR (3+ and 3+ to 4+) is excluded from the current study because of the uniform statement of both cardiologists and cardiac surgeons that it must be corrected at the time of revascularization. The term “IMR” in the current thesis refers only to “significant chronic IMR”.

Study exclusion criteria:

1. Patients with acute IMR as a result of a rupture of papillary muscle or chords;
2. Severe chronic IMR (4+) – a consensus exists regarding the surgical correction at the time of revascularization;

3. Mild chronic IMR (1+) – MV intervention is not recommended;
4. Patients with IHD and degenerative or other primary lesions of the mitral morphology presented with regurgitation;
5. Previous cardiac surgery;
6. Contraindications for cardiac surgery;
7. Life expectancy less than 3 years.

The data of patients included and excluded from the current study is shown in Fig. IV.1.a.:

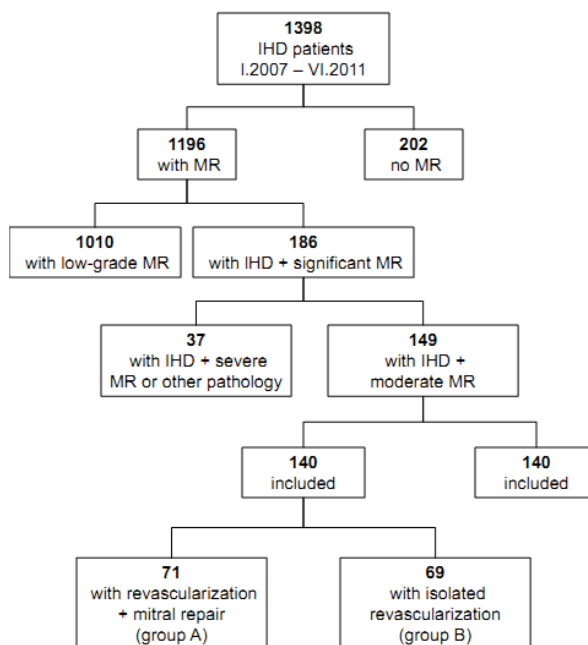


Figure IV.1.a. IHD patients subjected to cardiac surgery during the period January 2007 till June 2011 (Fig. 2.3.1.1.1.a from the thesis)

Out of all IHD patients subjected to surgical treatment in the Cardiac Surgery Department of the “St Marina” University Hospital, Varna, 1010 had mild (trivial,  $\leq 1+$  grade) MR and in other 186 patients significant chronic IMR was found. In 37 of them significant comorbidities dictated exclusion from the study. In 4 of the remaining 149 patients the MR was severe and in other 3 patients there was a rupture of the subvalvular apparatus, most often of one or more primary chords (it is difficult to be sure that the IHD is the primary cause of these ruptures). The last 7 patients were also excluded (due to severe IMR in 4 of them and structural changes of the mitral apparatus in 3 of them, which does not meet the criteria for chronic IMR). Calcinosi of the mitral annulus could possibly interfere with the MR



mechanism (changing the normal asymmetrical saddle-shaped mitral annulus) in another two patients, who were also excluded. So after meeting all criteria a total of 140 patients remained in the study. Seventy-one of them were subjected to combined surgery – revascularization and MVRRepair and these patients were included in group A. To the rest 69 patients isolated revascularization was performed and they formed group B of the study. This is illustrated in Fig. IV.1.a.

## **IV.2. Categorization of the patients in the study**

Three categorization problems in two classes were solved to categorize the patients. As a result the “Subdivision” variable (having four discretely – subgroups A1, A2, B1 and B2) can be defined and entered in the database for each patient.

### **IV.2.1. Selection of surgical treatment**

Patients with IHD, complicated by SIMR, could be subjected to either isolated revascularization or combination of revascularization and MVRRepair as shown on Fig. IV.1.a. The aim of the current paragraph is to formalize the process of treatment selection. It is the patient's decision through signing an informed consent form that finalizes the process. There are no patients in the current study that disagreed with the recommended treatment but had there been any, they would have been excluded from the study.

#### *IV.2.1.1. Categorization of information for the patients in groups A and B*

This problem can be informationally presented as a categorization of patients with IHD complicated by IMR into two groups – A (combined surgery – CABG + MVRRepair) and B (isolated revascularization – only CABG). Categorization of each patient is done in five steps as described below.

Algorithm 1 for choice of surgical treatment of patients with IHD complicated by significant IMR:

1. When the medical condition is severely impaired then the least aggressive procedure is selected in order to improve the cardiac performance by means of revascularization without the additional risks of combined surgery. In such cases the categorization in group B is undoubted. Therefore the following primary criteria for inclusion in group B and exclusion from group A can be defined:

- impaired medical condition with concomitant pathologies (respiratory diseases with abnormal external respiration parameters, peripheral arterial disease, cerebrovascular disease) especially in advanced age;
- subjectively judged life expectancy less than 4 years;
- severe left ventricular dysfunction with EF less than 25% and signs of heart failure;
- relative contraindications for cardiac surgery using cardiopulmonary bypass or indications for the less-invasive and less aggressive OPCAB procedure.

When any of these primary criteria is met then the patient is categorized in group B and subjected to isolated revascularization so the algorithm ends.

2. After not severely impaired medical condition is diagnosed then the significance of the mitral regurgitation is evaluated. If it is highly significant then categorization in group A is undoubted because the persisting of MR would worsen the prognosis. Therefore the secondary criteria for group A inclusion and group B exclusion can be defined:

- 3+ grade IMR;
- 2+ - 3+ grade IMR with RV more than 30 ml;
- 2+ - 3+ grade with RV less than 30 ml but with vena contracta at least 7 mm.

When any of the secondary criteria is met then the patient is categorized in group A and subjected to combined surgery so the algorithm ends.

3. So far it is found that neither the medical condition of the patient is severely impaired, nor the mitral regurgitation is highly significant. If the mitral regurgitation is diagnosed as slightly significant then the categorization in group B is undoubted, because the mitral repair would unnecessarily increase the surgical risk without significant benefit on the postoperative state. Therefore the presence of 1+ to 2+ grade IMR can be assumed as a tertiary criterion for group B inclusion and group A exclusion.

When the tertiary criterion is met then the patient is categorized in group B and subjected to isolated revascularization so the algorithm ends.

4. So far it is found that both surgical alternatives are relevant for a patient who is not in a seriously impaired medical condition and his mitral regurgitation is moderately significant. The categorization is performed using a list of parameters checking if their constellation composes any of the typical clinical pictures of group A or group B, which are described below.

*Group A typical clinical picture includes:* 2+ to 3+ grade IMR, regurgitant volume between 20 and 30 ml, vena contracta between 4 and 7 mm, tenting area between 1.5 and 2.5 cm<sup>2</sup>, tenting height between 10 and 20 mm, coaptation line between 1 and 4 mm, presence of tethering, subjectively judged life expectancy more than 5 years.

*Group B typical clinical picture includes:* 2+ grade IMR, regurgitant volume between 10 and 20 ml, vena contracta between 3 and 4 mm, tenting area between 0.8 and 1.5 cm<sup>2</sup>, tenting height between 6 and 10 mm, coaptation line between 3 and 5 mm, absence of tethering.

If the preoperative clinical picture of the patient reproduces the typical clinical picture of any of the groups then the patient is categorized in the corresponding group and the algorithm ends.

5. So far it is found that the patient is not in a seriously impaired medical condition, has moderately significant mitral regurgitation and his clinical picture does not reproduce any of the typical clinical pictures of both A and B groups. In this case the two surgical alternatives are again relevant. The cardiac team expertly decides which of the typical clinical pictures the patient resembles more. When the echocardiographic criteria for evaluating the MR and left ventricular remodeling are ambivalent then the final decision could be based on "stress echocardiography" that demonstrates the dynamic changes of the MR. The general medical condition and eventually the concomitant diseases are also considered. If the "stress test" does not provoke worsening of MR and when the expected result from mitral repair is a higher surgical risk and insignificant benefit then isolated revascularization is preferred, possibly off-pump (i.e. inclusion in group B). If the IMR grade worsens at "stress test" and significant benefit is expected from mitral repair with acceptable, relatively low surgical risk then the patient is included in group A. In the same group are also categorized patients of active age in whom the best possible recovery of work efficiency and physical activities is sought. Depending on the expert decision of the cardiac team the patient is categorized in the corresponding group and the algorithm ends.

#### *IV.2.1.2. Categorization of information for the patients in group A*

According to Algorithm 1 the patients with combined surgery can be categorized into group A in three different ways, corresponding to points 2, 4 or 5. It is obvious that group A is highly inhomogeneous. For the purpose of this study these patients are informationally divided into two subgroups – A1 and A2. In subgroup A1 are patients in relatively preserved cardiac and general medical condition where the aim of surgery is maximal recovery of the heart (reverse remodeling of the left heart chambers) and return to normal activities is anticipated. In subgroup A2 remain patients in more seriously impaired cardiac and general condition, where the aim of the mitral repair is to reduce the signs of heart failure caused by IHD. The expectation for these patients is that the surgical intervention will stop or slow down the process of left heart chambers remodeling rather than induce a reversal of this remodeling. This problem could be informationally presented as a categorization into two subgroups – A1 (relatively preserved condition) and A2 (relatively impaired condition) of the patients in group A (patients with IHD complicated by significant IMR, subjected to CABG + MVRepair).

Categorization of each group A patient is made in four steps as described below.

Algorithm 2 for categorization of patients with IHD complicated by significant IMR, who were included in group A (subjected to CABG + MVRepair):

1. If a patient is categorized in group A according to Algorithm 1, point 2, then he is not in a severely impaired medical condition and has highly significant IMR. The categorization is made using a set of parameters and checking if their constellation represents the typical primary clinical picture of subgroup A1 or A2 as described below.

The typical primary clinical picture of subgroup A1 includes: stable angina, no preceding MI, EF > 45%, preserved general condition, absence of comorbidities that could worsen the prognosis, LVEDV\_Index 75 ml/m<sup>2</sup> B.S.A. or less, LVESV\_Index 35 ml/m<sup>2</sup> B.S.A. or less.

The typical primary picture of subgroup A2 includes: unstable angina, preceding MI, EF < 40%, presence of comorbidities that worsen the prognosis, LVEDV\_Index more than 80 ml/m<sup>2</sup> B.S.A., LVESV\_Index more than 40 ml/m<sup>2</sup> B.S.A., LA\_Volume\_Index more than 40 ml/m<sup>2</sup> B.S.A..

If the preoperative clinical picture of the patient reproduces any of the typical primary clinical pictures of A1 or A2 subgroups then the patient is categorized in the corresponding subgroup and the algorithm ends.

2. If a patient is categorized in group A according to Algorithm 1, point 2, then he is not in a severely impaired medical condition and has highly significant IMR. So far it is found that his clinical picture does not represent any of the typical clinical pictures of subgroups A1 or A2. In this case the cardiac team expertly decides which of the typical primary pictures of subgroup A1 or A2 the patient resembles more. This decision is based on the overall echocardiographic evaluation (demonstrating predominantly preserved or impaired function of the left chambers and the advancement of the ischemic remodeling) as well as on the general condition and comorbidities.

Depending on the expert decision of the cardiac team the patient is categorized in the corresponding subgroup and the algorithm ends.

3. If a patient is categorized in group A according to Algorithm 1, points 4 or 5, then his mitral regurgitation is not highly significant. The categorization is made using a set of parameters and checking if their constellation represents the typical secondary clinical picture of subgroup A1 or A2 as described below.

