INTERNATIONAL CLINICAL RESEARCH CENTER

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ZÁNĚTLIVÁ KARDIOMYOPATIE

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Brno 2013

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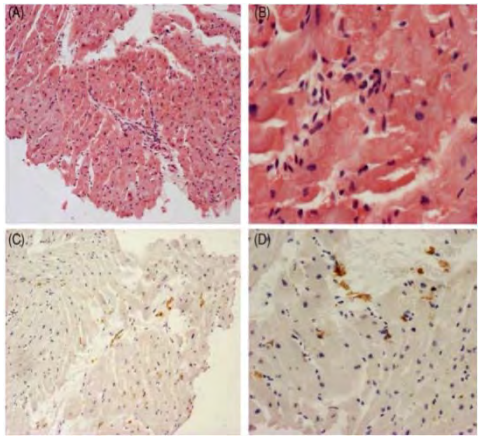
ZÁNĚTLIVÁ KARDIOMYOPATIE

- **Myokarditida je akutní či chronický zánět myokardu způsobený řadou toxinů či infekčních agens**

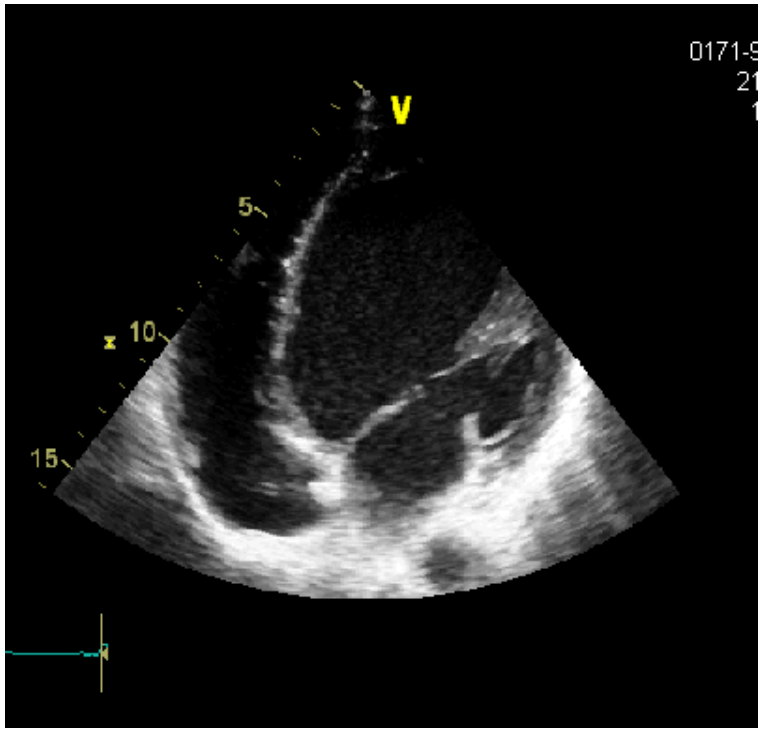
- **Zánětlivá kardiomyopatie (ZKMP) = myokarditida spojená s poruchou funkce myokardu (funkce LK)**



Caforio et al. Eur Heart J 1997

MORFOLOGICKÁ vs (IMUNO-)HISTOLOGICKÁ DG.

- **DKMP** → **myokarditida / ZKMP**
- **HKMP**
- **RKMP**
- **ARVC**



Etiologie myokarditid

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STATE-OF-THE-ART PAPER

Update on Myocarditis

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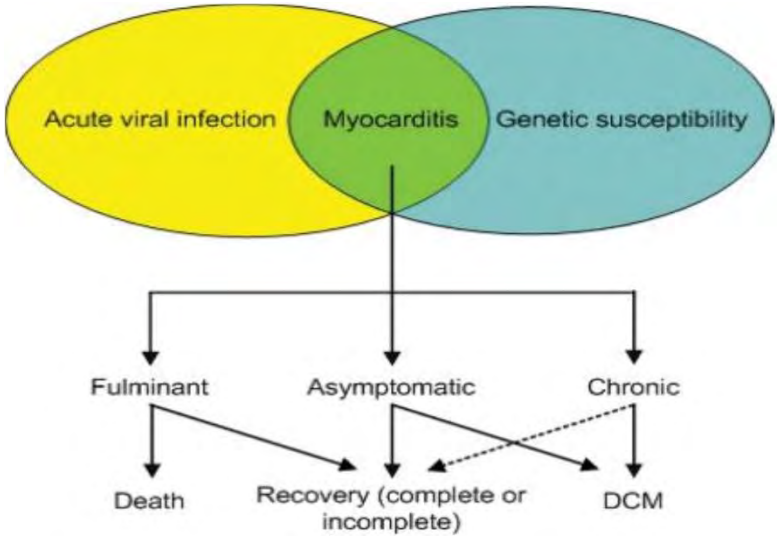
Udo Sechtem, MD,† Leslie T. Cooper, MD,§ Michael Böhm, MD*

Homburg/Saar, Stuttgart, and Tübingen, Germany; and Rochester, Minnesota

Etiology	Subgroups Examples
Infectious	Bacterial: *Chlamydia, Corynebacterium diphtheria, Legionella, Mycobacterium tuberculosis, Mycoplasma, Staphylococcus, Streptococcus A, Streptoccocus pneumoniae* Fungal: *Actinomyces, Aspergillus, Candida, Cryptococcus* Helminthic: *Echinococcus granulosus, Trichinella spiralis* Protozoal: *Toxoplasma gondii, Trypanosoma cruzi* Viral: Adenoviruses, Echoviruses, Enteroviruses (e.g., Coxsackieviruses), Herpes Viruses (Human Cytomegalovirus, Epstein-Barr virus, Human Herpesvirus 6), Hepatitis C Virus, Human Immunodeficiency Virus (HIV), Influenza A virus, Parvovirus B19 Rickettsial: *Coxiella burnetti, Rickettsia typhi* Spirochetal: *Borrelia burgdorferi, Leptospira, Treponema pallidum*
Autoimmune diseases	Celiac disease, Churg-Strauss syndrome, Crohn's disease, dermatomyositis, giant cell myocarditis, hypereosinophilic syndrome, Kawasaki disease, lupus erythematodes, lymphofollicular myocarditis, rheumatoid arthritis, sarcoidosis, scleroderma, ulcerative colitis
Hypersensitivity reactions to drugs	Penicillin, ampicillin, cephalosporins, tetracyclines, sulfonamids, antiphlogistics, benzodiazepines, clozapine, loop and thiazide diuretics, methyldopa, smallpox vaccine, tetanus toxoid, tricyclic antidepressants
Toxic reactions to drugs	Amphetamines, anthracyclines, catecholamines, cocaine, cyclophoshamide, 5-fluorouracil, phenytoin, trastuzumab
Toxic	Ethanol
Others	Arsenic, copper, iron, radiotherapy, thyreotoxicosis

Myokarditidy

- **u 90% lidí nevznikne myokarditida přes infekci „kardiotropními viry“**



Dennert et al. Acute viral myocarditis. Eur Heart J. 2008, 29(17): 2073–2082.

Epidemiologie

- **u 40-50% pts s chronickou DKMP byly nalezeny v EMB imunohistologické zn. myokarditidy**
- **ve 25-40% nalezen virový genom**

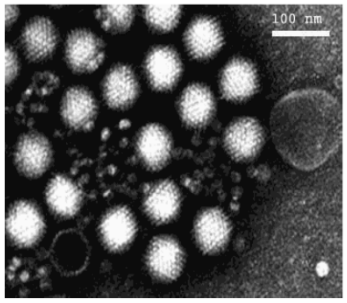
Cooper LT. The heat is off. Immunosupresion for myocaditis revisited. Eur Heart J 2009;30:1936-1939.

- **ve 48% EMB u DKMP nalezen zánět**

Kühl et al. Immunohistological evidence for chronic intramyocardial inflammatory proces in dilated cardiomyopathy. Heart 1996;75:295-300

- **virový genom nalezen v 67%** *(51% PVB19 + 22% HHV6)*

Kühl et al. High prevalence of viral genomes and multiple viral infections in the myocardium of adults with „idiopatic“ left ventricular dysfunction. Circulation. 2005;111:887-893



Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases

Alida L. P. Caforio[1†*], Sabine Pankuweit[2†], Eloisa Arbustini[3], Cristina Basso[4], Juan Gimeno-Blanes[5], Stephan B. Felix[6], Michael Fu[7], Tiina Heliö[8], Stephane Heymans[9], Roland Jahns[10], Karin Klingel[11], Ales Linhart[12], Bernhard Maisch[2], William McKenna[13], Jens Mogensen[14], Yigal M. Pinto[15], Arsen Ristic[16], Heinz-Peter Schultheiss[17], Hubert Seggewiss[18], Luigi Tavazzi[19], Gaetano Thiene[4], Ali Yilmaz[20], Philippe Charron[21], and Perry M. Elliott[13]

Eur Heart J (2013) doi: 10.1093/eurheartj/eht210
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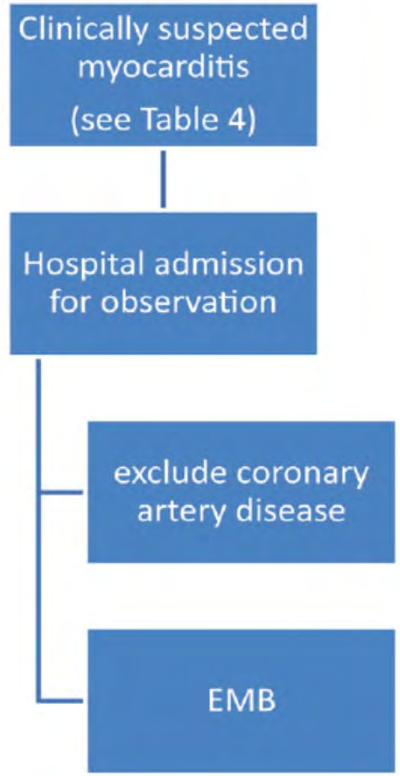
Table 4 Diagnostic criteria for clinically suspected myocarditis

