SAVREMENI KRITIČKI PRISTUP DIJAGNOZI AKUTNIH VIRUSNIH MIOKARDITA I INFLAMATORNIH KARDIOMIOPATIJA U KLINIČKOJ PRAKSI – FOKUS NA ULOGE EHOKARDIOGRAFIJE I ANTIVIRUSNIH ANTITELA.

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Sažetak: ZNAČAJ PROBLEMA: Dijagnoza akutnog virusnog miokarditisa je jedna od dijagnoza koje se najteže postavljaju u kardiologiji i medicini uopšte. Ehokardiografija i kardiomagnetna rezonaca imaju presudnu ulogu u kliničkoj dijagnozi a serumski titar antivirusnih antitela na kardiotropne viruse još uvek se neopravdano koristi za dijagnozu miokardita u svakodnevnoj praksi. **CILJEVI ISTRAŽIVANJA:** Analizirati učestalost i značaj ehokardiografskih parametara u dijagnozi klinički suspektnog akutnog virusnog miokardita, utvrditi kakvu ulogu ima dinamika titra antivirusnih antitela (AVA) za dijagnozu miokardita i izvršiti komparaciju virusne serologije u odnosu na ehokardiografske parametre dijastolne i sistolne funkcije leve komore. **METODOLOGIJA:** Urađena je retrogradna transverzalna studija u desetogodišnjem periodu od 2006. do 2015. godine, gde je analizirano 126 konsekutivnih pacijenata iz baze podataka Internističke ordinacije "Dr Bastać", sa radnom dijagnozom klinički suspektnog virusnog miokarditisa. Oni su klinički, EKG, ehokardiografski i serološki praćeni 4 do 8 nedelja zbog dinamike titra AVA. Ispitivana grupa (A) podeljena je na podgrupe: A1 sa povišenim titrom AVA klase IgM kod 43 (32%) ispitanika i podgrupu A2 bez povišenog titra IgM od 83 (68%) pacijenata. Kontrolna grupa zdravih (B) od 103 osobe je bila komparabilna. Statistička obrada je rađena u bazi EXCELL putem deskriptivne statistike, Studentovog-T testa i Hi² testa. **REZULTATI:** Klinički suspektan miokarditis (≥2 ESC kriterijuma) imalo je126 pacijenata. Dijastolna disfunkcija leve komore u 39/126 (31%) pacijenata je bio dominantni ehokardiografski kriterijum za klinički suspektan miokardit. Snižena ejekciona frakcije (EF<50%) izmerena je kod 19/126 (15%), praćena sa dilatacijom leve komore. Regionalna sistolna disfunkcija utvrđena je u 21/126 (17%) a promene u teksturi miokarda u 17 (13%) ispitanika. Klinička verovatnoća virusne etiologije je dijagnostički potkrepljena povišenim titrom antitela klase IgM kod 43 (32%) ispitanika (A1) gde dominiraju IgM antitela na virus Parvo B 19 u 36/43 pacijenata (84%). Većina je bila bez povišenog titra IgM antitela A2 (68%). Jasna dinamika titra IgM antitela zabeležen je u 23 osobe, pad titra IgM uz rast IgG titra (serokonverzija) u 13 bolesnika. Određivanje antisrčanih-autoantitela (AHA) je urađeno kod težih 17 slučajeva, od toga je 9 imalo pozitivna AHA. Komparacijom podgrupa A1 i A2 nije nađena statistički značajna razlika u ehokardiografskim parametrima. Grupa A klinički suspektnog miokardita u odnosu na kontrolnu grupu B ima stistički visoko značajno niže parametre globalne sistolne (EF=59,1±7,6 vs. 63±7,9; p<0,001), longitudinalne sistolne (S´=6,9±1,3 vs. 9,9±2,1) i dijastolne funkcije (E/e´11,9±4,8 vs. 8,7±4,6; p<0,001), te visoko statistički značajno povećanje teledijastolne dimenzije leve komore, indeksa mase miokarda i dimenzije leve pretkomore. **ZAKLJUČAK:** Dijagnoza akutnih virusnih miokardita u kliničkoj praksi postavlja se na osnovu kliničke slike, EKG i ehokardiografije koje upućuju na miokardit uz isključenje kardioloških komorbiditeta, na osnovu ESC kriterijuma za suspektan klinički miokarditis. A je imala visoko stistički značajno niže parametre sistolne i dijastolne funkcije u odnosu na kontrolnu grupu B. Normalan EKG i ehokardiografija ne mogu da služe za isključenje dijagnoze miokardita. Komparacijom A1 i A2 nije nađena statistički značajna razlika u ehokardiografskim parametrima Senzitivnost IgM titra na kardiotropne viruse je niska i ne treba je koristiti u rutinskoj dijagnozi miokardita.

Ključne reči: Akutni virusni miokarditis, Inflamatorna kardiomiopatija, serumska antitela na kardiotropne viruse, ehokardiografija, sistolna disfunkcija leve komore, dijastolna disfuncija leve komore

MODERN CRITICAL APPROACH TO THE DIAGNOSIS OF ACUTE VIRAL MYOCARDITIS AND INFLAMMATORY CARDIOMYOPATHIES IN CLINICAL PRACTICE - FOCUS ON THE ROLES OF ECHOCARDIOGRAPHY AND ANTIVIRUS ANTIBODIES.

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Summary: SIGNIFICANCE OF THE PROBLEM: The diagnosis of acute viral myocarditis is one of the diagnoses most difficult to make in cardiology and medicine in general. Echocardiography and cardiomagnetic resonance play a crucial role in the clinical diagnosis and the serum titer of antiviral antibodies to cardiotropic viruses is still unjustifiably used for the diagnosis of myocarditis in everyday practice. **RESEARCH OBJECTIVES:** To analyze the frequency and significance of echocardiographic parameters in the diagnosis of clinically suspected acute viral myocarditis, to determine the role of antiviral antibody titer (AVA) dynamics for the diagnosis of myocarditis and to compare viral serology and echocardiographic function versus echocardiographic function. **METHODOLOGY:** A retrograde transverse study was performed in the ten-year period from 2006. to 2015, where 126 consecutive patients from the database of the Office of Internal medicine ''Dr. Bastać'' were analyzed, with a working diagnosis of clinically suspected viral myocarditis. They were clinically, ECG, echocardiographically and serologically monitored for 4 to 8 weeks due to the dynamics of AVA titer. The examined group (A) was divided into subgroups: A1 with elevated AVA class IgM titer in 43 (32%) subjects and subgroup A2 without elevated IgM titer in 83 (68%) patients. The control group of healthy (B) of 103 subjects was comparable. Statistical processing was done in the EXCELL database via descriptive statistics, Student's-T test and Chi² test. **RESULTS:** 126 patients had clinically suspected myocarditis (≥2 ESC criteria). Diastolic left ventricular dysfunction in 39/126 (31%) patients was the dominant echocardiographic criterion for clinically suspected myocarditis. Reduced ejection fraction (EF <50%) was measured at 19/126 (15%), followed by left ventricular dilatation. Regional systolic dysfunction was found in 21/126 (17%) and changes in myocardial texture in 17 (13%) subjects. The clinical probability of viral etiology was diagnostically supported by elevated titer of IgM antibodies in 43 (32%) subjects (subgroup A1) where IgM antibodies to Parvo B 19 virus predominate in 36/43 patients (84%). Most were without elevated titer of IgM antibody- subgroup A2 83 (68%). Clear dynamics of IgM antibody titer was observed in 23 persons, a decrease in IgM titer with an increase in IgG titer (seroconversion) in 13 patients. Determination of anti-heart autoantibodies (AHA) was done in 17 severe cases, of which 9 had positive AHA. A comparison of subgroups A1 and A2 did not reveal a statistically significant difference in echocardiographic parameters. The whole group A of clinically suspected myocarditis compared to control group B has statistically highly significantly lower parameters of global systolic (EF=8,7±4,6 vs. 63±7,9; p<0,001), longitudinal systolic (S´=6,9±1,3 vs. 9,9±2,1) and diastolic function (E/e´11,9±4,8 vs. 8,7±4,6; p<0,001), and a highly statistically significant increase in left ventricular telediastolic dimension, myocardial mass index, and left atrial size. **CONCLUSION:** The diagnosis of acute viral myocarditis in clinical practice is made on the basis of the clinical picture, ECG and echocardiography that indicate myocarditis with the exclusion of cardiac comorbidities, based on the ESC criteria for suspected clinical myocarditis. The whole group A had highly statistically significantly lower parameters of systolic and diastolic function compared to control group B. Normal ECG and echocardiography cannot serve to exclude the diagnosis of myocarditis. Comparison of subgroups A1 and A2 did not reveal a statistically significant difference in echocardiographic parameters.

UVOD

Klinička slika miokarditisa je raznovrsna [1]. Miokarditis (MY) može biti uzrok iznenadne srčane smrti kod mladih odraslih osoba bez poznatih srčanih oboljenja u 20%, idiopatske ventrikularne tahikardije (VT) u 30%, akutne srčane insuficijencije u 10% [2,3]. MY je jedan od vodećih uzroka iznenadne srčane smrti i dilatacione kardiomiopatije (DCM) u mladih osoba [4,5]. U kliničkoj seriji iznenadne srčane smrti, MY je treći vodeći uzrok posle hipertrofične kardiomiopatije i kong enitalnih i aterosklerotskih bolesti koronarnih arterija [6]. Autopsijske studije pokazuju da je MY je čest uzrok DCM kod biopsijom dokazanog miokardita ali sa velikom varijacijom od serije do serije: od 0,5% do 67%, medijana je 10,3%. Zbog mogućnosti klinički tihog toka bolesti i retke biopsije miokarda, tačna učestalost: incidenca i prevalenca MY i inflamatorne kardiomiopatije (ICM) nije poznata [7,8].

Miokarditis (MY) ili inflamacija miokarda može biti rezultat multiplih uzroka, ali je uobičajeno vezana za infektivne agense i više od 20 virusa koji oštećuju miokard direktnom invazijom, produkcijom kardiotoksičnih supstanci i inflamacijom, sa ili bez perzistentne infekcije kao i autoimune rekacije na srčane epitope [7,9,10,11]. AVMY je jedan od najvećih izazova u pogledu kako dijagnoze, tako i terapije [7,12]. Klinička klasifikacija AVMY [7,13]:

1. Moguć subklinički akutni miokarditis (tipični virusni sindrom bez srčanih simptoma a sa EKG promenama, pozitivnim biomarkerima CKMB i troponin, uz ehokardiografski nalaz: pad EF i regionalne anomalije pokretljivoisti zidova leve komore i promene u teksturi miokarda)
2. Verovatan klinički akutni miokarditis (sve predhodno+ simptomi: bol, kratkoća daha, palpitacije etc.)
3. Definitivni miokarditis (potvrdjen patohistološki, imunohistohemijski i PCR virusni genom putem EMB)
   Ova klasifikacija još uvek nije revidirana putem kardiomagnetne rezonance (CMR), što bi bilo neophodno.

Termin ICM uveden 1995. godine od strane Svetske zdravstvene organizacije [14] i podrazumeva miokarditis sa sistolnom disfunkcijom i/ili dilatacijom leve komore, ali on ne opisuje fenotip i ne definiše uročnika [15]. Po toku se virusni miokarditisi dele na subakutni i hronični, često se govori o njima ali retko se dokazuju [15].

Postoji promena najčešće vrste uzročnika virusnih miokarda, ranije su to bili Koksaki B virusi i adenovirusi a poslednje dve decenije Parvo B19, herpes virus tip 6, hepatitis C virus, a sada ređe koksaki B virusi, adenovirusi, Epštajn-Bar-ov virus i Citomegalovirus. [7,11,12]. Miokarditis takođe može da se razvije u bolesniika sa HIV infekcijom, hepatitisom C ili Lajmskom bolešću [7,11,12]. Najskorije od 2019. u toku COVID 19 epidemije javljaju se dokazani slučajevi miokarditisa izazvanog virusom SARS CoV-2, ali se o tome još nedovoljno zna [16-20].

Najveći broj bolesnika sa akutnim virusnim miokarditisom se oporavi bez sekvela, ali jedan deo bolesnika progredira u hroničnu inflamatornu i dilatacionu kardiomiopatiju, srčanu insuficijenciju i bude kandidat za transplantaciju srca [1,5,12,13,15].

Do danas ne postoji takozvani neinvazivni zlatni standard za dijagnozu AVMY zbog niske specifičnosti i senzitivnosti tradicionalnih dijagnostičkih testova, ali razvoj kardiomagnetne rezonance je obećavajući [12,21,22]. Endomikardna biopsija sa patohistološkim pregledom i prisustvom virusnog genoma jesu najpouzdanije metode, ako se dobiju reprezentativni uzorci miokarda [7,9] i ona omogućavaju primenu terapijskog algoritma, ali je ova invazivna dijagnostika uglavnom rezervisana za teže i nejasne slučajeve inflamatornih kardiomiopatija. Zato klinička slika, EKG, biomarkeri i imaging metode, prvenstveno u praksi najlakše izvodljiva ehokardiografija i sve više magnetna rezonanca, mogu u vidu mozaika da komplementarno slože dijagnozu miokardita na osnovu kliničke slike i različitih dijagnoističkih kategorija sa ESC skorom od 2 i više bodova [11,12].

