UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA

FACULTY OF MEDICINE

COMPARATIVE STUDY ON THE EVOLUTION AND DISEASES OF PATIENT PROGNOSIS WITH DILATED CARDIOMYOPATHY VERSUS NONISCHEMIC

DOCTORATE THESIS

(summary)

SCIENTIFIC COORDINATOR:

Prof. PhD Paulina Lucia Ciurea

PHD STUDENT:

Dr. Tudoraşcu Raul Petrişor

CRAIOVA

2013

TABLE OF CONTENTS

Key words: dilated cardiomyopathy, evolution, prognosis, survival

INTRODUCTION

Dilated cardiomyopathy is a syndrome characterized by heart dilatation and impairment of systolic function of the ventricle or both and is a major health problem, being the third leading cause of heart failure, which justifies the investment in research to find the most effective methods of early diagnosis and treatment. However, dilated cardiomyopathy remains the leading cause of heart transplantation worldwide.

The prognosis of patients with dilated cardiomyopathy can be extremely variable in the etiology affecting in an important measure, the evolution of these patients.

The major theme of research concerned in this study is benchmarking the evolution and prognosis of patients with ischemic dilated cardiomyopathy versus nonischemic.

The paper is divided into two parts: the general part which contains current data about the etiopathogenesis and positive diagnosis of dilated cardiomyopathy and the special which includes: the study objectives, materials and methods, results obtained from the comprehensive assessment of patients with dilated cardiomyopathy, discussion of results and research findings.

MATERIAL AND METHOD

STUDY PURPOSE AND OBJECTIVES

The study objective was generally the identification of optimal factors influencing both the evolution and prognosis of patients with ischemic dilated cardiomyopathy versus nonischemic.

The main aim of the study was to investigate investigating evolutionary differences and the CMD prognosis of patients with ischemic etiology compared to other forms aiming to establish models of algorithms for evaluating the prognosis of these patients, with important implications for determining long-term therapeutic conduct.

The study focused on the evaluation and benchmarking of key of clinical, biological and imaging prognostic markers used in monitoring patients with CMD according to current recommendations.

The major theme of research concerned in this study is benchmarking the evolution and prognosis of patients with ischemic dilated cardiomyopathy versus nonischemic.

EXPLORATION PROTOCOL

The study was prospective in nature, and covers a period of four years, at Craiova Cardiology Center - Emergency County Hospital Craiova. Biological Investigations were carried out in the Laboratory of Emergency County Hospital Craiova, and the imaging of the Center of Cardiology Craiova.

There have been included in the target group and have agreed to enter the study a total of 180 people, divided into 2 groups, subjects from the population of patients with dilated cardiomyopathy with chronic ischemic and nonischemic etiology assisted in the same specialized cardiology clinic, in same period of the research, by the same medical staff, throughout the survey period. The monitoring was conducted over 48 months, to highlight differences in the evolution and prognosis of patients with ischemic versus nonischemic cardiomyopathy.

PATIENT SELECTION CRITERIA

For the composition of groups of patients included in the study, was analyzed the casuistry of the Cardiology Center of the Emergency County Hospital Craiova. They were formed two groups - one group of patients with ischemic etiology dilated cardiomyopathy and a group of patients with nonischemic etiology dilated cardiomyopathy hospitalized in the same period in the clinic.

The study was prospective in nature, with duration of 4 years (2008-2012), with admission of 180 patients with dilated cardiomyopathy, which met the criteria of the European Society of Cardiology on the diagnosis of idiopathic dilated cardiomyopathy:

1. FE a VS <45% and / or shortening fraction <25%, assessed by echocardiography, angiography
2. Diastolic diameter of VS > 117% compared to the normal value, adjusted for age and body size.

The inclusion in the CMD ischemic group requires demonstration of an extensive coronary disease accompanied by ventricular and systolic dysfunction (stenosis more than 70% of one or more of the epicardial coronary vessels major) remodeling, with the following features: an ejection fraction less than 35%, the diastolic diameter VS over 6.5 cm, coronary disease at angiography and demonstrable ischemia.