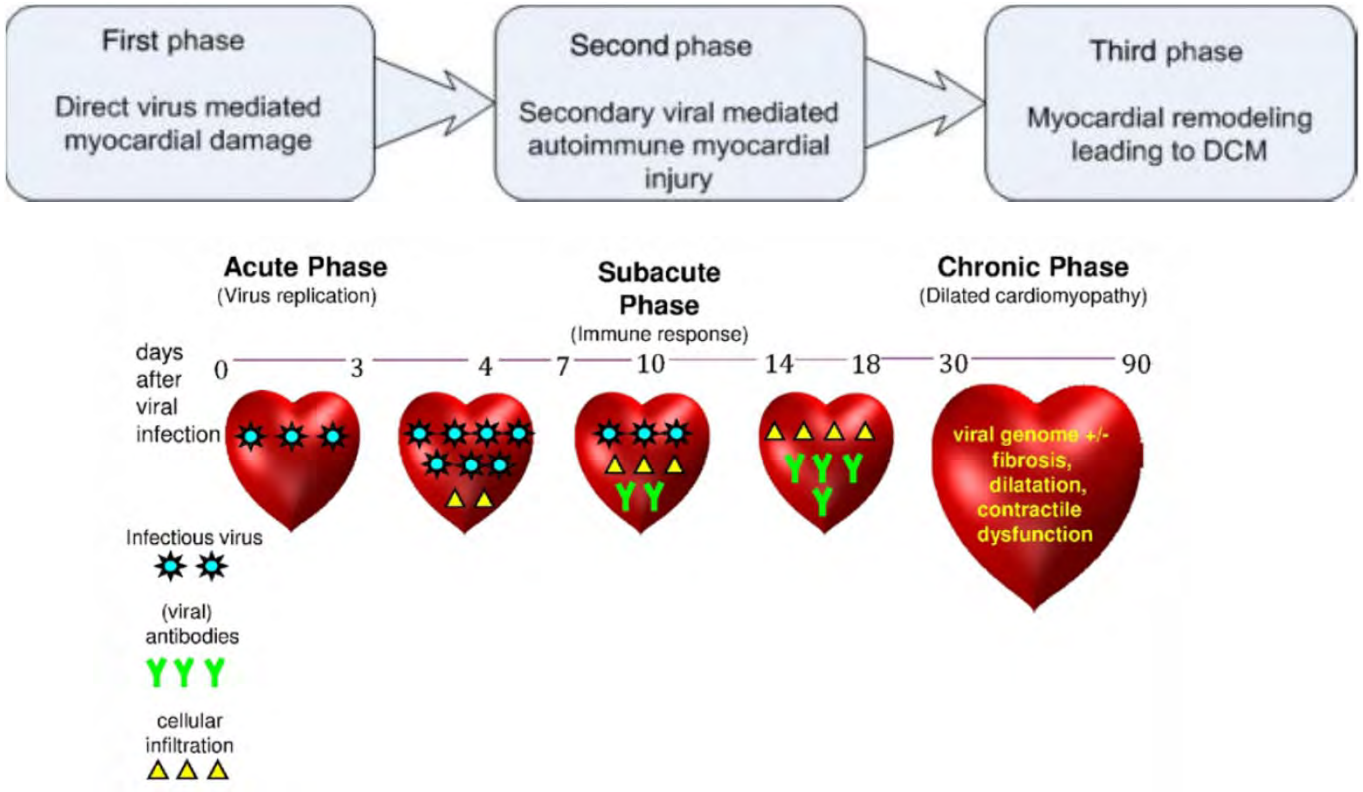
Clinical presentations[a]
Acute chest pain, pericarditic, or pseudo-ischaemic
New-onset (days up to 3 months) or worsening of: dyspnoea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs
Subacute/chronic (>3 months) or worsening of: dyspnoea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs
Palpitation, and/or unexplained arrhythmia symptoms and/or syncope, and/or aborted sudden cardiac death
Unexplained cardiogenic shock
Diagnostic criteria
I. ECG/Holter/stress test features
Newly abnormal 12 lead ECG and/or Holter and/or stress testing, any of the following: I to III degree atrioventricular block, or bundle branch block, ST/T wave change (ST elevation or non ST elevation, T wave inversion), sinus arrest, ventricular tachycardia or fibrillation and asystole, atrial fibrillation, reduced R wave height, intraventricular conduction delay (widened QRS complex), abnormal Q waves, low voltage, frequent premature beats, supraventricular tachycardia
II. Myocardiocytolysis markers
Elevated TnT/TnI
III. Functional and structural abnormalities on cardiac imaging (echo/angio/CMR)
New, otherwise unexplained LV and/or RV structure and function abnormality (including incidental finding in apparently asymptomatic subjects): regional wall motion or global systolic or diastolic function abnormality, with or without ventricular dilatation, with or without increased wall thickness, with or without pericardial effusion, with or without endocavitary thrombi
IV. Tissue characterization by CMR
Oedema and/or LGE of classical myocarditic pattern (see text)

Clinically suspected myocarditis if ≥1 clinical presentation and ≥1 diagnostic criteria from different categories, in the absence of: (1) angiographically detectable coronary artery disease (coronary stenosis ≥ 50%); (2) known pre-existing cardiovascular disease or extra-cardiac causes that could explain the syndrome (e.g. valve disease, congenital heart disease, hyperthyroidism, etc.) (see text). Suspicion is higher with higher number of fulfilled criteria.
[a]If the patient is asymptomatic ≥2 diagnostic criteria should be met.



Patogenetické souvislosti

- **až 2/3 případů DKMP jsou důsledkem předchozí myokarditidy**



Dennert Eur Heart J 2008
Kindermann JACC 2012

Myocarditis

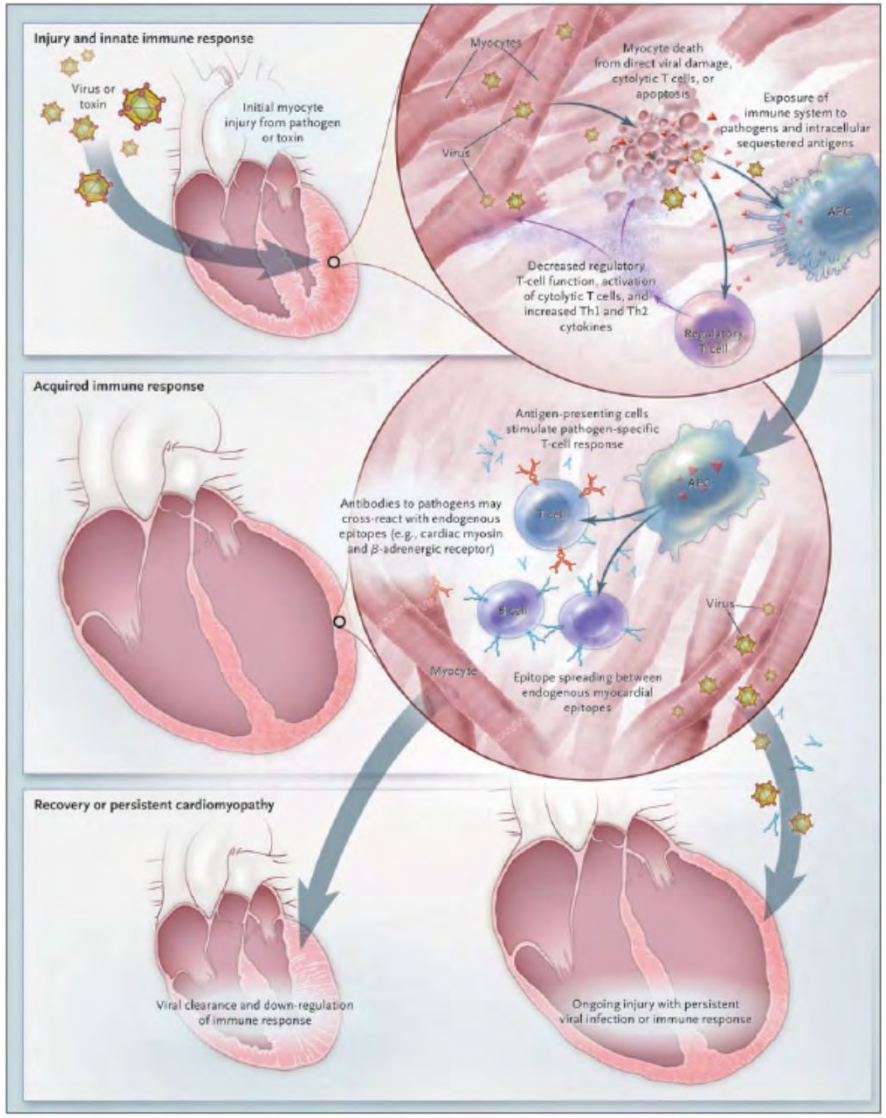
Leslie T. Cooper, Jr., M.D.

N Engl J Med 2009;360:1526-38.

1. FÁZE
přímé poškození myocytů virem a nespecifickou imunitní reakcí

2. FÁZE
poškození myokardu specifickou (auto)imunitní reakcí

3. FÁZE
Zhojení a restituce funkce
Vývoj dilatační kardiomyopatie



Diagnostika myokarditid / ZKMP

- **EKG, RTG S+P, ECHO, katetrizace**

- **Magnetická rezonance**

  nejdůležitější neinvazivní dg metoda

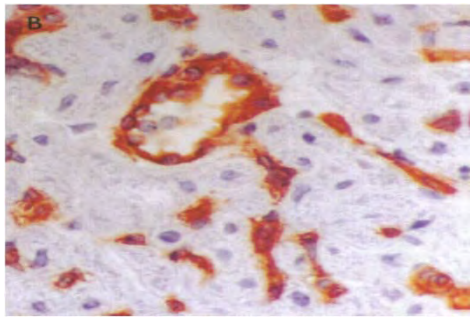
Cardiovascular Magnetic Resonance in Myocarditis: A JACC White Paper

Matthias G. Friedrich, MD,* Udo Sechtem, MD,‡ Jeanette Schulz-Menger, MD,§ Godtfred Holmvang, MD,‖ Pauline Alakija, MD,† Leslie T. Cooper, MD,¶ James A. White, MD,# Hassan Abdel-Aty, MD,§ Matthias Gutberlet, MD,** Sanjay Prasad, MD,†† Anthony Aletras, PHD,‡‡ Jean-Pierre Laissy, MD,§§ Ian Paterson, MD,‖‖ Neil G. Filipchuk, MD,* Andreas Kumar, MD,* Matthias Pauschinger, MD,¶¶ Peter Liu, MD,## for the *International Consensus Group on Cardiovascular Magnetic Resonance in Myocarditis*

Cardiovascular magnetic resonance (CMR) has become the primary tool for noninvasive assessment of myocardial inflammation in patients with suspected myocarditis. The International Consensus Group on CMR Diagnosis of Myocarditis was founded in 2006 to achieve consensus among CMR experts and develop recommendations on the current state-of-the-art use of CMR for myocarditis. The recommendations include indications for CMR in patients with suspected myocarditis, CMR protocol standards, terminology for reporting CMR findings, and diagnostic CMR criteria for myocarditis (i.e., "Lake Louise Criteria").