The typical secondary clinical picture of subgroup A1 includes: no MI in the past, EF > 40%, preserved general condition, absence of comorbidities that worsen the prognosis, LVEDV\_Index 80 ml/m<sup>2</sup> B.S.A. or less, LVESV\_Index 40 ml/m<sup>2</sup> B.S.A. or less, LA\_Volume\_Index 40 ml/m<sup>2</sup> B.S.A. or less.

The typical secondary picture of subgroup A2 includes: preceding MI, EF < 35%, impaired general condition, presence of comorbidities that worsen the prognosis, LVEDV\_Index more than 85 ml/m<sup>2</sup> B.S.A., LVESV\_Index more than 45 ml/m<sup>2</sup> B.S.A., LA\_Volume\_Index more than 45 ml/m<sup>2</sup> B.S.A.

If the preoperative clinical picture of the patient represents the typical secondary clinical picture of any of A1 or A2 subgroups then the patient is categorized in the corresponding subgroup and the algorithm ends.

4. If a patient is categorized in group A according to Algorithm 1, points 4 or 5, then his mitral regurgitation is not highly significant. So far it is found that his preoperative clinical picture does not represent any of the typical secondary pictures of subgroups A1 and A2. Then the cardiac team expertly decides which of the typical secondary pictures of subgroup A1 or A2 the patient resembles more. This decision is again based on the overall echocardiographic evaluation (demonstrating predominantly preserved or impaired function of the left chambers and the advancement of the ischemic remodeling) as well as on the general condition and comorbidities.

Depending on the expert decision the patient is categorized into the corresponding subgroup and the algorithm ends.

The logic of the Algorithm 2 is based on the following medical considerations:

- If the ischemic remodeling of the heart is in an early stage then categorization in subgroup A1 is undoubted;
- Similarly, if the ischemic remodeling of the heart is advanced then categorization in subgroup A2 is also undoubted;
- If a patient is categorized in group A according to Algorithm 1 point 2, he has IMR of higher grade, than it would have been, had the patient been categorized according to Algorithm 1, point 4 or 5. Therefore if the ischemic remodeling of the heart is moderate, then a patient, categorized in group A according to Algorithm 1, point 2 should be further categorized in subgroup A2, whereas one categorized in group A according to Algorithm 1, point 4 or 5 should be categorized in subgroup A1.

The number of patients representing the typical primary or secondary clinical pictures of subgroup A1 is 24. The number of patients representing the typical primary or secondary clinical pictures of subgroup A2 is 35. The number of patients not representing any of the typical primary or secondary clinical pictures of both subgroups A1 and A2 is 12. A total of 6 out of these 12 are categorized in subgroup A1 and the other 6 – in subgroup A2. So finally there are 30 patients in subgroup A1 and 41 patients in subgroup A2.

#### *IV.2.1.3. Categorization of information for the patients in group B*

According to Algorithm 1 the patients subjected to isolated revascularization (CABG) can be categorized in group B in four different ways, according to points

1, 3, 4 or 5 of the algorithm. It is obvious that group B is quite inhomogeneous. For the purpose of this study these patients are informationally divided into two subgroups – B1 and B2.

In subgroup B1 are patients in a relatively preserved cardiac and general condition, when the expectation is that isolated revascularization (avoiding the risks of combined surgery) would result in significant benefit in terms of cardiac performance (eventually left heart chambers reverse remodeling over time) that would allow the patient to return to his normal activities. In subgroup B are patients in a relatively impaired cardiac and general condition, subjectively judged life expectancy less than 4 years, where the aim is treatment of the ischemic heart disease and heart failure as a result from IHD complicated by SIMR by means of the least aggressive procedure. Some of these patients were operated without extracorporeal circulation (OPCAB) to reduce the surgical risk. The aim of surgery for some patients was coping with the unstable angina. This problem can be informationally presented as a categorization into two subgroups – B1 (relatively preserved condition) or B2 (relatively impaired condition) of patients from group B (patients with IHD complicated by significant chronic IMR, subjected to isolated CABG procedure).

Categorization of each patient is performed in five steps as described below.

Algorithm 3 for categorization of patients with IHD complicated by significant chronic IMR, subjected to CABG:

1. If a patient is categorized in group B according to Algorithm 1, point 1, then his medical condition is severely impaired. Then this patient is categorized in subgroup B2 and the algorithm ends.

2. If a patient is categorized in group B according to Algorithm 1, point 4 or 5 then his medical condition is not severely impaired and his IMR is not slightly significant. The categorization is made using a set of parameters and checking if their constellation composes the typical primary clinical picture of subgroup B1 or B2 as described below.

- The typical primary picture of B1 subgroup includes: stable angina, no MI in the past, EF > 45%, preserved general condition, absence of comorbidities that worsen the prognosis, no restrictions for using cardiopulmonary bypass, LVEDV\_Index 75 ml/m<sup>2</sup> B.S.A. or less, LVESV\_Index 35 ml/m<sup>2</sup> B.S.A. or less, LA\_Volume\_Index 35 ml/m<sup>2</sup> B.S.A. or less.

- The typical primary picture of B2 subgroup includes: unstable angina, preceding MI, EF < 40%, impaired general condition, presence of comorbidities that worsen the prognosis, LVEDV\_Index > 80 ml/m<sup>2</sup> B.S.A., LVESV\_Index > 40 ml/m<sup>2</sup> B.S.A., LA\_Volume\_Index > 40 ml/m<sup>2</sup> B.S.A., occasionally with restrictions for using cardiopulmonary bypass.

If the patient's clinical picture represents any of the typical primary clinical pictures of subgroups B1 or B2 then this patient is categorized in the corresponding subgroup and the algorithm ends.

3. If a patient is categorized in group B according to Algorithm 1, point 4 or 5 then his medical condition is not severely impaired and his IMR is not slightly significant. So far it is found that his clinical picture does not represent any of the typical primary clinical pictures of B1 or B2 subgroups. In this case the cardiac team expertly decides which of the typical primary pictures the patient resembles more. This decision is based on the overall echocardiographic evaluation (demonstrating predominantly preserved or impaired function of the left chambers

and the advancement of the ischemic remodeling) as well as on the general condition and comorbidities.

Depending on the expert decision of the cardiac team the patient is categorized in the corresponding subgroup and the algorithm ends.

4. If a patient is categorized in subgroup B according to Algorithm 1, point 3, then his medical condition is not seriously impaired and his MR is slightly significant. The categorization is made using a set of parameters and checking if their constellation represents any of the typical secondary clinical pictures of B1 or B2 subgroups as described below.

The typical secondary picture of B1 subgroup includes: no MI in the past, EF > 40%, preserved general condition, absence of comorbidities that worsen the prognosis, no restrictions for using cardiopulmonary bypass, LVEDV\_Index 80 ml/m<sup>2</sup> B.S.A. or less, LVESV\_Index 40 ml/m<sup>2</sup> B.S.A. or less, LA\_Volume\_Index 40 ml/m<sup>2</sup> B.S.A. or less.

The typical secondary picture of B2 subgroup includes: preceding MI, EF < 35%, impaired general condition, presence of comorbidities that worsen the prognosis, LVEDV\_Index > 85 ml/m<sup>2</sup> B.S.A., LVESV\_Index > 45 ml/m<sup>2</sup> B.S.A., LA\_Volume\_Index > 45 ml/m<sup>2</sup> B.S.A., occasionally with restrictions for using cardiopulmonary bypass.

If the patient's clinical picture represents any of the typical secondary clinical pictures of B1 or B2 subgroups then this patient is categorized in the corresponding subgroup and the algorithm ends.

5. If a patient is categorized in subgroup B according to Algorithm 1, point 3, then his medical condition is not seriously impaired and his MR is slightly significant. So far it is found that his clinical picture does not represent any of the typical secondary clinical pictures of B1 or B2 subgroups. Then the cardiac team expertly decides which of the typical secondary pictures the patient resembles more. This decision is again based on the overall echocardiographic evaluation (demonstrating predominantly preserved or impaired function of the left chambers and the advancement of the ischemic remodeling) as well as on the general condition and comorbidities.

Depending on the expert decision of the cardiac team the patient is categorized in the corresponding group and the algorithm ends.

The logic of Algorithm 3 is based on the following six medical considerations:

- If a patient is categorized in subgroup B according to Algorithm1, point 1, then his medical condition is severely impaired and categorization in subgroup B2 is undoubted;
- If the ischemic remodeling is at an early stage then categorization in subgroup B1 is undoubted for a patient who has been categorized in group B according to Algorithm 1, points 3, 4 or 5;
- Similarly, if the ischemic remodeling is advanced then categorization in subgroup B2 is also undoubted for a patient, who has been categorized in group B according to Algorithm 1, points 3, 4 or 5;
- If a patient is categorized in group B according to Algorithm 1, point 4 or 5, then he has IMR of higher grade, than it would have been, had the patient been categorized according to Algorithm 1, point 3. Therefore if the ischemic remodeling of the heart is moderate, then a patient, categorized in group B according to Algorithm 1, point 4 or 5 should be further categorized in subgroup

B2, whereas one categorized in group B according to Algorithm 1, point 3 should be categorized in subgroup B1;

- The MR of a patient categorized in group B according to Algorithm 1, point 4 or 5 is significantly lower compared to the MR of a patient categorized in group A according to Algorithm 1, point 2. In the second case lowering the MR is one of the targets of surgical treatment, whereas in the first case the MR would be a complication regarding the isolated revascularization. For these reasons the typical primary clinical pictures of subgroups B1 and B2 are similar to the typical primary pictures of subgroups A1 and A2.

- The MR of a patient categorized in group B according to Algorithm 1, point 3, is significantly lower compared to the MR of a patient categorized in group A according to Algorithm 1, point 4 or 5. In the second case lowering the MR is one of the targets of surgical treatment, whereas in the first case the MR would be a complication regarding the isolated revascularization. For these reasons the typical secondary pictures of subgroups B1 and B2 are similar to the typical secondary pictures of subgroups A1 and A2.

The number of patients representing the typical primary or secondary picture of B1 subgroup is 32. The number of patients representing the typical primary or secondary picture of B2 subgroup is 28. The number of patients not representing any of the typical primary or secondary clinical pictures of both B1 and B2 subgroups is 9. A total of 4 out of these 9 are categorized in B1 subgroup and the other 5 – in B2 subgroup. So finally there are 36 patients in subgroup B1 and 33 patients in subgroup B2.

#### **IV.2.2. Surgical treatment of the patients included in the study**

The type and volume of the surgical procedure are discussed by the cardiac team but the final decision is made by the operating surgeon.

The standard surgical approach is longitudinal median sternotomy. Cardiopulmonary bypass was instituted through aortic and bicaval cannulation for patients with combined procedure or through right atrial cannulation using a single two-stage venous cannula for on-pump isolated revascularization. The patient was cooled down to 34°C or at rare occasions 32°C, the aorta was cross-clamped and cardioplegic arrest was achieved using cold crystalloid cardioplegic solution infused into the aortic root (with the exception of 12 patients from group B who were operated using the OPCAB technique for isolated revascularization). After performing the distal anastomoses, additional cardioplegic solution was infused through the venous grafts. In patients with MVRepair the approach to the mitral valve was below the interatrial groove (in 75% of all cases). In cases when indications for tricuspid repair also existed the preferred surgical approach was oblique right atriotomy and incision of the interatrial septum (transseptal approach in the remaining 25% - predominantly through the fossa ovalis and advancing towards the right superior pulmonary vein when necessary. This approach was also used in cases of small left atrium (< 45 mm from standard view) or in cases of hypertrophic and dilated left ventricle when the mitral procedure could be difficult using the left atrial approach. The MV is inspected using the technique of Alain Carpentier.