MONITORED PARAMETERS

The study design assumed the registration of: dilated cardiomyopathy patients with ischemic and nonischemic, duration of the disease, NYHA heart failure, disease progression; collection of laboratory samples, perform standard EKG, heart ultrasound (including Doppler), thoracic mediastina pleural pulmonary radiography.

STATISTICAL ANALYSIS

Statistic indicators. Of central tendency indicators were analyzed: the arithmetic average, mode, median and of scattering data of the indicators the standard deviation, standard error of the average, 95% confidence interval of the average.

Statistical tests used Chi square test, ANOVA test, and risk analysis used relative risk for it is expressed the confidence interval 95% and the level of statistical significance.

Database has been managed with Excel, from Microsoft Office package, and statistical analysis has benefited from dedicated statistical programs Epi Info 2000 and MedCalc.

RESULTS AND DISCUSSION

STRUCTURE OF GROUPS OF PATIENTS

The study group consisted of 180 subjects grouped according to the type of medical condition that caused hospitalization in two groups: patients with DCM of ischemic etiology, and patients with nonischemic etiology dilated cardiomyopathy.

CLINICAL AND BIOLOGICAL PROFILE OF CASES WITH CMD ISCHEMIC AND NONISCHEMIC

The average age of cases with ischemic DCM (57.02 ± 9.09 years) was higher by almost three years compared to the cases with nonischemic DCM (54.22 ± 9.94 years).

By evaluating the disease duration was observed a significantly lower value ($p = 0.008$) in cases with nonischemic DCM (4.05 ± 2.95 years) compared with ischemic etiology of CMD (5.25 ± 3,1years).

But it was not noticed a significant difference according to NYHA class distribution in the two groups (p=0.42). The most common cases of IC were classified in NYHA class III classification and less than 5% in class IV (4.3% for CMD ischemic and 1.2 CMD nonischemic).

Although the average number of hospitalizations did not differ significantly (p = 0.168) in individuals with ischemic etiology (9.48 ± 2.91) and nonischemic etiology ones (8.92 ± 2.47).

Diastolic and systolic blood pressure were significantly different in the two groups (p <0.001), pointing out the profile of hypertensive patients with ischemic CMD unlike nonischemic etiology CMD cases with normal values of TA.

The metabolic profile of the CMD did not noticed significant differences in weight or body or mass index in the two etiologies, being however important and suggestive the differences in the lipid profile of the two groups. Thus, serum cholesterol, LDL cholesterol and triglyceride levels have higher values in individuals with ischemic CMD.

ECG changes were particularly relevant for objectifying the etiology of ischemic dilated cardiomyopathy, patients with CMD ischemic ST segment depression was found in 81% of cases unlike the etiology of nonischemic who experienced this change at only about one third of cases (37,2%).

Also, atrioventricular block was nearly three times more common in cases with ischemic CMD versus nonischemic CMD (p = 0.041), data were similar to those reported by other authors.

ANALYSIS OF PROGNOSTIC FACTORS ASSOCIATED

TO AN UNFAVORABLE EVOLUTION OF CMD

DEMOGRAPHIC ELEMENTS ANALYSIS AND THE ANALYSIS OF VARIABLES ASSOCIATED TO HOSPITALIZATION AND CHRONICITY IN THE CMD PROGNOSIS

Following the analysis of survival rates in the two groups one noticed a better survival rate for cases with nonischemic etiology of CMD, at which the survival at 4 years was over 75% (76.74%) as compared to the ischemic etiology which presented a survival at 4 years of 65% (65.96%).

The risk of death was almost 50% higher in individuals with ischemic etiology CMD, compared to nonischemic etiology (RR = 1.46; p = 0.11).

Although comparative analysis of survival rates showed no significant difference between the two sexes (p = 0.61), there was a trend that survival rates are generally better in women (76.47%) compared to males (69.86%), results comparable to those published by Miura K et al.