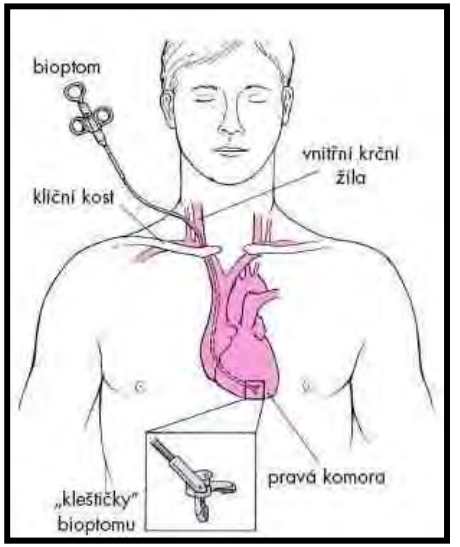
- **Endomyokardiální biopsie**

  „zlatý standard“ diagnostiky ZKMP



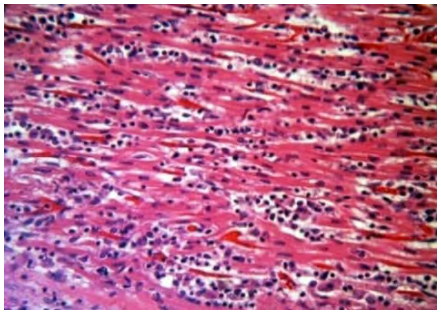
Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases

Alida L. P. Caforio[1†*], Sabine Pankuweit[2†], Eloisa Arbustini[3], Cristina Basso[4], Juan Gimeno-Blanes[5], Stephan B. Felix[6], Michael Fu[7], Tiina Heliö[8], Stephane Heymans[9], Roland Jahns[10], Karin Klingel[11], Ales Linhart[12], Bernhard Maisch[2], William McKenna[13], Jens Mogensen[14], Yigal M. Pinto[15], Arsen Ristic[16], Heinz-Peter Schultheiss[17], Hubert Seggewiss[18], Luigi Tavazzi[19], Gaetano Thiene[4], Ali Yilmaz[20], Philippe Charron[21], and Perry M. Elliott[13]



Diagnosis of myocarditis

Non-invasive imaging techniques such as cardiac magnetic resonance (CMR) imaging can be useful in making the diagnosis of myocarditis and for monitoring disease progression, but we strongly endorse the concept that EMB should be the gold standard for the diagnosis of definite myocarditis.[1–3] However, this implies that all patients with suspected myocarditis should undergo an EMB which is not routine practice; moreover, current guidelines recommend EMB only in a limited number of clinical scenarios that do not include some common

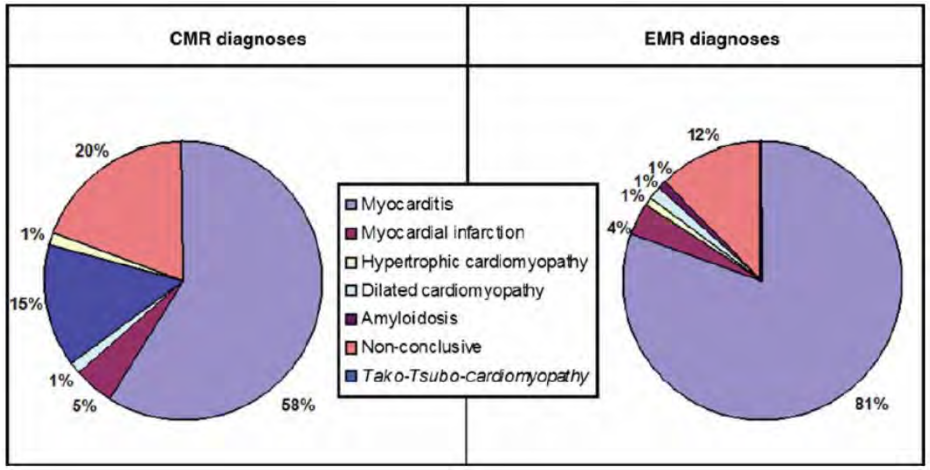


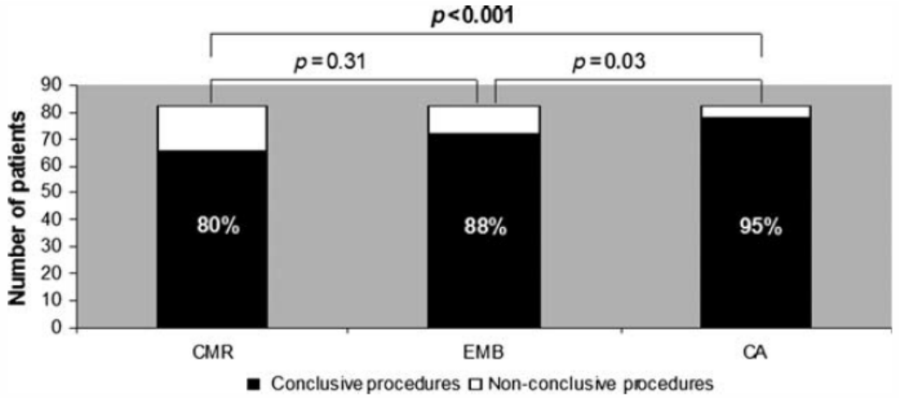
Recommendation

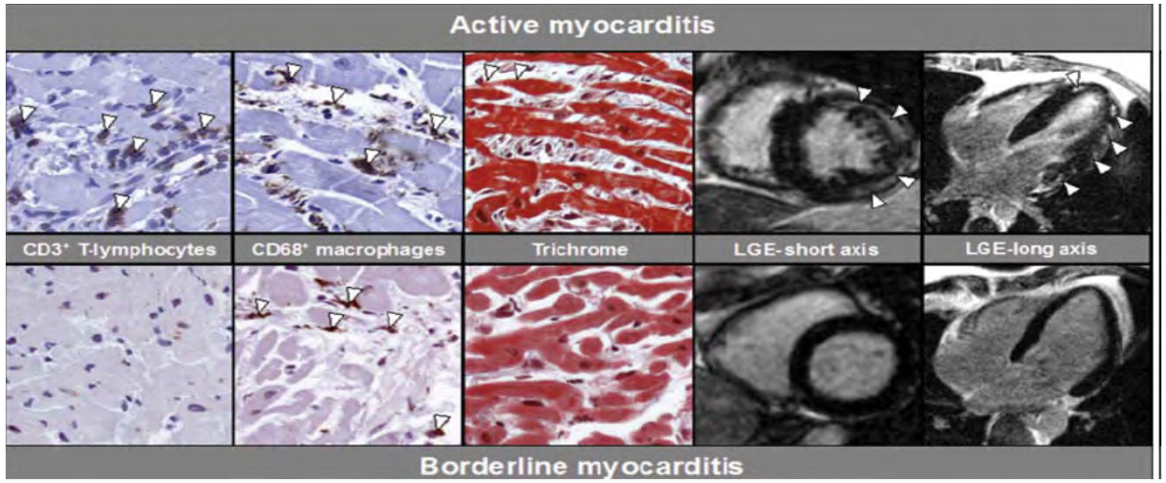
10. All patients with clinically suspected myocarditis should be considered for selective coronary angiography and EMB.

Diagnostic synergy of non-invasive cardiovascular magnetic resonance and invasive endomyocardial biopsy in troponin-positive patients without coronary artery disease

Hannibal Baccouche[1], Heiko Mahrholdt[1], Gabriel Meinhardt[1], Rimma Merher[1], Matthias Voehringer[1], Stefan Hill[1], Karin Klingel[2], Reinhard Kandolf[2], Udo Sechtem[1], and Ali Yilmaz[1]*







Imunohistologické hodnocení EMB

Immunohistological evidence for a chronic intramyocardial inflammatory process in dilated cardiomyopathy

U Kühl, M Noutsias, B Seeberg, H-P Schultheiss

Abstract

***Objective*—To determine whether immunohistochemical analysis of cardiac biopsies from patients presenting clinically as dilated cardiomyopathy (DCM) show a chronic inflammatory process.**

***Design*—Comparative case control study.**

***Setting*—Tertiary referral centre.**

***Patients*—Biopsies from 170 patients with DCM and 85 control patients with other cardiac diseases.**

***Results*—Nine patients had sufficient interstitial inflammatory cells to be called borderline myocarditis on conventional histology, leaving 161 patients with DCM. In 78 patients with DCM (48%) there were T lymphocytes in the myocardium. In 48 (62%) of these 78 T lymphocyte densities were in the range 2–14 per high power field (HPF), equivalent to 7–50 per mm² of tissue. In 43 (89%) interstitial and endothelial immune activation was demonstrated by MHC expression. In 30 patients with T cell counts in the range 1·5–2·0 per HPF, 80% also showed endothelial activation. Lymphocyte density correlated with increased expression of MHC class I and II antigens and the adhesion molecules ICAM, VCAM, ELAM, LFA-3, and GMP140. In all control biopsies the T lymphocyte density was less than 1·0 per HPF (less than 2–5 per mm² of tissue).**

***Conclusions*—Nearly half the patients with DCM had increased T lymphocyte density and immune activation of endothelial and interstitial cells in their cardiac biopsies. A chronic autoimmune process is still active within the myocardium in a significant percentage of patients with DCM. Immunohistochemical analysis of cardiac biopsies will enhance the sensitivity of cardiac biopsy and is essential for the diagnosis of myocarditis.**

(*Heart* 1996;75:295–300)

have been described.[5–10] Persistence of viral RNA has been demonstrated in endomyocardial biopsy specimens from some patients.[11 12]