Glavne tegobe AVMY su uobičajeno: umor, palpitacije, bol u grudima, nedostatak vazduha pri naporu a fizikalnim pregledom se otkriva tahikardija, oslabljen prvi ton S1 i često ritam S3 galopa i de novo mezosistolni šum [13,15,21]. Uobičajeni EKG nespecifični nalaz kod klinički suspektnog AVMY je najčešće sinusna tahikardija i razne disritmije: ventrikularne i supraventrikularne ekstrasistole, retko ventrikularna tahikardija i atrijalna fibrilacija i ređe bradikardija i srčani blokovi; EKG promene u ST segmentu i T talasu su dosta specifične za leziju miokarda: tranzitorne

The sensitivity of IgM titer to cardiotropic viruses is low and should not be used in routine diagnosis of myocarditis.
key words: Acute viral myocarditis, inflammatory cardiomyopathy, serum antibodies to cardiotropic viruses, echocardiography, left ventricular systolic dysfunction, left ventricular diastolic dysfunction

INTRODUCTION

The clinical picture of myocarditis is diverse [1]. Myocarditis (MY) can be the cause of sudden cardiac death in young adults without known heart disease in 20%, idiopathic ventricular tachycardia (VT) in 30%, acute heart failure in 10% [2,3]. MY is one of the leading causes of sudden cardiac death and dilated cardiomyopathy (DCM) in young people [4,5]. In the clinical series of sudden cardiac death, MY is the third leading cause after hypertrophic cardiomyopathy and congenital and atherosclerotic coronary artery disease. [6]. Autopsy studies show that MY is a common cause of DCM in biopsy-proven myocarditis but with large variation from batch to batch: from 0.5% to 67%, the median is 10.3%. Due to the possibility of clinically silent disease and infrequent myocardial biopsy, the exact frequency: incidence and prevalence of MY and inflammatory cardiomyopathy (ICM) is unknown [7,8]. Myocarditis (MY) or myocardial inflammation can be the result of multiple causes, but is commonly associated with infectious agents and more than 20 viruses that damage the myocardium by direct invasion, production of cardiotoxic substances, and inflammation, with or without persistent infection and autoimmune reactions to cardiac epitopes [7,9,10,11]. AVMY is one of the biggest challenges in terms of both diagnosis and therapy [7,12]. Clinical classification of AVMY [7,13]:

1. Possible subclinical acute myocarditis (typical viral syndrome without cardiac symptoms and with ECG changes, positive biomarkers of CK-MB and troponin, with echocardiographic findings: decreased EF and regional anomalies of left ventricular wall mobility and changes in myocardial texture)
2. Probable clinical acute myocarditis (all previous + symptoms: pain, shortness of breath, palpitations, etc.)
3. Definitive myocarditis (confirmed pathohistological, immunohistochemical and PCR viral genome via EMB)

This classification has not yet been revised by cardiomagnetic resonance imaging (CMR), which would be necessary. The term ICM was introduced in 1995 by the World Health Organization [14] and involves myocarditis with systolic dysfunction and/or left ventricular dilatation, but it does not describe the phenotype and does not define the cause [15]. By their course, viral myocardites are divided into subacute and chronic, they are often talked about but rarely proven[15].

There is a change in the most common types of viral myocarditis, previously Coxsackie B viruses and adenoviruses, and in the last two decades Parvo B19, herpes virus type 6, hepatitis C virus, and now less commonly Coxsackie B viruses, adenoviruses, Epstein-Barr virus and Cytomegalovirus [7,11,12]. Myocarditis can also develop in patients with HIV infection, hepatitis C or Lyme disease. [7,11,12]. Proven cases of myocarditis caused by the SARS CoV-2 virus have been occurring since 2019 during the COVID 19 epidemic, but not enough is known about it [16-20].

Most patients with acute viral myocarditis recover without sequelae, but some patients progress to chronic inflammatory and dilated cardiomyopathy, heart failure, and become candidates for heart transplantation [1,5,12,13,15].

To this day, there has not existed the so-called non-invasive gold standard for AVMY diagnosis due to the low specificity and sensitivity of traditional diagnostic tests, but the development of cardiomagnetic resonance imaging is promising [12,21,22]. Endomycardial biopsy with pathohistological examination and the presence of viral genome is the most reliable method, if representative myocardial samples are obtained [7,9] and it allows the application of a therapeutic algorithm, but this invasive diagnosis is mostly reserved for more severe and unclear cases of inflammatory cardiomyopathies. Therefore, the clinical picture, ECG, biomarkers and imaging methods, primarily in practice the easiest echocardiography and increasingly magnetic resonance imaging, can, in the form of a mosaic, complement the diagnosis of myocarditis based

promene u ST segmentu i T talasu, depresija ili elevacija ST segmenta, duboki negativni T talasi, blok leve grane Hissovog snopa i nekad slika infarkta miokarda [13,15, 21].

Laboratorijski se otkrivaju povišeni srčani troponini a postoje i noviji markeri. Kod dece sa fulminantnim miokarditisom, viši nivo kreatinina, laktata i aspartat-transaminaze (AST) u serumu povezan je sa povećanim mortalitetom u bolnici [23]. Natriuretički peptid (NT-pro-BNP) je povišen kod dece sa akutnom ICM-om i generalno brzo opada pri oporavku funkciju leve komore [24]. Kod odraslih su veće koncentracije interleukina-10 povezane sa povećanim rizikom od smrti. Zabeleženo je da antitela na miokard (AHA) predviđaju povećan rizik od smrti ili potrebu za transplantacijom [25]. Titrovi cirkulišućih virusnih antitela nisu u dobroj korelaciji sa tkivnim virusnim genomima i zbog niske senzitivnosti retko su za korisni za dijagnostičku upotrebu u praksi [11,12,26].

NEINVAZIVNE SLIKOVNE TEHNIKE SNIMANJA (imaging). Koncept imidžinga je evoluirao od monomodaliteta u multimodalitet imidžing strategiju gde svaki test dodaje informacije koje povećavaju specifičnost dijagnostičkog markera za dijagnozu miokarditisa. Transtoraksna Ehokardiografija (TTE) je najdostupnija metoda uz bolesničku postelju a kojom može da se posumnja na miokarditis. Ehokardiografski znaci klinički suspektnog AVMY su variabilni i heterogeni: najčešće disfunkcija leve komore uz poremećaje regionalne segmentne kinetike, dilatacija leve komore ili perikardni izliv, retko intrakardijalni tromb ali nalaz može da bude i normalan [11,12,27]. Kada je ehokardiografski prozor neadekvatan, važan korak u dijagnostici je transezofagusna ehokardiografija [28]. Imidžing deformacije putem spekl treking strejn ehokardiografije (speckle tracking strain) obično pokazuje snižen longitudinalni patern deformacije miokarda ali to je takođe nespecifičan znak bolesti miokarda. Prednost metode je što može da prepozna rane promene funkcije miokarda pre nego što ih vidimo uz pomoć „običnih" ili konvencionalnih metoda koje se zasnivaju na merenju ejekcione frakcije leve komore (EF) [29,30,31,32,33]. Sniženje globalne longitudinalne deformacije (GLS) ima dijagnostičku vrednost i utiče na prognozu bolesti kod inflamatorne kardiomiopatije i srčane insuficijencije. Srčana magnetna rezonanca (CMR) je korisna u postavljanju

dijagnoze AVMY i za praćenje napredovanja bolesti, a prisustvo kasnog nakupljanja gadolinijuma (LGE) je najbolji nezavisni prediktor za srčani mortalitet [21,34,35]. CMR pokazuje a vezivanje gadolinijuma u medijalnom delu miokarda leve komore i subepikardno, što se potpuno razlikuje od nalaza kod ishemijske kardiomiopatije [9,11,12,35].

Endomiokardna biopsija (EMB) sa patohistološkim pregledom i prisustvom virusnog genoma putem PCR i imunohistohemijskih dokaza inflamacije jesu najpouzdanije metode i omogućavaju primenu terapijskog algoritma, ali je ova invazivna dijagnostika uglavnom rezervisna za teške slučajeve i kardiomiopatije [7,9]. Ako uzorci miokarda nisu reprezentativni mogući su lažno negativni nalazi EMB. Ipak većina autoriteta podržava koncept da EMB treba da bude zlatni standard za dijagnozu definitivnog miokarditisa. [7,9,11,12].

U osnovi lečenja AVMY je lečenje srčane insuficijencije i aritmija. Specifično lečenje za fulminantni i akutni AVMY je antivursna terapija a za posvirusni hronični autoreaktivni miokarditis je imunosupresivna terapija kortikosteroidima i ciklosporinom [36] te u najnovije vreme CD3 muromonab-om [22].

CILJEVI ISTRAŽIVANJA: Analizirati vrstu i značaj ehokardiografskih parametara i karakteristika u dijagnozi klinički suspektnih akutnih virusnih miokarditisa u svakodnevnoj praksi. Utvrditi kakvu ulogu ima dinamika titra antivirusnih antitela za dijagnozu klinički suspektnog akutnog virusnog miokarditisa i izvršiti komparaciju virusne serologije u odnosu na ehokardiografske parametre dijastolne i sistolne funkcije leve komore.

MATERIJAL I METODE

Urađena je retrogradna transverzalna studija u desetogodišnjem periodu od 2006. do 2015. godine gde je izdvojeno iz baze podataka Internističke ordinacije "Dr Bastać", 126 konsekutivnih pacijenata klinički suspektnih na akutni virusni miokardit (grupa A) koji su klinički, ehokardiografski i serološki praćeni zbog dinamike titra antitela na kardiotropne viruse. Ispitivana grupa (A) je bila prosečne starosti 43,3± 8,9 godina, indeksa telesne mase BMI 27,8 ± 5,9 , dominira ženski pol-78 (62%). Srednje vrednosti sistolnog i dijastolnog pritiska na dolasku su bile -127 ± 14 /78 ± 11 mmHg. Kontrolna grupa (B) je bila komparabilnih

on the clinical picture and various diagnostic categories with an ESC score of 2 or more points [11,12].

The main symptoms of AVMY are common: fatigue, palpitations, chest pain, shortness of breath on exertion; physical examination reveals tachycardia, weakened first S1 tone and often S3 gallop rhythm and de novo mesosystolic murmur [13,15,21]. The usual ECG nonspecific finding in clinically suspected AVMY is most commonly sinus tachycardia and various dysrhythmias: ventricular and supraventricular extrasystoles, rarely ventricular tachycardia and atrial fibrillation, and less frequently bradycardia and heart blocks; ECG changes in the ST segment and T wave are quite specific for myocardial lesions: transient changes in the ST segment and T wave, depression or elevation of the ST segment, deep negative T waves, block of the left branch of the His bundle and sometimes images of myocardial infarction [13,15,21].

Elevated cardiac troponins are detected in the laboratory and there are also newer markers. In children with fulminant myocarditis, higher levels of creatinine, lactate and aspartate transaminase (AST) are associated with increased hospital mortality [23]. Natriuretic peptide (NT-pro-BNP) is elevated in children with acute ICM and generally declines rapidly in recovery of left ventricular function [24]. In adults, higher concentrations of interleukin-10 are associated with an increased risk of death. Myocardial antibodies (AHAs) have been reported to predict an increased risk of death or the need for transplantation. [25]. Circulating viral antibody titers do not correlate well with tissue viral genomes and are rarely useful for diagnostic use in practice due to their low sensitivity [11,12,26].

NON-INVASIVE IMAGING TECHNIQUES. The concept of imaging has evolved from a monomodality to a multimodality imaging strategy where each test adds information that increases the specificity of the diagnostic marker for the diagnosis of myocarditis. Transthorax Echocardiography (TTE) is the most available method at the patient's bed, which can be used to suspect myocarditis. Echocardiographic signs of clinically suspected AVMY are variable and heterogeneous: most often left ventricular dysfunction with regional segmental kinetic disorders, left ventricular dilatation or pericardial effusion, rarely intracardiac

thrombus, but the finding can be normal, too [11,12,27]. When the echocardiographic window is inadequate, an important step in diagnostics is transesophageal echocardiography [28]. Imaging of deformation by speckle tracking echocardiography (speckle tracking strain) usually shows a reduced longitudinal pattern of myocardial deformation but it is also a non-specific sign of myocardial disease.The advantage of the method is that it can recognize early changes in myocardial function before we see them using "ordinary" or conventional methods based on measuring the ejection fraction of the left ventricle (EF) [29,30,31,32,33]. Reduction of global longitudinal deformation (GLS) has a diagnostic value and affects the prognosis of the disease in inflammatory cardiomyopathy and heart failure. Cardiac magnetic resonance imaging (CMR) is useful in diagnosing AVMY and for monitoring disease progression, and the presence of late gadolinium accumulation (LGE) is the best independent predictor of cardiac mortality [21,34,35]. CMR shows a gadolinium binding in the medial part of the left ventricular myocardium and subepicardially, which is completely different from the findings in ischemic cardiomyopathy [9,11,12,35].

Endomyocardial biopsy (EMB) with pathohistological examination and the presence of viral genome by means of PCR and immunohistochemical evidence of inflammation is the most reliable method and allows the application of a therapeutic algorithm, but this invasive diagnosis is mostly reserved for severe cases and cardiomyopathies [7,9]. If myocardial samples are not representative, false-negative EMB findings are possible. Yet most authorities support the concept that EMB should be the gold standard for the diagnosis of definitive myocarditis [7,9,11,12].

The basis of AVMY treatment is the treatment of heart failure and arrhythmias. Specific treatment for fulminant and acute AVMY is antiviral therapy and for post-viral chronic autoreactive myocarditis the treatment is immunosuppressive therapy with corticosteroids and cyclosporine [36] and more recently with CD3 muromonab [22].

