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Doctoral Thesis

Summary

CURRENT APPROACH IN THE TREATMENT OF ISCHEMIC HEART FAILURE

Phd Student: Bolea (Batâr) Florina Gabriela

Doctoral Advisor: Prof. Univ. Dr. Ioan Manițiu

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Content

PhD thesis contains 152 pages, has an iconography made up of 46 figures and 24 tables.

The thesis is divided into three main parts: the general part includes the current state of knowledge, which includes special contributions from personal references.

The bibliography includes a total of 248 references. Keywords: heart failure, ischemic heart disease, nicorandil, pharmacotherapy, revascularization

Current state of knowledge

1.1 Definition

Ischemic heart failure is a clinical syndrome characterized by symptoms typical (dyspnea, fatigue) can be accompanied by signs (jugular turgid, peripheral edema, crackles) [1] having as a cause of cardiac dysfunction coronary heart disease resulting in a decreased cardiac output and / or pressure intracardiac elevated at rest or during exercise. Coronary heart disease is a consequence of myocardial damage from inadequate oxygen supply to the need. Myocardial ischemia usually occurs in the context of coronary atherosclerosis but can reflect a dynamic component of the coronary vascular resistance [2].

Ischemic heart disease grouping several categories of conditions, namely stable coronary disease, unstable angina, myocardial infarction and sudden cardiac death [3]. Describes the situation where ischemic cardiomyopathy myocardial ischemia, myocardial dysfunction causes the clinical manifestations of heart failure. Heart failure is classified using various criteria. Of these the most common is the left ventricular ejection fraction and NYHA functional class.

1.2. Epidemiology

Cardiovascular diseases are the leading cause of death among both women and men worldwide. Heart failure is a major public health problem, with a prevalence of over 5.8 million in the US and 23 million worldwide.

1.3 Etiopathogenesis

Myocardial ischemia is the result of an imbalance between supply and demand of myocardial oxygen. Ischemia is considered myocellular hypoxia or condition that results when oxygen supplied to a region of the heart muscle is insufficient for the needs. Reduction of acute coronary flow and therefore myocardial oxygen supply is typically mechanism of acute coronary syndrome. In this case, recent injuries to the plaque (for example rupture, erosion, bleeding), thrombosis often overlapping and / or microembolism lead to endothelial dysfunction and increased reactivity, reducing coronary blood flow that will lead to acute ischemic myocyte injury . In contrast, a sharp increase in the oxygen demand in the context of a limited ability to increase the oxygen supply, the ischemia mechanism is usually chronic coronary disease [4].

Mechanisms of myocardial ischemia: fixed or dynamic stenosis of epicardial coronary artery dysfunction, epicardial coronary microvascular spasm focal or diffuse. The main cause of

myocardial oxygen deficient intake is epicardial coronary artery atherosclerosis, the main vessels of the coronary circulation conductance. Conventional risk factors for developing ischemic heart disease are hypertension, hypercholesterolemia, diabetes, obesity, smoking and family history of ischemia. They affect prognosis, probably through their effect on atherosclerotic disease progression.

Myocardial ischemia depresses ventricular performance, at a coronary flow reductions of 50%, which is directly proportional to the severity of ischemia. Ventricular segmental performance is changed, the corresponding trunk artery territory infarction affected. It is influenced systolic and diastolic function of left ventricular. In patients with ischemic cardiomyopathy it is important to recognize the hibernating myocardium and stunning myocardium because these processes are reversible ischemic in compared to fibrosis and necrotic tissue [5]. The consequence of myocardial infarction is ventricular remodeling comprising both infarcted area and the non-infarct involves changes in left ventricle size, shape and thickness of its walls that will affect LV function.

1.4 Investigation

A suspected ischemic cardiomyopathy requires a full assessment of the patient both in terms of assessment of ventricular dysfunction and to determine the extent of ischemia and its reversibility. Therefore, using a wide range of investigations, from the usual laboratory at the complex invasive and non-invasive imaging. Laboratory tests are part of routine blood counts, ionogram, creatinine, glucose, total cholesterol, LDL

cholesterol, HDL cholesterol, triglycerides, liver enzymes, protein status and analysis of urine analysis. Natriuretic peptides are hormones secreted cardiac and cerebral. The current used in the practice of BNP and NT-proBNP . These markers significantly rise under increased intracardiac filling pressures, as is often the case in acute coronary syndromes and heart failure.

The rest electrocardiogram (ECG) is part of the standard evaluation of a patient suspected of having heart failure, and a patient diagnosed with HF in the history is presented to a decompensation. Sinus tachycardia or supraventricular arrhythmias occurring in decompensated heart failure. There are changes that provide valuable information about ischemic etiology of HF, QRS's morphological changes that occur in ischemic pathology both ventricular depolarization and repolarization.

Chest radiography remains a useful evaluation in HF, especially when the clinical presentation is ambiguous. A alveolar opacity in the form of "butterfly" is the classic pattern of pulmonary congestion that occurs in HF.

Echocardiography is the most common used examination, widely available in patients with suspected HF. It provides instant information on cavities volumes, left ventricular systolic and diastolic function, thickness parietal, valve function and pulmonary hypertension [6].

Echocardiography is a term used to sum all using ultrasound imaging techniques including echocardiography two-dimensional / three-dimensional, pulsed and continuous Doppler, color Doppler, tissue Doppler imaging (TDI), contrast echocardiography and imaging deformation (strain and strain rate).