One proposed pathogenetic mechanism for DCM is that acute viral myocarditis develops into a chronic autoimmunological process directed against cryptic myocardial epitopes or viral neo-antigens in genetically predisposed patients.[13 14]

About 90% of adults with acute viral myocarditis recover completely. A few slowly progress to cardiac dysfunction. In patients admitted to hospital with chronic heart failure dating back at least several months or even years light microscopy of endomyocardial biopsies often shows only non-specific fibrosis and these cases are categorised as DCM. The diagnosis of a chronic inflammatory process is, however, difficult to establish by light microscopy. Cellular infiltrates are often sparse and may be missed by sampling error.[15 16] In sections stained with haematoxylin and eosin it is not possible to distinguish unequivocally between non-inflammatory cells (for example, fibroblasts or pericytes) and infiltrating lymphocytes.[17 18]

Immunohistological techniques have now been successfully introduced to identify more accurately cellular infiltrates in myocardial biopsies and this study determines the fre-

> 7 CD3+ a/nebo > 5 CD68+ /mm2
a/nebo zvýšená exprese HLA

PATIENTS

We studied 170 patients with dilated cardiomyopathy (116 men, 54 women, mean (SD) age 50·1 (14·3) years). They had had symptoms for more than six months (6 months–10 years) without any clinical history

Imunohistologické hodnocení EMB

Herz © Urban & Vogel 2000

Definition of Inflammatory Cardiomyopathy (Myocarditis): On the Way to Consensus

A Status Report

Bernhard Maisch, Irene Portig, Arsen Ristic, Günther Hufnagel, Sabine Pankuweit[1]

Abstract

This article reviews the current state of consensus reached for the diagnosis of myocarditis and dilated cardiomyopathy on the basis of conventional histopathological and immunohistochemical methods for inflammatory infiltrates in addition to molecular biological methods for persistence of viral genome in endomyocardial biopsies.

Additionally, a brief overview is presented stating the current knowledge on effector mechanisms of the immune system in myocarditis and dilated cardiomyopathy.

Key Words: Myocarditis · Dilated cardiomyopathy with and without inflammation · Effector systems of the immune system · Viral heart disease

> 14 leukocytů/mm2 (LCA resp. CD45+)

Imunohistologické hodnocení EMB

Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: the TIMIC study

Andrea Frustaci[1,2]*, Matteo A. Russo[3,4], and Cristina Chimenti[1,2,4]

[1]Cardiovascular and Respiratory Sciences Department, La Sapienza University, Viale del Policlinico 155, 00161 Rome, Italy; [2]Molecular and Cellular Cardiology Laboratory, National Institute for Infectious Diseases 'Lazzaro Spallanzani', Rome, Italy; [3]Experimental Medicine Department, La Sapienza University, Rome, Italy; and [4]IRCCS San Raffaele La Pisana, Rome, Italy

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See page 1936 for the editorial comment on this article (doi:10.1093/eurheartj/ehp172)

Aims To evaluate the efficacy of immunosuppression in virus-negative inflammatory cardiomyopathy.

Methods and results This randomized, double-blind, placebo-controlled study included 85 patients with myocarditis and chronic (>6 months) heart failure unresponsive to conventional therapy, with no evidence of myocardial viral genomes. Patients received either prednisone 1 mg kg^{-1} day^{-1} for 4 weeks followed by 0.33 mg kg^{-1} day^{-1} for 5 months and azathioprine 2 mg kg^{-1} day^{-1} for 6 months (43 patients, Group 1) or placebo (42 patients, Group 2) in addition to conventional therapy for heart failure. Primary outcome was the 6 month improvement in left-ventricular function. Group 1 showed a significant improvement of left-ventricular ejection fraction and a significant decrease in left-ventricular dimensions and volumes compared with baseline. None of Group 2 patients showed improvement of ejection fraction, that significantly worsened compared with baseline. No major adverse reaction was registered as a result of immunosuppression.

Conclusion These data confirm the efficacy of immunosuppression in virus-negative inflammatory cardiomyopathy. Lack of response in 12% of cases suggests the presence of not screened viruses or mechanisms of damage and inflammation not susceptible to immunosuppression.

Keywords Inflammatory cardiomyopathy • Immunosuppressive therapy • Heart Failure • Ejection Fraction • NYHA class

> 14 leukocytů/mm2 a/nebo > 7 T-lymfocytů/mm2

FNUSA ICRC

„new“ diagnostic criteria

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Alida L. P. Caforio[1†*], Sabine Pankuweit[2†], Eloisa Arbustini[3], Cristina Basso[4], Juan Gimeno-Blanes[5], Stephan B. Felix[6], Michael Fu[7], Tiina Heliö[8], Stephane Heymans[9], Roland Jahns[10], Karin Klingel[11], Ales Linhart[12], Bernhard Maisch[2], William McKenna[13], Jens Mogensen[14], Yigal M. Pinto[15], Arsen Ristic[16], Heinz-Peter Schultheiss[17], Hubert Seggewiss[18], Luigi Tavazzi[19], Gaetano Thiene[4], Ali Yilmaz[20], Philippe Charron[21], and Perry M. Elliott[13]

Definitions

Myocarditis (WHO /ISFC[1]):

Inflammatory disease of the myocardium diagnosed by established histological, immunological and immunohistochemical criteria**.*

**N.B. established histological Dallas criteria[12] defined as follows:*

'histological evidence of inflammatory infiltrates within the myocardium associated with myocyte degeneration and necrosis of non-ischaemic origin[12]'.

***N.B. unspecified immunohistochemical criteria[1], we propose an abnormal inflammatory infiltrate to be defined as follows:*

'≥ 14 leucocytes/mm^2 including up to 4 monocytes/mm^2 with the presence of CD 3 positive T-lymphocytes ≥ 7 cells/mm^2'.[15,18,19]

Inflammatory Cardiomyopathy (WHO /ISFC[1]):

Myocarditis in association with cardiac dysfunction.

N.B. Inflammatory cardiomyopathy, involved in the pathogenesis of DCM, includes idiopathic, autoimmune and infectious subtypes.[1]

> 14 LCA+/mm2 s maximálně 4 monocyty (CD68+) a SOUČASNĚ > 7 CD3/mm2

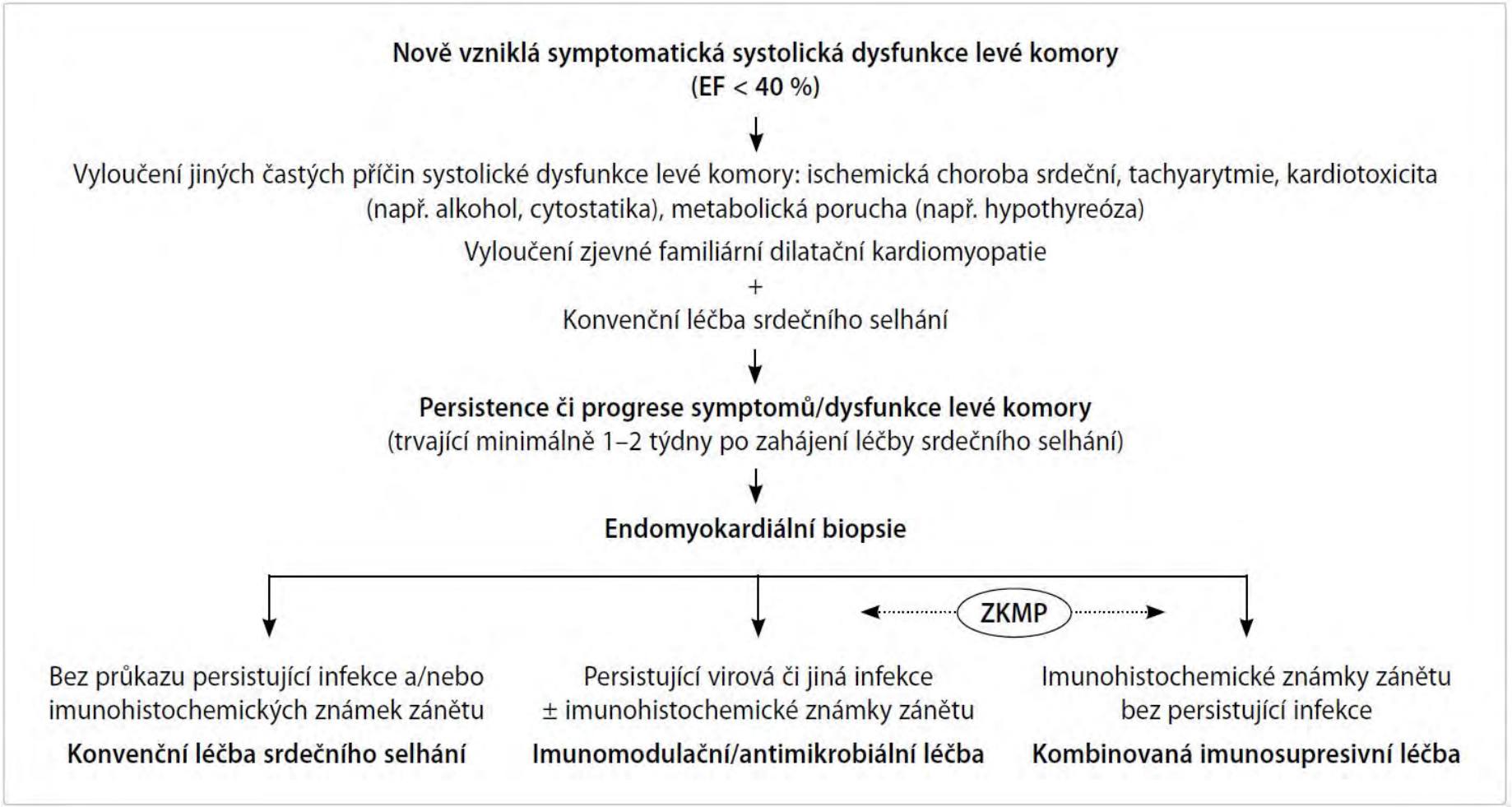
impaired by abnor-

N.B. DCM includes idiopathic, familial/genetic, viral and/or immune, alcoholic/toxic subtypes.[1]