RESEARCH OBJECTIVES: To analyze the type and significance of echocardiographic parameters and characteristics in the diagnosis of clinically suspected acute viral myocarditis in everyday practice. To determine the role of

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karakteristika: 103 osobe prosečne starosti 46±12 godina, indeksa telesne mase BMI 29,3±6,4, 53 osobe (52%) ženskog pola. Srednje vrednosti sistolnog i dijastolnog pritiska na dolasku su bile 136 ± 14 / 71 ± 11 mmHg. **Kriterijumi isključivanja** Odsustvo hipertenzije, poznate koronarne bolesti, valvularnih mana drugih relevantnih bolesti i sa niskom pre-test verovatnoćom (PTP) <15% na ishemijsku bolest srca. **Kriterijumi**

uključivanja: korišćeni su najpre kriterijumi Dennerta i saradnika iz 2007.godine [7] a kasnije su re-evualirani putem kriterijuma Radne grupe za bolesti miokarda i perikarda Evropskog udruženja kardiologa iz 2013. godine za klinički suspektan miokarditis [11]. Bilo je potrebno da imaju najmanje 2 kriterijuma: najmanje jedan iz grupe kliničkih prezentacija i najmanje jedan iz grupe dijagnostičkih kategorija što je prikazano na TABELI 1 [11]:

TABELA 1. Kriterijumi Radne grupe za bolesti miokarda i perikarda Evropskog udruženja kardiologa iz 2013. godine za klinički suspektan miokarditis [11]

ESC KRITERIJUMI ZA KLINIČKI SUSPEKTAN MIOKARDITIS:	
JEDAN ILI VIŠE ≥1-KRITERIJUMA KLINIČKIH PREZENTACIJA (1-5)	≥ 1 DG KRITERIJUMA IZ RAZLIČITIH KATEGORIJA (I-IV),
1. SLIČNA AKUTNOM KORONARNOM SINDROMU	I. EKG: EKG/HOLTER/ STRES TEST- nove abnormalnosti, bilo šta od sledećeg: 1. blok I-III stepena ili blok grane, 2. ST/T promene-ST elevacija/depresija ili bez, inverzija T talasa 3. sinusni arrest, VT ili komorski flater i asistolija, 4. AF, 5. redukovana amplituda R zubca, 6. intraventrikularni blok 7. Q zubac 8. niska voltaža 9. česte VES 10. PSVT
2. De novo ILI POGORŠAVAJUĆA SRČANA INSUFICIJENCIJA u odsustvu koronarne bolesti i drugih poznatih uzroka srčen slabosti	II. MARKERI MIOKARDIOCITOLIZE (troponini I, T)
3. HRONIČNA SRČANA INSUFICIJENCIJA 4 .PALPITACIJE I/ILI NEOBJAŠNJENI SIMPTOMI ARITMIJE I/ILI PRESINKOPA I SINKOPA I/ILI REANIMIRANI PACIJENTI	III FUNKCIONALNE I STRUKTURNE ANOMALIJE MIOKARDA- EHOKARDIOGRAFIJA , CMR, PET, PET CT SKEN Nove, drugačije, neobjašnjene LV i/ili RV strukturne i funkcijske abnormalnosti: 1. regionalni poremećaji kinetike segmenata ili 2. globalne sistolne ili dijast. anomalije sa ili bez: 3. dilatacije komora, sa ili bez 4. povećane debljine zida, sa ili bez 5.perikardnog izliva i sa ili bez 6.endokavitarnog tromba
5. NEOBJAŠNJENI KARDIOGENI ŠOK	IV. KARAKTERIZACIJA TKIVA na Kardiomagnetnoj rezonanci (CMR) –edem, kasno nakupljanje gadolinijuma mezomikardno ili subepikardno (LGE) klasični miokardni obrazac
Ako je pacijent asimptomatičan- 2 ili više kriterijuma iz različitih Dg. kategorija	

METODOLOGIJA. Uz rutinske kliničke metode: anamneza i fizikalni pregled, EKG, antropometrija, osnovna biohemija krvi, svima je rađena ehokardiografija i serologija IgM i IgG antivirusnih antitela. U pojedinačnim slučajevima je rađena radiografija toraksa , te troponin T, pro BNP i D dimer. Vrlo retko je finalizovan predloženi pregled na kardio-magnetnoj rezonanci, dok je endomiokardna biopsija urađena samo kod 2 pacijenta.

EHOKARDIOGRAFIJA. Ehokardiografski pregledi su obavljani pomoću aparata marke „*Toshiba Power Vision 6000*", *Toshiba Xario CV* i *GE Vivid 7* multifrekventnim sektorskim sondama od 2,0 do 4,5 MHz sa harmonskom slikom (harmonic imaging). Svi ispitanici su podvrgnuti pregledu standardnim protokolom prema tada važećim preporukama [37,38] a

interpretirani su u svetlu najnovijih preporuka za standarde u izvođenu ehokardiografije [39,40]. Ehokardiografski pregledi su vršeni metodama konvencionalne M-mode i dvodimenzionalne (B-mod) ehokardiografije, a takođe je izvršena i Doppler analiza transmitralnog protoka tokom dijastole, kao i pregled metodom pulsnog tkivnog (Tissue) Doppler-a. Od strukturnih parametara, izmereni su između ostalih: dijametar leve pretkomore (LA), teledijastolni dijametar leve komore (LVEDD), telesistolni dijametar leve komore (LVESD), debljina zadnjeg zida leve komore (PWTd) i interventrikularnog septuma u dijastoli (IVSTd). Kriterijum za dilatacija leve komore bio je teledijastolna dimenzija leve komore ≥54mm za žene i ≥59mm za muškarce) [37]. Volumeni leve komore i ejekcione frakcije

antiviral antibody titer dynamics for the diagnosis of clinically suspected acute viral myocarditis and to compare viral serology in relation to echocardiographic parameters of diastolic and systolic function of the left ventricle.

MATERIAL AND METHODS

A retrograde transverse study was performed in the ten-year period from 2006 to 2015, where 126 consecutive patients clinically suspected of acute viral myocarditis, were isolated from the database of the Office of Internal medicine ''Dr. Bastać'', having been clinically, echocardiographically and serologically monitored due to the dynamics of antibody titers to cardiotropic antibodies. The examined group had an average age of 43.3 ± 8.9 years, body mass index BMI 27.8 ± 5.9, dominated by female gender-78 (62%). Mean values of systolic and diastolic pressure on arrival were -127 ± 14/78 ± 11 mmHg. The control group had

comparable characteristics: 103 persons with average age 46 ± 12 years, body mass index BMI 29.3 ± 6.4, 53 persons (52%) female. Mean systolic and diastolic pressure on arrival were 136 ± 14/71 ± 11 mmHg

Exclusion criteria: Absence of hypertension, known coronary heart disease, valvular defects of other relevant diseases and with low pre-test probability (PTP) <15% on ischemic heart disease. **Inclusion criteria:** the criteria of Dennert et al. from 2007 were used first [7] and later were re-evaluated through the criteria of the Working Group on Myocardial and Pericardial Diseases of the European Society of Cardiology from 2013 for clinically suspected myocarditis [11]. 2 criteria at least were required: one at least from the group of clinical presentations and one at least from the group of diagnostic categories as shown in the **TABLE1** [11]

TABLE 1. The criteria of the Working Group on Myocardial and Pericardial Diseases of the European Society of Cardiology from 2013 for clinically suspected myocarditis [11]

ESC CRITERIA FOR CLINICALLY SUSPECT MYOCARDITIS:	
ONE OR MORE ≥1-CRITERIA OF CLINICAL PRESENTATIONS (1-5)	≥ 1 DG CRITERIA FROM DIFFERENT CATEGORIES (I-IV),
1. SIMILAR TO ACUTE CORONARY SYNDROME	I. ECG: ECG / HOLTER / STRESS TEST- new abnormalities, any of the following: 1. block I-III degree or branch block, 2. ST / T changes-ST elevation / depression or without, T wave inversion 3. sinus arrest, VT or ventricular flutter and asystole, 4. AF, 5. reduced amplitude of R tooth, 6.intraventricular block 7. Q tooth 8. low voltage 9. frequent VES 10. PSVT
2. De novo OR EXCESSIVE HEART FAILURE in the absence of coronary heart disease and other known causes of heart failure	II. MYOCARDIOCYTOLYSIS MARKERS (troponins I, T)
3. CHRONIC HEART FAILURE 4 .PALPITATIONS AND/OR UNEXPLAINED SYMPTOMS OF ARRHYTHMIA AND/OR PRESINCOPE AND SYNCOPE AND/OR RESUSCITATED PATIENTS	III FUNCTIONAL AND STRUCTURAL ANOMALIES OF THE MYOCARDIUM - ECHOCARDIOGRAPHY, CMR, PET, PET CT SCAN New, different, unexplained LV and/or RV structural and functional abnormalities: 1. regional disorders of segment kinetics or 2. global systolic or diastolic anomalies with or without: 3.ventricular dilatation, with or without 4. increased wall thickness, with or without 5.pericardial effusion and with or without 6.endocavitary thrombus
5. UNEXPLAINED CARDIOGENIC SHOCK	IV. TISSUE CHARACTERIZATION on Cardiomagnetic Resonance (CMR) -edema, late gadolinium accumulation mesomicardially or subepicardially (LGE) classic myocardial pattern
If the patient is asymptomatic - 2 or more criteria from different Dg. categories	

METHODOLOGY. In addition to routine clinical methods: anamnesis and physical examination, ECG, anthropometry, basic blood biochemistry, echocardiography and serology of IgM and IgG antiviral antibodies were performed

on all of them. In individual cases, radiography of the thorax was performed, as well as troponin T, pro BNP and D dimer. Very rarely, the proposed examination on cardio-magnetic resonance imaging was completed, while

leve komore (EF) su automtski izračunavani putem Teicholtz metode i biplejn Simpsonovog pravila [37] a zatim su izračunati masa leve

komore (LVM) formulom po Devereux-u i indeks mase leve komore (LVMI).

$$(\text{LVMI (g/m}^2) = [(TDD + ZZd + IVSd)^3 - TDD^3] \times 1.05 - 13.4 / BSA \text{ (m}^2) \quad [37]$$

Normalna masa miokarda je za muški pol do 224 g a za ženski do 162g. Indeks mase miokarda je za ženski pol manje od 95 g/m², za muški manje od 115 g/m². Dijastolna funkcija je procenjena merenjem maksimalne brzine rane (E) i kasne (A) faze komorskog punjenja, vreme decelacije E brzine (DTE, normalno 160-200 ms), kao i izračunavanjem odnosa E/A (normalno E/A ≥0.8). Tehnikom tkivnog Doppler-a, izvršena su merenja tkivnih dijastolnih (e´) i sistolnih brzina (S´) miokarda na septalnoj i lateralnoj strani mitralnog anulusa i uzimana je srednja vrednost (e´), a potom je izračunat odnos E/e´ [38], kao surogat pritiska punjenja leve komore Dijastolna funkcija je kategorizovana kao:

(a) normalna (E/A ≥0.8 - <1.5, vreme decelacije E brzine-DTE >160 ms, srednji E/e´≤8);

(b) Stepen 1, oštećena relaksacija (E/A <0.8, DTE >200 ms, srednji E/e´≤8);

(c) Stepen 2, Pseudonormalizacija (E/A ≥0.8 and <1.5, DTE 160–200 ms, srednja E/e´ = 9–12);

(d) Stepen 3, Restiktivni obrazac (E/A ≥1.5, DTE <160 ms, srednja E/e´ ≥13).

Regionalni poremećaji u kontraktilnosi leve komore jesu segmentne hipokinezije, akinezije, diskinezije. Promene u teksturi miokarda; hiperehogene ektenzivne subendokardne ili transmuralne zone su jasan nalaz dok ovalne hiperehogene zone miokarda- najčešće u intraventrikularnom septumu su

kontraverzan parametar. Značajne su samo ekstenzivne zone ili 3 manje zone prečnika ≥3mm ili pak transmuralno zahvatanje (znaci fibroze i cicatrixa) uz hipokineziju. Na osnovu gore navedenih kriterijuma se postavljao klinički suspektan miokarditis–tim pacijentima se (do 2015.) rutinski određivao serumski nivo antitela IgM I IgG na Parvo B19, Koksaki i Adenovrus, a izuzetno i na ređe potencijalne izazivače (Ebštajn Bar virus, citomegalovirus, virus influence, hepatitis C) određivan iz 2 uzorka uparenih seruma na 2 do 8 nedelja. Antivirusna antitela i antisrčana antitela su određivana enzimo-imunološkom metodom (ELISA). **Na osnovu pozitivnosti IgM antivirusnih antitela ispitivana grupa (A) je podeljena na podgrupe:** A1 sa povišenim titrom antitela klase IgM kod 43 (32%) ispitanika (PODGRUPA A1) i A2 bez povišenog titra IgM antitela (Grupa A2)- 83 (68%) pacijenata. (PODGRUPA A2). Statistička obrada je rađena u bazi EXCEL putem metoda deskriptivne statistike, Studentovog-T testa i Hi² testa.

REZULTATI

Klinički suspektan miokarditis (grupa A) sa ≥2 ESC kriterijuma imalo je 126 pacijenata (GRUPA A). Najčešći simptomi su bile palpitacije 107/126 (85%), bol u grudima 83/126 (66%) i zamaranje, osećaj umora, nedostatak vazduha i dispneja na napor 62/126 (49%) u raznim kombinacijama (TABELA2)

TABELA 2. Simptomi, fizikalni znaci i EKG promene kod pacijenata grupe A sa suspektnim miokarditisom i/ili inflamatornom kardiomiopatijom

Simptomi i fizikalni znaci kod klinički suspektnog miokarditisa - kliničke prezentacije	Grupa A N=126	%
SIMPTOMI - KLINIČKE PREZENTACIJE		
I. Palpitacije	106	84%
II. Bol u grudima: anginozni, perikardni ili pseudishemični	83	66%
III. Zamaranje, osećaj umora, Dispneja-nedostatak vazduha pri naporu	62	49%
IV. Simptomi i znaci hronične srčane insuficijencije	21	17%
V. Životno ugrožavajuća stanja: Akutna srčana insuficijencija	3	2%
FIZIKALNI ZNACI		
Tahikardija >90/min u miru	106	84%
Bradikardija<50/min u miru	3	2,4%
Nepravilan srčani ritam-disritmije	102	81%
Mukli tonovi/ritam galopa	3	2.4%
De novo sistolni šum	2	1,6%

endomyocardial biopsy was performed in only 2 patients.