Transthoracic echocardiography (TTE) is the method of choice for assessment of myocardial systolic and diastolic function of both the right and the left ventricle. Echocardiography is an important investigation in the diagnosis and monitoring of patients with heart failure. It provides information on the geometry of the left ventricle, cardiac systolic and diastolic function , complications assessment, evaluation regional wall motion. Assessment of LV systolic function using LVEF calculation method Simpson modified biplane. Measurement of heart rate and systolic measurement plane excursion of the mitral annulus (MAPSE) are determined for systolic function.

Assessment of LV diastolic function: high filling pressures are the main physiological consequence of diastolic dysfunction. Filling pressures are considered high when the mean pressure in pulmonary capillary wedge pressure (PCWP) is> 12 mm Hg or when PEDVS is> 16 mm Hg right atrial (RA) are used to determine the systolic blood pressure in Pulmonary Artery [7]. Evaluation of transmitral diastolic flow using pulsed Doppler LV considers filling pressures. The first line measurements of the flow are: early filling diastolic velocity (E) and the fill late diastolic filling velocity (A), E / A ratio, deceleration time of the E wave (TDE) and the isovolumetric relaxation time (IVRT) [8]. Additional measurements include the wave length (obtained from the mitral ring) and diastolic filling time.

The evaluation wall movement of LV: visual evaluation (contractility normal / hypokinesia / akinesia / dyskinesia) based on the visual estimation of a thickening and displacement of the parietal wall may be sufficient in determining the immediate ischemia but it is insufficient for the size of the infarction and the area affected. A semi-quantitative method is left ventricular wall motion index; each segment is assigned a score based on a visual assessment of the contractility (0-5). Wall motion contractility index is the ratio of the sum of the scores assigned to each segment considered and examined the number of segments, thus integrating the kinetics kinetics as an index of global segmentation [9].

Quantitative methods of assessment of segmental function of myocardial velocities are the evaluation of myocardial deformation. There are two main ways echocardiography to assess myocardial deformation: tissue Doppler imaging (TDI) and speckle tracking. Myocardial deformation is defined as the fractional change in length of a myocardial segment relative to the original length and expressed as a percentage. The rate of deformation is the temporal derivative thereof and provides information on the velocity of the deformation, expressed in [sec-1]. In the case of clinical application of the complex three-dimensional deformation of the heart is described, typically the longitudinal parts, the circumferential and radial components of the wall.

Stress echography is the best imaging method, in terms of cost-effectiveness and cost-benefit assessment noninvasive ischemia or myocardial viability, providing data diagnostic and prognostic with good accuracy (detects coronary artery disease with sensitivity 83% and a

specificity of 85%). Stressors that can be used in stress echocardiography to unmask coronary stenosis: exercise, dobutamine, dipyridamole, adenosine, ergonovine.

Cardiac magnetic resonance imaging has classical indications for anatomical evaluation of the heart and large vessels, and recently it has received a central role for myocardial characterization, with applications in the study of myocardial viability and post-infarct imaging.

Magnetic resonance is the gold standard technique in quantifying volumes and ventricular mass due to its three-dimensional nature which is not based on geometric simulation [10]. The accuracy of the measurements in determining the volume and mass of the left ventricle has been demonstrated by numerous in vivo and in vitro studies. In recent years, CMR has developed a technique for evaluating myocardial ischemia and viability. In the chronic phase of ischemic heart disease CMR becomes the basic exploration in stratifying and guiding the therapeutic intervention [11].

The use contrast CMR and stress RMC with dobutamine is recommended post-infarction due to the increased risk of recurrence of ischemic events. The distribution volume of gadolinium is much higher in scar tissue than in viable myocardium. When testing with dobutamine the hibernating myocardium which can benefit from revascularization is highlighted. For the determination of viable myocardium, the acquisition of late contrast images (10-30 minutes after gadolinium injection) is used.

Determination of viable myocardium and scar tissue by CMR has been shown to be a predictive factor in response to cardiac resynchronization therapy.

Myocardial scintigraphy is a cornerstone in the evaluation of patients with suspected ischemic heart disease, due to its high diagnostic accuracy, and has the ability to define the degree, severity and localization of myocardial infusion abnormalities, contributing largely to clinical management.

Coronarography is the "gold standard" investigation for establishing the presence and severity of ischemic coronary artery disease. It is used to evaluate patients with systolic dysfunction when there is a high degree of clinical suspicion of ischemic etiology [12].

Coronarography is an invasive exploration of coronary arteries used for anatomical diagnosis of ischemic heart disease. It is performed using catheters that are introduced by the femoral or radial artery to the level of the coronary arteries, with contrast injection and radiological incidence.

Coronary angiography is recommended in patients with HF who have angina refractory to drug therapy [13], provided that the patient is compatible with coronary revascularization. Coronary angiography is also recommended in patients with a history of symptomatic ventricular arrhythmias or with resuscitated cardiac arrest. Coronary angiography should be considered in patients with HF and intermediate to high pre-test probability of having coronary heart disease and ischemia, in non-invasive stress tests, to determine ischemic etiology and severity of coronary heart disease.

In evaluating the functional capacity of the patient with heart failure, there is often debate about assessing the functional capacity with the help of CPT or the 6-minute walking test (6MWT). 6MWT has the advantage of being easy to achieve and at a minimal cost. However, CPT, unlike 6MWT, allows to assess gas exchange. This is why it is particularly relevant for patients with HF, who tend to be older with comorbidities that can lead to pulmonary or orthopedic limitations.