Zánětlivá kardiomyopatie: aktuální pohled na diagnostiku a léčbu

Petr Kuchynka, Tomáš Paleček, Stanislav Šimek, Ivana Vítková*, Jana Schramlová**, Dagmar Hulínská**, Viktor Aster***, Gabriela Dostálová, Sudheera Magage, Michael Aschermann, Aleš Linhart

*II. interní klinika kardiologie a angiologie, *Ústav patologie, Všeobecná fakultní nemocnice a 1. lékařská fakulta Univerzity Karlovy, **Státní zdravotní ústav, ***III. klinika infekčních a tropických nemocí, Fakultní nemocnice Na Bulovce a 1. lékařská fakulta Univerzity Karlovy, Praha, Česká republika*



Hodnocení EMB na našem pracovišti

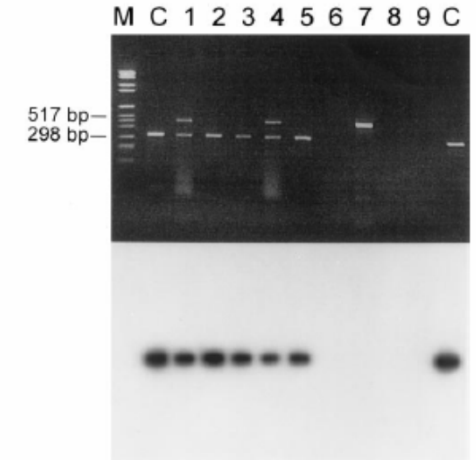
1) histologie a imunohistologie

(detekce zánětlivé infiltrace,
zvýšená exprese HLA DR)

> 14 leukocytů/mm2 a/nebo > 7 T-lymfocytů/mm2

2) molekulárně-genetické vyš. (přítomnost nukleové kyseliny patogenů v myokardu)

- Parvovirus B19 (PVB19)
- Human herpes virus 6 (HHV6)
- Enteroviry (EV- coxackie + echoviruses)
- Adenovirus (AV)
- Cytomegalovirus (CMV)
- Ebstein-Barr virus (EBV)
- Herpes simplex virus (HSV1)
- Borrelia burgdoferi



Original Research Article

Impact of inflammatory infiltration and viral genome presence in myocardium on the changes of echocardiographic parameters

Jan Krejčí[a,*], Hana Poloczková[a], Petr Hude[a], Tomáš Freiberger[b], Eva Němcová[b,d], Víta Žampachová[c], Alžběta Sirotková[c], Radka Štěpánová[d], Lenka Špinarová[a], Petr Němec[b,d], Jiří Vítovec[a]

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[b]Center of Cardiovascular and Transplant Surgery, Brno, Czech Republic
[c]1st Department of Pathologic Anatomy, St. Anne's University Hospital and Masaryk University, Brno, Czech Republic
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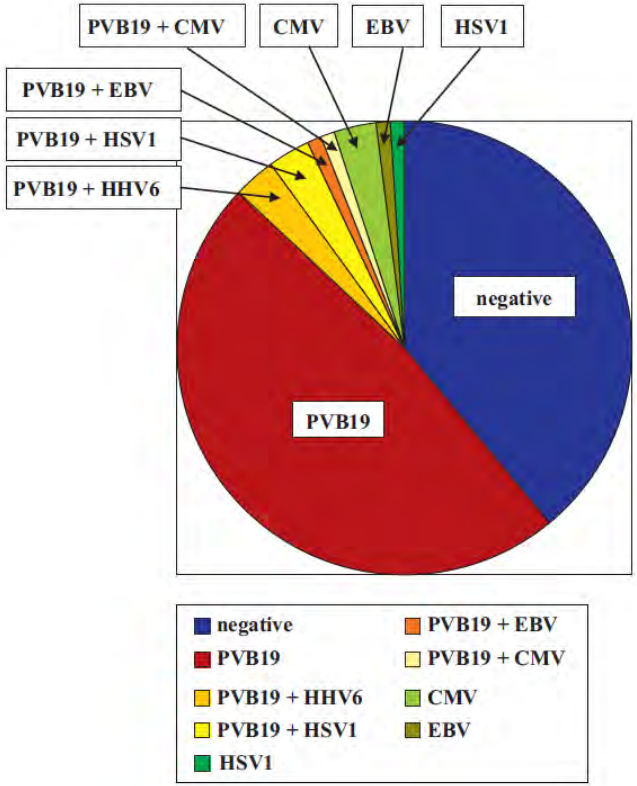
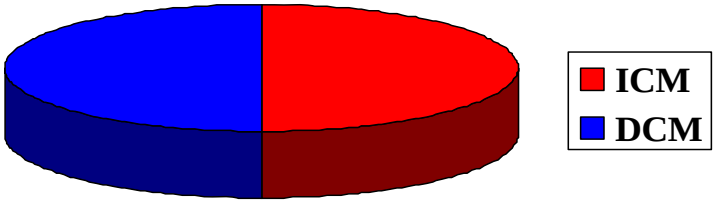
Results: According to immunohistological (IH) assessment findings were positive (IH+) in 35 patients (i.e. 50%); thus the inflammatory infiltration was present in myocardium. In remaining patients the findings were negative (IH−). At 6 months follow-up, in the group of IH+ patients the LVEF improved from 25±9% to 39±11% and NYHA class declined from 2.8±0.5 to 1.7±0.6 (both $p<0.001$). In IH− group change in LVEF (from 23±8% to 27±10%) in contrast to the change of NYHA class (from 2.5±0.5 to 2.1±0.7; $p<0.05$) was not found statistically significant. Comparing changes in the parameters between both groups, the IH+ group has significantly more improved in LVEF ($p<0.01$) as well as in the NYHA class ($p<0.001$). Viral genome was detected (PCR was positive, PCR+) in 43 patients (i.e. 61%). At 6 months follow-up, there were statistically significant changes of LVEF in PCR+ group (from 25±8% to 34±12%; $p<0.01$) and also in PCR− group (from 22±8% to 32±12%; $p<0.001$).



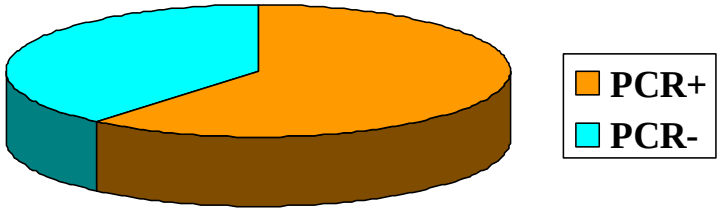
Patients group

- 70 patients (standard heart failure therapy)
- Males 56 (80%); females 14 (20%)

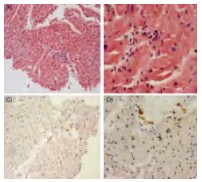
- 35 IH+ ICM (50%)
- 35 IH- DCM (50%)



- 43 PCR+ (61%)
- 27 PCR- (39%)

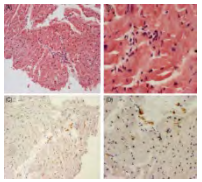


ICM - 6-month follow-up



	baseline	6-M	p
NYHA	2.8 ± 0.5	1.7 ± 0.6	< 0.001
LVEF (%)	25 ± 9	39 ± 11	< 0.001
DD (mm)	64 ± 9	60 ± 9	0.001
SD (mm)	56 ± 10	49 ± 10	< 0.001
RV (mm)	34 ± 6	32 ± 5	0.123
s´ (cm/s)	5.3 ± 2.0	6.7 ± 2.1	0.002
e´ (cm/s)	6.5 ± 1.9	6.8 ± 2.1	0.449
E/e´	12.7 ± 4.5	10.6 ± 5.2	0.004
s´tri (cm/s)	10.2 ± 2.0	13.2 ± 3.9	0.001
TAPSE (mm)	19.8 ± 4.2	22.6 ± 2.8	0.017

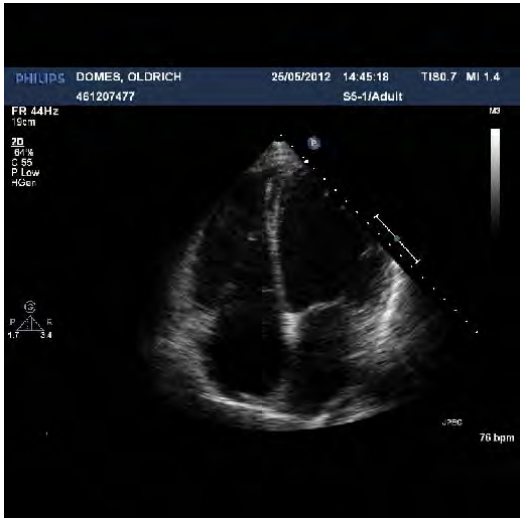
DCM - 6-month follow-up

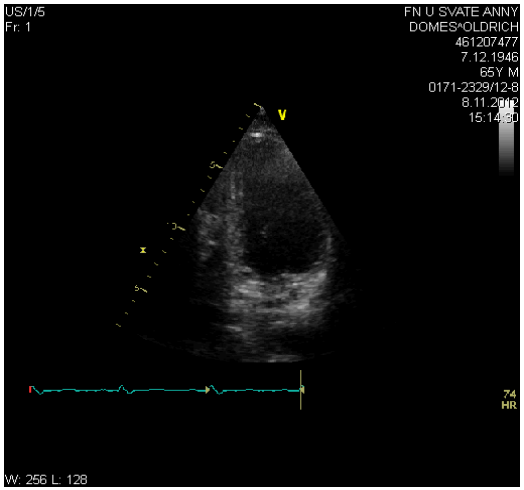


	baseline	6-M	p
NYHA	2.5 ± 0.5	2.1 ± 0.7	0.042
LVEF (%)	23 ± 8	27 ± 10	0.219
DD (mm)	69 ± 8	67 ± 9	0.016
SD (mm)	61 ± 8	58 ± 9	0.004
RV (mm)	37 ± 5	34 ± 6	0.055
s´ (cm/s)	4.9 ± 1.5	5.5 ± 1.3	0.108
e´ (cm/s)	5.5 ± 2.1	6.0 ± 1.8	0.340
E/e´	15.9 ± 8.9	10.1 ± 2.7	0.001
s´ tri (cm/s)	10.8 ± 2.8	11.2 ± 2.3	0.920
TAPSE (mm)	20.0 ± 4.6	20.2 ± 3.7	0.709

