нарушений физического и психического здоровья людей развитого техногенного общества. В контексте проблемы первичного стресс-индуцированного бесплодия, которое возникает на фоне наличия острых и хронических стрессов, наибольший научный интерес составляет исследование баланса половых гормонов. В данной статье освещено содержание уровня прогестерона у женщин со значительными стрессовыми нагрузками, что, в сочетании с другими провоцирующими факторами, приводит к развитию стресс-индуцированного бесплодия.
Ключевые слова: прогестерон, стресс-индуцированное бесплодие, репродуктивный возраст.

Bulavenko O.V., Lyovkina O.L

PROGESTERONE BLOOD CONTENT ANALYSIS IN PRIMARY STRESS-INDUCED INFERTILITY WOMEN

Summary. *Acute problem of modern society medicine is a problem of stress, as reason of often physical and psychological disorders of developed technogenic society. In context of primary stress-induced infertility, which develops on background of acute or chronic stresses the biggest scientifical interest presents sex-hormonal balance investigation. In this article we expose progesterone content in women with considerable stress loadings, which together with other provocative factors may lead to stress-induced infertility.*
Key words: *progesterone, stress-induced infertility, reproductive age.*

Булавенко Ольга Василівна - д.мед.н., проф., зав. кафедрою акушерства і гінекології №2 Вінницького національного медичного університету ім. М.І. Пирогова; +38(067)6231671; remedivin@gmail.com
Льовкіна Олена Леонідівна - к.мед.н, асистент кафедри акушерства і гінекології №2 Вінницького національного медичного університету ім. М.І. Пирогова; +38(067)7471707; elevkina@mail.ua

Cherniuk S.V.
State institution "National scientific centre "M.D. Strazhesko Institute of cardiology" NAMS of Ukraine (Narodnogo opolchenia str., 5, Kiev, Ukraine, 03680)

SEARCH FOR PROGNOSTIC MARKERS OF HEART FAILURE IN PATIENTS WITH CLINICALLY SUSPECTED MYOCARDITIS

Summary. *Prediction of myocarditis clinical course remains one of the most challenging problems in present cardiology. The purpose of the study was to build the prognostic model of persistent heart failure and to detect its early predictors in patients with myocarditis. We established the following predictors of sustained HF: high concentration of CD16+ cells, high antimyocardial antibody titer and pronounced blasttransformation lymphocyte activity, presence of non-sustained ventricular tachycardia, impairment of left ventricular (LV) ejection fraction and longitudinal global systolic strain, increased LV end-diastolic volume index, and presence of typical changes on cardiac magnetic-resonance imaging observed on the 1st month after the disease onset. By the use of discriminant analysis a prognostic model was built that is characterized by high sensitivity and specificity and could be used on the 1st month after myocarditis onset for the early prediction of HF persistence after 12 months of follow-up.*
Keywords: *myocarditis, heart failure, predictors, prognostic model.*

Introduction

Diagnosis of myocarditis for the present day remains one of the most challenging in the contemporary clinical practice. The disease does not have any specific clinical features and establishing of the right diagnosis frequently needs the use of expensive cardiac imaging and invasive techniques as also complex diagnostic approach and expert teems [8, 9, 14]. The real incidence of myocarditis remains unclear due to high amount of fast spontaneous resolve of myocardial inflammation in some cases and subclinical course of the disease [11, 13]. It is necessary to say that myocarditis is an actual social problem because the disease predominantly affects the young people of working age and could result in the development of sustained congestive heart failure (HF) as also in life-threatening states, such as cardiogenic shock, pulmonary edema, ventricular tachycardia and fibrillation, complete atrio-ventricular block, thromboembolism and others [5, 9, 14, 15]. Recently obtained data indicate the 5-year mortality in diffuse myocarditis with left ventricular (LV)

systolic dysfunction and clinical features of congestive HF up to 45% [8, 12].

The official diagnostic algorithms and guidelines for the diagnosis and treatment of this disease are still not managed not only by the European Society of cardiology (ESC) but also in other highly developed countries such as United States, Canada, Japan and others. Today for the use in clinical practice we have only the position statement of the ESC Working group on myocardial and pericardial diseases published by A.L.P. Caforio et al. in the year 2013 [7]. Now we also have Lake Louise Criteria for the diagnosis of myocarditis that are based on the results of cardiac magnetic-resonance imaging (MRI) and its analysis [2, 3, 4, 6]. Endomyocardial biopsy (EMB) with immunohistologic evaluation of infiltrative cells and polymerase chain reaction remains the "gold standard" but its use in real clinical practice is strictly limited [16]. Currently we have lack of information about the early predictors that could explain further clinical

course of myocarditis as also prognostic markers of long-term persistent congestive HF remain unstudied.