The risk of death was almost 6 times higher in individuals with ischemic CMD with a longer disease duration of 5 years and almost 5 times in those with nonischemic CMD with the same period of the disease.

The risk of death was almost double in cases with nonischemic CMD with more than 10 hospitalizations (RR = 9.1; CI95% 2.88 -28.68; P <0.001) versus those with ischemic CMD (RR = 4 42; CI95% 2.12 to 9.2; P <0.001).

SURVIVAL ANALYSIS BASED ON CLINICAL ELEMENTS

The risk of death of cases located in stage III compared to those in II NYHA stage was 14 times higher, and for those at the onset of the study already in IV NYHA stage - 32 times.

The average values of heart rate expressed significant differences between the 2 groups, pointing out cases tendency to tahicardizare in deceased pulse rate, more pronounced in the group of cases with nonischemic CMD.

The risk of death was identified with the emergence in the evolution of some acute cardiovascular events almost 8 times higher compared to cases with no acute cardiovascular events (rr = 7.74; CI 95% 4.53 to 13.23; p <0.001).

SURVIVAL ANALYSIS ACCORDING TO SOME LABORATORY EXAMINATIONS

The cases of survival at 4 years therefore expressed much lower values, suggesting, like the results of the study made by michael arad md and dov freimark dov md., that the low serum value nt-probnp is an independent factor of survival. thus, for those with ischemic CMD, the value at 4 years was almost 2 times lower (6598.49 ± 3482.76 pg / ml; range 1300-21000 pg / ml), and those with nonischemic etiology CMD – the average value of nt-probnp at 4 years was nearly 4 times lower (3571.21 ± 2074.08 pg / ml; range 450-14000 pg / ml) as compared to the mean of deceased cases ($p < 0.001$).

SURVIVAL DEPENDING ON ECOGRAPHICAL VARIABLES

Ejection fraction was lower in cases of dead compared to those who survived 4 years, results similar to those published by Fruhwald FM et al and Miura K et al.

It was, also, identified a deeper importance of the progonisis role of FE in nonischemic etiology cases of CMD, which confirms the observations of the study published by Jacek Grzybowski MD et al.

Evaluation of left ventricular posterior wall thickness has identified a significant difference ($p < 0.001$) between dead cases (11.48 ± 1.23 mm) and those who survived (12.79 ± 1.12 mm), regardless of etiology CMD is in itself an unfavorable prognostic factor.

Small mitral regurgitation allowed maximum survival. the trend of decrease in survival was strongly conditioned by advancing the degree of mitral regurgitation ($R2 = 0.99$).

And for cases with nonischemic CMD, the mitral regurgitation grade was a similar important prognostic factor, a conclusion supported by Raluca Ianula et al. in a study published in 2011, according to which the mitral insufficiency is an independent prognostic factor for deterioration of the disease and risk of death in patients with nonischemic CMD.

The risk of death of cases regardless of the etiology of CMD at fluid levels above 2 mm was 5 times higher as compared to those with levels of pericardial fluid of 1-2 mm (RR = 5; IC95% 3.34 TO 7, 41; $P<0.001$).

SURVIVAL ACCORDING TO ELECTROCARDIOGRAPHIC VARIABLES

The risk of death in cases that presented ventricular arrhythmias was almost 4 times higher as compared to the risk of death in cases without ventricular arrhythmia (RR = 4.06; CI95% 2.89 to 5.8; p = 0.001) in contradiction to the study published by Huang SK et al, whereby ventricular tachycardia appear to predict short-term prognosis of patients with idiopathic CMD.

Atrial fibrillation influenced survival decrease with the CMD cases regardless of etiology, the survival in the context of their presence being 53.25% as opposed to cases without constant atrial fibrillation episodes in which the survival was over 80% (84.47%) .