Difference between IH+ / IH- groups
(in favor of IH+/ICM group)

	p
NYHA	0.001
LVEF (%)	0.002
DD (mm)	0.317
SD (mm)	0.048
RV (mm)	0.669
s´ (cm/s)	0.082
e´ (cm/s)	0.880
E/e´	0.848
s´ tri (cm/s)	0.003
TAPSE (mm)	0.040





Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases

Alida L. P. Caforio[1†*], Sabine Pankuweit[2‡], Eloisa Arbustini[3], Cristina Basso[4], Juan Gimeno-Blanes[5], Stephan B. Felix[6], Michael Fu[7], Tiina Heliö[8], Stephane Heymans[9], Roland Jahns[10], Karin Klingel[11], Ales Linhart[12], Bernhard Maisch[2], William McKenna[13], Jens Mogensen[14], Yigal M. Pinto[15], Arsen Ristic[16], Heinz-Peter Schultheiss[17], Hubert Seggewiss[18], Luigi Tavazzi[19], Gaetano Thiene[4], Ali Yilmaz[20], Philippe Charron[21], and Perry M. Elliott[13]

Terapeutická doporučení

Recommendations

14. Patients with a life-threatening presentation should be sent to specialized units with capability for haemodynamic monitoring, cardiac catheterization, and expertise in EMB.
15. In patients with haemodynamic instability, a mechanical cardio-pulmonary assist device may be needed as a bridge to recovery or to heart transplantation.
16. Cardiac transplantation should be deferred in the acute phase, because recovery may occur, but can be considered for haemodynamically unstable myocarditis patients, including those with giant cell myocarditis, if optimal pharmacological support and mechanical assistance cannot stabilize the patient.
17. Management of ventricular dysfunction should be in line with current ESC guidelines on heart failure.
18. ICD implantation should be deferred until resolution of the acute episode.
19. Arrhythmia management outside the acute phase should be in line with current ESC guidelines on arrhythmia and device implantation.

Léčba - antivirotická

Interferon-β Treatment Eliminates Cardiotropic Viruses and Improves Left Ventricular Function in Patients With Myocardial Persistence of Viral Genomes and Left Ventricular Dysfunction

Uwe Kühl, PhD; Matthias Pauschinger, MD; Peter Lothar Schwimmbeck, MD; Bettina Seeberg; Conny Lober, MD; Michel Noutsias, MD; Wolfgang Poller, MD; Heinz-Peter Schultheiss, MD

Background—Viral infections are important causes of myocarditis and may induce cardiac dysfunction and finally lead to dilated cardiomyopathy. We investigated whether interferon (IFN)-β therapy is safe and may achieve virus clearance and prevent deterioration of left ventricular (LV) function in patients with myocardial virus persistence.

Methods and Results—In this phase II study, 22 consecutive patients with persistence of LV dysfunction (history of symptoms, 44±27 months) and polymerase chain reaction–proven enteroviral or adenoviral genomes were treated with 18×10^6 IU/week IFN-β (Beneferon) subcutaneously for 24 weeks. Histological and immunohistological analysis of endomyocardial biopsies was used to characterize myocardial inflammation. LV diameters and ejection fraction were assessed by echocardiography and angiography, respectively. During the treatment period, IFN-β was well tolerated by all patients. No patient deteriorated. Clearance of viral genomes was observed in 22 of 22 of patients after antiviral therapy. Virus clearance was paralleled by a significant decrease of LV end diastolic and end systolic diameters, decreasing from 59.7±11.1 to 56.5±10.0 mm ($P<0.001$) and 43.2±13.6 to 39.4±12.1 mm ($P<0.001$), respectively. LV ejection fraction increased from 44.6±15.5% to 53.1±16.8% ($P<0.001$).

Conclusions—A 6 months, IFN-β treatment was safe in patients with myocardial enteroviral or adenoviral persistence and LV dysfunction and resulted in elimination of viral genomes (22 of 22 patients) and improved LV function (15 of 22 patients). (***Circulation.*** **2003;107:2793-2798.)**

Key Words: cardiomyopathy ■ viruses ■ biopsy ■ heart failure

22 pacientů
Symptomy 44 měsíců
Léčba 24 týdnů

TABLE 2. Clinical, Hemodynamic, Virological, and Immunohistological Data of Patients Before and After IFN-β Treatment

	Before IFN-β	After IFN-β	P
Echocardiography			
LVEDD (n=22)	59.7±11.1*	56.5±11.1*	<0.001
LVESD (n=22)	43.4±13.6*	39.4±12.1*	<0.001
LV angiography			
LVEF (n=22)	44.7±15.5*	53.1±16.8*	<0.001
Endomyocardial biopsy			
Molecular biology (PCR)			
Enterovirus	15	0	<0.001
Adenovirus	7	0	<0.05
Histology			
Myocarditis	0	0	
Borderline myocarditis	0	0	
Immunohistology			
Inflammation (n=7) CD3, cells/mm²	19.2±4.8*	6.0±4.6*	<0.05
No inflammation (n=15) CD3, cells/mm²	2.6±1.8*	2.9±3.1*	NS
NYHA	2.5±0.6*	1.7±0.7*	<0.05

	$LVEF_{baseline}$ <50% (n=12)			$LVEF_{baseline}$ >50% (n=10)		
N=22	Baseline	Follow-Up	*P*	Baseline	Follow-Up	*P*
LVEF, %	33.6±11.2	43.9±17.2	<0.001	58.0±6.7	64.1±7.2	<0.05
LVEDD	67.2±9.4	62.2±10.0	<0.001	50.8±4.4	49.7±4.2	0.20
LVESD	52.3±11.9	47.0±10.9	<0.001	32.6±4.8	30.3±5.0	<0.05

Léčba - antivirotická

Basic Science and Experimental Studies

Interferon β-1b Therapy in Chronic Viral Dilated Cardiomyopathy—Is There a Role for Specific Therapy?

OLIVER ZIMMERMANN, MD,[1,*] CHRISTOPH RODEWALD, MD,[1,*] MICHAEL RADERMACHER, MD,[1] MARTIN VETTER,[1] JULIANE M. WIEHE, PhD,[1] MAGDALENA BIENEK-ZIOLKOWSKI,[1] VINZENZ HOMBACH, MD,[1] AND JAN TORZEWSKI, MD[2]

Ulm, Germany; Immenstadt, Germany

ABSTRACT

Background: Myocardial biopsy can be used for the detection of viral genome in dilated cardiomyopathy (DCM). Pilot studies have previously reported beneficial effects on clinical outcome and safety of an antiviral therapy using interferon β-1b in chronic viral DCM.

Methods and Results: Myocardial biopsies were taken from patients with DCM. Using polymerase chain reaction and Southern Blot analysis, viral genome could be detected in 49% of patients. In 42 patients with viral infection, off-label use with interferon β-1b was initiated. A further 68 patients formed the control group. The outcome was evaluated after follow-up with echocardiography, exercise electrocardiogram, and New York Heart Association class. A total of 81 men and 29 women with a median left ventricular ejection fraction of 34% were included. The follow-up period was 36 months. In 33 (79%) patients with interferon β-1b treatment, minor adverse reactions occurred, but no major adverse events were reported. No significant benefit for interferon β-1b treatment on clinical outcome could be detected during follow-up.

Conclusions: Off-label use with interferon β-1b in patients with viral DCM is feasible and safe under routine clinical practice. Concerning the herein evaluated clinical outcome parameters, promising results from pilot studies could not be confirmed. High prevalence of parvovirus B19 (92%) might influence the results. (*J Cardiac Fail 2010;16:348–356*)

Conclusions: Off-label use with interferon β-1b in patients with viral DCM is feasible and safe under routine clinical practice. Concerning the herein evaluated clinical outcome parameters, promising results from pilot studies could not be confirmed. High prevalence of parvovirus B19 (92%) might influence the results. (*J Cardiac Fail 2010;16:348–356*)

Léčba - imunomodulační

Controlled Trial of Intravenous Immune Globulin in Recent-Onset Dilated Cardiomyopathy

Dennis M. McNamara, MD; Richard Holubkov, PhD; Randall C. Starling, MD; G. William Dec, MD; Evan Loh, MD; Guillermo Torre-Amione, MD; Alan Gass, MD; Karen Janosko, RN, MSN; Tammy Tokarczyk, RN, BSN; Paul Kessler, MD; Douglas L. Mann, MD; Arthur M. Feldman, MD, PhD; for the Intervention in Myocarditis and Acute Cardiomyopathy (IMAC) Investigators

Background—This prospective placebo-controlled trial was designed to determine whether intravenous immune globulin (IVIG) improves left ventricular ejection fraction (LVEF) in adults with recent onset of idiopathic dilated cardiomyopathy or myocarditis.

Methods and Results—Sixty-two patients (37 men, 25 women; mean age ±SD 43.0±12.3 years) with recent onset (≤6 months of symptoms) of dilated cardiomyopathy and LVEF ≤0.40 were randomized to 2 g/kg IVIG or placebo. All underwent an endomyocardial biopsy before randomization, which revealed cellular inflammation in 16%. The primary outcome was change in LVEF at 6 and 12 months after randomization. Overall, LVEF improved from 0.25±0.08 to 0.41±0.17 at 6 months ($P<0.001$) and 0.42±0.14 ($P<0.001$ versus baseline) at 12 months. The increase was virtually identical in patients receiving IVIG and those given placebo (6 months: IVIG 0.14±0.12, placebo 0.14±0.14; 12 months: IVIG 0.16±0.12, placebo 0.15±0.16). Overall, 31 (56%) of 55 patients at 1 year had an increase in LVEF ≥0.10 from study entry, and 20 (36%) of 56 normalized their ejection fraction (≥0.50). The transplant-free survival rate was 92% at 1 year and 88% at 2 years.