The *purpose* of the study was to build the prognostic model of persistent heart failure and to detect its early predictors in patients with myocarditis.

Material and methods

We included 82 patients with clinically suspected myocarditis that were treated in the department of non-coronary diseases and rheumatology of State institution "National scientific centre M.D. Strazhesko Institute of cardiology" NAMS of Ukraine between the years 2014 - 2016. At inclusion all patients had LV systolic dysfunction according to the Classification, standards of diagnosis and treatment of heart diseases in Ukraine - LV ejection fraction (EF) $\leq$ 45% and HF functional class II or higher according to New York Heart Association classification [1]. The average age was (39,7±2,9) years. All patients underwent for examinations twice: in the acute stage on the 1st month after the disease onset and after 12 months of follow-up.

Diagnosis of clinically suspected myocarditis was based on the presence of clinical features and diagnostic criteria according to the position statement of the ESC Working group on myocardial and pericardial diseases [7]. The diagnosis was confirmed by cardiac MRI. Included patients received only the standard treatment of congestive HF that consisted of ACE-inhibitors, β-blockers, antagonists of mineral-corticoid receptors and diuretics [10, 11, 12]. Anticoagulants and anti-arrhythmic drugs were prescribed by the indications. No one among included patients received immunosuppressive or immune-modulate treatments.

The functional class (FC) of HF according to NYHA was assessed on the base of appropriate recommendations and by the results of 6-minute walking test [10].

We studied peripheral blood concentrations of immunoglobulines class G and M (IgM and IgG), CD8+, CD16+ and CD19+ cells. Cardiospecific immunologic studies included measurement of average antimyocardial antibody (AMA) titers and assessment of blast transformation lymphocyte activity against myocardium (BTLAm) in the specimens of peripheral serum.

By the use of 24-hour ECG Holter monitoring system Philips Digitrack TM-plus 3100A we studied frequency of ventricular extrasystoles (VE) and incidence of non-sustained ventricular tachycardia (NSVT). We performed transthoracic 2-dimensional echocardiography (EchoCG) and speckle-tracking by the ultrasound apparatus Aplio Artida SSH - 880 CV, Toshiba Medical System Corporation (Japan) with the measurement of LV end-diastolic volume index (LV EDVi) and LV EF in four chamber position, longitudinal global systolic strain (LGSS), circumferential global systolic strain (CGSS) and radial global systolic strain (RGSS). Cardiac MRI was performed by the use imaging system Toshiba Vantage Titan HSR 1,5 Tesla (Japan) with assessment of hyperemia on T1-weighted images, edema on T2-weighted images and fibrosis on T1 delayed enhancement. Tomovist was used as a contrast. MRI images

were assessed according to Lake Louise Criteria - the sole for today imaging criteria of myocarditis.

For statistic processing we used program pack Statistica 6. By the use of Student criteria and having dynamic changes of studied parameters we established the most significant variables that could have influence on HF class after 12 months and evaluated their odds ratio (OR) and confidence interval (CI). The prognostic model was built using the most significant variables with help of discriminant analysis. Correlation analysis was performed by Pierson's pair correlation coefficient.

Results. Discussion

We established reliable direct correlation between concentrations of cardiospecific immunologic markers - AMA titer and RBTLm activity on the 1st month after the onset of myocarditis and HF class after 12 months (table 1). Among the markers of cell immunity we found reliable correlation of the HF 1-year persistence only with concentration of CD16+.

Correlation analysis of persistent HF with instrumental parameters obtained on the 1st month after myocarditis onset showed its strong correlations with LV EF and LV EDVi - r = -0,78; p <0,01 and r = 0,72; p <0,02 respectively. We also found direct correlation between the data obtained by novel imaging techniques (speckle tracking EchoCG, cardiac MRI) and persistent HF (table 1).

Thus, correlation analysis showed that high autoimmune activity and significant impairment of contractile function of LV during the 1st month after myocarditis onset could lead to development of persistent HF.

Table 2 demonstrates the role of investigated parameters taken on the 1st month after the disease onset in

Table 1. Correlation between laboratory and instrumental data obtained on the 1st month and persistence of HF ≥ II FC after 12 months in patients with myocarditis.