Suture annuloplasty a modo Paneth was used to correct the MR in 9 patients during the period January 2007 – April 2008 (12.7% of the patients included in the study). After this period this technique is abandoned because it did not meet the

conception for restoration of the asymmetrical 3-dimensional form of the mitral annulus making the long-term outcome unclear.

The commonly used surgical technique for SIMR correction included implantation of an annuloplasty ring (in 87.3%). Rigid rings (Carpentier-Edwards rigid Classic annuloplasty ring) were used in 5.6%, semirigid rings (Physio Edwards Lifesciences or Physio II) – in 54.9%, asymmetrical semirigid rings (Carpentier-McCarthy-Adams IMR Etlogix Annuloplasty Ring) – in 11.3%, flexible rings (Sovering Mitral ring, Sorin) – in 4.2% and semirings (band – Medtronic Colvin-Galloway Future Band) - in 11.3%. The sizing of the implant included echocardiographic evaluation prior the procedure as well as direct measurement of the AML during the intraoperative MV inspection and was followed by downsizing by one or two sizes. The complex mechanism of IMR sometimes makes the simple restrictive annuloplasty for IMR correction inadequate. In such cases some additional surgical maneuvers were necessary – artificial chords (GoreTex 4/0 – in two patients, 2.8%), commisuroplasty (of the postero-medial commissure in 9.9% of all cases of mitral repair), Alfieri edge-to-edge stitch in 14.1% or combinations of these. The last two techniques are considered final options for valve sparing and correction of the regurgitation without valve replacement. During the late period of the study these techniques were rarely applied. Combination of the additional procedures was necessary in only two patients (2.8%) of the combined CABG + MVRepair procedures. Neither fixed-size 6.5 cm or 4 cm annuloplasty bands fixed to the posterior mitral annulus nor „sandwich plasty“ or papillary muscle sling for approximation of the dislocated papillary muscles was used. None of the novel interventions on the LV myocardium or other papillary muscle approximation techniques were performed. Solitary cases of augmentation patch plasty of a mitral leaflet using autologous pericardium when the tethering was significant were excluded from the study. These techniques need further investigation.

In all MVRepair patients the left atrial appendage was excluded from circulation using purse-string or continuous suture after implantation of the annuloplasty ring. In cases of inadequate closure at control intraoperative TOE then the appendage was additionally sutured or ligated from the outside of the heart. The reason for this aggressive approach to the left atrial appendage is the high rate of perioperative arrhythmic episodes in these patients. Dilated LA is also a well-known risk factor for developing atrial fibrillation in the late postoperative period.

Proximal anastomoses were performed using partial aortic clamping after completion of mitral repair and removal of the aortic cross-clamp. Mean cross-clamp time was  $82 \pm 17$  min for group A (combined procedure) and was significantly longer ( $p_{\text{value}} < 0.05$ ) compared to the mean time in group B (isolated revascularization) which was  $53 \pm 20$  min.

Both durations of intensive care unit stay and hospital stay are presented when discussing the influence of the mitral repair (paragraph 2.4.3.). Early (30-day) mortality was 2.8% in group A (both lethal cases were from A2 subgroup) versus 0% in group B.



### IV.3. Statistical analysis

The statistical procedures and the necessary mathematical algorithms used in the thesis were created in the thesis of master Neli K. Mihaylova under the supervision of Assoc. Prof. Natalia D. Nikolova, PhD.

#### IV.3.1. Samples selection

Samples for three clusters of tests can be selected based on the database information.

##### *IV.3.1.1. First cluster tests samples selection*

Both samples are one-dimensional and contain values of a selected continuous variable. The patients in the first sample differ from these in the second sample by exactly one factor. The influence of this factor upon the selected continuous variable can be evaluated through comparison of the samples.

##### *IV.3.1.2. Second cluster tests samples selection*

Both samples are one-dimensional and contain values of a selected discrete variable. The patients in the first sample differ from these in the second sample by exactly one factor. The influence of this factor upon the selected discrete variable can be evaluated through comparison of the samples.

##### *IV.3.1.3. Third cluster tests samples selection*

This is a two-dimensional sample that contains the values of a given generalized continuous three-dimensional parameter in two time points. The second time point precedes the first, and the allowed variations for the pair "first time point – second time point" are three in total: either "early postoperative – preoperative", or "late postoperative – preoperative" or "late postoperative – early postoperative". The influence of the surgical procedure upon the selected generalized continuous three-dimensional parameter can be evaluated through assessment of the change in the two time points.

#### IV.3.2. Description of the used statistical tests

*First cluster tests* – first cluster tests are seventeen and are divided into five groups: one group for continuous distributions and one group for each of the following – mean values, medians, dispersions and interquartile ranges.

- *First group tests of First cluster* aims to find differences in the continuous distributions of the two general samples. This group consists of three statistical tests – Bootstrap Kuiper test, analytical Kuiper test and analytical Mann-Whitney-Wilcoxon test. The latter is performed using the "ranksum" function of MATLAB.

- *Second group tests of First cluster* aims to find differences in the mean values of the two general samples. This group consists of four statistical tests – two-way and one-way Bootstrap test of means, two-way and one-way analytical Welch t-test. The latter two are performed using the "ttest2" function of MATLAB.

- *Third group tests of First cluster* aims to find differences in the medians of the two general samples. This group consists of two tests – two-way and one-way Bootstrap test of medians (Efron and Tibshirani 1993; Nikolova et al. 2013b).

- *Fourth group test of First cluster* aims to find differences in the dispersions of the two general samples. This group consists of four statistical tests – two-way

and one-way Bootstrap test of dispersions, two-way and one-way analytical F-test. The latter are performed using the “vartest2” function of MATLAB.

- *Fifth group tests of First cluster* aims to find differences in the interquartile ranges of the two general samples. This group consists of four statistical tests – two-way and one-way Bootstrap test of interquartile ranges, two-way and one-way analytical Ansari-Bradley test. The latter two tests are performed using the “ansaribradley” function of MATLAB.

*Second cluster tests* – This group consists of four statistical tests – two-way and one-way Bootstrap test of equality of proportions, two-way and one-way analytical hypergeometrical test of equality of proportions. In the latter two tests the  $p_{value}$  is estimated through integration of hypergeometrical distribution using the “higecdf” function of MATLAB.

*Third cluster tests* – these tests use a single two-dimensional sample of a continuous variable, measured in two time points, called moment 1 and moment 2. After extraction of moment 2 values from moment 1 values the result is a one-dimensional sample of the change. The third cluster tests are six and divided into two groups: one group for the mean and the other group for the median of the change.

- *First group tests of Third cluster* consists of four statistical tests – two-way and one-way Bootstrap test for nulity of the mean as well as two-way and one-way analytical Student t-test. The latter two tests are performed using the “ttest” function of MATLAB.

- *Second group tests of Third cluster* consists of two statistical tests – two-way and one-way Bootstrap test for nulity of the median.

## V. RESULTS AND DISCUSSION

The results of the current thesis can be presented as the solutions of two qualitative and four quantitative problems.

### V.1. First qualitative problem: Database set up

A database was designed and collected containing information regarding 140 patients of the Bulgarian population, suffering from IHD complicated by hemodynamically significant chronic IMR. Some of these patients had 1+ to 2+ grade or 2+ grade IMR and were subjected to isolated surgical revascularization, forming *group B*. The remaining had 2+ or higher grade IMR. They are the patients whose 1-year and 5-year survival without surgical treatment (based on medical publications) are up to twice lower compared to patients without any IMR. The surgical procedure combining revascularization and an adequate mitral repair relieves the volume overload of the left heart chambers, and this is a prerequisite for their reverse remodeling. These patients form *group A*. On the other hand the combined surgery – CABG + MVRRepair is related to higher perioperative risk. This requires a most exact notion regarding the effects of the treatment in this population of Bulgarian patients and selection of diagnostic and prognostic criteria

which to serve as a basis for construction of an algorithm for evidence-based decision making in each individual.

Values of 53 discrete and continuous variables were entered for each patient in the database.

The discrete variables are 16: 1) "subgroup of the patient" having four discretely: 0 – subgroup A1, 1 – subgroup A2, 2 – subgroup B1 and 3 – subgroup B2; 2) "gender" having two discretely: 0 – male and 1 – female; 3) "emergency" having 3 discretely: 0 – elective surgery, 1 – urgent surgery and 2 – emergent surgery; 4) "diabetes mellitus" having two discretely: 0 – no diabetes and 1 – diabetes; 5) "history of cerebrovascular disease" having 2 discretely: 0 – no evidence of cerebrovascular disease and 1 – history of a cerebrovascular incident disregarding any neurological symptoms; 6) "renal failure" having two discretely – 0 – no renal failure, 1 – renal failure; 7) "AP" having two discretely: 0 – stabile AP and 1 – unstable angina; 8) "preoperative arrhythmia" having 3 discretely: 0 – no history of arrhythmia, 1 – history of episodes of arrhythmia, atrial fibrillation or flutter, 2 – permanent arrhythmia at hospitalization; 9) "NYHA functional class" having 6 discretely: 0 – no heart failure, 1 – class I heart failure, 2 – class II heart failure, 3 – class III heart failure, 4 – class IV heart failure, 5 – acute heart failure; 10) "history of MI" – having 5 discretely: 0 – no MI, 1 – chronic MI, 2 – subacute MI, 3 – non-Q wave AMI, 4 – Q-wave AMI; 11) "previous percutaneous intervention" having 2 discretely: 0 – no previous PCI, 1 – previous PCI; 12) "left main stenosis" having two discretely: 0 – no left main stenosis, 1 – left main stenosis; 13) "preoperative MV tethering" having 3 discretely: 0 – no MV tethering, 1 – asymmetrical tethering, 2 – symmetrical MV tethering; 14) "real preoperative MR grade" having 8 discretely: 0 – 0 grade MR, 1 – 0 – 1+ grade MR, 2 – 1+ grade MR, 3 – 1+ – 2+ grade MR, 4 – 2+ grade MR, 5 – 2+ – 3+ grade MR, 6 – 3+ grade MR, 7 – >3+ grade MR; 15) "early postoperative real grade of MR" having 8 discretely: 0 – 0-grade MR, 1 – 0 – 1+ grade MR, 2 – 1+ grade MR, 3 – 1+ – 2+ grade MR, 4 – 2+ grade MR, 5 – 2+ – 3+ grade MR, 6 – 3+ grade MR, 7 – >3+ grade MR; 16) "late postoperative real grade of MR" having 8 discretely: 0 – 0-grade MR, 1 – 0 – 1+ grade MR, 2 – 1+ grade MR, 3 – 1+ – 2+ grade MR, 4 – 2+ grade MR, 5 – 2+ – 3+ grade MR, 6 – 3+ grade MR, 7 – >3+ grade MR.

The continuous variables are 37: 1) "age of the patient"; 2) „SYNTAX Score“; 3) "length of stay in the intensive care unit"; 4) "length of hospital stay"; 5) "preoperative LVEDV index"; 6) "early postoperative LVEDV index"; 7) "late postoperative LVEDV index"; 8) "preoperative LVESV index"; 9) "early postoperative LVESV index"; 10) "late postoperative LVESV index"; 11) "preoperative LA volume index"; 12) "early postoperative LA volume index"; 13) "late postoperative LA volume index"; 14) "preoperative regurgitant volume"; 15) "early postoperative regurgitant volume"; 16) "late postoperative regurgitant volume"; 17) "preoperative vena contracta"; 18) "early postoperative vena contracta"; 19) "late postoperative vena contracta"; 20) "preoperative coaptation line"; 21) "early postoperative coaptation line"; 22) "late postoperative coaptation line"; 23) "preoperative tenting area"; 24) "early postoperative tenting area"; 25) "late postoperative tenting area"; 26) "preoperative tenting height"; 27) "early postoperative tenting height"; 28) "late postoperative tenting height"; 29) "preoperative PISA radius"; 30) "early postoperative PISA radius"; 31) "late postoperative PISA radius"; 32) "preoperative EF"; 33) "early postoperative EF"; 34) "late postoperative EF"; 35) "preoperative modified EF"; 36) "early postoperative modified EF"; 37) "late postoperative modified EF".