Conclusions—These results suggest that for patients with recent-onset dilated cardiomyopathy, IVIG does not augment the improvement in LVEF. However, in this overall cohort, LVEF improved significantly during follow-up, and the short-term prognosis remains favorable. (***Circulation***. **2001;103:2254-2259.**)

Conclusions—These results suggest that for patients with recent-onset dilated cardiomyopathy, IVIG does not augment the improvement in LVEF. However, in this overall cohort, LVEF improved significantly during follow-up, and the short-term prognosis remains favorable. (***Circulation***. **2001;103:2254-2259.**)

Imunosupresivní léčba

Randomized, Placebo-Controlled Study for Immunosuppressive Treatment of Inflammatory Dilated Cardiomyopathy

Two-Year Follow-Up Results

Romuald Wojnicz, MD; Ewa Nowalany-Kozielska, MD; Celina Wojciechowska, MD; Grażyna Glanowska, MD; Przemysław Wilczewski, MD; Tomasz Niklewski, MD; Marian Zembala, MD, PhD; Lech Poloński, MD, PhD; Marius M. Rozek, MD; Jan Wodniecki, MD, PhD

Background—Previous studies have shown disappointing results for immunosuppressive treatment in patients with dilated cardiomyopathy. Therefore, we studied the effectiveness of such therapy in patients with HLA upregulation on biopsy.

Methods and Results—Of 202 patients with dilated cardiomyopathy, 84 patients with increased HLA expression were randomized to receive either immunosuppression or placebo for 3 months; they were then followed for 2 years. After 2 years, there were no significant differences in the primary end point (a composite of death, heart transplantation, and hospital readmission) between the 2 study groups (22.8% for the immunosuppression group and 20.5% for the placebo). The secondary efficacy end point included changes in ejection fraction, end-diastolic diameter, end-diastolic volume, end-systolic volume and NYHA class; left ventricular ejection fraction increased significantly in the immunosuppression group compared with the placebo group (95% CI, 4.20 to 13.12; $P<0.001$) after 3 months of follow-up. The early favorable effects of immunosuppressive therapy on left ventricular volume, left ventricular diastolic dimension, and New York Heart Association class were also present. This improvement was maintained in the immunosuppression group at 2 years (ejection fraction: 95% CI, 6.94 to 19.04; $P<0.001$). In addition, on the basis of the protocol-specified definition of improvement, 71.8% patients in the immunosuppression group versus 20.9% patients in the placebo group met the criteria of improvement after 3 months ($P<0.001$). At the end of the follow-up period, 71.4% patients from the immunosuppression group versus 30.8% patients from the placebo group were improved ($P=0.001$).

Conclusions—These data demonstrate a long-term benefit of immunosuppressive therapy in patients with dilated cardiomyopathy and HLA upregulation on biopsy specimens. Thus, restoration of immunosuppressive therapy for such patients should be considered. (***Circulation***. 2001;104:39-45.)

Key Words: cardiomyopathy ■ myocarditis ■ heart failure ■ immunohistochemistry ■ HLA antigens

84 pac.
Symptomy delší než 6měsíců
Léčba 3 měsíce:
PRE 1mg/kg/den…0,2mg/kg/den
AZA 1mg/kg/den

Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: the TIMIC study

Andrea Frustaci[1,2]*, Matteo A. Russo[3,4], and Cristina Chimenti[1,2,4]

[1]Cardiovascular and Respiratory Sciences Department, La Sapienza University, Viale del Policlinico 155, 00161 Rome, Italy; [2]Molecular and Cellular Cardiology Laboratory, National Institute for Infectious Diseases 'Lazzaro Spallanzani', Rome, Italy; [3]Experimental Medicine Department, La Sapienza University, Rome, Italy; and [4]IRCCS San Raffaele La Pisana, Rome, Italy

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See page 1936 for the editorial comment on this article (doi:10.1093/eurheartj/ehp172)

Aims	To evaluate the efficacy of immunosuppression in virus-negative inflammatory cardiomyopathy.
Methods and results	This randomized, double-blind, placebo-controlled study included 85 patients with myocarditis and chronic (>6 months) heart failure unresponsive to conventional therapy, with no evidence of myocardial viral genomes. Patients received either prednisone 1 mg kg^{-1} day^{-1} for 4 weeks followed by 0.33 mg kg^{-1} day^{-1} for 5 months and azathioprine 2 mg kg^{-1} day^{-1} for 6 months (43 patients, Group 1) or placebo (42 patients, Group 2) in addition to conventional therapy for heart failure. Primary outcome was the 6 month improvement in left-ventricular function. Group 1 showed a significant improvement of left-ventricular ejection fraction and a significant decrease in left-ventricular dimensions and volumes compared with baseline. None of Group 2 patients showed improvement of ejection fraction, that significantly worsened compared with baseline. No major adverse reaction was registered as a result of immunosuppression.
Conclusion	These data confirm the efficacy of immunosuppression in virus-negative inflammatory cardiomyopathy. Lack of response in 12% of cases suggests the presence of not screened viruses or mechanisms of damage and inflammation not susceptible to immunosuppression.
Keywords	Inflammatory cardiomyopathy • Immunosuppressive therapy • Heart Failure • Ejection Fraction • NYHA class

85 pac.

Symptomy delší než 6měsíců
Léčba 6 měsíců:
PRE 1mg/kg/den…0,33mg/kg/den
AZA 2mg/kg/den

Original Research Article

Czech Inflammatory Cardiomyopathy Immunosuppression Trial (CZECH-ICIT): Randomized, multicentric study comparing the effect of two regimens of combined immunosuppressive therapy in the treatment of inflammatory cardiomyopathy: The aims and design of the trial

Tomáš Paleček[a,c], *Jan Krejčí*[b,c,*], *Ladislav Pecen*[c], *Hana Kostková*[c], *Petr Kuchynka*[a,c], *Hana Poloczková*[b,c], *Adam Svobodník*[c], *on behalf of CZECH-ICIT Investigators*

Potvrdíme, že přidání IS léčby ke standardní léčbě srd. selhání přináší nemocným se ZKMP prospěch?

Jsou oba IS režimy stejně účinné ?

Jaký bude efekt IS léčby u skupiny nemocných se symptomy kratšími 6 měsíců?

Jaký bude efekt IS léčby u nemocných s nízkou virovou náloží PVB19?

Peripartální kardiomyopatie

European Journal of Heart Failure (2010) 12, 767–778
doi:10.1093/eurjhf/hfq120

POSITION STATEMENT

Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Working Group on peripartum cardiomyopathy

Karen Sliwa[1]*, Denise Hilfiker-Kleiner[2], Mark C. Petrie[3], Alexandre Mebazaa[4], Burkert Pieske[5], Eckhart Buchmann[6], Vera Regitz-Zagrosek[7], Maria Schaufelberger[8], Luigi Tavazzi[9], Dirk J. van Veldhuisen[10], Hugh Watkins[11], Ajay J. Shah[12], Petar M. Seferovic[13], Uri Elkayam[14], Sabine Pankuweit[15], Zoltan Papp[16], Frederic Mouquet[17], and John J.V. McMurray[18]

- **Srdeční selhání vznikající na konci těhotenství či v prvních měsících po porodu u ženy bez předchozího srdečního onemocnění**

Peripartum Myocarditis and Cardiomyopathy

Mark G. Midei, MD, Samuel H. DeMent, MD, Arthur M. Feldman, MD, PhD, Grover M. Hutchins, MD, and Kenneth L. Baughman, MD

Can peripartum cardiomyopathy be familial?

A.-E. Baruteau *, G. Leurent, J.-M. Schleich, R. Gervais, J.-C. Daubert, P. Mabo

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Received 18 February 2008; received in revised form 12 March 2008; accepted 10 May 2008
Available online 9 August 2008

Evaluation of Bromocriptine in the Treatment of Acute Severe Peripartum Cardiomyopathy

A Proof-of-Concept Pilot Study

Karen Sliwa, MD, PhD; Lori Blauwet, MD; Kemi Tibazarwa, MD; Elena Libhaber, PhD; Jan-Peter Smedema, MD, MMed(Int); Anthony Becker, MD; John McMurray, MD, FESC; Hatice Yamac, MD; Saida Labidi, MSc; Ingrid Struman, PhD; Denise Hilfiker-Kleiner, PhD

Peripartum Cardiomyopathy as a Part of Familial Dilated Cardiomyopathy

Karin Y. van Spaendonck-Zwarts, MD; J. Peter van Tintelen, MD, PhD; Dirk J. van Veldhuisen, MD, PhD; Rik van der Werf, MD; Jan D.H. Jongbloed, PhD; Walter J. Paulus, MD, PhD; Dennis Dooijes, PhD; Maarten P. van den Berg, MD, PhD

Inhibition of Cardiac Myocyte Apoptosis Improves Cardiac Function and Abolishes Mortality in the Peripartum Cardiomyopathy of Gαq Transgenic Mice

Yukihiro Hayakawa, MD, PhD; Madhulika Chandra, MD; Wenfeng Miao, MD, PhD; Jamshid Shirani, MD; Joan Heller Brown, PhD; Gerald W. Dorn II, MD; Robert C. Armstrong, PhD; Richard N. Kitsis, MD

Cardiac Angiogenic Imbalance Leads to Peri-partum Cardiomyopathy

Ian S. Patten[1,2,9], Sarosh Rana[3,9], Sajid Shahul[4,10], Glenn C Rowe[1,10], Cholsoon Jang[1], Laura Liu[1], Michele R. Hacker[3], Julie S. Rhee[3], John Mitchell[4], Feroze Mahmood[4], Phil Hess[4], Caitlin Farrell[1], Nicole Koulisis[1], Eliyahu V Khankin[5], Suzanne D. Burke[5], Igor Tudorache[6], Johann Bauersachs[7], Federica del Monte[1], Denise Hilfiker-Kleiner[7], S. Ananth Karumanchi[5,8], and Zoltan Arany[1,*]

High prevalence of viral genomes and inflammation in peripartum cardiomyopathy

Burkhard D. Bültmann, MD,[a,*,†] Karin Klingel, MD,[a,†] Michael Näbauer, MD,[c] Diethelm Wallwiener, MD,[b] Reinhard Kandolf, MD, PhD[a]

Institute of Pathology[a] and Department of Gynecology and Obstetrics,[b] University Hospital of Tübingen, Germany; Department of Medicine I, Ludwig-Maximilian University, München, Germany[c]

ETIOLOGIE NENÍ JASNÁ !!

1) myokarditida
2) oxidativní stres - prolactin-cathepsin D - 16kDa prolaktin
3) autoimunita
4) vystupňovaná apoptóza
5) hemodynamický stres
6) hormonální vlivy
7) genetické faktory

Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2012; 156:XX.