Studied marker on the 1st month	Correlation with HF ≥ II FC after 12 months
IgM	r = 0,26; p >0,05
IgG	r = 0,12; p >0,05
CD8+	r = 0,06; p >0,05
CD16+	r = 0,42; p <0,05
CD19+	r = 0,12; p >0,05
AMA titer	r = 0,66; p <0,02
BTLAm	r = 0,64; p <0,01
VE	r = 0,06; p >0,05
NSVT	r = 0,24; p >0,05
LV EF	r = -0,78; p <0,01
LV EDVi	r = 0,72; p <0,02
LGSS	r = 0,52; p <0,02
CGSS	r = 0,32; p >0,05
RGSS	r = -0,05; p >0,05
MRI changes (edema + hyperemia)	r = 0,66; p <0,01

Table 2. The role of immunologic and instrumental markers for HF persistence after 12 months in patients with myocarditis.

Studied marker on the 1st month	OR
IgM	0,87 (CI 0,77 - 1,49; p>0,05)
IgG	0,76 (CI 0,70 - 1,34; p>0,05)
CD8$^+$	1,12 (CI 0,81 - 1,57; p>0,05)
CD16$^+$	1,86 (CI 1,28 - 2,54; p<0,05)
CD19$^+$	0,81 (CI 0,69 - 1,55; p>0,05)
AMA titer	3,26 (CI 1,71 - 4,40; p<0,01)
BTLAm	4,12 (CI 2,39 - 6,24; p<0,01)
VE	1,16 (CI 0,81 - 1,79; p>0,05)
NSVT	2,06 (CI 1,38 - 3,44; p<0,05)
LV EF	5,36 (CI 3,57 - 7,33; p<0,02)
LV EDVi	4,56 (CI 3,08 - 6,99; p<0,01)
LGSS	3,09 (CI 1,98 - 4,80; p<0,01)
CGSS	1,31 (CI 0,76 - 2,10; p>0,05)
RGSS	0,68 (CI 0,51 - 1,09; p>0,05)
MRI changes (edema + hyperemia)	8,03 (CI 6,42 - 10,40; p<0,01)

development of HF persistence. The most significant role was established for high values of CD16$^+$, AMA titer, BTLAm activity, presence of NSVT, impairment of LV EF and LGSS, increased LV EDVi, and presence of typical MRI changes. On the other hand, such immune markers of humoral autoimmune response as IgM and IgG, and cell autoimmune response - CD8$^+$ and CD19$^+$ concentrations as also parameters of speckle tracking - CGSS and RGSS did not show pronounced influence on HF persistence.

Examinations in dynamics with the help of discriminant analysis allowed us to build mathematic model that could be used for early prediction of HF persistence during 12 months after the onset of myocarditis. The model consists of parameters with the highest values of OR for HF persistence and Wilks' Lambda and lowest values of Student's criterion p. The base of the model comprises two equations that on the 1st month from the disease onset give an opportunity to evaluate the probability in percentage of HF persistence: Y_1 - for improvement of HF NYHA FC to I or its absence after 12 months, Y_0 - for persistence of HF $\geq$ II FC. Thus by the use of this model even in the early stages of the disease we can assess likelihood of bad or good prognosis for patients with myocarditis.

Y_1 = -44,9 + 12,3 x CD16$^+$ + 7,26 x NSVT + 0,78 x AMA titer + 3,04 x BTLAm + 0,18 x LV EDVi - 0,43 x LGSS - 0,24 x LV EF

Y_0 = -58,1 + 11,5 x CD16$^+$ + 5,06 x NSVT + 0,66 x AMA titer + 2,88 x BTLAm + 0,16 x LV EDVi - 0,45 x LGSS - 0,26 x LV EF

Probability in percentage of HF improvement to NYHA class I or absence of HF after 12 months could be estimated by the formula: $Y_1/(Y_1 + Y_0)$ x 100%

Probability in percentage of HF?II FC persistence after 12 months could be estimated by the formula: $Y_0/(Y_1 + Y_0)$ x 100%

The sensitivity of the model is 84%, specificity - 78%, positive predictive value - 80%, negative predictive value - 86%.

Conclusions and future perspectives

1. We established predictors of HF 1-year persistence in patients with clinically suspected myocarditis: high values of CD16+, AMA titer, RBTLm activity, presence of NSVT, impairment of LV EF and LGSS, increased LV EDVi and presence of typical MRI changes that include edema and hyperemia on the 1st month after the disease onset.

2. With the help of discriminant analysis we built a prognostic model that is characterized by high sensitivity and specificity and could be used on the 1st month after myocarditis onset for the early prediction of HF persistence after 12 months of follow-up.