Echocardiography. Echocardiographic examinations were performed using Toshiba Power Vision 6000, Toshiba Xario CV and GE Vivid 7 multifrequency sector probes from 2.0 to 4.5 MHz with harmonic imaging. All subjects underwent standard protocols, according to the then valid recommendations [37,38]and they were interpreted in the light of the latest recommendations for standards in performing echocardiography [39,40]. Echocardiographic examinations were performed by conventional M-mode and two-dimensional (B-mode) echocardiography, and Doppler analysis of transmitral flow during diastole was performed, as well as pulse tissue Doppler examination.Of the

structural parameters, left ventricular diameter (LA), left ventricular telediastolic diameter (LVEDD), left ventricular telesystolic diameter (LVESD), posterior left ventricular wall thickness (PWTd), and interventricular septum IV were measured. The criterion for left ventricular dilatation was the telediastolic dimension of the left ventricle ≥54mm for women and ≥59mm for men) [37]. Left ventricular volumes and left ventricular ejection fractions (EF) were automatically calculated using the Teichholz method and biplane Simpson method [37] and then the left ventricular mass (LVM) was calculated by the Devereux formula and the left ventricular mass index (LVMI).

$$(\text{LVMI (g/m}^2) = [(TDD + ZZd + IVSd)^3 - TDD^3] \times 1.05 - 13.4 / BSA(m^2)\ [37]$$

Normal myocardial mass is up to 224 g for males and up to 162 g for females. Myocardial mass index is less than 95 g/m² for females and less than 115 g/m² for males. Diastolic function was assessed by measuring the maximum velocity of the early (E) and late (A) phases of ventricular filling, the deceleration time of the E velocity (DTE, normally 160-200 ms), and by calculating the E/A ratio (normal E/A ≥0.8). Using the tissue Doppler technique, measurements of tissue diastolic (e') and systolic velocities (S´) of the myocardium on the septal and lateral sides of the mitral annulus were performed and the mean value (e') was taken, and then the ratio E/e'was calculated [38], as a surrogate for left ventricular filling pressure. Diastolic function is categorized as:
(a) normal (E/A ≥0.8 - <1.5, E-DTE deceleration time> 160 ms, mean E/e'≤8);
(b) Grade 1, impaired relaxation (E/A <0.8, DTE> 200 ms, mean E/e'≤8);
(c) Grade 2, Pseudonormalization (E A ≥0.8 and <1.5, DTE 160–200 ms, mean E/e'= 9–12);
(d) Grade 3, Restrictive pattern (E/A ≥1.5, DTE <160 ms, mean E e'≥13).

Regional disorders in left ventricular contractility are segmental hypokinesia, akinesia, dyskinesia. Changes in myocardial texture; hyperechoic extensive subendocardial or transmural zones are a clear finding while oval hyperechoic zones of the myocardium- most often in the intraventricular septum are a controversial parameter. Only extensive zones or 3 smaller zones with a diameter of ≥3 mm or transmural

involvement (signs of fibrosis and cicatrix) with hypokinesia are significant.Based on the above criteria, clinically suspected myocarditis was established - until 2015, these patients were routinely tested for serum IgM and IgG antibodies to Parvo B19, Coxsackie and Adenovirus, and exceptionally to less potential agents (Ebstein Bar virus, cytomegalovirus, influenza virus, hepatitis C) it was determined from 2 samples of paired sera at 2 to 8 weeks. Antiviral antibodies and anti-heart antibodies were determined by enzyme-linked immunosorbent assay (ELISA). **Based on the positivity of IgM antiviral antibodies, the examined group (A) was divided into subgroups:** A1 with elevated IgM antibody titer in 43 (32%) subjects (SUBGROUP A1) and A2 without elevated IgM antibody titer (Group A2) - 83(68%) patients (SUBGROUP A2). Statistical processing was done in the EXCEL database using the methods of descriptive statistics, Student's-T test and Chi² test.

RESULTS

126 patients (GROUP A) had clinically suspected myocarditis (KSVMy with ≥2 ESC criteria). The most common symptoms were palpitations 107/126 (85%), chest pain 83/126 (66%) and fatigue, feeling tired, shortness of breath and dyspnea on exertion 62/126 (49%) in various combinations (TABLE 2)

Perikardno trenje	2	1,6%
EKG PROMENE		
BILO KOJE	112	89%
TACHYCARDIA SINUALIS	106	84%
ARRHYTHMIA EXTRASYSTOLICA VENTRICULARIS VES	78	62 %
ARRHYTHMIA EXTRASYSTOLICA SUPRAVENTRICULARIS	34	27%
DIFUZNA DEPRESIJA ST SEGMENTA	33	26%
NEGATIVNI T TALASI	30	24%
BLOK LEVE GRANE HISSOVOG SNOPA	9	7%
SINUSNA BRADIKARDIJA <50 SA AV BLOKOM GRADUS I	6	5%
AV BLOKOVI DRUGOG II I TREĆEG III STEPENA	3	2,5%
NORMALAN EKG	14	11%

U fizikalnom nalazu kod suspektnog miokardita (TABELA 2) dominirala je tahikardija 106/126 (84%), nepravilan srčani ritam 102/126 (81%) a dosta ređe su bile teže kliničke forme: znaci srčane dekompenzacije 21/126 (17%), (kasnoinspiratorni pukoti na plućima, tahipneja, dispneje u miru. nabrekle vene na vratu, kasnoinspiratorni pukoti na plućima, hepatomegalija, periferni edemi). Objektivni, fizikalni nalaz je bio normalan u 14 /126 (11%) ispitanika.

Od 126 slučajeva grupe A većina je imala neke EKG promene-112/126 (89%), a sa normalnim EKG je bilo samo 14/126 (11%) ali kod njih su nađene ehokardiografske promene. Analizom EKG-a (TABELA 2) registruje se visoka učestalost nespecifičnih poremećaja-disritmija: sinusna tahikardija u 112/126 (89%), ventrikularne ekstrasistole 78/126 (62%), supraventrikularne ekstrasistole 24/126 (19%) i elektropatoloških promena za klinički suspektan miokarditis: difuzna depresija ST segmenta 33/126 (26%), difuzno negativni T talasi 30/126 (24%) i blok leve grane Hisovog snopa u 9 (7%) bolesnika.

Analizom parametara merenih transtorakalnom ehokardiografijom (TTE), u zastupljenosti ehokardiografskih kriterijumima za klinički suspektan miokardit grupe A (TABELA 3) dominirala je dijastolna disfunkcija leve komore u 39/126 (31%), od toga je 17 (14%) imalo težu dijastolnu disfunkciju gradus III.

Globalna sistolna disfunkcija leve komore kvantifikovana putem ejekcione frakcije leve komore (EF) manje od 50% (EF<50%) nađena je kod 19/126 (15%) i kod svih je bila prisutna blaga do umerena dilatacija leve komore i kriterijumi za inflamatornu kardiomiopatiju (ICM). Povećana masa miokarda leve komore i indeks mase miokarda leve komore (LVMI) usled mogućeg edema miokarda registrovan je u 16 pts (13%) od ovih 19 pacijenata. Regionalna sistolna disfunkcija (hipokinezija 2 ili više miokardnih segmenata leve komore) koji najčešće nisu po distribuciji perfuzije koronaranih arterija, utvrđena je u 21/126 (17%), uz prisutan cicatrix u 11 pacijenata najčešće infero-postero-lateralno. Akinezije miokarda nije bilo u ispitivanoj grupi a diskinezija septuma je bila prisutna u bloku leve grane (nije uzimana u obzir) kod 9 bolesnika (7%). Promene u teksturi miokarda- ekstenzivne hiperehogene zone miokarda i fibroza-cicatrix nadjene su u 17 (13%) ispitanika. Ipak 24/126 (19%) pacijenata je imalo potpuno normalan ehokardiografski nalaz ali uz kliničke i EKG kriterijume za miokarditis.

TABELA 3. EHOKARDIOGRAFSKI PARAMETRI U INDIVIDUALNOJ DISTRIBUCIJI kod klinički suspektnog miokardita (grupa A)

EHOKARDIOGRAFSKI PARAMETRI	GRUPA A, N=126 pacijenata	PROCENAT
Patološki nalaz na ehokardiografiji	102	81%
Normalan ehokardiografski nalaz	24	(19%)
Dijastolna disfunkcija reperzentovana odnosom -E/e' ≥9	39	(31%)
Teška dijastolna disfunkcija gradus III (E/e´prim ≥13) u 17 pacijenata,	17	13,5%
Regionalna sistolna disfunkcija uz normalnu EF hipokinezija segmenata miokarda	21	(17%)
Promene u teksturi miokarda-signifikantne hiperehogene zone (fibroza-cicatrix)	17	13,5%)
Sistolna disfunkcija – EF <50% i Dilatacija leve komore	19	(15%)
Povećana masa miokarda	16	(13%)

TABLE 2. **Symptoms, physical signs, and ECG changes in 126 patients with suspected myocarditis and/or inflammatory cardiomyopathy**

Symptoms and physical signs in clinically suspected myocarditis - clinical presentations	Group A N=126	%
SYMPTOMS - CLINICAL PRESENTATIONS		
I. Palpitations	106	84%
II. Chest pain: anginal, pericardial or pseudischemic	83	66%
III. Fatigue, feeling tired, Dyspnea - lack of air on exertion	62	49%
IV. Symptoms and signs of chronic heart failure	21	17%
V. Life-threatening conditions: Acute heart failure	3	2%
PHYSICAL SIGNS		
Tachycardia> 90 / min at rest	106	84%
Bradycardia <50 / min at rest	3	2,4%
Irregular heart rhythm-dysrhythmias	102	81%
Muffled tones / gallop rhythm	3	2.4%
De novo systolic murmur	2	1,6%
Pericardial friction	2	1,6%
ECG CHANGES		
ANY	112	89%
TACHYCARDIA SINUALIS	106	84%
ARRHYTHMIA EXTRASYSTOLICA VENTRICULARIS VES	78	62 %
ARRHYTHMIA EXTRASYSTOLICA SUPRAVENTRICULARIS	34	27%
DIFFUSE ST-SEGMENT DEPRESSION	33	26%
NEGATIVE T WAVES	30	24%
HISS BUNDLE LEFT BRANCH BLOCK	9	7%
SINUS BRADICARDIA <50 WITH AV BLOCK GRADUS I	6	5%
SECOND II AND THIRD III DEGREE AV BLOCKS	3	2,5%
NORMAL ECG	14	11%

The physical finding in KSVMy (TABLE 2) was dominated by tachycardia 106/126 (84%), irregular heart rhythm 102/126 (81%) and much less frequent were more severe clinical forms: signs of cardiac decompensation 21/126 (17%), (late inspiratory crackles in the lungs, tachypnea, dyspnea at rest, swollen veins in the neck, late inspiratory cracklesin the lungs, hepatomegaly, peripheral edema). Objective, physical findings were normal in 14/126 (11%) subjects

Of the 126 cases of clinically suspected myocarditis, most had some ECG changes-112/126 (89%), and with a normal ECG there were only 14/126 (11%) but echocardiographic changes were found in them. ECG analysis (TABLE 2) registers a high frequency of nonspecific disorders-dysrhythmias: sinus tachycardia in 112/126 (89%), ventricular extrasystoles 78/126 (62%), supraventricular extrasystoles 24/126 (19%) and electropathological changes for clinically suspected myocarditis: diffuse ST segment depression 33/126 (26%), diffuse negative T waves 30/126 (24%) and His bundle left branch block in 9 (7%) patients.

The analysis of parameters measured by transthoracic echocardiography (TTE), in the presence of echocardiographic criteria for KSVMy (TABLE 3) was dominated by left ventricular diastolic dysfunction in 39/126 (31%), of which 17 (14%) had severe diastolic dysfunction grade III.

Global left ventricular systolic dysfunction quantified by left ventricular ejection fraction (EF) less than 50% (EF <50%) was found in 19/126 (15%) and all had mild to moderate left ventricular dilatation and criteria for inflammatory cardiomyopathy (ICM). Increased left ventricular myocardial mass and left ventricular myocardial mass index (LVMI) due to possible myocardial edema were registered in 16 (13%) of these 19 patients. Regional systolic dysfunction (hypokinesia of 2 or more left ventricular myocardial segments), which, most commonly by distribution are not coronary artery perfusion, was found in 21/126 (17%), with cicatrix present in 11 patients, most commonly infero-postero-lateral.Myocardial akinesia was not present in the study group and septal dyskinesia was present in the left branch block (not taken into account) in 9 patients (7%). Changes in the texture of the myocardium - extensive hyperechoic zone of the myocardium and fibrosis-cicatrix were found in 17 (13%) subjects. However, 24/126 (19%) patients had a completely normal echocardiographic finding,

Perikardni izliv-Myopericarditis	4	(3%)
Mitralna regurgitacija zbog disfunkcije papilarnih mišića	3	3%

Kod pacijenata sa klinički suspektnim miokarditisom je klinička verovatnoća virusne etiologije je dijagnostički potkrepljena povišenim titrom antitela klase IgM kod 43 (32%) ispitanika-(podgrupa A1) (GRAFIKON 1) dok je većina je bila bez povišenog titra IgM antitela (Grupa A2)-83 (68%) pacijenata.

GRAFIKON 1. Distribucija IgM serološke pozitivnosti kod 43 (34%) od 126 ispitivanih pacijenata na suspektnu skorašnju infekciju virusom i dokaz autoimunog odgovora putem povišenog serumskog titra AHA antitela
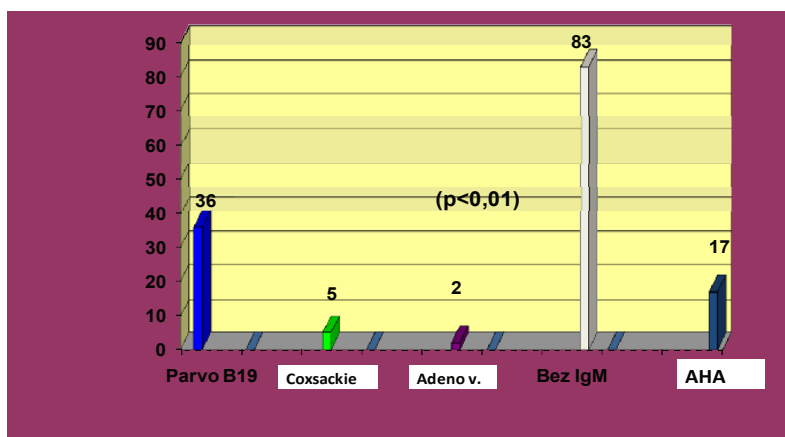
Postoji dominacija IgM antitela na virus Parvo B 19 u 36/43 (84%) pacijenata (p<0,01) a samo u 5/43 (12%) slučajeva na Coxsackie B i u 2/43 (5%) pacijenta na Adenovirus. Većina pacijenata je bila bez povišenog titra IgM antitela-(podgrupa A2) od 83 (68%) pacijenata a oko polovine njih -41/126 (32%) ima samo povišen serumski titar IgG antitela na kardiotropne koji nema dijagnostički značaj sam za sebe, bez dinamike titra IgM antitela.