1.5 Positive diagnosis

A detailed history must always be made. HF is uncommon in a patient without a medical history (for example, a potential cause of cardiac injury), while certain features, particularly myocardial infarction, greatly increase the likelihood of ischemic HF in a patient with symptoms and signs.

Cardiac imaging plays a central role in diagnosing and guiding the treatment of heart failure.

1.6 Treatment of heart failure

In patients with ischemic heart failure goals of treatment are to improve the clinical status of the HF, the functional capacity and quality of life, and reduce hospitalization and mortality prevention.

Pharmacological treatment

- one intervention that has proved unequivocally beneficial in improving symptoms and prolonging life in patients with LV dysfunction is treatment with ACE inhibitors [14]. In recent decades were conducted numerous clinical trials using this class of drugs that assessed their effects on survival (mortality, morbidity and the rate of rehospitalization) in patients with systolic heart failure chronic
- β-blockers improve survival in patients with systolic heart failure chronic reduce hospitalizations and increase the functional capacity and are suitable for the treatment of all patients with stable HF class NYHA II-IV, with ischemic etiology, with LVEF <40%, in the absence of contraindications;
- aldosterone antagonists - spironolactone and eplerenone blocks the receptors which bind aldosterone and with different degrees of affinity for other receptors of steroid hormones (corticosteroids, androgens). Spironolactone or eplerenone are recommended for all symptomatic patients with LVEF <35% ;
- diuretics are recommended to relieve the signs and symptoms of congestion in patients with HFREF, but their effect on morbidity and mortality has not been studied in randomized clinical trials

- Digoxin is recommended primarily in patients with HF and atrial fibrillation for rate control
- Ivabradine should be considered to reduce the risk of hospitalization in HF and cardiovascular death in symptomatic patients with LVEF ≤ 35% in sinus rhythm and resting heart rate ≥ 70 despite treatment with a beta-blocking dose recommended in the guidelines
- Sacubitril / neprilysin Valsartan combined with an inhibitor of angiotensin receptor blocker. As inhibitors of neprilysin, an enzyme degrading natriuretic peptides biologically active, this combination increases the levels of natriuretic peptides assets, resulting effects of natriuretic, diuretic and vasodilating [1]
- Nicorandil is a drug with properties similar to nitrate and activation of the channel ATP-sensitive potassium (K + ATP). By virtue of this dual mechanism of action, the drug acts as a vasodilator coronary and peripheral and reduces preload and afterload. Nicorandil remains a useful therapy for patients with angina. Also, the drug showed potential cardioprotective effects when used as part of an intervention strategy immediately after acute myocardial infarction in patients with increased risk.

Interventional therapy

- Revascularization: coronary artery bypass (CABG) and percutaneous coronary intervention (PCI) are myocardial revascularization options used to correct coronary artery obstruction and, therefore, their use in patients with ischemic cardiomyopathy improves the pain and prognosis of the patient. Revascularization improves patient survival especially in the presence of LV dysfunction

- With devices (ICD, CRT):

ICD indications in patients with ischemic cardiomyopathy are for primary and secondary prevention of sudden cardiac death.

RCT is one of the most important recent therapeutic acquisitions in HF treatment. About 20-30% of HF patients associate varying degrees of intra / interventricular asynchrony leading to decreased systolic LV efficiency with decreased cardiac output. RCT improves cardiac performance in selected patients, and improves symptoms and well-being and reduces morbidity and mortality [15]. Cardiac resynchronization indications are: NYHA class III / IV, FEVS≤35, QRS> 120ms

1.7 Prognosis

Estimating the prognosis of morbidity, disability and death helps patients, their families and clinicians decide on the right type and time for certain treatments (especially the decision to of advanced therapies) and assist in planning the use of health and social services resources.

Personal contributions

Heart failure is a major cause of mortality and morbidity with a prevalence of 2-3%, being the cause of 5% of hospitalizations. The number of cases of heart failure is constantly increasing due to the cumulative effect of aging of the population but also becuse of improving the survival of patients with cardiovascular diseases due to the revascularization therapy of coronary heart disease.

Epidemiological studies estimate that approximately 70% of cases of chronic heart failure have ischemic etiology. When talking about atherosclerosis prophylaxis, the essential purpose is to prevent or delay the occurrence of these changes, the source of important and usually irreversible complications. Myocardial tissue loss following a miocardial infarction, respectively in the presence of chronic ischemia, is one of the triggering factors for ventricular remodeling and heart failure. It has become necessary to identify effective diagnostic methods that identify the ischemic substrate of heart failure in order to establish an appropriate therapeutic attitude.

This paper aims to characterize the profile of the patient with heart failure through usual investigations (electrocardiogram, laboratory tests) as well as through imaging tests useful in characterizing the structure and function of the heart (echocardiography) and its substrate (coronarography) together with the exercise testing (cardiopulmonary test and 6-minute walk test).

Another aim of this research is to improve the prognosis of patients with ischemic heart failure through the use of established drug therapies through clinical trials, adequate myocardial revascularization but also innovative medication. The efficacy of Nicorandil treatment was evaluated in a small group of patients

The present work was structured in three studies, the first retrospective on 111 patients offering a characterization of the pathology in question, and the second study discusses the revascularization strategy and the third approaches the medical therapy. The last includes a prospective, on a small cohort of patients studying the use of a potassium channel activator in the treatment of heart failure.