It is obvious for today that non-invasive distinguishing of myocarditis and prediction of its further clinical course is a challenging problem of present cardiologic science. For better understanding of this problem we need more investigations in this field that includes management of multicenter randomized clinical trials with rigorous selection of patients. In our opinion more attention must be paid to studies that could search for early predictors of severe clinical course of myocarditis.

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Чернюк С.В.

ПОИСК ПРОГНОСТИЧЕСКИХ МАРКЕРОВ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ У ПАЦИЕНТОВ С КЛИНИЧЕСКИ ПОДОЗРЕВАЕМЫМ МИОКАРДИТОМ

Резюме. *Прогнозирование клинического течения миокардита является одной из наиболее сложных задач современной кардиологии. Целью работы было построение прогностической модели персистирующей сердечной недостаточности (СН) и выявление ее предикторов у пациентов с клинически подозреваемым миокардитом. В результате проведенных исследований нами были установлены следующие предикторы сохранения СН через 12 месяцев от начала заболевания: высокая концентрация $CD16^+$ клеток, высокий титр антител к миокарду, повышение активности реакции бласттрансформации лимфоцитов, индуцированных миокардом, наличие пароксизмов нестойкой желудочковой тахикардии, низкие величины фракции выброса и продольной глобальной систолической деформации миокарда левого желудочка (ЛЖ), увеличение индекса конечно-диастолического объема ЛЖ, наличие типичных для миокардита изменений при магнитно-резонансной томографии сердца (отек и гиперемия), выявленные в первый месяц от дебюта миокардита. При помощи дискриминантного анализа построена прогностическая модель, характеризующаяся высокой чувствительностью и специфичностью, и при помощи которой уже в первый месяц от начала заболевания можно предсказать процентную вероятность сохранения СН через 12 месяцев.*
Ключевые слова: *миокардит, сердечная недостаточность, предикторы, прогностическая модель*

Чернюк С.В.

ПОШУК ПРОГНОСТИЧНИХ МАРКЕРІВ СЕРЦЕВОЇ НЕДОСТАТНОСТІ У ПАЦІЄНТІВ З КЛІНІЧНО ПІДОЗРЮВАНИМ МІОКАРДИТОМ

Резюме. *Прогнозування клінічного перебігу міокардиту на сьогоднішній день є одним з найскладніших завдань сучасної кардіології. Метою роботи була побудова прогностичної моделі персистування серцевої недостатності (СН) та виявлення її предикторів у пацієнтів з клінічно підозрюваним міокардитом. В результаті проведених досліджень нами були встановлені наступні предиктори збереження СН через 12 місяців від початку захворювання: висока концентрація $CD16^+$ клітин, високий титр антитіл до міокарду, підвищення активності реакції бласттрансформації лімфоцитів, індукованих міокардом, наявність пароксизмів нестійкої шлуночкової тахікардії, низькі величини фракції викиду і повздовжньої глобальної систолічної деформації лівого шлуночка (ЛШ), збільшення індекса кінцево-діастолічного об'єму ЛШ, наявність характерних для міокардита змін при магнітно-резонансній томографії (набряк і гіперемія), що виявляються в перший місяць від початку захворювання. За допомогою дискримінантного аналізу побудовано прогностичну модель, що характеризується високою чутливістю і специфічністю, і за допомогою якої вже в перший місяць від дебюту міокардиту можна спрогнозувати вірогідність збереження СН через 12 місяців.*
Ключові слова: *міокардит, серцева недостатність, предиктори, прогностична модель.*

Cherniuk Sergii - research associate, department of non-coronary heart diseases and rheumatology, PhD., State Institution "National scientific center "Institute of cardiology named by M.D. Strazhesko" National Academy of medical sciences of Ukraine, Kyiv; +38(050)7015965; vertebrata@bigmir.net

Бартюк Р.С., Московко С.П.

Вінницький національний медичний університет імені М.І. Пирогова, кафедра нервових хвороб з курсом нейрохірургії (вул. Пирогова, 56, м.Вінниця, Україна, 21018)

ЗМІНИ ЦЕРЕБРОВАСКУЛЯРНОЇ АУТОРЕГУЛЯЦІЇ У ХВОРИХ НА МІГРЕНЬ

Резюме. *Порушення судинної ауторегуляції є важливим компонентом патогенезу мігрені. Проаналізовано характер змін цереброваскулярних реакцій у відповідь на навантаження у здорових осіб та хворих на мігрень. Показано відмінності стану цереброваскулярної реактивності між даними групами. Отримані результати свідчать про гетерогенність судинних змін у хворих відносно односпрямованих реакцій у здорових.*
Ключові слова: *мігрень, цереброваскулярна ауторегуляція, реактивність церебральних судин.*