The variable clinical course of peripartum cardiomyopathy

Jan Krejci[a], Petr Hude[a], Lenka Spinarova[a], Vita Zampachova[b], Alzbeta Sirotkova[b], Tomas Freiberger[c], Eva Nemcova[c], Jiri Vitovec[a]

Background. In Europe, peripartum cardiomyopathy (PPCM) is a rare disorder, often difficult to diagnose and it has a variable clinical course. The aim of this report was to describe and discuss the individual variability of this disorder and its management.
Patients and Methods. Three cases of PPCM manifesting as severe heart failure are compared. Common was the presence of myocardial inflammation detected by endomyocardial biopsy. Different were treatment methods and clinical course. Modern therapeutic concepts such as immunosuppressive therapy and bromocriptin administration are discussed, as well as non-pharmacological approaches.
Conclusion. In the differential diagnostics of dyspnea associated with pregnancy and childbirth, PPCM should be considered. The potentially severe course of the disease requires hospitalization with the possibility of comprehensive heart failure treatment, including non-pharmacological approaches such as device therapy and heart transplantation.

Key words: peripartum cardiomyopathy, myocarditis, echocardiography, endomyocardial biopsy, therapy

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http://dx.doi.org/10.5507/bp.2012.080

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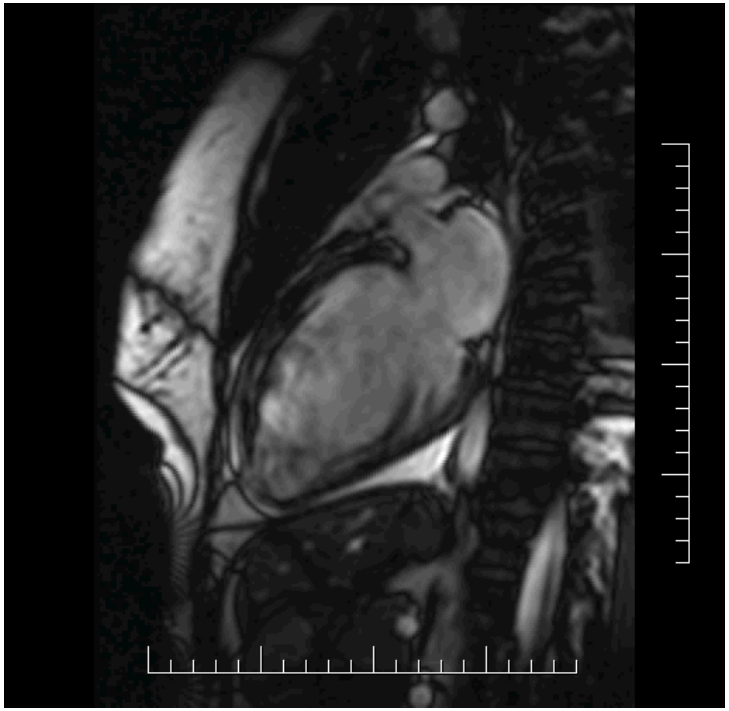
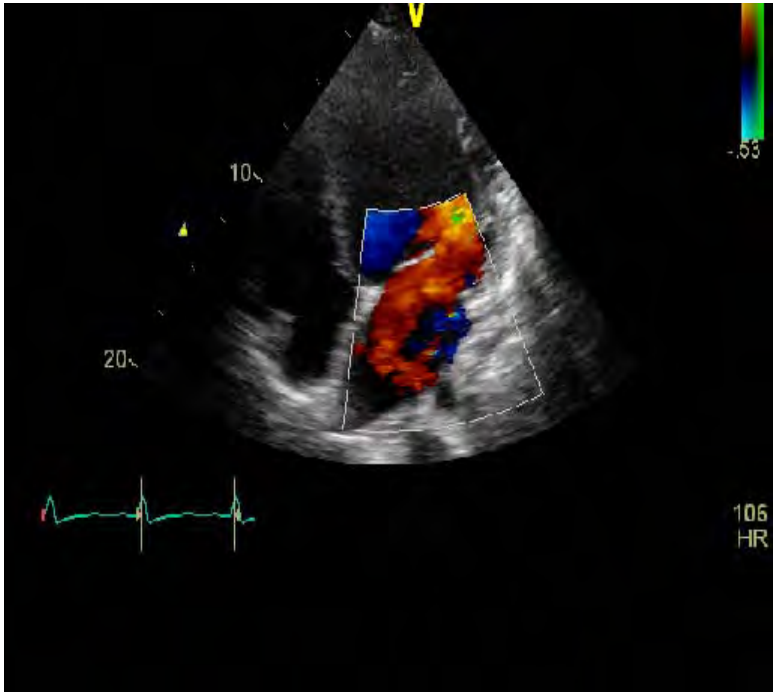
Corresponding author: Jan Krejci, e-mail: jan.krejci@fnusa.cz

Peripartální kardiomyopatie

- v 6 případech ze 7 myokarditidu
- z 10 pacientek 2 po OTS
- 1 zemřela NS



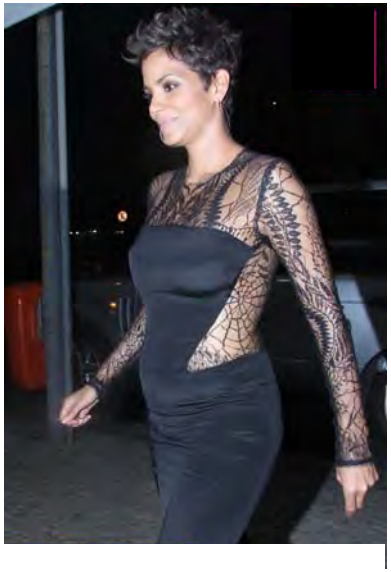


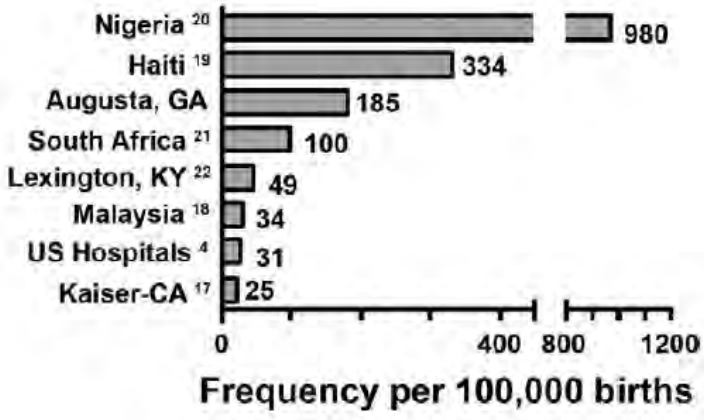
Peripartální kardiomyopatie

African-American Women Have a Higher Risk for Developing Peripartum Cardiomyopathy

Mindy B. Gentry, MD,* James K. Dias, PHD,† Antonio Luis, MD,* Rakesh Patel, MD,* John Thornton, MD,* Guy L. Reed, MD*‡

Augusta, Georgia; and Memphis, Tennessee





Prognóza PPCM

- **Mortalita 2-15%**
- **Nutnost HTx 10%**

ORIGINAL ARTICLE

Predictors of outcome in 176 South African patients with peripartum cardiomyopathy

Lori A Blauwet,[1] Elena Libhaber,[2,3] Olaf Forster,[4] Kemi Tibazarwa,[2,5] Alex Mebazaa,[6] Denise Hilfiker-Kleiner,[7] Karen Sliwa[2]

International Journal of Cardiology 154 (2012) 27–31

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journal homepage: www.elsevier.com/locate/ijcard

Predictors of left ventricular recovery in a cohort of peripartum cardiomyopathy patients recruited via the internet

Jordan G. Safirstein [a,*], Angela S. Ro [b], Sreeram Grandhi [b], Lin Wang [b], James D. Fett [c], Cezar Staniloae [b]

Journal of Cardiac Failure Vol. 18 No. 1 2012

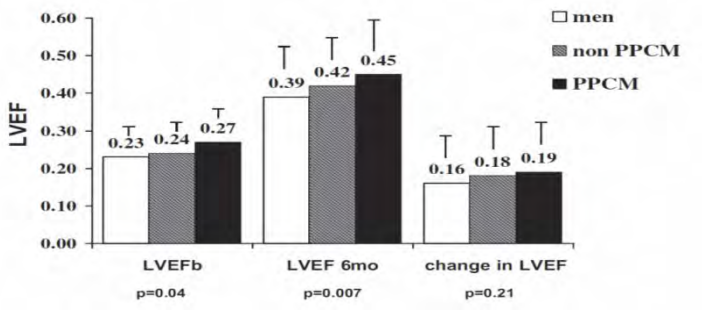
Myocardial Recovery in Peripartum Cardiomyopathy: Prospective Comparison With Recent Onset Cardiomyopathy in Men and Nonperipartum Women

LESLIE T. COOPER, MD,[1] PAUL J. MATHER, MD,[2] JEFFREY D. ALEXIS, MD,[3] DANIEL F. PAULY, MD, PhD,[4] GUILLERMO TORRE-AMIONE, MD, PhD,[5] ILAN S. WITTSTEIN, MD,[6] G. WILLIAM DEC, MD,[7] MARK ZUCKER, MD,[8] JAGAT NARULA, MD, PhD,[9] KEVIN KIP, PhD,[10] AND DENNIS M. MCNAMARA, MD, MS,[11] FOR THE IMAC2 INVESTIGATORS

Rochester, Minnesota; Philadelphia, Pennsylvania; Rochester and New York, New York; Gainesville and Tampa, Florida; Houston, Texas; Baltimore, Maryland; Boston, Massachusetts; Newark, New Jersey; and Pittsburgh, Pennsylvania

21% RECOVERY (černošky)

78% RECOVERY (90%bělošek)



Terapie PPCM

- **Léčba srdečního selhání** (v těhotenství KI ACEI/ARB, spironolacton/eplerenon – možno hydralazin, nitráty, nitroproprusid, dobu, dopa)

- ***Imunomodulační léčba*** *(imunosuprese, gamaglobuliny)*
- ***Pentoxifyllin*** *(omezení produkce TNFα)*
- ***Bromokriptin*** *(omezení apoptózy)*

- **Antikoagulační léčba** (protrombogenní stav postpartálně)

- **ICD, CRT, LVAD, HTx**