The present study aims to achieve the following objectives:

1. Characterization of the profile of patients with heart failure of ischemic etiology according to the severity of the symptomatology

2. Analysis of myocardial revascularization strategy in terms of age, associated pathology, localization of coronary lesions.

3. Evaluation of drug therapy and implementation of recommendations of the European Society of Cardiology, 2016 Heart failure guideline, for this cohort of patients

Materials and methods

The present study is an observational one, a retrospective that included patients admitted to the Cardiology Clinic of the Sibiu County Emergency Clinical Hospital between January 1 and December 31, 2017.

Patients were selected by consulting the electronic database of the SCJU Sibiu. The selection process consisted of identifying the outpatients diagnosed with heart failure who had performed coronarography during the twelve months at the CVASIC Research Center within the SCJ Sibiu.

Inclusion criteria:

- coronarography performed at the CVASIC Center which showed at least one coronary lesion> 50%,

- symptomatology characteristic of heart failure at the time of admission to the Cardiology Clinic.

Exclusion criteria:

- significant primary valvulopathies that can determine the symptomatology of HF

- causes other than ischemic that explain the symptomatology.

111 patients were selected and were monitored until 1.05.2019, whose data were processed and analyzed. Patient data were collected from the discharge sheet which included: laboratory test results, ECG, echocardiography, pathological history, treatment at discharge.

The length of the hospitalization and the evolution of the post-discharge (death and re-hospitalization in the Cardiology clinic) were registered until May 1, 2019.

Data were collected regarding the treatment received at discharge and the adherence to the 2016 Heart Failure Guideline of the European Society of Cardiology was analyzed.

We have structured this part into three studies that followed clinical, echocardiographic, angiographic elements from the perspective of revascularization therapy and drug therapy.

2.1. Clinical, echocardiographic and angiographic implications on symptomatology in patients with ischemic etiology

Results and discussions

The study included 111 patients, ranging in age from 41 to 86 years, with a mean 62.68 ± 0.98 years.

All the characteristics of the study population and all the parameters followed in this group of patients were expressed according to the NYHA Functional Class at admittion, thus describing 3 groups: Class I and II were grouped and the others were constituted in different lots.

The mean length of hospitalization is 8.5 ± 0.415 days with a minimum of 2 days and a maximum of 29, being longer for patients who presented with a more severe symptomatology, who are in Functional Class NYHA III and IV than those with moderate symptomatology.

The mean length of hospitalization was different in the three classes, so the worse the hospitalization symptoms, the longer the hospitalization. The group of patients in the Nyha II class had an average of 8 days hospitalization, while the average hospitalization of patients admitted to the Nyha IV class was 11 days. The mean length of hospitalization in our study was higher than in other studies of heart failure, where the average duration of hospitalization is 6 days

Diabetes was found in 41.37% of NYHA Class II patients, 36.3% of NYHA Class III patients and 33.3% of NYHA Class IV patients.

The presence of diabetes among comorbidities was present in 38.73% of the patients included in the study without significant differences with the results of other similar studies. In the ASPIRE IV study [18], the incidence of diabetes in patients with heart failure of ischemic etiology was 38.5% with no differences between the stages of heart failure and in the MERIT-IF study the incidence of diabetes was 37.3%.

The presence of hypertension was in 62.12% of the patients in the study, compared to the Spanish Heart Failure Registry, where the incidence of hypertension in patients with heart failure is 55.9% [16] and in the EURObservational Registry it is 58% [17]. The incidence of

hypertension in patients with heart failure in the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) registry was 62%

The presence of stroke in the study patients was 8.10% with a higher incidence in the HYHA Class II heart failure group 10.34%.

In the group with severe heart failure the incidence of myocardial infarction in the personal history was higher (44.44%) than in the other groups (31.37%).

It has been observed that atrial fibrillation is associated with NYHA Functional Class III and IV in an increased percentage, so rhythm disorders are associated with severe heart failure. The same results were observed in other studies where the sinus rhythm is present at 87.7%, the percentage being 100% in stage II and decreasing with the aggravation of the symptomatology [18].

From these data it can be interpreted that atrial fibrillation may be a consequence of progression of heart failure or aggravation of symptoms may be the consequence of atrial fibrillation, the connection between them being bidirectional, complex and difficult to evaluate.

The presence of acute coronary syndrome at the time of inclusion in the study was evaluated. 21.6% of patients had acute coronary syndrome at study entry. 58% of patients with SCA were in NYHA Class II, 42% in NYHA Class III None in Nyha Class IV.

Echocardiography was performed in 98 patients evaluating the systolic function of the left ventricle by ejection fraction and diastolic function of LV. The ejection fraction of the left ventricle mean was 45.1%. Systolic dysfunction of LV was present in 70% of the patients included in the study. It was noted that no patient in Functional Class Nyha IV had LVEF> 50%.

There were significant differences in terms of symptom severity in the three groups based on LVEF, so a negative correlation between LVEF and the NYHA functional class was found, which is explained by the fact that the severity of the symptomatology is higher as LVEF is reduced.

Regarding diastolic dysfunction there were differences between the three groups of patients ($p = 0.021$), so that in the NYHA II group the dysfunction was mild (altered relaxation: 80% of patients) and in the groups with severe symptoms diastolic dysfunction was more advanced.