Jasna dinamika titra IgM je zabeležena kod 23/126 (18%) ispitivane osobe a pad titra uz rast IgG titra (serokonverzija) u 13/126 (10%) bolesnika, dok je bez uhvaćene dinamike titra bilo 7 bolesnika (GRAFIKON 2).

GRAFIKON 2. Dinamika titra IgM antitela na kardiotropne viruse i serokonverzija Igm u IgG kod 43 pacijenata podgrupe A1
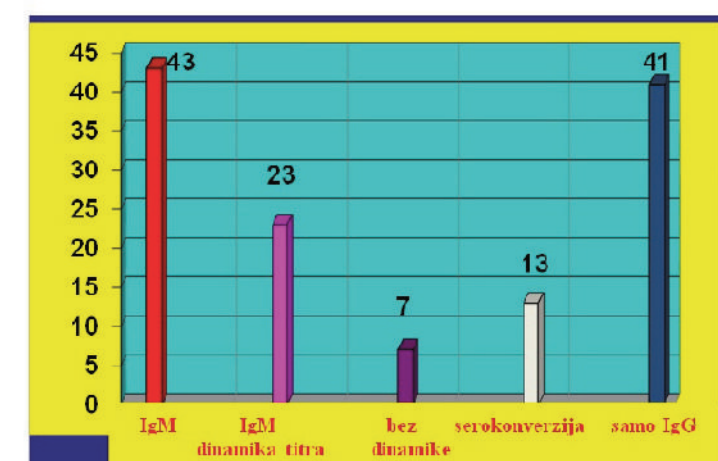
but with clinical and ECG criteria for myocarditis..

TABLE 3. ECHOCARDIOGRAPHIC PARAMETERS IN INDIVIDUAL DISTRIBUTION in clinically suspected myocarditis

ECHOCARDIOGRAPHIC PARAMETERS	GROUP A, N=126 patients	PERCENTAGE
Pathological findings on echocardiography	102	81%
Normal echocardiographic findings	24	(19%)
Diastolic dysfunction represented by the ratio -E / e '≥9	39	(31%)
Severe diastolic dysfunction grade III (E / e´prim ≥14)	17	13,5%
Regional systolic dysfunction with normal EF (hypokinesia of myocardial segments)	21	(17%)
Changes in the texture of the myocardium-significant hyperechogenic zone (fibrosis-cicatrix)	17	13,5%)
Systolic dysfunction - EF <50% and Left ventricular dilatation EDD> 54 or 58mm),)	19	(15%)
Increased myocardial mass	16	(13%)
Pericardial effusion-Myopericarditis	4	(3%)
Mitral regurgitation due to papillary muscle dysfunction	3	3%

In patients with clinically suspected myocarditis, the clinical probability of viral etiology was diagnostically supported by elevated IgM antibody titer in 43 (32%) subjects- (subgroup A1) (CHART 1) while most were without elevated IgM antibody titer (Group A2) - 83 (68%) patients.

CHART 1. Distribution of IgM serological positivity in 43 (34%) of 126 patients examined for suspected recent virus infection and evidence of autoimmune response via elevated AHA antibodies serum titer
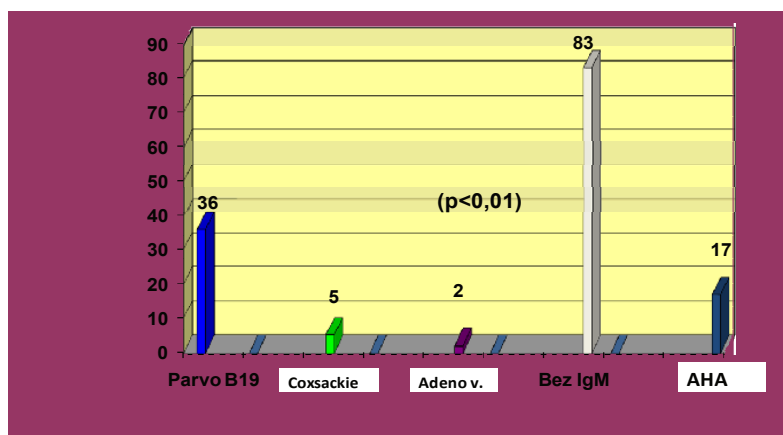
There is a predominance of IgM antibodies to Parvo B 19 virus in 36/43 (84%) patients (p <0.01) and only in 5/43 (12%) cases to Coxsackie B and in 2/43 (5%) patients to Adenovirus. The majority of patients were without elevated IgM antibody titer - subgroup A2 of 83 (68%) patients and about half of them - 41/126 (32%) have only elevated serum titer of IgG antibodies to cardiotropic which has no diagnostic significance on its own, without IgM antibody titer dynamics.

Clear IgM titer dynamics was recorded in 23/126 (18%) subjects and a decrease in titer, with an increase in IgG titer (seroconversion) in 13/126 (10%) patients, while there were 7 patients without captured titer dynamics (CHART 2)

Povišen titar IgG antitela nema dijagnostički značaj sam za sebe, bez dinamike titra IgM antitela. U grupi A2 bez IgM povišen serumski titar IgG antitela na kardiotropne viruse imalo je 41/126 (32%) (grafikon 2), najčešće na parvo B19, adenovirus i koksaki B. Čak 42/126 bolesnika (33%) nije imala povišen titar ni IgM ni IgG antivirusnih antitela, ali su imali jasne kriterijume (2 i više) za klinički miokardtitis a od njih je 8 imalo povišena

antisrčana antitela i znake inflamatorne CMP. Određivanje antisrčanih autoantitela (AHA) koje je novijeg datuma urađeno kod težih slučajeva 17 inflamatorne kardiomiopatije (GRAFIKON 1) i od toga su 8 njih imali antimiokardna autoantitela, ali njihova uloga nije još definisana.
Kvantitativni ehokardiografski parametri kod pacijenata sa klinički suspektnim miokarditisom su prikazani na TABELI 4 i GRAFIKONIMA 3 i 4.

TABELA 4. Kvantitativni ehokardiografski parametri u odnosu na virusnu serologija kod klinički suspektnog miokardita

KVANTITATIVNI EHOKARDIOGRAFSKI Xsr±SD	Cela grupa (A) N=126	podgrupa A1 N=43/126 (34,1%) POZITIVNA IgM	podgrupa A2 N=83/126 (66%) NEGATIVNA IgM	kontrolna grupa B N=103	Statistički Značajnost razlika studentov T-test p NS=NESIGNIFIKANTNA
DIJASTOLNA DISFUNKCIJA REPREZENTOVANA ODNOSOM E/e´	11,9± 4,8	12,3±5,3	11,6±4,7	8,7±4,6	A vs B, <0,001 A1 VS A2 0,400 , NS A1 VS B <0,001 A2 vs B, 0,00019
LONGITUDINALNA SISTOLNA FUNKCIJA(TKIVNI DOPLER)- SISTOLNA BRZINA LATERALNOG ANULUSA S´	6,9± 1,3	7,2 ± 1,4	6,9± 1,2	9,9± 2,1	A vs B <0,001 A1 VS A2 0,300 , NS A1 Vs B- <0,0001 A2 vs B- <0,0001
DIMENZIJA LEVE PRETKOMORE (mm)	42,87±4,60	43,39 ±4,43	42,35 ±4,74	37,92± 3,72	A vs B <0,001 A1 VS A2. 0,113, NS A1 VS B <0,001 A2 vs B, <0,001
EJEKCIONA FRAKCIJA leve komore EF (%)	59,1±7,6	59,7±6,9	58,7±8,2	63±7,9	A VS B <0,001 A1 vs A2- 0,554 NS A1 Vs B- 0,0004 A2 vs B- 0,0001
DIMENZIJA LEVE KOMORE TDD (mm)	52,84± 5,85	53,58± 6,05	52,10 ±5,57	49,56±4,26	A vs B <0,001 A1 VS A2 0,076 NS A1 VS B <0,001 A2 vs B, 0,0004
INDEKS MASE MIOKARDA g/m²	121,8±28,5	123,3±29,6	119,5±30,9	98,1± 20.2	A vs B <0,001 A1 vs A2 0,425 NS A1 VS B <0,001 A2 vs B <0,001

GRAFIKON 3. kvantitativni ehokardiografski parametri tkivnog Dopplera: dijastolna funkcije i longitudinalna sistolna funkcija u odnosu na virusnu serologija kod klinički suspektnog miokardita
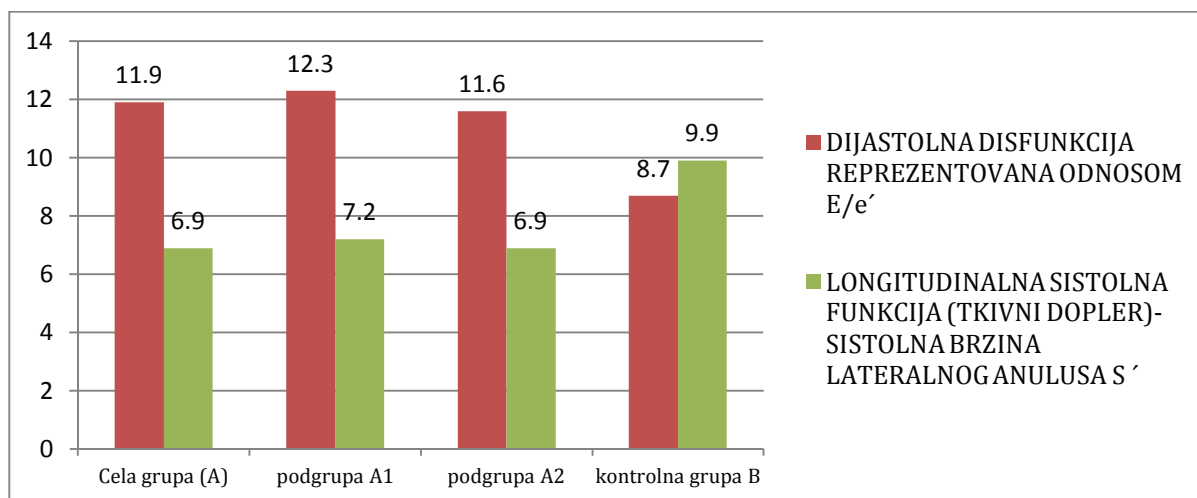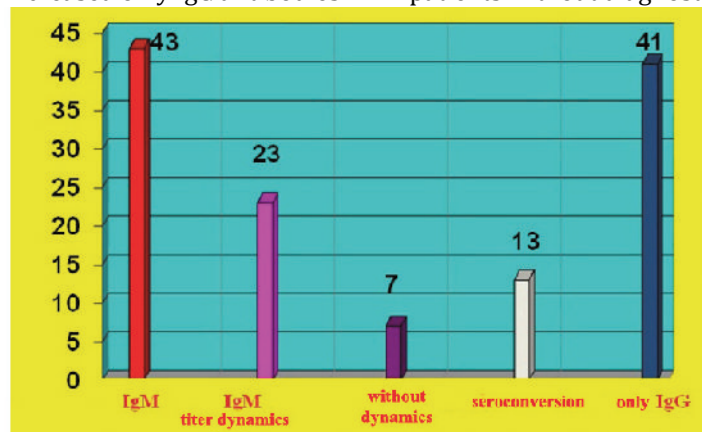
CHART 2. Dynamics of IgM antibody titer to cardiotropic viruses and IgM seroconversion to IgG in 43 patients and increased only IgG antibodies in 41 patients without diagnostic significance

Elevated IgG antibody titer has no diagnostic significance on its own, without IgM antibody titer dynamics. In group A2 without IgaM, 41/126 (32%) had elevated serum IgG antibodies to cardiotropic viruses, most often to parvo B19, adenovirus and coxsackie B. As many as 42/126 patients (33%) did not have elevated IgM or IgG titers. antiviral antibodies, but had clear criteria (2 and more) for clinical myocarditis and 8 of them had elevated anti-heart antibodies and signs of inflammatory CMP.

Determination of anti-heart autoantibodies (aha) was performed more recently in severe cases of 17 inflammatory cardiomyopathy (CHART 1) of which 8 had antimyocardial autoantibodies, but their role has not yet been defined.

Quantitative echocardiographic parameters in patients with clinically suspected myocarditis are shown in TABLE 4 and CHARTS 3 and 4.