When a certain parameter is measured prior the operation, early and late postoperatively then the three variables altogether form a generalized three-dimensional parameter. In this way 12 generalized three-dimensional parameters were formed in the database. One of them ("real MR grade") is a generalized discrete three-dimensional parameter and the rest 11 are generalized continuous three-dimensional parameters: 1) "LVEDV index"; 2) "LVESV index"; 3) "LA volume index"; 4) "regurgitant volume"; 5) "vena contracta"; 6) "coaptation line"; 7) "tenting area"; 8) "tenting height"; 9) "PISA radius"; 10) "EF"; 11) "modified EF".

## **V.2. Second qualitative problem: Categorization of patients into groups and subgroups**

The collection of values of the discrete variable "subgroup of the patient" required selection of the type of surgical treatment of each patient, i.e. categorization of the study patients into *group A* (revascularization and MVR repair) or *group B* (isolated revascularization). In addition the patients from both groups were categorized into subgroups of patients in relatively preserved general medical and cardiac condition (A1 and B1 respectively) or into subgroups of patients in relatively impaired general medical and cardiac condition (A2 and B2 respectively). The process of categorization of the patients into groups and subgroups was formalized through hierarchical algorithms including on the one hand inclusion and exclusion criteria and on the other hand typical clinical pictures. As a result all patients in the study were categorized into: *group A*, comprising 71 patients, and *group B*, comprising 69 patients. In addition *group A* was informationally divided into *subgroup A1* with 30 patients and *subgroup A2* with 41 patients. Similarly *group B* was informationally divided into *subgroup B1* with 36 patients and *subgroup B2* with 33 patients.

## **V.3. First quantitative problem: Comparison of the preoperative state of the subgroups**

Both A and B groups are highly inhomogeneous and direct comparison of either preoperative or postoperative state was therefore impossible. The dichotomy of each group, performed in the second qualitative problem, aims mainly at deriving homogeneous subgroups. The aim of the first quantitative problem is to compare the preoperative condition of A1 patients to the preoperative condition of B1 patients as well as the preoperative condition of A2 patients to the preoperative condition of B2 patients. For solving the first quantitative problem were used 738 statistical tests.

The general medical states of the patients in A1 and B1 subgroups as well as A2 and B2 subgroups are compared by 6 variables. Out of these variables only the "age of the patient" is a continuous parameter. The remaining five variables are discrete: 1) "gender"; 2) "emergency"; 3) "diabetes mellitus"; 4) "history of cerebrovascular disease"; 5) "renal failure".

The following conclusions have been drawn:

- comparison of the general medical state between subgroups A1 and B1 found that:

- patients in A1 subgroup have statistically insignificant higher risks compared to patients in B1 subgroup according to 3 discrete factors: “diabetes mellitus”, “history of cerebrovascular disease” and “emergency”;
- patients in A1 subgroup have equal risk compared to patients in B1 subgroup according to one discrete factor: “renal failure”;
- patients in A1 subgroup have statistically borderline lower risks compared to patients in B1 subgroup according to 2 factors: “gender” and “age of the patient”;
- The preoperative general medical state of both A1 and B1 subgroups is virtually the same;
- comparison of the general medical state between subgroups A2 and B2 found that:
  - patients in subgroup A2 have statistically insignificant higher risks compared to patients in B2 subgroup according to one discrete factor: “history of cerebrovascular disease”;
  - patients in subgroup A2 have equal risk compared to patients in subgroup B2 according to 3 discrete factors: “emergency”, “diabetes mellitus” and “renal failure”;
  - patients in A2 subgroup have statistically borderline lower risks compared to patients in B2 subgroup according to one discrete factor: “gender”;
  - patients in A2 subgroup have statistically borderline lower risks compared to patients in B2 subgroup according to one continuous parameter: “age of the patient”;
  - the general medical state of patients in subgroups A2 and B2 is virtually the same, although patients in B2 subgroup have slightly higher risks compared to patients in subgroup A2.

The cardiac state of the patients in A1 and B1 subgroups as well as A2 and B2 subgroups was compared by 18 variables. Out of them 8 are discrete variables: 1) “AP”; 2) “preoperative arrhythmia”; 3) “NYHA functional class”; 4) “history of MI”; 5) “previous percutaneous intervention”; 6) “left main stenosis”; 7) “preoperative MV tethering”; 8) “preoperative real MR grade”. The remaining 10 variables are continuous: 1) “SYNTAX Score”; 2) “preoperative LVEDV index”; 3) “preoperative LVESV index”; 4) “preoperative LA volume index”; 5) “preoperative regurgitant volume”; 6) “preoperative vena contracta”; 7) “preoperative coaptation line”; 8) “preoperative tenting area”; 9) “preoperative tenting height”; 10) “preoperative PISA radius”.

The following conclusions have been drawn:

- comparison of the cardiac state between subgroups A1 and B1 found that:
  - patients in A1 subgroup have medically significant and statistically proved higher risk compared to patients in B1 subgroup according to 8 factors: “preoperative MV tethering”, “preoperative real MR grade”, “preoperative LVESV index”, “preoperative regurgitant volume”, “preoperative vena contracta”, “preoperative tenting area”, “preoperative tenting height” and “preoperative PISA radius”;
  - patients in A1 subgroup have medically significant but statistically borderline higher risk compared to patients in B1 subgroup according to 2 continuous variables: “preoperative LVEDV index” and “preoperative LA volume index”;

- patients in A1 subgroup have medically significant but statistically unproved higher risk compared to patients in B1 subgroup according to 2 discrete variables: "preoperative arrhythmia" and "previous percutaneous intervention";
- patients in A1 subgroup have medically significant but statistically unproved lower risk compared to patients in B1 subgroup according to 3 discrete variables: "AP", "NYHA functional class" and "history of MI";
- patients in A1 subgroup have medically significant and statistically proved lower risk compared to patients in B1 subgroup according to 1 continuous variable: "SYNTAX Score";
- patients in A1 subgroup have significantly higher risk related to their cardiac state compared to patients in subgroup B1;
- comparison of the cardiac state between subgroups A2 and B2 found that:
  - patients in A2 subgroup have medically significant and statistically proved higher risk compared to patients in B2 subgroup according to 11 variables: "preoperative MV tethering", "preoperative LVEDV index", "preoperative LVESV index", "preoperative LA index", "preoperative real MR grade", "preoperative vena contracta", "preoperative regurgitant volume", "preoperative coaptation line", "preoperative tenting area", "preoperative tenting height" and "preoperative PISA radius";
  - patients in A2 subgroup have medically significant but statistically unproved higher risk compared to patients in B2 subgroup according to 1 discrete variable: "preoperative arrhythmia";
  - there is no medical difference between patients in A2 subgroup and patients in B2 subgroup according to 2 discrete variables: "history of MI" and "previous percutaneous intervention";
  - patients in A2 subgroup have medically significant but statistically unproved lower risk compared to patients in B2 subgroup according to 2 discrete variables: "AP" and "left main stenosis";
  - patients in A2 subgroup have medically significant and statistically borderline lower risk compared to patients in B2 subgroup according to 1 continuous variable: "SYNTAX Score";
  - patients in A2 subgroup have medically significant and statistically proved lower risk compared to patients in B2 subgroup according to 1 discrete variable: "NYHA functional class";
  - patients in A2 subgroup have significantly higher risk related to their cardiac state compared to patients in B2 subgroup.

The general conclusions regarding the general medical state and the cardiac state of the patients are:

- patients in A1 subgroup have statistically proven higher preoperative risk profile compared to patients in B1 subgroup;
- patients in A2 subgroup have statistically proven higher preoperative risk profile compared to patients in B2 subgroup.

#### V.4. Second quantitative problem: Comparison of the variables “EF” and “modified EF”

In the first quantitative task in the database set-up a new parameter was introduced regarding the medical state of patients with MR, which is called “modified EF” and is defined as the stroke volume minus the regurgitant volume as a percentage of the LVEDV.

$$\begin{aligned}\text{Calculated\_Real\_EF (\%)} &= (\text{SV}_{\text{LV}} - \text{RV}_{\text{MV}}) / \text{LVEDV} \times 100 = \\ &= (\text{LVEDV} - \text{LVESV} - \text{RV}_{\text{MV}}) / \text{LVEDV} \times 100 ,\end{aligned}$$

where  $\text{SV}_{\text{LV}}$  is the stroke volume of the LV, measured in ml,  $\text{RV}_{\text{MV}}$  is the regurgitant volume through the MV, measured in ml and LVEDV and LVESV are measured in ml.

The aim is a parameter to be created measuring the physiological function of the LV taking into account the fact that eliminating or lowering the RV dramatically improves the perfusion because of the increase of the effective amount of blood ejected from the LV into the aorta and the body with each LV contraction. The introduced parameter can be considered as a generalization of the widely used “EF”, because in the absence of MR (and hence no RV) these two continuous variables will be equal. On the contrary, in the presence of MR the “modified EF” would demonstrate the effectiveness of each heart stroke whereas the “EF” would reflect the contractility of the LV.

It is assumed that the patients benefit from a mitral repair. This assumption will be undoubtedly proved later. The aim of the second quantitative problem is to compare the generalized continuous three-dimensional parameters “EF” and “modified EF” by their sensitivity to the benefit from the mitral repair compared to the isolated revascularization. The sensitivity of each of the parameters is evaluated on one hand in patients from A1 and B1 subgroups and on the other hand in patients from A2 and B2 subgroups using two methods. The **first method** requires subsequent comparison of the preoperative values and of the late postoperative values of a parameter for a selected couple of subgroups. The joint analysis of both comparisons gives information about the criterion sensitivity towards the subgroups. The **second method** requires analysis of the late postoperative changes compared to the preoperative values separately for each subgroup. The joint analysis of the observed changes in the subgroups also gives information about the criterion sensitivity towards the volume of surgery. The first method gives more information but the information using the second method is less dependent on the individual characteristics of the patients.

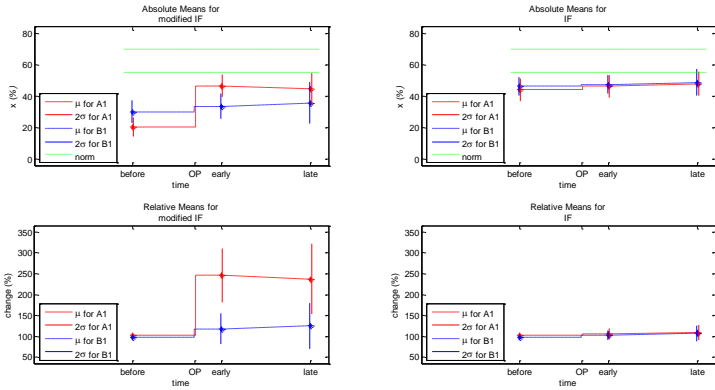


Figure V.4.a. Changes of means and standard deviations of modified EF (left) and EF (right) in A1 and B1 subgroups

At Fig. V.4.a the diagrams on the left show that the means of the modified EF changed dramatically immediately after the combined surgery in A1 subgroup (a 120% increase compared to baseline) and this early result persisted in the late postoperative period with negligible difference (trend to decrease) (the red line). This change was far less significant in group B1 and the trend was towards late postoperative increase compared to the preoperative values (blue line). The diagrams on the right show that the commonly used EF was insignificantly increased after surgery but this increase was not medically significant in both A1 (CABG + MVRepair) and B1 (isolated CABG) subgroup. These facts lead to the conclusion that the modified EF is the only parameter demonstrating the benefit of the surgical intervention and that the mitral repair in A1 subgroup has lead to a far greater change compared to B1 subgroup where no annuloplasty was performed.