All patients had a coronarography at the time of entry into the study with at least one arterial lesion. 42.34% of the patients had tricoronary lesions and 34.23% had bicoronary lesions. 23.45% had a single coronary lesion, of which 57.75 were in the Nyha II class.

Angiographic features of coronary lesions can have a major influence on the severity of the symptoms of heart failure. The localization of significant hemodynamic stenosis determines the myocardial territory affected by ischemia.

The number of vessels affected was not correlated with the severity of the symptomatology in our study, so patients with mild symptomatology had uniroronary, bicoronary and tricoronary

lesions. However, patients with tricoronary lesions were in functional class III and IV predominantly.

The most affected coronary artery in most patient groups is the anterior descending artery, the incidence of ADA being 80%, except for NYHA Class IV where the most affected is the right coronary artery (88.8%).

The survival curves of patients were compared according to the classification in the NYHA Functional Class upon admission.

No statistically significant differences were observed between the three groups of patients with regard to the cumulate endpoint, re-admission or death ($p = 0.260$).

The severity of the symptoms from hospitalization is a prognostic factor for the evolution of the patients. These results are reinforced by data from the literature supporting the Nyha Class as a strong prognostic factor in patients with heart failure.

2.2 Therapeutic revascularization strategy in the study population

Results and discussions

In our study, age did not play a role in choosing the therapeutic strategy for the coronary artery lesions. Both patients under the age of 65 as well as the elderly received equally revascularization, surgical intervention or optimal drug therapy. The study by Davierwala et al did not observe an age-appropriate revascularization strategy [19], also the revascularization guide of the European Society of Cardiology 2018 did not include in the criteria of choosing the age revascularization therapy [20].

Depending on the presence of the ACS at the time of inclusion in the study, the group of patients was divided into two groups. In the group presenting with ACS at the hospitalization, the patients benefited more from PCI compared to the other therapeutic strategies ($p = 0.027$), so that 70.8% of the patients were interventionally revascularized 16.6% received indication of by -pass and 12.5% were treated conservatively.

The outcomes of the patients was analyzed through a survival study that had as a cumulative endpoint the reintegration for symptomatology due to heart failure and death. This study reveals that patients who presented, with acute coronary syndrome had statistically significant fewer events during the follow-up period.

Patients with a history of myocardial infarction were surgically revascularized, statistically significant ($p = 0.05$) than patients without a previous infarction.

The majority of patients without chronic kidney disease were percutaneous revascularized (50%), but only 21% of the patients with conical renal disease had PCI, the majority had surgical revascularization.

Patients with diabetes have benefited, to a greater extent, from surgical revascularization compared to the other therapeutic methods.

ARTS II study comparing the evolution of patients who were revascularized by PCI with stent vs bare metal. Sirolimus-eluting stent vs. By-pass in diabetic patients resulted in superiority of drug eluding stents to bare metal, but inferiority to by-pass [21]. Similar results also had the FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) trial [22] demonstrating superiority of surgery in diabetic patients.

Surgical revascularization was the therapeutic solution for patients with systolic dysfunction of the left ventricle.

Data comparing surgical revascularization with drug therapy exist from the STICH trial. An analysis of this study showed that surgical therapy can be performed with acceptable 30-day mortality rates (5.1%) in patients with VS dysfunction (FEVS ≤35%). An extension of the follow-up of the STICH trial (STICHES) by 10 years, has a significant benefit in the survival of the by-pass combined with the drug therapy compared to the drug therapy alone [23].

Patients with left coronary artery disease were referred for surgical revascularization in 71.42% of cases.

Significant statistical differences were found between revascularization therapy according to the number of coronary lesions ($p = 0.000$). As the patients with one lesion were treated conservatively and with PCI, the bicoronary lesions were percutaneously revascularized in half of the cases and in only 13% of the patients the revascularization was performed surgically. Tricoronary patients received surgical treatment in 81% of cases.

Current evidence indicates that PCI is an appropriate by-pass alternative in affecting TACS with mild and intermediate anatomical complexity. In patients with LCA disease and low anatomical complexity, there is evidence that findings on major clinical endpoints are similar for PCI and bypass. In those with LCA disease and high anatomical complexity, studies show better survival at surgical revascularization.

2.3 Drug therapy for ischemic heart failure

2.3.1. Adherence to ESC Gudelines

Results and discussions

The therapy of the study population is classified according to the mechanism of action: beta-blockers (66.6%), conversion enzyme inhibitors and ARBs (66.6%), diuretics (47%), anti-

aggregates (aspirin and ADP receptor inhibitors, P2Y12) (83%), anticoagulants (18%), nitrates (49.5%).

Adherence indices were calculated for each class with IA recommendations of 2016 Hear Failure Guideline, drug but also for all three classes (overall adherence index).

- Beta blocker adherence index 78.36 ± 2.63%

- The adherence index to ACEI / ARBs is 76.02 ± 2.71%

- The diuretic adherence index is 82.06 ± 2.98%

- The overall adherence index is 72.96 ± 2.45%.

There is a statistically significant difference between systolic dysfunction of the left ventricle and the level of treatment adherence to the guidelines, so patients with LVEF> 50% (heart failure with ejection fraction preserved) have a lower adherence level and patients with LVEF reduced (heart failure with systolic dysfunction of the left ventricle) have a better adherence to the guidelines.