TABLE 4. Quantitative echocardiographic parameters in relation to viral serology in clinically suspected myocarditis

QUANTITATIVE ECHO-CARDIOGRAPHIC Xsr±SD	The whole group (A) N=126	Subgroup A1 N=43/126 (34,1%) POSI-TIVE IgM	Subgroup A2 N=83/126 (66%) NEGATIVE IgM	Control group B N=103	Statistically Significant difference student's T-test p NS=UNSIGNIFICANT
DIASTOLIC DYSFUNCTION REPRESENTED BY RELATIONSHIP E/e´	11,9± 4,8	12,3±5,3	11,6±4,7	8,7±4,6	A vs B, <0,001 A1 VS A2 0,400 , NS A1 VS B <0,001 A2 vs B, 0,00019
LONGITUDINAL SYSTOLIC FUNC-TION (TISSUE DOPPLER) - SYSTOLIC RATE OF THE LATERAL ANULUS S´	6,9± 1,3	7,2 ± 1,4	6,9± 1,2	9,9± 2,1	A vs B <0,001 A1 VS A2 0,300 , NS A1 Vs B- <0,0001 A2 vs B- <0,0001
LEFT ATRIAL SIZE (mm)	42,87±4,60	43,39 ±4,43	42,35 ±4,74	37,92± 3,72	A vs B <0,001 A1 VS A2. 0,113, NS A1 VS B <0,001 A2 vs B, <0,001
LEFT VENTRICULAR EJECTION FRACTION-EF (%)	59,1±7,6	59,7±6,9	58,7±8,2	63±7,9	A VS B <0,001 A1 vs A2- 0,554 NS A1 Vs B- 0,0004 A2 vs B- 0,0001
LEFT VENTRICULAR DIMENSION TDD (mm)	52,84± 5,85	53,58± 6,05	52,10 ±5,57	49,56±4,26	A vs B <0,001 A1 VS A2 0,076 NS A1 VS B <0,001 A2 vs B, 0,0004
LEFT VENTRICULAR MYOCARDI-AL MASS INDEX g/m²	121,8±28,5	123,3±29,6	119,5±30,9	98,1± 20.2	A vs B <0,001 A1 vs A2 0,425 NS A1 VS B <0,001 A2 vs B <0,001

GRAFIKON 4. Ehokardiografski parametri sistolne funkcije i dimenzija leve komore i pretkomore u odnosu na virusnu serologija kod klinički suspektnog miokardita
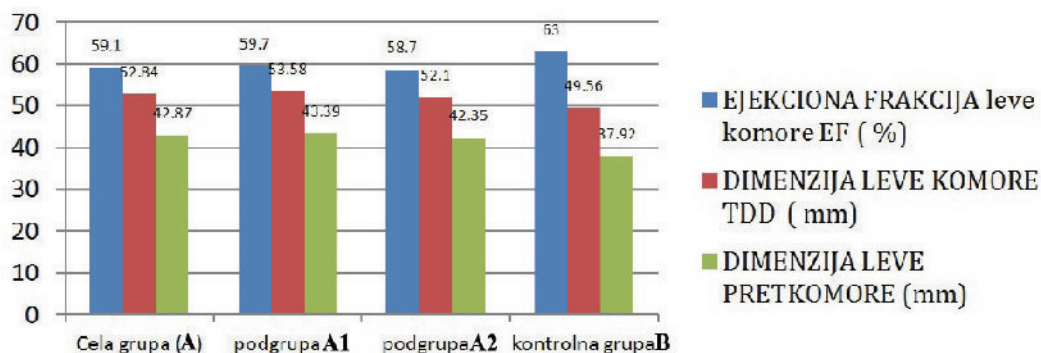
Cela grupa A klinički suspektnog miokardita u odnosu na kontrolnu grupu B ima statistički visoko značajno snižene parametre sistolne funkcije (EF=59,1±7,6% vs. 63±7,9%; p<0,001) (tabela 4 i grafikon 3) uključujući i longitudinalnu sistolnu funkciju S´ putem tkivnog doplera 6,9±1,3 cm/s vs. 9,9±2,1; p<0,001 (tabela 4 i grafikon 4).

Dijastolna disfunkcija (E/e´11,9±4,8 vs. 8,7±4,6; p<0,001) prikazana na tabela 4 i grafikonu 3, je visoko značajno izražena u ispitivanoj grupi vs kontrolna grupa. Povećanje teledijastolne dimenzije leve komore (TDD, EDD), indeksa mase miokarda (LVMI) i dimenzije leve pretkomore (TABELA 4 i GRAFIKON 4) je statistički visoko značajno povećana u grupi klinički suspektnog miokarditisa. Cela grupa klinički suspektnog

miokardita ima indeks mase miokarda statistički značajno veći, što se objašnjava edemom miokrda a ne hipertrofijom kao u hipertenziji.

Komparacijom podgrupa A1 i A2 nije nađena statistički značajna razlika,. između IgM pozitivnih i IgM negativnih pacijenata u odnosu na na kvantitativne ehokardiografske promene (TABELA 4 i GRAFIKONI 3 i 4) što znači da povišen titar IgM antitela i serokonverzija ne ukazuju na stepen oštećenja miokarda i samim tim na težu formu miokarditisa.

Kvalitativne ehokardiografske promene su prikazane na GRAFIKONU 5. Ove promene se ne javljaju u kontrolnoj grupi, što ukazuje na njihovu dobru specifičnost. Kao iza kvantitativne ehokardiografske parametre nema statistički značajne razlike između podgrupa A1 i A2 (Xi2 test nesignifikantne razlike).

CHART 3. Quantitative echocardiographic parameters of tissue Doppler: diastolic function and longitudinal systolic function in relation to viral serology in clinically suspected myocarditis
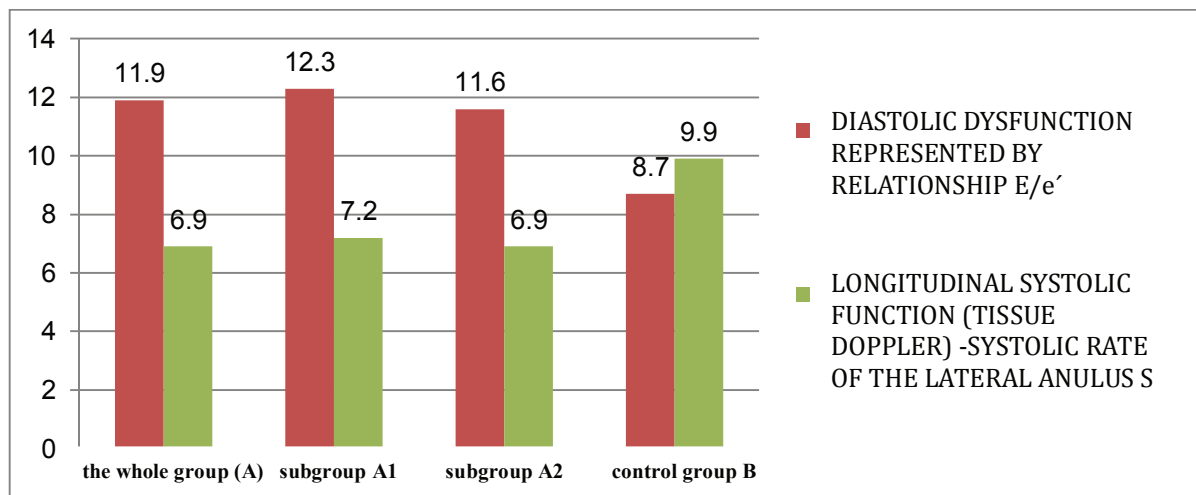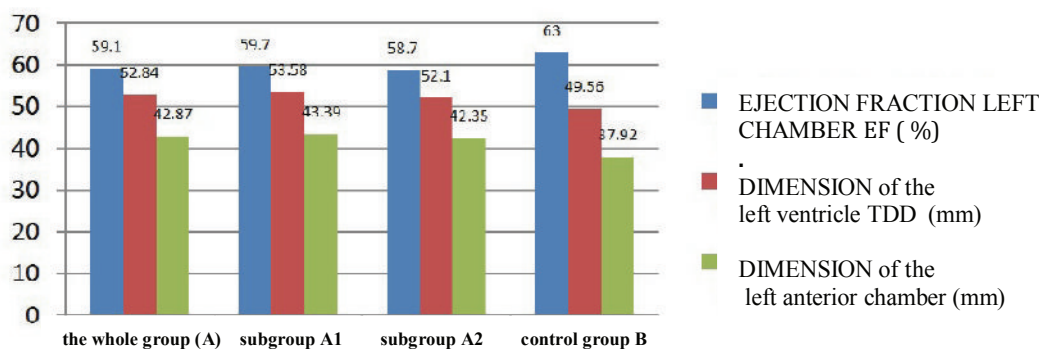

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CHART 4. Echocardiographic parameters of left ventricular and atrial systolic function and dimensions in relation to viral serology in clinically suspected myocarditis

The whole group A of clinically suspected myocarditis compared to control group B had statistically highly significantly reduced parameters of systolic function (EF = 59.1 ± 7.6% vs. 63 ± 7.9%; p <0.001) (Table 4 and Chart 3) including longitudinal systolic function S´ via tissue Doppler 6.9 ± 1.3 cm / s vs. 9.9 ± 2.1; p <0.001 (Table 4 and Chart 4).

Diastolic dysfunction (E/e´11.9 ± 4.8 vs. 8.7 ± 4.6; p <0.001) shown in Table 4 and Graph 3, was highly significant in the study group vs. control group. The increase in left ventricular telediastolic dimension (TDD, EDD), myocardial mass index (LVMI) and left atrial size (TABLE 4 and CHART 4) was statistically significantly increased in the group of clinically suspected myocarditis. The whole group A of clinically

suspected myocarditis has a myocardial mass index statistically significantly higher, which is explained by myocardial edema and not hypertrophy as in hypertension.

Comparison of subgroups A1 and A2 did not find a statistically significant difference between IgM positive and IgM negative patients in relation to quantitative echocardiographic changes (TABLE 4 AND CHARTS 3 AND 4), which means that elevated IgM antibody titer and seroconversion do not indicate the degree of myocardial damage and thus to a more severe form of myocarditis.

Qualitative echocardiographic changes are shown in CHART 5. These changes do not occur in the control group, which indicates their good specificity. As for quantitative

GRAFIKON 5. Kvalitativne ehokardiografske promene kod klinički suspektnog miokarditisa
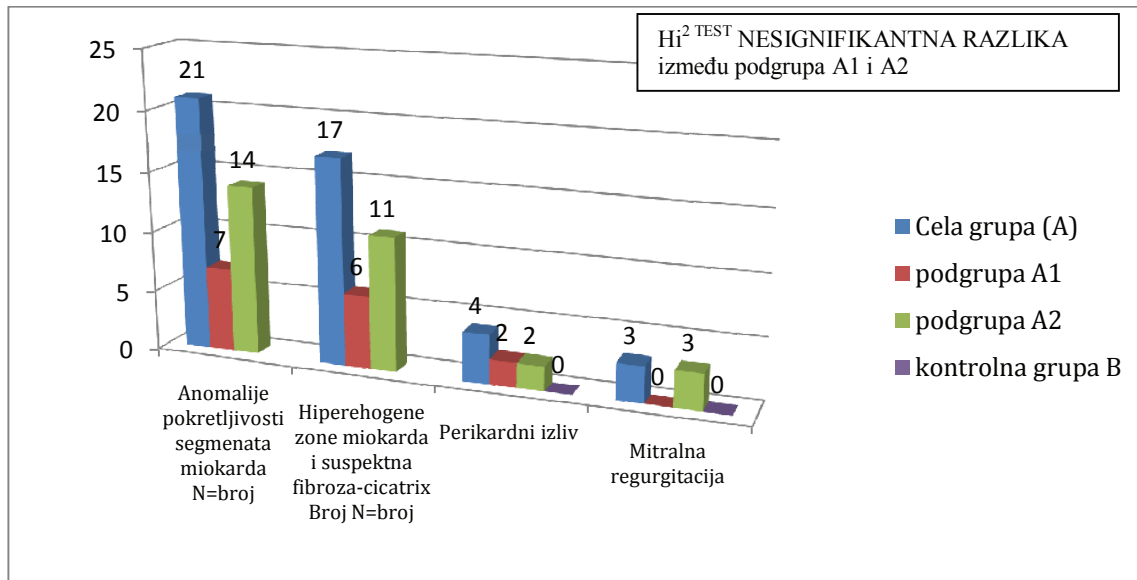
DISKUSIJA

Do danas ne postoji takozvani zlatni standard za dijagnozu akutnog miokarditisa zbog niske specifičnosti i senzitivnosti tradicionalnih dijagnostičkih testova. Endomikardna biopsija sa patohistološkim pregledom, imunohistohemijom i prisustvom virusnog genoma jesu najpouzdanije metode i omogućavaju primenu terapijskog algoritma, ali je ova invazivna dijagnostika uglavnom rezervisana za teže i nejasne slučajeve dilatacionih i/ili inflamatornih kardiomiopatija. Akutni virusni miokarditis je generalno blaga i samoograničavajuća posledica sistemske infekcije kardiotropnim virusima [41]. Međutim, pacijenti mogu razviti privremeno ili trajno oštećenje srčane funkcije, uključujući akutnu kardiomiopatiju sa hemodinamskom kompromItacijom ili teške aritmije. Akutni fulminatni miokardit je redak, javlja se prvenstveno u dece kao kardiogeni šok ili edem pluća a prepoznavanje na vreme spašava život. EF se najčešće se vraća skoro u normalu ali rezidualna dijastolna disfunkcija može da limitira veće napore kod nekih koji su preležali fulminantni miokardit [13]. Proporcija dilatacionih kardiomiopatija (DCM) zbog virusne infekcije ostaje kontraverzna [42]. U najvećoj seriji od 1426 osoba dečijeg uzrasta miokarditis je uzrok DCM u 34% [43]. Precizno predviđanje KV rizika u ranijim fazama miokardita posebno je važno zbog pravovremene identifikacije visokorizičnih bolesnika [15].

Najveći broj objavljenih studija retko ima uključene i inicijalne i follow-up biopsije [44,45,46] i ima samo iznesene inicijalne nalaz EMB na početku simptoma. Serije bez EMB imaju postavljenu dijagnozu hroničnog miokardita na osnovu kliničke prezentacije, povišene inflamatorne markere i imidžing karakterizaciju kod pacijenata sa normalnom koronarografijom [47]. Predhodne studije procenjuju da se 30% DCM razvija iz miokardita [45,46,48,49].

Pacijenti sa akutnim miokarditisom uobičajeno se prezentuju sa bolom u grudima, dispenjom ili sa oba simptoma uz tahikardije i disritmije [1,13,50,51,52]. U nedavnoj seriji od 245 pacijenata sa klinički sumnjivim miokarditisom, najčešći simptomi su bili umor (82%), dispneja pri naporu (81%), aritmije (55%, supraventrikularna i ventrikularna), palpitacije (49%) i bol u grudima u mirovanju (26%) [53]. Ovo je saglasno sa našim rezultatima, gde su aritmije i palitacije dominirale u 84%, dok je bol u grudima bio duplo češći (66%). Virusni prodrom groznice, mijalgije i respiratornih simptoma javlja se u između 20% i 80% slučajeva, pacijent može lako propustiti da prijavi prodrome, pa se na to ne može osloniti u dijagnozi.

Od naših 126 slučajeva klinički suspektnog miokardita većina je imala neke elektropatološke EKG promene-112/126 (89%),

echocardiographic parameters, there is no statistically significant difference between

subgroups A1 and A2 (Xi2 test of insignificant difference).