In nonischemic etiology cases, atrial fibrillation plays a very powerful role in shaping survival. The risk of death of cases with this complication was more than 20 times higher than those who had no arrhythmic event (RR = 24; CI95% 3.36 to 171.3; p <0.0001); these results support the study made by Thomas Hofmann, MD et al, according to which the presence of atrial fibrillation significantly increases the risk of death in patients with idiopathic CMD.

Left bundle branch block as a complication expressed for cases with this complication a survival of 50% as compared to BRS cases, in which the survival was over 80%.

The risk of death of cases with BRS regardless of the etiology of CMD was 3 times higher than those without BRS, results comparable to those of a study conducetd by William C. Roberts, who identified in CMD patients who died, an increased frequency of left bundle branch block and complete atrial fibrillation.

Even if the mean values of QT gap in deceased cases were higher with only 4%, the difference was highly statistically significant, which supports the conclusion of a study conducted by Lindsay M Ryerson, MD demonstrating that the combination of QT prolongation gap increases the risk of death of CMD patients.

CONCLUSIONS

1. As a consequence of the analysis of survival rates in the two groups there was noticed a superiority for nonischemic etiology cases of CMD, the risk of death being approximately 50% higher in individuals with ischemic etiology CMD, as compared to nonischemic etiology.

2. Although there is no significant difference between the two sexes in rates of survival, there was a tendency that the survival rates to be generally better in females as compared to males, observing that females may represent a prognosis factor favorable especially for nonischemic etiology.

3. Regardless of sex, cases with nonischemic CMD showed better survival rates as compared to ischemic CMD.

4. The results of the study show that survival rates were higher in cases with low age, low duration of the disease evolution and a small number of hospitalizations per year.

5. Although the mean number of hospitalizations did not differ significantly in individuals with ischemic etiology and for those with nonischemic etiology, one noticed a stronger correlation between the number of hospitalizations and disease duration in patients with nonischemic CMD as compared with other cases.

6. Patients with ischemic CMD present an altered lipid profile, with a significantly higher atherogenic index as compared to subjects with nonischemic CMD.

7. Cardiac decompensation assessed by NYHA staging was one of the most important and eloquent CMD prognostic factors, the risk increasing all along with the functional class, and the presence during the follow-up period of the study of acute cardiovascular events correlated best with the unfavorable prognosis.

8. Among biological parameters, the best correlation with the risk of death showed thhe serum value of NT-proBNP, and in terms of ultrasound parameters - the ejection fraction value and the degree of mitral regurgitation dictated pacients' prognosis.

9. Electrocardiographic changes, best correlated with patients' prognosis and the risk of death, were ventricular arrhythmias, atrial fibrillation, left bundle branch block and QT gap.

Identifying the clinical and laboratory and imaging profile associated with increased evolving risk has a particular importance in tracing the evolution and prognosis of patients with dilated cardiomyopathy according to the etiology, and establishing *some models of algorithms for evaluating the prognosis of patients with CMD* presents important implications for determining long-term stages of therapeutic conduct.

CURRICULUM VITAE

1. Personal Information

- *Surname and given name: TUDORAŞCU RAUL PETRIŞOR*
- *Address: Craiova, Dolj, N. BANESCU, Bldg. D9a, Flat no. 14*
- *Phone number: 0726398092*
- *E-mail: petridiana@yahoo.com*
- *Date of birth: 14.06.1977*
- *Marital status: married*

2. Professional Experience

- *2004-2008 internship doctor County Emergency Clinical Hospital of Craiova*

3. Education and training

- *2009 cardiolology consultant*
- *2004-2008 internship in cardiolology*
- *1997-2003 Faculty of General Medicine, UMF of Craiova*
- *1993-1997 Tudor Vladimirescu Academic High School*

4. Skills and competences

- *Native tongue - Romanian*
- *Foreign languages – English, French*
- *Echocardiography*
- *Computer literacy*

5. Thesis profile works*– 2 articles in extenso first aid - 4 abstracts*