Our study illustrates the local adherence of the pharmacological treatment recommendations to the current indications of the ESC guideline. The results place the degree of adherence lower than other studies performed on subjects with similar characteristics. Thus the overall adherence index is 73%, compared to the one in the ASPIRE IV study in the German cohort, which has an index of 96. The β-blocker adherence index is 78%, compared to 90% the withdrawals from ASPIRE IV. IECA adherence in our group is 76%, also lower than in the ASPIRE IV group. However, our results show a higher adherence to the MAHLER study in terms of β-blocking adherence (58% MAHLER), but also of the global index 60%.

There is a higher adherence in patients with HFrEF compared to those with HFpEF. A possible explanation for this observation is the difficulty of managing patients with HFpEF due to the limited data in evidence-based medicine, the recommendations of the guides being relative.

2.3.2 Effects of Nicorandil treatment in patients with ischemic heart failure

The purpose of this research is to demonstrate the improvement of outcomes in patients with ischemic substrate for heart failure after treatment with Nicorandil. Thus the present paper has the following objectives:

1. Characterization of the two groups of patients following the clinical and biological parameters

2. Analysis of echocardiographic parameters in the patient group

3. Evaluation of effort capacity in patients with heart failure depending on the treatment

4. Establishing the existence of possible associations between biological, functional parameters and effort capacity in patients with ischemic heart failure

Materials and methods

The current study is conducted prospectively, on a batch of 12 patients diagnosed with heart failure, admitted to the Cardiology Clinic of the Sibiu County Emergency Clinical Hospital between August and October 2016.

Inclusion criteria:

- diagnosis of functional class heart failure Nyha II-III;

- ischemic etiology of heart failure by coronarography;

- sinus rhythm;

- presence of systolic dysfunction;

- the possibility of carrying out the stress test on the cycling meter.

Exclusion criteria:

- the presence of significant primary valves;

- severe symptomatology Nyha Class IV

- major cardiovascular events in the last month.

12 patients were selected who were randomly divided into two groups. The first group, known as the Nicorandil Group, received treatment with Nicorandil 20 mg twice daily for 5 days. All patients received standard treatment for heart failure (beta blockers, conversion enzyme inhibitors , mineralocorticoids and diuretics). No patients received treatment with a positive inotropic effect (dopamine, dobutamine, levosimentan, noradrenaline).

The BNP level was evaluated for each patient at study entry and on the fifth day using the Biosite Triage MeterPro analyzer and Quidel Triage Profiler SOB Panel immunofluorescence kits.

All patients underwent an echocardiographic evaluation by the same cardiologist. Siemens Acuson CV70 ultrasound with P4-2 probe was used. 2D, M-mode, continuous color Doppler, pulsed Doppler, Tissue Doppler modes were used.

Each patient underwent maximal or limited symptoms of cardiopulmonary stress testing on the fifth day after study entry. The Cortex Metalyser General Electric was used. Patients were monitored for ECG in 12 derivatives during the effort. The stress test was performed on the e-Bike cycloergometer, with an incremental load of 8-12W / min, depending on the estimation of the effort capacity of each patient.

The 6-minute walk test was performed for each patient previously discharged. In the type of the walking test, the distance made in 6 minutes was noted, the initial oxygen saturation, at 2 minutes, at 4 minutes at 6 minutes and at 2 minutes after stopping.

Patients were followed for 16 months. The number of days from external to the worsening of symptoms with hospitalization needs was evaluated.

Results and Discussions

The mean age of the Nicorandil group was 63.83 ± 4.19 years, and the age of the non-nicorandil group 69.67 ± 5.2 years.

The leght of hospitalization was compared in the two groups of patients. The mean length of hospitalization in the Nicorandil-treated group was shorter than in the control case but without statistical significance (7.17 ± 0.833 and 7.33 ± 0.760 respectively).

Several parameters characterizing the systolic function of the left ventricle were evaluated and compared between the two groups.

The global LVEF was evaluated by the modified Simpson method applied in the four-chamber apical window. The mean value in the Nicorandil group was 39.33 ± 15.17 and in the control group 39.83 ± 14.75 without any statistical significance ($p = 0.95$).

The measurement of the MAPSE parameter was performed in the apical window four chambers in the M mode. The mean value of MAPSE in the Nicorandil group was 11.20 ± 2.55 and in the control group 12.08 ± 5.12 without the statistically significant difference ($p = 0.378$).

In our study, several measurements were used to analyze in detail the systolic function of the left ventricle. The mitral annular plane (MAPSE) systolic excursion is an echocardiographic marker derived in the M mode of the longitudinal function of the left ventricle.

Diastolic dysfunction of the left ventricle was evaluated using the E / A ratio of the transmitral diastolic flow and the E / e 'ratio. Significant statistical differences were observed between the two groups of patients ($p = 0.05$), so that the patients in the Nicorandil group had more advanced diastolic dysfunction, half of them having a restrictive transmitral diastolic profile. In the control group no patient had a restrictive profile, 83% had a altered relaxation profile. The mean value of

the ratio E / e 'in the Nicorandil group was 8.13 ± 0.77 and in the control group 6.62 ± 2.24, without statistically significant differences (p = 0.177).

In this study, BNP levels were measured in each patient at the time of entry into the study and on fifth day. The regression of the BNP was calculated as the difference between the BNP level on admission and the BNP level on fifth day.

We observe a greater reduction of the BNP level on the fifth day in the case of the Nicorandil group (221) compared to the control group (-30), a reduction that has statistical significance (p = 0.038).