CHART 5. Qualitative echocardiographic changes in clinically suspected mycarditis
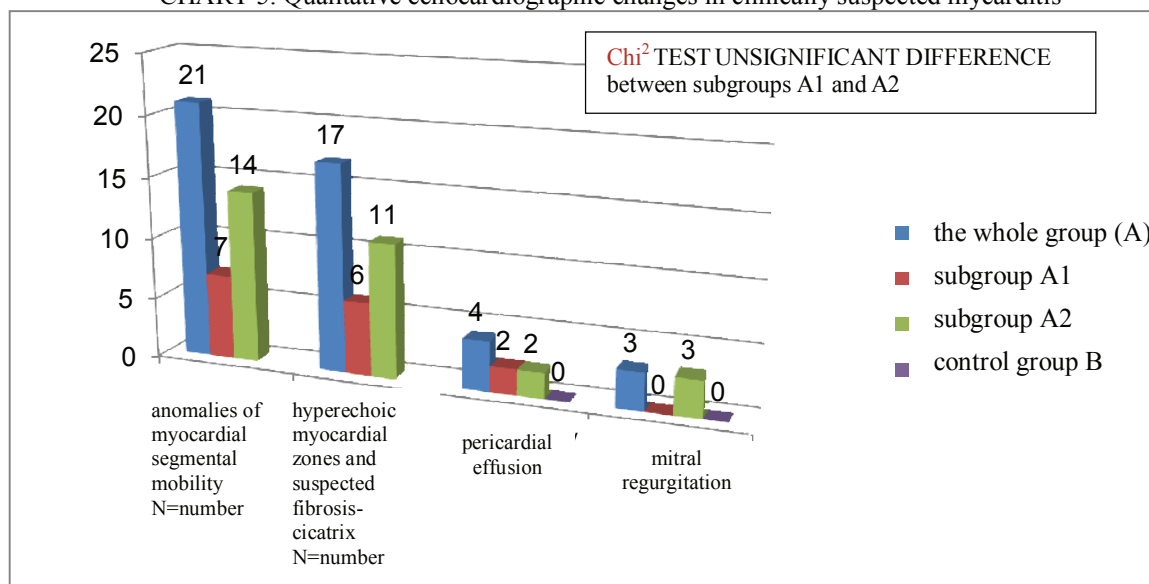
DISCUSSION

To this day, there has not existed the so-called gold standard for the diagnosis of acute myocarditis due to the low specificity and sensitivity of traditional diagnostic tests. Endomycardial biopsy with pathohistological examination, immunohistochemistry and the presence of viral genome is the most reliable method and allows the application of a therapeutic algorithm, but this invasive diagnosis is mainly reserved for more severe and unclear cases of dilated and / or inflammatory cardiomyopathies. Acute viral myocarditis is generally a mild and self-limiting consequence of systemic infection with cardiotropic viruses [41]. However, patients may develop temporary or permanent impairment of cardiac function, including acute cardiomyopathy with hemodynamic compromise or severe arrhythmia. Acute fulminate myocarditis is rare, it occurs primarily in children as cardiogenic shock or pulmonary edema, and recognizing it in time saves lives. EF usually returns almost to normal but residual diastolic dysfunction may limit greater exertion in some who have experienced fulminant myocarditis [13]. The proportion of dilated cardiomyopathies (DCM) due to viral infection remains controversial [42]. In the largest series of 1426 children, myocarditis was the cause of

DCM in 34% [43]. Accurate prediction of CV risk in the earlier stages of myocarditis is especially important due to the timely identification of high-risk patients [15].

The largest number of published studies rarely involve both initial and follow-up biopsies [44,45,46] and have only outlined the initial finding of EMB at the onset of symptoms. EMB-free series have been diagnosed with chronic myocarditis based on clinical presentation, elevated inflammatory markers, and image characterization in patients with normal coronary angiography [47]. Previous studies have estimated that 30% of DCM develops from myocarditis [45,46,48,49].

Patients with acute myocarditis usually present chest pain, dyspnea, or both, with tachycardia and dysrhythmias. [1,13,50,51,52]. In a recent series of 245 patients with clinically suspected myocarditis, the most common symptoms were fatigue (82%), exercise dyspnea (81%), arrhythmias (55%, supraventricular and ventricular), palpitations (49%), and chest pain at resting (26%) [53]. This is consistent with our results, where arrhythmias and palitations dominated in 84%, while chest pain was twice as common (66%). Viral prodrome of fever, myalgia and respiratory symptoms occurs in between 20% and 80% of cases, the patient can

a sa normalnim EKG je bilo 14/126 (11%) te on ne može da posluži za isključenje miokardita. Ipak kod ovih 14 pacijenata su postojale ehokardiografske promene I kriterijumi kliničke prezentacije. Disritmije nemaju specifičnost za miokardit, dok EKG znaci oštećenja miokarda depresija ili elevacija ST, blok leve grane Hisovog snopa govore u prilog lezije miokarda ali ne ukazuju na uzrok. Procena senzitivnosti EKG za miokarditis na oko 47%, dok je specifičnost vrlo niska [52]. Troponin na primer ima još nižu senzitivnost za miokarditis 34% ali dobru specifičnost preko 89% [52].

Analizom parametara merenih transtorakalnom ehokardiografijom u kriterijumima za klinički suspektan miokarditis dominirala je dijastolna disfunkcija leve komore, koju reprezentuje odnos E/e´prim≥9 u 39/126 (31%), od toga je 17 (14%) pacijenata, oko polovine imalo težu dijastolnu disfunkciju gradus III (E/e´prim ≥14). U jednoj seriji od 147 patienta sa jako redukovanom EF (23 ± 8%), dijastolnu disfunkciju je imalo 42%, ali su to bili teži bolesnici sa inflamatornom kardiomiopatijom. Poboljšanje dijastolne funkcije u 58% tih pacijenata posle lečenja i praćenja oko 6 meseci je prognostički važno, isto kao i poboljšanje EF i nosi rastuću prognostičku vrednost za stratifikaciju rizika [54]. Globalna sistolna disfunkcija leve komore (EF<50%) nađena je kod samo 19/126(15%) naših pacijenata i kod svih je bila prisutna blaga dilatacija leve komore i kriterijumi za inflamatornu kardiomiopatiju. Značajno je veći broj bolesnika sa sistolnom disfunkcijom u italijanskoj studiji kod biopsijom dokazanom miokarditu u seriji od 41 pts [55], gde je sistolna difunkcija leve komore bila prisutna u 69% a regionalni poremećaji u kontraktilnosti u 64%, hipertrofija leve komore zbog edema miokarda u 20%, promene u teksturi miokarda 23% , ventrikularnu tromb u 15% i restriktivni patern punjenja leve komore u 7%. Većina naših pacijenata je imala normalnu ejekcionu frakciju njih 107 pts ili 85%, što je važan prognostički faktor u većini relevantnih studija [56,57,58]. U registru jednog nemačkog centra na 210 EMB-dokazanih miokardita 50% ili tri puta više nego u našim rezulattima je imalo sniženu ejekcionu frakciju, zbog kliničkog spektra teških bolesnika sa miokarditom koji se šalju na EMB. Posle dvogodišneg praćenja i lečenja standardnom terapijom za srčanu insuficijenciju, 26% je normalizovalo EF a 27% je ostalo sa sniženom

EF [59]. Studija Grun S. i saradnika [56] sa serijom od 222 konsekutivna pts sa EMB dokazanim virusnim miokarditom, iznosi mortalitet od 19% sa medijanom 4,7 godina. Generalno oko 1/4 bolesnika sa EMB dokazanim virusnim miokarditom razvija se u pravcu pogoršanja srčane funkcije i budu podvrgnuti transplantaciji srca ili egzitiraju. [15]. Prediktori ishoda variraju u raznim studijama sa EMB: Perzistencija NYHA klase III do IV, dilatacija leve pretkomore i poboljšanje EF unutar 6 meseci jesu nezavisni prediktori dugoročnog ishoda [42]. Kinderman i saradnici iznose da visoka NYHA klasa, imunološki znaci inflamacije i nedostatak betablokatora u terapiji jesu prediktori lošeg ishoda a ne histološke karakateristike Dallas kriterijuma ili prisustvo virusnog genoma [10].

Regionalna sistolna disfunkcija po našim istraživanima bila je utvrđena u 21/126 (17%) i u ovim slučajevima mora se isključiti cicatrix posle asimptomatskog infarkta stres ehokardiografskim testom farmakološkim ili fizičkim opterećenjem a u inkonkluzivnim slučajevima MSCT ili invazivnom koronarografijom [60].

Ehokardiografija je odličan alat za dijagnozu i praćenje pacijenata sa miokarditom i DCM. Speckle tracking echokardiografija (slika deformacije miokarda) ima sve veći značaj u ranim stadijumima miokardita i detekciji progresije u kardiomiopatiju [50].

Promena vrste virusa izazivača miokardita je u skladu sa drugim studijama [7,8,11,12], dok jedna od ređih novijih studija iz Bugarske nalazi na serološku dominaciju Koksaki virusa kao mogućeg izazivača miokardita [61]. Jasna dinamika titra IgM je zabeležena kod malog broja pacijenata u 23/126 (18%) osoba sa dominacijom Parvo B19 antitela a pad titra uz rast IgG titra (serokonverzija) u 13/126 (10%) bolesnika. Povećanje dinamika titra cirkulišućih antivirusnih antitela od akutne ka subakutnoj i hroničnoj fazi može da potpomogne Dg virusnog miokardita sa mogućim spontanim oporavkom [13]. Senzitivnost antivirusnih antitela je niska i procenjena na osnovu više studija na 25-32% a specifičnost na 40% [52]. To govori za aktivni proces infekcije bilo gde u organizmu i ima doprinos mogućoj kauzalnoj dijagnozi samo uz jake dokaze zahvaćenosti miokarda putem važećih ESC kriterijuma za klinički suspektan miokarditis. U najznačajnijoj studiji na ovu temu,

easily fail to report prodromes, so one cannot rely on that in the diagnosis.

Of our 126 cases of clinically suspected myocarditis, most had some electropathological ECG changes-112/126 (89%), and with a normal ECG there were 14/126 (11%) so it cannot be used to rule out myocarditis. However, in these 14 patients there were echocardiographic changes and criteria for clinical presentation. Dysrhythmias have no specificity for myocarditis, while ECG signs of myocardial damage, depression or ST elevation, block of the left branch of the His bundle speak in favour of myocardial lesions, but do not indicate the cause. Estimation of ECG sensitivity for myocarditis is at about 47%, while the specificity is very low [52].Troponin, for example, has an even lower sensitivity for myocarditis of 34% but a good specificity of over 89% [52].

The analysis of parameters measured by transthoracic echocardiography in the criteria for clinically suspected myocarditis was dominated by left ventricular diastolic dysfunction, represented by the ratio E / e´prim≥9 in 39/126 (31%), of which 17 (14%) patients, about half had severe diastolic dysfunction grade III (E / e´prim ≥14). In one series of 147 patients with severely reduced EF (23 ± 8%), 42% had diastolic dysfunction, but these were more severe patients with inflammatory cardiomyopathy. Improvement of diastolic function in 58% of these patients after treatment and follow-up for about 6 months is prognostically important, as is improvement in EF and it carries increasing prognostic value for risk stratification [54]. Global left ventricular systolic dysfunction (EF <50%) was found in only 19/126 (15%) of our patients and all had mild left ventricular dilatation and criteria for inflammatory cardiomyopathy. There was a significantly higher number of patients with systolic dysfunction in the Italian study with biopsy-proven myocarditis in a series of 41 pts [55], where left ventricular systolic dysfunction was present in 69% and regional contractility disorders in 64%, left ventricular hypertrophy due to myocardial edema in 20%, changes in myocardial texture 23%, ventricular thrombus in 15%, and restrictive left ventricular filling pattern in 7%. Most of our patients had a normal ejection fraction of 107 pts or 85%, which is an important prognostic factor in most relevant studies [56,57,58]. In the registry of one German

centre on 210 EMB-proven myocarditis 50% or three times as many than in our results had a reduced ejection fraction, due to the clinical spectrum of severe patients with myocarditis who are sent for EMB. After two years of follow-up and treatment with standard therapy for heart failure, 26% normalized EF and 27% remained with decreased EF [59]. Study by Grün S et al. [56] with a series of 222 consecutive pts with EMB-proven viral myocarditis, gives the mortality rate of 19% with a median of 4.7 years. In general, about 1/4 of patients with EMB-proven viral myocarditis go towards worsening cardiac function and undergo or have a heart transplant or exit. [15]**.** Outcome predictors vary in various studies with EMB: NYHA class III to IV persistence, left atrial dilatation, and EF improvement within 6 months are independent predictors of long-term outcome [42]. Kinderman I et al. state that high NYHA class, immune signs of inflammation, and lack of beta-blockers in therapy are predictors of poor outcome rather than histological characteristics of the Dallas criteria or the presence of a viral genome [10].

Regional systolic dysfunction according to our research was determined in 21/126 (17%) and in these cases cicatrix must be excluded after asymptomatic infarction by stress echocardiographic test by pharmacological or physical load and in inconclusive cases by MSCT or invasive coronary angiography [60].

Echocardiography is an excellent tool for diagnosing and monitoring patients with myocarditis and DCM. Speckle tracking echocardiography (image of myocardial deformity) is of increasing importance in the early stages of myocarditis and detection of progression to cardiomyopathy [50].