Diagrams of medians and IQR of modified EF (left) and EF (right) are presented at Fig. V.4.b, and show similar changes and trends. This confirms that the modified EF much better demonstrates the beneficial effect of the mitral repair over the isolated revascularization. These benefits cannot be detected only analyzing the EF parameter.



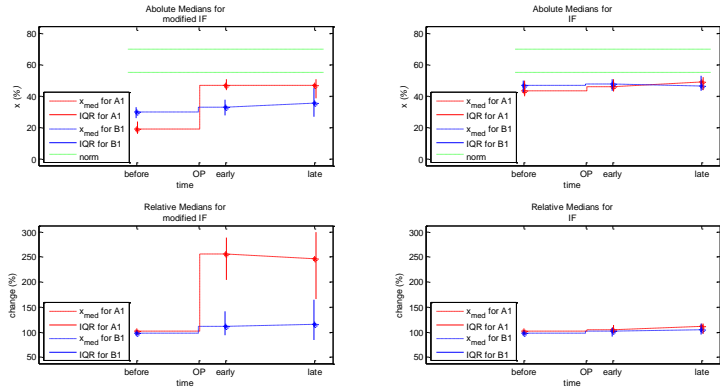


Figure V.4.b. Changes of medians and IQR of modified EF (left) and EF (right) in A1 and B1 subgroups.

For solving the second quantitative problem 184 statistical tests were performed. The following conclusions have been drawn after comparison between A1 and B1 subgroups (see Fig. V.4.a-V.4.b):

- Comparison between A1 and B1 subgroups using the first method demonstrates that the “EF” parameter has low sensitivity to the benefit from the annuloplasty, because only the preoperative median was borderline lower in A1 subgroup compared to B1 subgroup and after surgery it was borderline lower in B1 subgroup compared to A1 subgroup without sufficient medical significance in both cases;
- Comparison between A1 and B1 subgroups using the first method demonstrates that the “modified EF” has excellent sensitivity to the benefit from the annuloplasty because the characteristics of the position are statistically proved and medically significantly lower in A1 subgroup compared to B1 subgroup before the surgical procedure and change to statistically proved and medically significantly higher in A1 subgroup compared to B1 subgroup after surgery;
- Comparison between A1 and B1 subgroups using the second method demonstrates that the “EF” is far less sensitive regarding the benefit from the annuloplasty because the characteristics of position of the change after the valve repair in A1 subgroup are statistically significantly positive but with debatable medical importance and in B1 subgroup the mean of the change after isolated revascularization is statistically significant and similar to the mean of A1 subgroup, whereas the median of the change after isolated revascularization is insignificant;
- Comparison between A1 and B1 subgroups using the second method demonstrates that the “modified EF” is highly sensitive regarding the benefit from mitral repair, because the characteristics of position of the change after the annuloplasty in A1 subgroup are statistically strongly positive and huge, and the mean of the change in B1 subgroup after isolated revascularization is significantly positive, but six times smaller than the mean of the change in A1 subgroup (where the increase is about 120%), whereas the median of the change was not proved to be statistically nonnull;

- If the annuloplasty in A1 subgroup is successful compared to patients with isolated revascularization from B1 subgroup then the “modified EF” parameter is highly more sensitive to this fact than the “EF” parameter at least regarding A1 and B1 subgroups.

The benefit of the annuloplasty over the revascularization is better demonstrated by the “modified EF” parameter which rises immediately after surgery and shows a trend to additional increase at long-term follow up (Fig.V.4.c). The “EF” parameter is completely uninformative regarding this beneficial effect and even decreases immediately after surgery and can lead to misinterpretation of results and baseless disappointment of the combined procedure if no other parameters are taken into account.

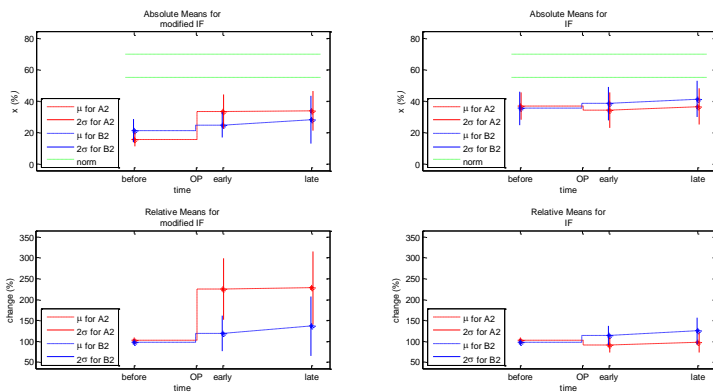


Figure V.4.c. Changes in means and standard deviations of the “modified EF” (left) and “EF” (right) in A2 and B2 subgroups

The “modified EF” parameter demonstrates the impact of annuloplasty much better than the “EF” parameter because its increase is medically significant in patients from A2 subgroup unlike patients from B2 subgroup where this increase is medically insignificant. This increase of medians and IQRs is noted immediately after surgery and persists with minor changes (decrease) in the late postoperative follow up (Fig.V.4.d). Unlike the “modified EF”, the widely used “EF” parameter exhibits insignificant change and even shows a “negative impact” of the annuloplasty in patients from A2 subgroup compared to B2 subgroup (the diagrams on the right side of Fig. V.4.d).

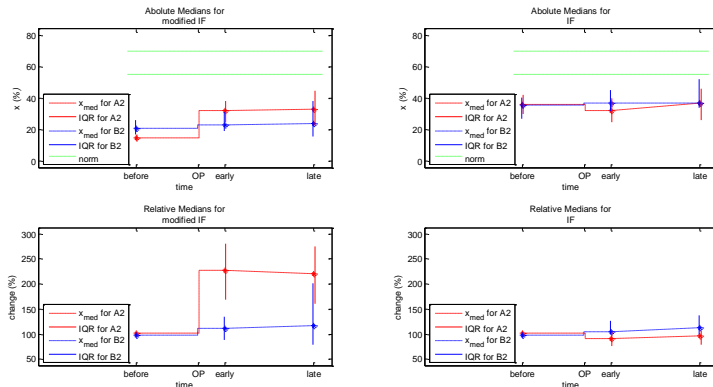


Figure V.4.d. Changes of medians and IQRs of “modified EF” (left) and “EF” (right) in A2 and B2 subgroups

The following conclusion has been drawn after comparison of A2 and B2 subgroups (Fig. V.4.c-V.4.d):

- Comparison of A2 and B2 subgroups using the first method showed that the “EF” parameter is anti-sensitive to the benefit of annuloplasty and demonstrates statistically insignificant negative impact because preoperative mean values were more favorable in A2 subgroup than in B2 subgroup, whereas the results were reciprocal after the surgery (Fig. V.4.c and Fig. V.4.d);
- Comparison of A2 and B2 subgroups using the first method showed that the “modified EF” is somewhat sensitive regarding the benefit of annuloplasty, because its preoperative mean was statistically significantly more unfavorable in A2 subgroup compared to B2 subgroup and the postoperative results were reciprocal, whereas the medians do not demonstrate significant changes neither before nor after surgery;
- Comparison of A2 and B2 subgroups using the second method showed that the “EF” is anti-sensitive to the benefit of annuloplasty demonstrating statistically significant negative impact, because the mean of the change after annuloplasty in A2 subgroup is negative whereas it is positive after isolated revascularization in B2 subgroup;
- Comparison of A2 and B2 subgroups using the second method showed that the “modified EF” is highly sensitive regarding the benefit from annuloplasty because the characteristics of position of the change after annuloplasty were huge (about 120% of preoperative values) and the characteristics of position of the change after isolated revascularization in B2 subgroup had controversial medical significance no matter they were significantly positive;
- If the annuloplasty is successful in A2 subgroup compared to patients with isolated revascularization from B2 subgroup then the “modified EF” parameter is highly more sensitive regarding this fact than the “EF” parameter at least for A2 and B2 subgroups. Besides in these subgroups the “EF” showed a negative impact of the annuloplasty, which is simply not true based on the entity of parameters in the third quantitative problem;

- The parameter “modified EF” can successfully replace the “EF” in the subsequent data analysis of the current study.

### **V.5. Third quantitative problem: Evaluation of the late postoperative effect of mitral annuloplasty in revascularized patients**

The aim of the third quantitative problem is to evaluate the effect of the mitral annuloplasty in patients who underwent surgical revascularization by comparison of the condition change of A1 and B1 subgroups as well as A2 and B2 subgroups.

The effect of mitral repair in patients subjected to surgical revascularization was evaluated using 13 variables. Two of them are continuous variables: “length of stay in the intensive care unit” and “length of hospital stay” and the remaining are generalized three-dimensional parameters. “MR grade” is a generalized discrete three-dimensional parameter and the other ten parameters are generalized continuous three-dimensional parameters: 1) “LVEDV index”; 2) “LVESV index”; 3) “LA volume index”; 4) “regurgitant volume”; 5) “vena contracta”; 6) “coaptation line”; 7) “tenting area”; 8) “tenting height”; 9) “PISA radius”; 10) “modified EF”. The two continuous parameters correlate with the cost of the treatment and for all generalized parameters the change between the preoperative and late postoperative values was analyzed.

The effect of annuloplasty was first analyzed by comparison of patients in A1 and B1 subgroups, and second, by comparison of patients in A2 and B2 subgroups. Two methods were used to analyze this effect for the generalized continuous three-dimensional parameters. The **first method** includes comparison of the preoperative values and then comparison of the late postoperative values of the parameter. The two parallel comparisons provide information about the effect of annuloplasty in patients subjected to revascularization. The **second method** includes separate analysis of the individual changes in a selected parameter in the late postoperative period compared to the preoperative value. The parallel comparison of the changes in the two groups also provides information about the effect of annuloplasty in patients subjected to revascularization; the information provided by the first method is greater in amount but the information by the second method is more independent on the patients' individual characteristics. The “MR grade” is a generalized discrete three-dimensional parameter so only the first method is used. Only values from the selected pair of subgroups were subsequently compared for both continuous parameters. They are informative only after the operation but can be analyzed together with equal preoperative values. This imaginary set-up allows formal applying of the second method of analysis of the effect of the annuloplasty for the two continuous parameters.