The prognostic values of BNP are well known, having independent predictive value on survival. A meta-analysis on the importance of the prognostic value of BNP showed that each increase of 100 pg / ml was associated with a 35% increase in the relative risk of death.

The effort capacity assessment was performed by two tests dedicated in this area, the Cardiopulmonary Exercise Test and the 6-minute walking test.

The maximum oxygen consumption rate in the study patients was measured and the means of the two groups was compared. Mean VO2 in the Nicorandil group was lower than in the control group (Nicorandil group 9.20 ± 1.09, respectively control group 11.20 ± 2.9). The maximum oxygen consumption was decreased in both groups below the threshold value of 14 ml / kg / min.

Respiratory reserve is an important independent prognostic parameter in patients with heart failure and is calculated as the ratio VE / VCO2, where VE is minute ventilation and VCO2 is the volume of expired carbon dioxide.

Respiratory reserve averages were compared in which two groups of patients. In the Nicorandil group the respiratory reserve is higher than the control group (slope VE / VCO2 is smaller), having statistical significance (p = 0.022). The mean value of the respiratory reserve in the Nicorandil group is 32.30 ± 2.58 and in the control group 37.70 ± 3.38.

The ventilation reserve illustrates the extent to which the minute ventilation reached values close to the maximum ventilation during TE. Its values are not influenced by age. The VE / VCO2 slope is a strong predictor of events in patients with heart failure [24]. A VE / VCO2 slope> 34 to 36 identifies high risk in HF patients and provides important prognostic, superior VO2max information [25].

The walking distance in six minutes was measured for each patient. The mean distances of the two groups were compared and it was observed that the Nicorandil-treated group had a greater mean distance (396 ± 87.1 meters) compared to the control group (320.83 ± 118 meters) without the difference being statistical. significant (p = 0.234).

The mean distance traveled by the patients in our study was 355 meters, higher in the nicorandil treatment group (396 meters) compared to the control group (320 meters). The mean distance traveled in the 6-minute walk test in the HF-ACTION trial was 377 meters, the test being performed in patients with heart failure and FEVS <50%, characteristics similar to those of our study population.

The filling pressures of the left ventricle were strongly negative correlated with the rate of oxygen consumption, as the filling pressures were higher, the maximum oxygen consumption was lower, having statistical significance (r = -0.787, p = 0.02). Several studies in the literature have demonstrated this correlation. The filling pressures estimated by the ratio E / e 'correlated strongly with the duration of the cardiopulmonary stress test, with statistical significance, so that the duration of the test was the longer the diastolic pressures in VS were lower (r = -0725, p = 0.042).

The relationship between the respiratory reserve and the distance traveled in the 6-minute walking test was analyzed and a statistically significant negative correlation was observed between the VE / VCO2 slope and the walking distance (r = -0.663, p = 0.037), so the respiratory reserve is higher distance traveled is greater. The data analyzed in our study show a significant correlation between walking distance during 6MWT and ventilatory efficiency measured during CPT (r = -0.663, p = 0.037). In Forman's study he published similar results on the correlation of the two parameters (r = –0, .26, p = 0.0001) [26], using the database of the HF-ACTION trial (Heart Failure). : A Controlled Trial Investigating Outcomes of Exercise Training).

General conclusions

1. The length of hospitalization in patients with heart failure correlates with the severity of the symptoms.

2. Atrial fibrillation is associated with worsening of symptoms.

3. Left ventricle ejection fraction is negatively correlated with the NYHA functional class.

4. The degree of diastolic dysfunction is directly correlated with the severity of the symptoms.

5. There is no correlation between the number of coronary lesions and the severity of the symptoms of heart failure.

6. There is no correlation between the location of coronary lesions and the severity of the symptoms of heart failure.

7. The revascularization strategy does not involve age in the decision-making plan.

8. Patients presenting with acute coronary syndrome are predominantly interventional revascularized.

9. The presence of myocardial infarction in the personal history inclines towards surgical revascularization.

10. Patients with chronic kidney disease were surgically revascularized.

11. Patients with diabetes were surgically revascularized.

12. Systolic dysfunction of the left ventricle inclined the surgical revascularization decision.

13. Coronary and bivascular disease was percutaneously corrected and trivascular disease was surgically resolved.

14. Stenosis of the left coronary artery was treated surgically.

15. There are no significant differences between the survival of the three revascularization approaches as the group was heterogeneous.

16. The classes of drugs used in the treatment of patients with heart failure are: ACEi / ARBs, diuretics, vasodilators, antithrombotics and β-blockers.

17. β-blockers were present in 66.6% of patients in the recommended therapy at discharge, being higher in patients with HFrEF.

18. Mortality was lower in patients taking β-blockers.

19. ACEi were indicated in 66.6% of patients at discharge, with lower mortality

20. Half of the patients were treated with diuretics without improving their prognosis.

21. The overall adherence to the recommendations of the heart failure management guide of the European Cardiology Society is 73%, being below the current European average.

22. The overall adherence to the recommendations of the guide is superior for HFrEF.

23. Nicorandil has a beneficial effect by improving exercise capacity in patients with ischemic heart failure.

Bibliografie

1. Ponikowski P, V. A. . 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure . European Heart Journal ,2016; 2129–2200.

2. Sabatine MS, C. C. Approch to the patient with chest pain. În Braunwalds Heart Disease. Philadelphia: Elsevier.2012; p. 1076.