The change in the type of myocarditis-causing virus is in line with other studies [7,8,11,12], while one of the few recent studies from Bulgaria finds the serological dominance of Coxsackie virus as a possible cause of myocarditis [61]. Clear dynamics of IgM titer was observed in a small number of patients in 23/126 (18%) persons with Parvo B19 antibody dominance and a decrease in titer with an increase in IgG titer (seroconversion) in 13/126 (10%) patients. Increasing the titer dynamics of circulating antiviral antibodies from acute to subacute and chronic phases may aid Dg viral myocarditis with possible spontaneous recovery [13]. The sensitivity of antiviral antibodies is low

Mahfoud F. i saradnici [26] su ispitivali serologija virusa i upoređivali je sa nalazom PCR putem endomikardne biopsije sa histološkim i imunohistohemijskim nalazom kod 124 pacijenta starosti 40 ± 15 godina sa sumnjom na miokarditis. Virusni genom je detektovan u miokardu lančanom reakcijom polimeraze. Akutnu virusnu infekciju kardiotropnim virusima dijagnostikovali su putem IgM u početnom uzorku ili serokonverzija IgG u narednom uzorku. Imunohistohemijski znaci upale bili su prisutni kod 54 pacijenta. Virusni genom je otkriven u miokardu 58 pacijenata (47%). Kod 20 pacijenata (16%), akutna virusna infekcija dijagnostikovana je serologijom, što je u skladu sa našim rezultatom od 18%. Ali samo kod 5 od 124 pacijenta (4%) postojali su serološki dokazi o infekciji istim virusom koju je otkrila EMB. Senzitivnost serologije virusa bila je samo 9% a specifičnost 77%. Nedostatak korelacije između serologije i EMB je dokaz protiv rutinske upotrebe virusne serologije kod svih pacijenata sa klinički suspektnim miokarditom. Senzitivnost virusne serologije je jako niska u odnosu na EKG i ehokardiografiju, a specifičnost umerena, te istu ne treba koristiti rutinski u evaluaciji miokarditisa, već u selekcionisanim slučajevima uz ESC kriterijume gde se ne radi CMR i EMB. Iz kliničkog iskustva se zna da je teško neke pacijente razuveriti da nemaju "Koksaki virus u srcu". Psihičko opterećenje pacijenata i vezivanja za "Koksaki bolest " za koji su ubeđeni da ga nose više godina samo na osnovu povećanih serumskih IgG antivirusnih antitela je kontraproduktivno sa socijalnomedicinskog stanovišta. Antisrčana antitela (AHA) nemaju ustanovljenu ulogu, jer se javljaju i u drugim bolestima (CAD, genetske CMP) a senzitivnost je slična kao i kod virusne serologije 25-30% i specifičnost oko 40% [52]. Međutim i sami patohistološki Dallas krititerijumi [52] bez imunohistologije i PCR imaju slabu senzitivnost 35 do 50% i dobru specifičnost 78 do 89%. Dopunjeni imunohistohemijom i PCR identifikacijom genoma virusa senzitivnost je zadovoljavajuća 65% do 70% a specifičnost 80 -100%. Nažalost čak i EMB ima lažno negativne nalaze, zavisno odakle su uzimani uzorci i da li je tehnički uzeto dovoljno tkiva.

Komparacijom grupe A1 i grupe A2 nije nađena statistički značajna razlika u ehokardiografskim parametrima, što znači da IgM antitela i serokonverzija ne ukazuju na teže forme miokarditisa. Nema do sada studija o ovom aspektu.

Cela grupa A klinički suspektnog miokarditisa u odnosu na kontrolnu grupu B ima stistički visoko značajno redukovane parametre globalne sistolne (EF=59,1±7,6 vs. 63±7,9; p<0,001) i longitudinalne sistolne funkcije (S´=6,9±1,3 vs 9,9± 2,1) što upućuje da ove suptilne promene mogu u svakodnevnoj kliničkoj praksi da nas navedu da mislimo na miokarditis. U individulanoj distrubuciji sistolna disfunkcija je upola manje zastupljena od dijastolne (15% Vs 31%). Dijastolna disfunkcija, uprkos kompleksnosti procene je još izraženije snižena u odnosu na kontrolnu grupu B, kada posmatramo najreprezentativniji parametar E/e´ (E/e´11,9±4,8 vs. 8,7±4,6; p<0,001). Dilatacija leve pretkomore i leve komore su visoko značajno povećanih srednjih vrednosti u odnosu na kontrolnu grupu. Masa miokarda i indeks mase miokarda su moguće merilo edema miokarda kod miokarditisa i značano su većih srednjih vrednosti u ispitivanoj grupi vs. kontrolna grupa (121,8±28,5 g/m^2 vs. 98,1±20,2, p<0,001) što je važno za postavljanje radne dijagnoze klinički suspektnog miokarditisa, praćenje toka bolesti i efekta lečenja. Sve ehokardiografske promene su, bez patognomoničnosti i specifičnosti za miokardit, ali imaju dobru dijagnostičku senzitivnost. Sposobnost ehokardiografskih parametara za predviđanje razvoja manifestne srčane insuficijencije mortaliteta i neželjenih KV događaja u populaciji inflamatorne kardiomiopatije je dokazana je u malom broju studija. Kod bolesnika sa klinički suspektnim miokarditom koji još nisu započeli lečenje srčane insuficijecije i/ili aritmija, potvrđena je povezanost i ejekcione frakcije i dijastolne disfunkcije sa KV mortalitetom [62,63,64]. Paradoksalno u skorašnjoj meta-analizi Chen-a WH. i saradnika prisustvo virusnog genoma ne pogoršava dugotrajnu prognozu pacijenata sa miokarditsom ili inflamatornom kardiomiopatijom. Ipak virus-pozitivni pacijenti koji nisu bili pod specifičnim antivirusnim tretmanom imaju lošiju prognozu od virus negativnih. Znači da rana dijagnoza prisustva virusne infekcije miokarda poboljšava prognozu pacijenata [64].

U ovom našem ispitivanju nismo imali konzistentne podatke o vrednost parametara kardijalnih biomarkera Troponina I i T kao i NT-pro BNP, što je objektivni nedostatak ove studije.

and estimated based on several studies at 25-32% and specificity at 40% [52]. This tells of the active process of infection anywhere in the body and contributes to a possible causal diagnosis only with strong evidence of myocardial involvement through valid ESC criteria for clinically suspected myocarditis. In the most significant study on this topic, Mahfoud F. et al [26] examined the serology of the virus and compared it with PCR findings by endomicardial biopsy with histological and immunohistochemical findings in 124 patients aged 40 ± 15 years with suspected myocarditis. The viral genome was detected in the myocardium by a polymerase chain reaction. Acute viral infection with cardiotropic viruses was diagnosed by IgM in the initial sample or IgG seroconversion in the next sample. Immunohistochemical signs of inflammation were present in 54 patients. The viral genome was detected in the myocardium of 58 patients (47%). In 20 patients (16%), acute viral infection was diagnosed by serology, which is in line with our result of 18%. But only 5 of 124 patients (4%) had serological evidence of infection with the same virus detected by EMB. The sensitivity of virus serology was only 9% and the specificity was 77%. The lack of correlation between serology and EMB is evidence against the routine use of viral serology in all patients with clinically suspected myocarditis. The sensitivity of viral serology is very low in relation to ECG and echocardiography, and the specificity is moderate, and it should not be used routinely in the evaluation of myocarditis, but in selected cases with ESC criteria where CMR and EMB are not performed. It is known from clinical experience that it is difficult to reassure some patients of not having the "Coxsackie virus in their heart". The mental burden of patients and attachment to "Coxsackie disease", which they are convinced to carry for many years only on the basis of increased serum IgG antiviral antibodies, is counterproductive from the social-medical point of view. Anti-heart antibodies (AHA) do not have an established role, because they occur in other diseases (CAD, genetic CMP) and the sensitivity is similar to viral serology 25-30% and specificity about 40% [52]. However, the pathohistological Dallas criteria itself [52] without immunohistology and PCR have low sensitivity 35 to 50% and good specificity 78 to 89%. Complemented by immunohistochemistry

and PCR identification of the virus genome, the sensitivity is satisfactory 65% to 70% and the specificity 80-100%. Unfortunately even EMB has false negative findings, depending on where the samples were taken and whether technically enough tissue was taken.

A comparison between group A1 and group A2 did not reveal a statistically significant difference in echocardiographic parameters, which means that IgM antibodies and seroconversion do not indicate more severe forms of myocarditis. There have been no studies on this aspect so far.

The whole group A of clinically suspected myocarditis in relation to the control group B has statistically highly significantly reduced parameters of global systolic (EF = 59.1 ± 7.6 vs. 63 ± 7.9; p <0.001) and longitudinal systolic function (S´ = 6.9 ± 1.3 vs 9.9 ± 2.1) which suggests that these subtle changes may lead us to think of myocarditis in everyday clinical practice. In individual distribution, systolic dysfunction is by half less represented than diastolic (15% Vs 31%). Diastolic dysfunction, despite the complexity of the assessment, is even more markedly reduced compared to control group B, when we look at the most representative parameter E/e´ (E/e´11.9 ± 4.8 vs. 8.7 ± 4.6; p <0.001). Dilatation of the left atrium and left ventricle are highly significantly increased mean values compared to the control group. Myocardial mass and myocardial mass index are possible measures of myocardial edema in myocarditis and are of significantly higher mean values in the examined group vs. control group (121.8 ± 28.5 g/m^2 vs. 98.1 ± 20.2, p <0.001) which is important for making a working diagnosis of clinically suspected myocarditis, monitoring the course of the disease and the effect of treatment. All echocardiographic changes are without pathognomonicity and specificity for myocarditis, but they have good diagnostic sensitivity. The ability of echocardiographic parameters to predict the development of manifest heart failure mortality and adverse CV events in the population of inflammatory cardiomyopathy has been proven in a small number of studies. In patients with clinically suspected myocarditis who have not yet started treatment for heart failure and / or arrhythmias, the association of both ejection fractions and diastolic dysfunction with CV mortality has been confirmed [62,63,64]. Paradoxically in a recent

Takodje tada nismo rutinski radili volumen indeks leve pretkomore (LAVI) koji je bolji pokazatelj dijatolne funkcije od dimenzije leve pretkomore. Ehokardiografija putem deformacije miokarda spekl-treking tehnologijom (myocardial strain) će dati jači eho alat u evaluaciji klinički suspektnog miokarditisa.

ZAKLJUČAK

Dijagnoza akutnih virusnih miokardita nije laka i postavlja se na osnovu kriterijuma za klinički suspektan miokarditis Evropskog udruženja kardiologa (ESC) koji uključuju kliničke prezentacije i 4 različite dijagnostičke kategorije, sa dominantnom ulogom EKG i ehokardiografije u svakodnevnoj kliničkoj praksi uz obavezno isključenje drugih kardiovaskularnih bolesti. Cela grupa klinički suspektnog miokarditisa A imala je visoko stistički značajno niže parametre sistolne i dijastolne funkcije u odnosu na kontrolnu grupu B. Dominirala je dijastolna disfunkcija leve komore u 31% gde je 17 pacijenata imalo težu dijastolnu disfunkciju gradus III i klinički srčanu insuficijenciju sa očuvanom ejekcionom frakcijom. Regionalna sistolna disfunkcija utvrđena je u 17% a globalna sistolna disfunkcija leve komore (EF<50%) kod 15% sa dilatacijom leve komore i kriterijumima za inflamatornu kardiomiopatiju. Promene u teksturi miokarda- hiperehogene zone miokarda i znaci fibroze-cicatrixu bili su prisutni u 13% ispitanika. te visoko značajno povećanje teledijastolne dimenzije leve komore, indeksa mase miokarda i dimenzije leve pretkomore Normalan ehokardiografski nalaz je imalo 24 (19%) pacijenta ali uz kliničke i EKG kriterijume za miokarditis. Ipak 81% pacijenata imalo je neku od ehokardiografskih patoloških promena, koje su specifičnije za dijagnozu od EKG promena. Normalan EKG i ehokardiografski nalaz ne mogu da služe za isključenje dijagnoze miokardita. Komparacijom podgrupa sa prisustvom dinamike titra antivirusnih IgM antitela (A1) i bez iste (A2) nije nađena statistički značajna razlika u ehokardiografskim parametrima. Senzitivnost IgM titra na kardiotropne viruse je jako niska i ne treba je koristiti u rutinskoj dijagnozi miokardita.

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meta-analysis of Chen WH. and associates the presence of the viral genome does not worsen the long-term prognosis of patients with myocarditis or inflammatory cardiomyopathy. However, virus-positive patients who have not received specific antiviral treatment have a worse prognosis than virus-negative ones. This means that early diagnosis of the presence of a viral myocardial infection improves the patient's prognosis [64].

In this study, we did not have consistent data on the value of the parameters of the cardiac biomarkers Troponin I and T as well as NT-pro BNP, which is an objective shortcoming of this study. Also at that time we did not routinely do a left atrial volume index (LAVI) which is a better indicator of diastolic function than the left atrial size. Echocardiography of myocardial deformation using speckle tracking technology (myocardial strain) will provide a stronger echo tool in the evaluation of clinically suspected myocarditis.

CONCLUSION

Diagnosis of acute viral myocarditis is not easy to make and is based on the criteria for clinically suspected myocarditis of the European Society of Cardiology (ESC), which include clinical presentations and 4 different diagnostic categories, with a dominant role of ECG and echocardiography in everyday clinical practice with necessary exclusion of other cardiovascular diseases. The whole group of clinically suspected myocarditis A had highly statistically significantly lower parameters of systolic and diastolic function compared to control group B. Diastolic left ventricular dysfunction dominated in 31% where 17 patients had severe diastolic dysfunction grade III and clinically heart failure with preserved ejection fraction. Regional systolic dysfunction was found in 17% and global left ventricular systolic dysfunction (EF <50%) in 15% with left ventricular dilatation and criteria for inflammatory cardiomyopathy. Changes in myocardial texture - hyperechoic myocardial zone and signs of fibrosis - cicatrix were present in 13% of subjects, and a highly significant increase in left ventricular telediastolic dimension, myocardial mass index and left atrial size. 24 (19%) patients had a normal echocardiographic finding, but with clinical and ECG criteria for myocarditis. However, 81% of patients had some of the echocardiographic pathological changes, which are more specific for diagnosis than ECG changes. A normal ECG and echocardiographic findings cannot be used to rule out a diagnosis of myocarditis. Comparison of subgroups with the presence of antiviral IgM antibody titer dynamics (A1) and without it (A2) did not reveal a statistically significant difference in echocardiographic parameters. The sensitivity of IgM titer to cardiotropic viruses is very low and should not be used in the routine diagnosis of myocarditis.

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