Solving the third quantitative problem 1124 statistical tests were used, 658 of them were new and the rest 466 were also used for the first and second quantitative problem. Based on these tests the following conclusions were drawn about A1 and B1 subgroups as described in Tables V.5.a – V.5.c:

- using the first method for comparison of revascularized patients from A1 and B1 subgroups were found:
  - 7 generalized three-dimensional parameters that demonstrated statistically proved and medically significant highly beneficial effect of the annuloplasty: “regurgitant volume”, “vena contracta”, “coaptation line”, “tenting height”, “PISA radius”, “modified EF” and “MR grade”;

- 2 generalized continuous three-dimensional parameters that demonstrated statistically proven and medically significant beneficial effect of the annuloplasty: "LVESV index" and "tenting area";
- 1 generalized continuous three-dimensional parameter that demonstrated both statistically and medically borderline beneficial effect of the annuloplasty: "LVEDV index";
- 1 generalized continuous three-dimensional parameter that did not demonstrate significant effect of the annuloplasty: "LA volume index";
- 2 continuous parameters that demonstrated statistically proved and medically significant slightly negative effect of the annuloplasty: "length of stay in the intensive care unit" and "length of hospital stay";
- using the second method for comparison of revascularized patients from A1 and B1 subgroups were found:
  - 4 generalized continuous three-dimensional parameters that demonstrated statistically proved and medically significant highly beneficial effect of the annuloplasty: "vena contracta", "regurgitant volume", "PISA radius" and "modified EF";
  - 3 generalized continuous three-dimensional parameters that demonstrated statistically proven and medically significant beneficial effect of the annuloplasty: "LVEDV index", "LVESV index" and "LA volume index";
  - 3 generalized continuous three-dimensional parameters that demonstrated statistically not proved and medically significant beneficial effect of the annuloplasty: "coaptation line", "tenting area" and "tenting height";
  - as a whole A1 subgroup patients were in a worse preoperative state compared to B1 subgroup patients whereas late postoperatively A1 subgroup patients were in a better state compared to B1 subgroup patients;
  - the hypothesis from the first quantitative problem was confirmed that patients from B1 subgroup can serve as a pseudo control group to patients from A1 subgroup;
  - the thesis was proved true that the effect of MVRepair is highly beneficial in patients subjected to surgical revascularization in relatively preserved general medical and cardiac state (subgroups A1 and B1);
  - the assumption in the second quantitative problem (regarding the beneficial effect of the annuloplasty) was proved true regarding A1 and B1 subgroups. The thesis in the second quantitative problem assuming that the "modified EF" is a far more reliable parameter about the surgical treatment of patients from A1 and B1 subgroups than the commonly used "EF" was therefore proved true.

Table V.5.a. Summary of the effect of the annuloplasty in A1 subgroup compared to B1 subgroup. Significantly nonnull, borderline nonnull and insignificantly nonnull characteristics of position are shown in red, blue and black color respectively. Beneficial effect, negative effect and absence of any effect are shown as +, - and 0 respectively. Highly significant, significant and slightly significant changes are demonstrated by 3, 2 or 1 sign respectively. (Table 2.4.3.2.a from the thesis)

Parameter	First method	Second method
LVEDV_Index	+	++
LVESV_Index	++	++
LA_Volume_Index	0	++
Vena_Contracta	+++	+++
RegVol	+++	+++
Coaptation_Height	+++	++
Tenting_Area	++	++
Tenting_Height	+++	++
PISAr	+++	+++
Calculated_Real_EF	+++	+++
Real_MR	+++	N.A.
ICU_LOS	-	N.A.
Hospital_LOS	-	N.A.

Table V.5.b. Calculations of the change in the analyzed parameters (late postoperative compared to preoperative values) in A1 subgroup. All characteristics of position are significantly nonnull and colored in red (Table 2.4.3.2.b of the thesis).

Parameter	Calculation	Unit	Mean of relative change	Mean of absolute change	STD of absolute change	Median of relative change	Median of absolute change	IQR of absolute change
LVEDV index		ml/m <sup>2</sup> B.S.A.	-11.2%	-6.74	11.2	-9.5%	-5.99	16.4
LVESV index		ml/m <sup>2</sup> B.S.A.	-16.8%	-5.68	8.04	-18.2%	-5.61	8.69
LA volume index		ml/m <sup>2</sup> B.S.A.	-11.4%	-6.17	14	-12.9%	-4	14.5
Vena contracta		mm	-86.1%	-4.59	1.35	-100.0%	-5	2
Regurgitant volume		ml	-86.7%	-22	6.23	-100.0%	-22	9
Coaptation line		mm	252.9%	4.55	1.94	166.7%	5	3
Tenting area		cm <sup>2</sup>	-52.1%	-1.02	0.541	-53.8%	-0.9	0.825
Tenting height		mm	-39.1%	-3.52	1.6	-41.7%	-4	3
PISA radius		cm	-79.6%	-0.548	0.253	-100.0%	-0.6	0.325
Modified EF		%	137.2%	24.2	12.6	145.8%	26	16.3

Table V.5.c. Calculations of the change in the analyzed parameters (late postoperative compared to preoperative values) in B1 subgroup. Significantly nonnull, borderline nonnull and insignificantly nonnull characteristics of the position are colored in red, blue and black respectively (Table 2.4.3.2.c of the thesis).

Calculation Parameter	Unit	Mean of relative change	Mean of absolute change	STD of absolute change	Median of relative change	Median of absolute change	IQR of absolute change
LVEDV index	ml/m <sup>2</sup> B.S.A.	-2.1%	-1.57	10.1	-3.1%	-1.12	12.8
LVESV index	ml/m <sup>2</sup> B.S.A.	-5.4%	-1.62	7.16	-4.1%	-1.5	8.88
LA volume index	ml/m <sup>2</sup> B.S.A.	-1.7%	-1.97	8.18	-2.7%	-1	9.5
Vena contracta	mm	-22.0%	-0.806	1.58	-25.0%	-1	2
Regurgitant volume	ml	-22.7%	-3.26	8.93	-25.0%	-4	12.2
Coaptation line	mm	18.0%	0.613	1.28	25.0%	1	1
Tenting area	cm <sup>2</sup>	-15.0%	-0.219	0.311	-20.0%	-0.3	0.4
Tenting height	Mm	-13.4%	-0.935	1.55	-16.7%	-1	2
PISA radius	Cm	-20.8%	-0.106	0.191	-14.3%	-0.1	0.2
Modified EF	%	25.0%	5.55	14.6	15.4%	5	21.2

Based on the results of the statistical tests described in Tables V.5.d – V.5.f, the following conclusions have been drawn regarding A2 and B2 subgroups:

- using the first method for comparison of revascularized patients from A2 and B2 subgroups were identified:
  - 7 generalized three-dimensional parameters that demonstrated statistically proved and medically significant highly beneficial effect of the annuloplasty: “vena contracta”, “regurgitant volume”, “coaptation line”, “tenting area”, “PISA radius”, “modified EF” and “real MR grade”;
  - 1 generalized continuous three-dimensional parameter that demonstrated statistically proved and medically significant beneficial effect of the annuloplasty: “tenting height”;
  - 1 generalized continuous three-dimensional parameter that demonstrated statistically proved and medically significant slightly beneficial effect of the annuloplasty: “LA volume index”;
  - 2 generalized continuous and 1 generalized discrete three-dimensional parameters that did not demonstrate any significant effect of the annuloplasty: “LVEDV index”, “LVESV index” and “length of hospital stay”;
  - 1 continuous parameter that demonstrated statistically proved and medically significant highly negative effect of annuloplasty: “length of stay in the intensive care unit”;
- using the second method for comparison of revascularized patients from A2 and B2 subgroups were identified:
  - 7 generalized continuous three-dimensional parameters that demonstrated statistically proved and medically significant highly beneficial effect of the annuloplasty: “vena contracta”, “regurgitant volume”, “tenting area”, “coaptation line”, “tenting height”, “PISA radius” and “modified EF”;

- 1 generalized continuous three-dimensional parameter that demonstrated statistically proved and medically significant beneficial effect of the annuloplasty: "LA volume index";
- 1 generalized continuous three-dimensional parameter that demonstrated statistically not proved but medically significant slightly negative effect of the annuloplasty: "LVEDV index";
- 1 generalized continuous three-dimensional parameter that demonstrated statistically proved and medically significant slightly negative effect of the annuloplasty: "LVESV index";
- as a whole A2 subgroup patients were in a worse preoperative state compared to B2 subgroup patients whereas late postoperatively A2 subgroup patients were in a better state compared to B2 subgroup patients;
- the hypothesis from the first quantitative problem was confirmed that patients from B2 subgroup can serve as a pseudo control group to patients from A2 subgroup;
- the thesis was proved true that the effect of MVRepair is highly beneficial in patients subjected to surgical revascularization in relatively impaired general medical and cardiac state (subgroups A2 and B2);
- the assumption in the second quantitative problem (regarding the beneficial effect of the annuloplasty) was proved true regarding A2 and B2 subgroups. The thesis in the second quantitative problem assuming that the "modified EF" is a far more reliable parameter regarding the surgical treatment of patients from A2 and B2 subgroups than the commonly used "EF" was therefore proved true.

Table V.5.d. Summary of the effect of the annuloplasty in A2 subgroup compared to B2 subgroup. Significantly nonnull, borderline nonnull and insignificantly nonnull characteristics of the position are shown in red, blue and black color respectively. Beneficial effect, negative effect and no effect are shown as +, - and 0 respectively. Highly significant, significant and slightly significant changes are demonstrated by 3 signs, 2 signs or 1 sign respectively. (Table 2.4.3.3.a from the thesis)

Parameter	First method	Second method
LVEDV_Index	0	-
LVESV_Index	0	-
LA_Volume_Index	+	++
Vena_Contracta	+++	+++
RegVol	+++	+++
Coaptation_Height	+++	+++
Tenting_Area	+++	+++
Tenting_Height	++	+++
PISAr	+++	+++
Calculated_Real_EF	+++	+++
Real_MR	+++	N.A.
ICU_LOS	--	N.A.
Hospital_LOS	0	N.A.



Table V.5.e. Calculations of the change in the analyzed parameters (late postoperative compared to preoperative values) in A2 subgroup. Significantly nonnull, borderline nonnull and insignificantly nonnull characteristics of the position are colored in red, blue and black respectively (Table 2.4.3.3.b of the thesis).

Calculation Parameter	Unit	Mean of relative change	Mean of absolute change	STD of absolute change	Median of relative change	Median of absolute change	IQR of absolute change
LVEDV index	ml/m <sup>2</sup> B.S.A.	-11.6%	-9.93	16.1	-7.7%	-6.19	19.6
LVESV index	ml/m <sup>2</sup> B.S.A.	-8.8%	-4.25	14.1	-5.5%	-3.7	19.1
LA volume index	ml/m <sup>2</sup> B.S.A.	-19.1%	-9.23	8.89	-20.0%	-10	9.25
Vena contracta	Mm	-84.6%	-5.23	1.23	-87.5%	-5	2
Regurgitant volume	ml	-83.4%	-26.4	10.5	-89.8%	-27	9
Coaptation line	Mm	295.2%	4.97	1.85	250.0%	5	2
Tenting area	cm <sup>2</sup>	-45.4%	-0.939	0.544	-43.5%	-0.9	0.475
Tenting height	Mm	-33.6%	-3.16	2.08	-33.3%	-3	2
PISA radius	Cm	-77.3%	-0.623	0.236	-77.8%	-0.7	0.4
Modified EF	%	127.9%	18.5	11.6	120.0%	19	19.5

Table V.5.f. Calculations of the change in the analyzed parameters (late postoperative compared to preoperative values) in B2 subgroup. Significantly nonnull, borderline nonnull and insignificantly nonnull characteristics of the position are colored in red, blue and black respectively (Table 2.4.3.3.c of the thesis).

Calculation Parameter	Unit	Mean of relative change	Mean of absolute change	STD of absolute change	Median of relative change	Median of absolute change	IQR of absolute change
LVEDV index	ml/m <sup>2</sup> B.S.A.	-9.5%	-7.44	11.9	-6.5%	-3.24	15.4
LVESV index	ml/m <sup>2</sup> B.S.A.	-16.2%	-7.8	11.2	-18.1%	-5.41	11.3
LA volume index	ml/m <sup>2</sup> B.S.A.	11.6%	3	6.77	12.5%	4	10.3
Vena contracta	mm	-22.1%	-0.84	1.65	0.0%	0	2
Regurgitant volume	ml	-20.0%	-2.6	8.14	-21.1%	-3	11.8
Coaptation line	mm	19.7%	0.64	1.35	25.0%	1	1.5
Tenting area	cm <sup>2</sup>	1.4%	0.004	0.44	0.0%	0	0.45
Tenting height	mm	2.9%	0.04	2.11	0.0%	0	2.5
PISA radius	cm	-16.2%	-0.088	0.209	0.0%	0	0.2
Modified EF	%	36.3%	6.88	13.7	17.6%	4	22.3

## V.6. Fourth quantitative problem: Evaluation of the early postoperative effect of annuloplasty in patients subjected to revascularization.