3. Wong, ND . Epidemiological studies of CHD and the evolution of preventive cardiology. Nature Reviews. Cardiology. 2014;11 (5): 276–89

4. Pepine C , Nichol WW. The Pathophysiology of Chronic Ischemic Heart D iseas . Clin. Cardiol. 2007: I4-I9

5. Mereuta A. Angina pectorala stabila. In: Ginhina C, editor. Mic tratat de cardiologie. 2nd ed. Editura Academiei Romane (2017), 270-286

6. Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007;28:2539–2550

7. Bouchard JL, Aurigemma GP, Hill JC, Ennis CA, and Tighe D.A. Usefulness of the pulmonary arterial systolic pressure to predict pulmonary arterial wedge pressure in patients with normal left ventricular systolic function. Am J Cardiol. 2008; 101: 1673–1676

8. Appleton CP, Jensen JL, Hatle LK, Oh JK. Doppler evaluation of left and right ventricular diastolic function: a technical guide for obtaining optimal flow velocity recordings. J Am Soc Echocardiogr. 1997; 10: 271–291

9. Jurcut R, Andrei O, Ghinghina C. Evaluarea ischemiei miocardice. In Ginghina C. Esențialul în ecocardiografie. 2ed. Ed Medicală Antaeus. 2013. P 75-109

10. Bellenger NG, Burgess M, Ray SG, et al: Comparison of left ventricular ejection fraction and volumes in heart failure by two-dimensional echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance: Are they interchangeable?. Eur Heart J 2000; 21:1387

11. Schwitter J,Aray A: Assessmant of cardiac ischaemia and viability: role os cardiovascular magnetic resonance. Eur Heart J 2011; 32: 799-813

12. Greenberg B, Kahn AM. Clinical assessment of heart failure. În Braunwalds Heart Disease. Philadelphia: Elsevier.2012; p. 505

13. Jolicœur EM, Dunning A, Castelvecchio S, Dabrowski R, Waclawiw MA, Petrie MC, Stewart R, Jhund PS, Desvigne-Nickens P, Panza JA, Bonow RO, Sun B, San TR, Al-Khalidi HR, Rouleau JL, Velazquez EJ, Cleland JGF. Importance of angina in patients with coronary disease, heart failure, and left ventricular systolic dysfunction: insights from STICH. J Am Coll Cardiol 2015;66:2092–2100.

14. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ, Cuddy TE et al . Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial. N Engl J Med. 1992;327:669–677.

15. Sohaib SMMA, Finegold JA, Nijjer SS, Hossain R, Linde C, Levy WC, Sutton R, Kanagaratnam P, Francis DP, Whinnett ZI. Opportunity to increase life span in narrow QRS cardiac resynchronization therapy recipients by deactivating ventricular pacing: evidence from randomized controlled trials. JACC Heart Fail 2015;3:327–336.

16. Maggioni AP, Dahlström U, Filippatos G, Chioncel, O, Leiro MC, Drozdz J. (2010), EURObservational Research Programme: The Heart Failure Pilot Survey (ESC-HF Pilot). European Journal of Heart Failure, 12: 1076-1084

17. Crespo-Leiro MG, Segovia-Cubero J, González-Costello J, Bayes-Genis A, López-Fernández S, Sanz-Julve M Adherence to the ESC Heart Failure Treatment Guidelines in Spain: ESC Heart Failure Long-term Registry .Rev Esp Cardiol. 2015;68(9):785–793

18. Morbach C, Wagner M, Güntner S, et al. Heart failure in patients with coronary heart disease: Prevalence, characteristics and guideline implementation - Results from the German EuroAspire IV cohort. BMC Cardiovasc Disord. 2017;17(1):108

19. Davierwala PM, Mohr FW. Myocardial revascularization: do age and sex matter?. J Thorac Dis. 2016;8(10):E1244–E1248.

20. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC Scientific Document 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019 Jan 7;40(2):87-165

21. A.P. Kappetein, S.J. Head, M.C. Morice, et al., SYNTAX Investigators Treatment of complex coronary artery disease in patients with diabetes: 5-year results comparing outcomes of bypass surgery and percutaneous coronary intervention in the SYNTAX trial Eur J Cardiothorac Surg, 43 (2013), pp. 1006-1013

22. P.W. Serruys, Y. Onuma, S. Garg, et al., for the ARTS II Investigators 5-year clinical outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the sirolimus-eluting stent in the treatment of patients with multivessel de novo coronary artery lesions J Am Coll Cardiol, 55 (2010), pp. 1093-110

23. M.E. Farkouh, M. Domanski, L.A. Sleeper, et al. Strategies for multivessel revascularization in patients with diabetes N Engl J Med, 367 (2012), pp. 2375-2384

24. Jaussaud J, Aimable L, Douard H. The time for a new strong functional parameter in heart failure: the VE/VCO2 slope. Int J Cardiol 2011;147:189–90.

25. Cornelis J, Taeymans J, Hens W, Beckers P, Vrints C, Vissers D. Prognostic respiratory parameters in heart failure patients with and without exercise oscillatory ventilation—a systematic review and descriptive meta-analysis. Int J Cardiol 2015;182:476–86

26. Forman DE, Fleg JL, Kitzman DW, et al. 6-min walk test provides prognostic utility comparable to cardiopulmonary exercise testing in ambulatory outpatients with systolic heart failure. J Am Coll Cardiol. 2012;60(25):2653–2661