The aim of the fourth quantitative problem is to demonstrate the typical changes in the medical condition of the patients from each subgroup in their early postoperative period compared to the preoperative state. The results allow: a) improved effectiveness in the distribution of medical resources and adequate attention to patients who present with from the typical early postoperative clinical

picture; b) realistic prognosis about the expected duration of the hospital treatment, the time and extent of recovery and eventually returning to the professional activities; c) the relatives can evaluate the success of the operation several days after surgery. The expected clinical picture in the early postoperative period differs from the late postoperative because in the first several postoperative days no reverse remodeling of the left heart chambers can be anticipated. This process is due to the reduced volume overload and requires some time.

For a realistic description of the change of condition in the early postoperative period 10 generalized continuous three-dimensional parameters were used: 1) "LVEDV index"; 2) "LVESV index"; 3) "LA volume index"; 4) "regurgitant volume"; 5) "vena contracta"; 6) "coaptation line"; 7) "tenting area"; 8) "tenting height"; 9) "PISA radius"; 10) "modified EF".

Changes in each of the generalized continuous three-dimensional parameters in the early postoperative period compared to the preoperative values were analyzed separately in each of the four subgroups. For solving the fourth quantitative problem 240 statistical tests were performed. Based on the results, tables containing the changes of the characteristics of the position were created. The following conclusions were drawn:

- The following change was found in the early postoperative clinical picture of A1 subgroup patients subjected to combined surgery compared to the preoperative:

- 4 generalized continuous three-dimensional parameters showed statistically significant improvement and their values reached close to the theoretical maximum: "vena contracta", "regurgitant volume", "coaptation line" and "PISA radius";

- 4 generalized continuous three-dimensional parameters showed statistically significant improvement and their values reached within the normal range: "LVEDV index", "LVESV index", "tenting area" and "tenting height";

- 2 generalized continuous three-dimensional parameters showed statistically significant improvement but their values remained out of the normal range: "LA volume index" and "modified EF".

- The following change was found in the early postoperative clinical picture of B1 subgroup patients subjected to isolated revascularization compared to the preoperative:

- 3 generalized continuous three-dimensional parameters showed statistically significant improvement and their values reached within the normal range: "LVEDV index", "LA volume index" and "coaptation line";

- 1 generalized continuous three-dimensional parameter showed statistically insignificant improvement but its values reached within the normal range: "LVESV index";

- 6 generalized continuous three-dimensional parameters showed statistically significant improvement but their values remained out of the normal range: "vena contracta", "regurgitant volume", "tenting area", "tenting height", "PISA radius" and "modified EF".

- The following change was found in the early postoperative clinical picture of A2 subgroup patients subjected to combined surgery compared to the preoperative:

- 4 generalized continuous three-dimensional parameters showed statistically significant improvement and their values reached close to the

theoretical maximum: “vena contracta”, regurgitant volume”, “coaptation line” and “PISA radius”;

- 1 generalized continuous three-dimensional parameter showed statistically significant improvement and its values reached within the normal range: “tenting height”;

- 5 generalized continuous three-dimensional parameters showed statistically significant improvement but their values remained out of the normal range: “LVEDV index”, “LVESV index”, “LA volume index”, “tenting area” and “modified EF”.

- The following change was found in the early postoperative clinical picture of B2 subgroup patients subjected to isolated revascularization compared to the preoperative:

- 2 generalized continuous three-dimensional parameters showed statistically insignificant improvement but their values reached within the normal range: “LVESV index” and “coaptation line”;

- 7 generalized continuous three-dimensional parameters showed statistically significant improvement but their values remained out of the normal range: “LVEDV index”, “vena contracta”, “regurgitant volume”, “tenting area”, “tenting height”, “PISA radius” and “modified EF”;

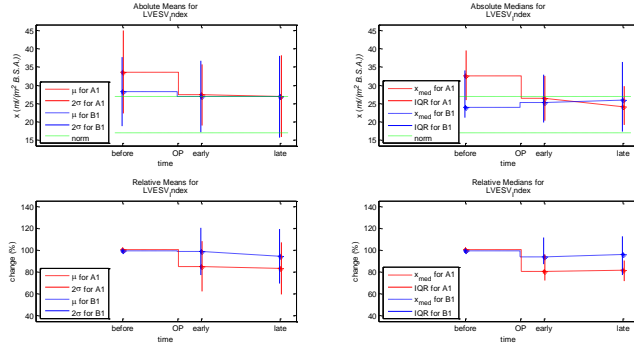
- 1 generalized continuous three-dimensional parameter showed statistically insignificant improvement and its values remained out the normal range: “LA volume index”.

## **V.7. Left heart chambers reverse remodeling**

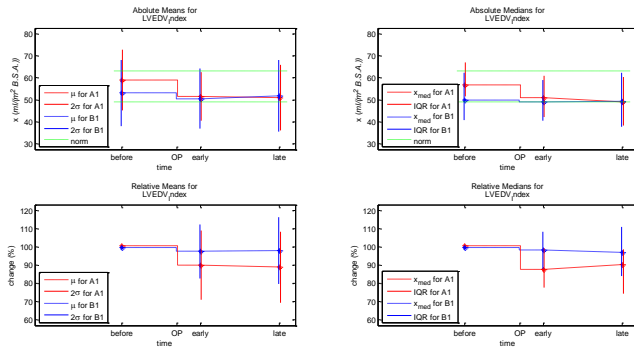
Left heart chambers reverse remodeling is a process expressed by decrease of the sizes and volumes of the left heart chambers after surgical revascularization. According to Gelsomino et al. reverse remodeling is present when the LVESV index decreases with 15% or more compared to baseline. The reverse remodeling can be assumed one of the main targets of the surgical treatment of patients with significant CIMR.

Diagrams in Fig. V.7.a demonstrate that LV reverse remodeling is present only in A1 subgroup where the decrease of means and medians of the LVESV index is by 16.8% and 18.2% respectively (Table V.5.b). This decrease is observed immediately after surgery and persists and even progresses further although slightly in the late follow up of A1 subgroup. The reverse remodeling is related to the decrease of volume overload after mitral repair and revascularization. Reverse remodeling is not present in B1 subgroup which means that the decrease of the LVESV index is less than 15% compared to baseline (Table V.5.b).

Despite the statistically significant decrease of the characteristics of position of the LVESV index its decrease does not reach 15% (Table V.5.b and Table V.5.c) and therefore does not meet the “responders” criteria in both A1 and B1 subgroups (see Fig. V.7.b).

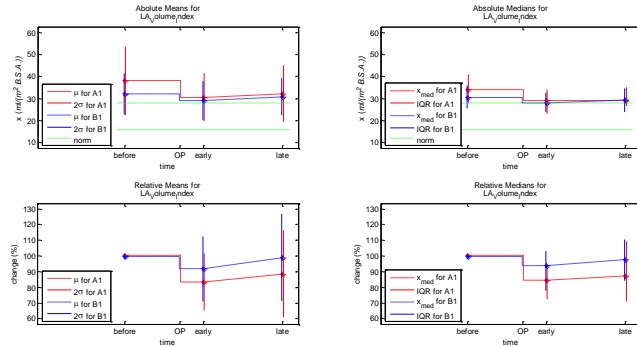


V.7.a. Changes in the characteristics of position of the LVESV index in A1 and B1 subgroups



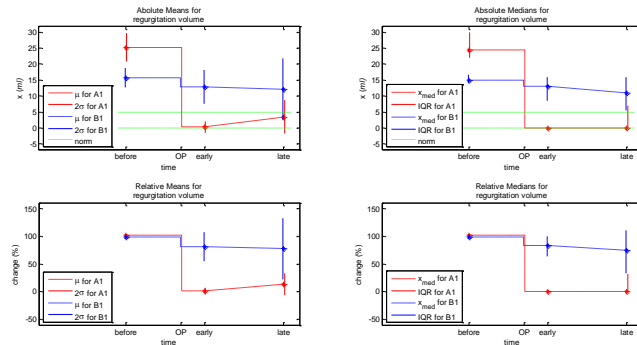
V.7.b. Changes in the characteristics of position of the LVEDV index in A1 and B1 subgroups

No LA reverse remodeling was found using the LA volume because the LA volume index reduction did not reach 15% (Tables V.5.b and V.5.c). However the reduction in A1 subgroup is more than 10% and is expected to be beneficial to the postoperative status in terms of likelihood of preserving the sinus rhythm. This expectation is discouraged by the fact that after the early reduction of LA volume index, which was greater in A1 subgroup and insignificant in B1 subgroup, there was an increase again in the later postoperative period (Fig. V.7.c).



### V.7.c. Changes in the characteristics of position of the LA volume index in A1 and B1 subgroups

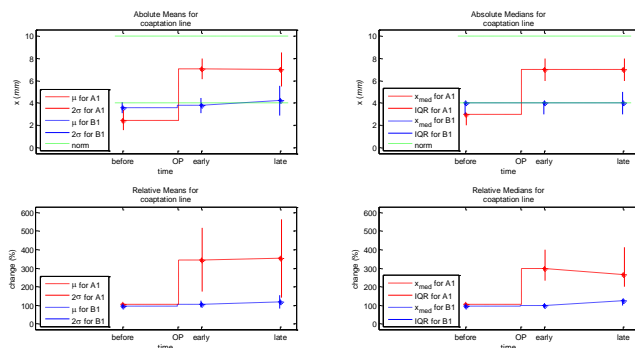
Reduction of both means and medians of the regurgitant volume was huge in A1 subgroup and this was an expected result, but it was also statistically significant in B1 subgroup (Tables V.5.b and V.5.c). The explanation of this result is that the revascularization itself improves the RV in patients with relatively preserved LV function but if combined with MVRepair it leads to more than fourfold improvement of the RV. The change of the means was registered immediately after surgery and trended to slight RV increase during the follow-up (Fig. V.7.d). Medians also decreased immediately after surgery, stayed virtually the same during the follow-up and even trended to additional decrease in B1 subgroup. No relapse of MR with RV equal of or higher than preoperative values was found.



### V.7.d. Changes in the characteristics of position of the regurgitant volume in A1 and B1 subgroups

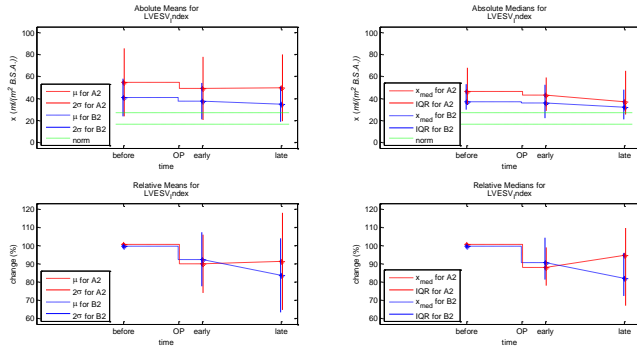
The coaptation line of MV leaflets is one of the parameters representing the effectiveness of the surgical correction of CIMR. As expected it increased

significantly in A1 subgroup patients but also in B1 subgroup patients, although the A1 increase was about fifteen times greater (Tables V.5.b and V.5.c). This increase in both means and medians was found immediately after surgery and stayed virtually the same during the follow-up of both A1 and B1 subgroups (Fig. V.7.e). The relative values of medians in A1 subgroup trended to slight decrease during the long-term follow-up which is related to the ischemic pathogenesis of MR and the progress of LV remodeling in some patients.



V.7.e. Changes in the characteristics of position of the coaptation line in A1 and B1 subgroups

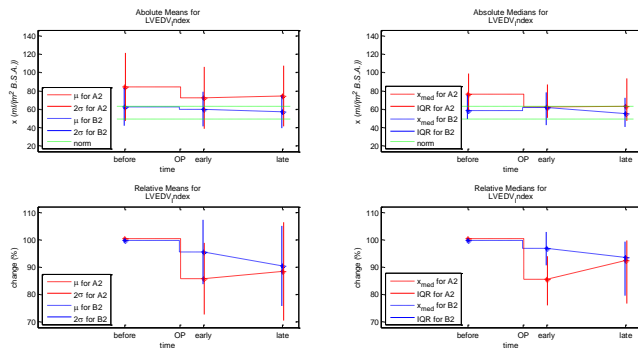
The decrease of LVESV showed borderline statistical significance in A2 subgroup patients and was statistically significant in B2 subgroup patients (Tables V.5.e and V.5.f). This result can be interpreted as a lack of reverse remodeling in A2 subgroup patients (they can be termed stable or non-responders) and presence of reverse remodeling in B2 subgroup patients (responders). It is interesting to note that after initial decrease immediately after surgery the relative medians of LVESV increased in A2 subgroup but decreased further in B2 subgroup which can be interpreted as a progressive remodeling in A2 subgroup patients and reverse remodeling in B2 subgroup patients (Fig. V.7.f).



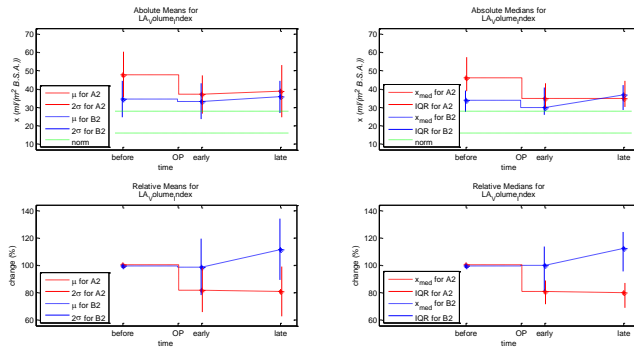
V.7.f. Changes in the characteristics of position of the LVESV index in A2 and B2 subgroups

Despite the statistically significant decrease of both means and medians of LVEDV index, the values defining LV reverse remodeling were not reached (Tables V.5.e and V.5.f). Dynamics of the changes in the characteristics of position were presented in the diagrams before (Fig. V.7.g). After an initial decrease immediately after surgery, both relative means and medians trended to increase in A2 subgroup during the long-term follow-up, whereas the same values in B2 subgroup trended to decrease further.

There was, as expected, a statistically significant decrease of values of LA volume index in A2 subgroup patients where the correction of MR resulted in relief of LA volume overload immediately after surgery (Fig. V.7.h). This effect remained during the long-term follow-up. There was no such decrease, again as expected, in B2 subgroup patients (except of the minimal decrease of absolute medians of LA volume index immediately after surgery) (Tables V.5.e and V.5.f), because their mitral regurgitation remained uncorrected.

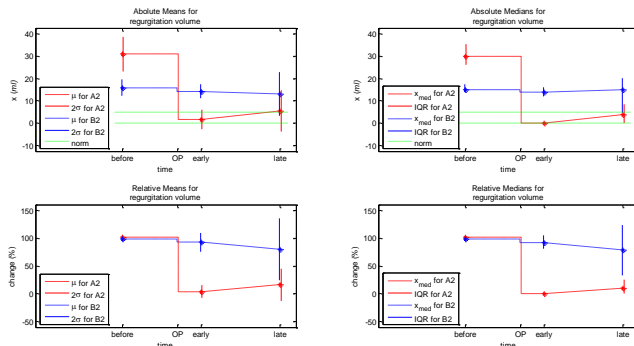


V.7.g. Changes in the characteristics of position of the LVEDV index in A2 and B2 subgroups



V.7.h. Changes in the characteristics of position of the LA volume index in A2 and B2 subgroups

Immediately after surgery there was a statistically significant and well expressed decrease of both means and medians of the RV in A2 subgroup patients but minimal and borderline significant decrease in B2 subgroup patients (Tables V.5.e and V.5.f). The dynamic changes of this parameter during the long-term follow-up were different: there was a trend towards increase of RV in A2 subgroup patients and a trend towards decrease in B2 subgroup patients (Fig. V.7.i).

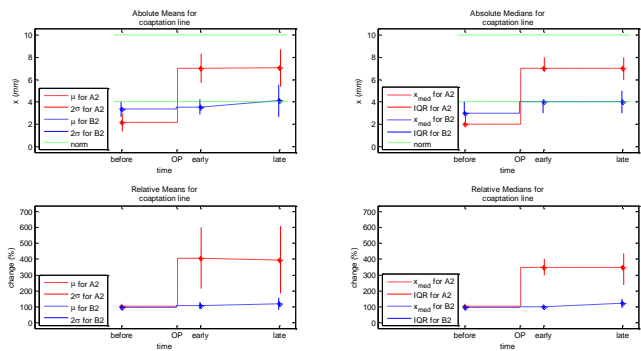


V.7.i. Changes in the characteristics of position of the regurgitant volume in A2 and B2 subgroups

The coaptation line of MV leaflets is one of the parameters representing the effectiveness of the surgical correction of CIMR. It increased statistically significantly, as expected, in A2 subgroup patients but a statistically significant increase was also found in B2 subgroup patients, although the A2 increase is about fifteen times greater (Tables V.5.e and V.5.f). This increase of both means



and medians was registered immediately after surgery and remained virtually the same during the long-term follow-up of both A2 and B2 subgroups with the relative medians of B2 subgroup showing a slight trend towards increase. (Fig. V.7.j).



V.7.j. Changes in the characteristics of position of the coaptation line in A2 and B2 subgroups

## **VI. GENERAL CONCLUSIONS OF THE STUDY**

The results of the study can be summarized into a single fundamental theoretical and two equally important practical conclusions:

- the analysis of the results of surgical treatment of different groups of IHD patients complicated by SIMR contributes to a more precise and individualized approach to each patient category and results in an improvement of the survival and quality of life of these patients;
- a little more conservative approach is required when scheduling patients in relatively impaired general and cardiac state for surgical revascularization combined with MVRepair, based on the lack of stable trend towards left heart chambers reverse remodeling in these patients and the higher surgical risks compared to isolated revascularization;
- patients with IMR in a relatively preserved general and cardiac state should be subjected to combined surgery (revascularization and MVRepair) based on the well expressed trend towards long-term left heart chambers reverse remodeling.

## VII. CLAIMS FOR CONTRIBUTION

As a result of the current thesis the following contributions are claimed:

1. A database was designed representing a Bulgarian group of patients with ischemic heart disease complicated by ischemic mitral regurgitation; the database contains data about 140 patients each described by 37 continuous and 16 discrete parameters; 33 of the continuous and 3 of the discrete parameters form triplets representing the values of a single parameter measured prior the operation, in the early and in the late postoperative period. The collected data take into account the social and communal characteristics of the Bulgarian population.

2. A hierarchical algorithm was formalized using inclusion and exclusion criteria as well as typical clinical pictures, aiming at selection of surgical treatment of IHD patients complicated by ischemic mitral regurgitation, which were categorized in either group A (subjected to combined revascularization and mitral repair) or group B (subjected to isolated revascularization).

3. Homogenization of groups A and B was achieved through segmentation of each group into two subgroups; this required the designing of:

a. A hierarchical algorithm using typical clinical pictures aiming at informational categorization of A group patients (IHD patients complicated by chronic significant ischemic mitral regurgitation, subjected to combined revascularization and mitral repair) into either A1 subgroup (relatively preserved general medical and cardiac state) or A2 subgroup (relatively impaired general medical and cardiac state);

b. A hierarchical algorithm using typical clinical pictures aiming at informational categorization of B group patients (IHD patients complicated by chronic significant ischemic mitral regurgitation, subjected to isolated revascularization) into either B1 subgroup (relatively preserved general medical and cardiac state) or B2 subgroup (relatively impaired general medical and cardiac state).

4. It was found that B1 and B2 groups can serve as pseudo control groups for A1 and A2 subgroups respectively because based on 738 statistical tests comparing 11 continuous and 13 discrete parameters it was undoubtedly proved that:

a. The preoperative state in A1 subgroup was worse than the B1 subgroup preoperative state;

b. The preoperative state in A2 subgroup was worse than the B2 subgroup preoperative state.

5. A new diagnostic parameter was introduced called "modified ejection fraction", which is useful in the evaluation of influence of MR on the effectiveness of the cardiac function. The undoubted advantage of the introduced parameter over the commonly used diagnostic parameter "ejection fraction" in the evaluation of the benefit of mitral annuloplasty was proved by 184 statistical tests.

6. A beneficial effect of the mitral annuloplasty compared to the pseudo control groups was found, because based on 1124 statistical tests comparing 10 generalized continuous three-dimensional parameters, 1 generalized discrete three-dimensional parameter and 2 continuous parameters it was undoubtedly proved that:

a. The late postoperative state of A1 subgroup patients was better than the late postoperative state of B1 subgroup patients and signs of left ventricular reverse remodeling were present;

b. The late postoperative state of A2 subgroup patients was better than the late postoperative state of B2 subgroup patients and signs of left ventricular reverse remodeling were virtually not present.

7. Early postoperative clinical pictures of A1, A2, B1 and B2 subgroup patients were designed and the changes in the early postoperative period compared to the preoperative period were proved using 240 statistical tests on 10 generalized continuous three-dimensional parameters. The designed clinical pictures facilitate the distribution of medical resources with early attention on patients with expected complicated early postoperative period.

## VIII. Publications on the thesis subject

Basic concepts of the current thesis have previously been published in the following papers:

1. Panayotov, P., Danov, V., Slavov, M. (2008) "Ischemic Mitral Regurgitation". *Heart-Lung* 14 (1-2): 42-47.

2. Panayotov, P., Slavov, M., Panayotova, D. (2009) "Early Results of Combined Surgical Treatment of Ischemic Mitral Regurgitation in the Department of Cardiac Surgery in "St Marina" University Hospital, Varna". *Heart-Lung* 15 (3-4): 37-42.

3. Panayotov, P., Slavov, M., Panayotova, D., Peychev, Y., Hadziev, V. (2010) "Influence of surgical approach to the mitral valve on the early postoperative rhythm and conduction disorders". *Heart-Lung* 16 (1-2): 36-45.

4. Panayotov, P., Slavov, M., Panayotova, D., Nikolova, N. D. (2011). "Left atrial reverse remodeling after surgical revascularization and mitral repair". *Heart-Lung* 17 (1-2).

5. Panayotov, P., Slavov, M., Panayotova, D., Peychev, Y., Kornovski, V. (2012) "Influence of correction of significant ischemic mitral regurgitation on the rhythm and conduction disorders after surgical coronary revascularization". *Bulgarian cardiology*, XVIII (Appendix 2): 30.

6. Simov, D., Konstantinov, P., Panayotov, P., Softova, E. (2007) "Asymptomatic course of a giant left atrial myxoma. Transseptal excision." *Contemporary medicine*, 58 (3): 56 – 59.