INTERNATIONAL CLINICAL RESEARCH CENTER

„CREATING THE FUTURE OF MEDICINE“

ZÁNĚTLIVÁ KARDIOMYOPATIE

Jan Krejčí

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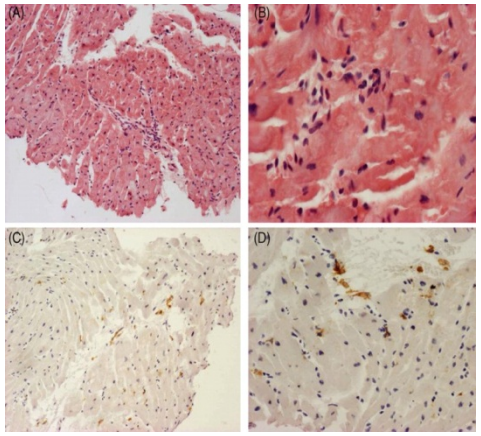
DEFINICE

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

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



Caforio et al. Eur Heart J 1997

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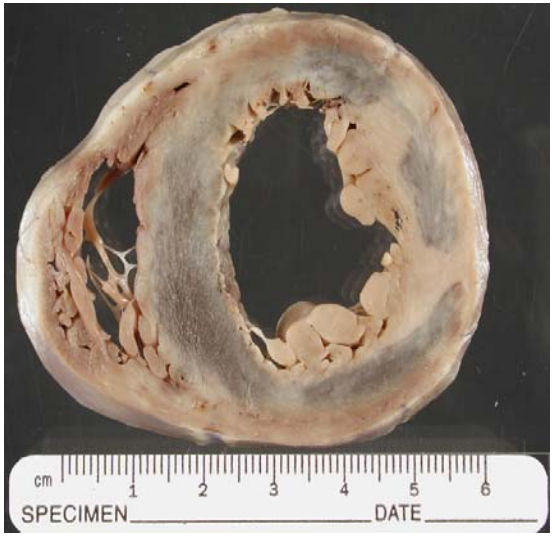
Etiologie myokarditid

- **infekční (nejčastěji virové)**
- **autoimunitní (SLE, FR, m.Crohn, sklerodermie, rejekce štěpu po OTS…)**
- **toxické (léky – cytostatika, kokain, jedy hadů, škorpionů, chemikálie, hormonální – tyreotoxikóza**
- **těhotenství – peripartální kardiomyopatie**



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Etiologie myokarditid

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STATE-OF-THE-ART PAPER

Update on Myocarditis

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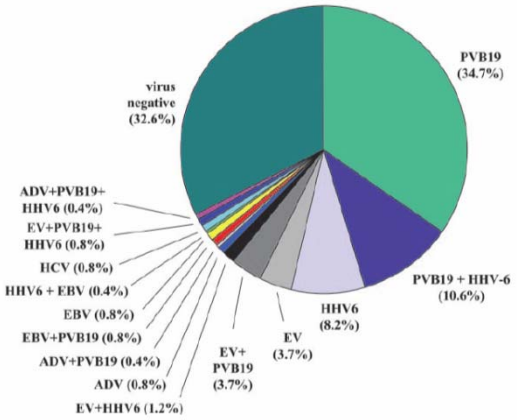
Homburg/Saar, Stuttgart, and Tübingen, Germany; and Rochester, Minnesota

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

Nejčastější etiologická agens

- **viry**
  - parvoviry (51,4%)
  - HHV6 (21,6%)
  - enteroviry (*coxackie B+A, echoviry* – 9,4%)
  - EBV (2%), adenoviry (1,6%), CMV (0,8%)
- 27,3% vícečetná infekce (n=245, DKMP)



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

- **spirochety** – borrelia burgdorferi

(literárně okolo 1%, v souboru Kuchynky a spol. 22%)

- ***paraziti*** – *Chagasova nemoc*

(na světě v roce 2008 asi 16-18 mil. nakažených, 2/3 chronicky nemocných mají kardiální postižení, každoročně na ni zemře 20.000 nemocných)

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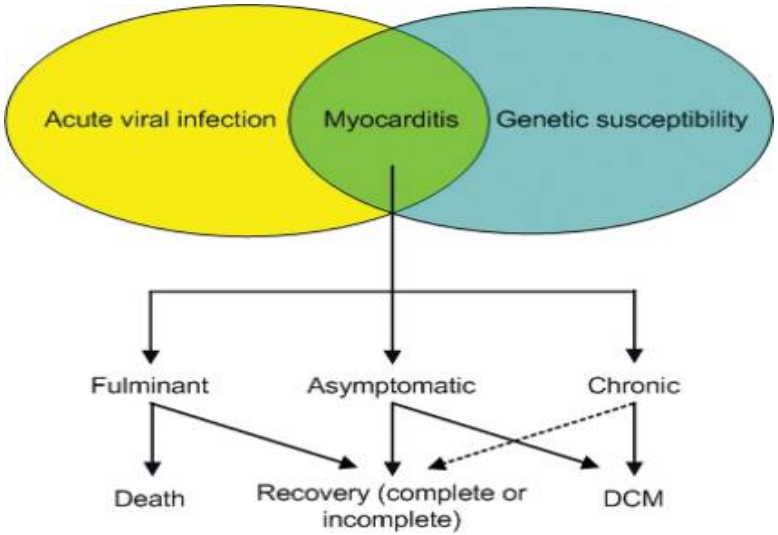
Myokarditidy

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



Dennert et al. Acute viral myocarditis. Eur Heart J. 2008, 29(17): 2073–2082.
Liu PP, Mason JW. Advances in the understanding of myocarditis. Circulation 2001;104:1076-1082.

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Epidemiologie

- **u 40-50% pts s chronickou DKMP byly nalezeny v EMB imunohistologické zn. myokarditidy**

- **ve 25-40% nalezen virový genom**

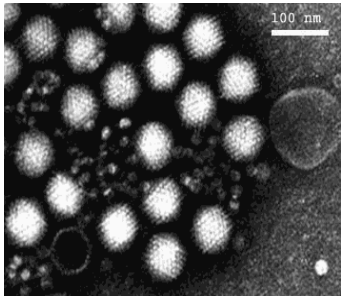
Cooper LT. The heat is off. Immunosupresion for myocaditis revisited. Eur Heart J 2009;30:1936-1939.

- **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



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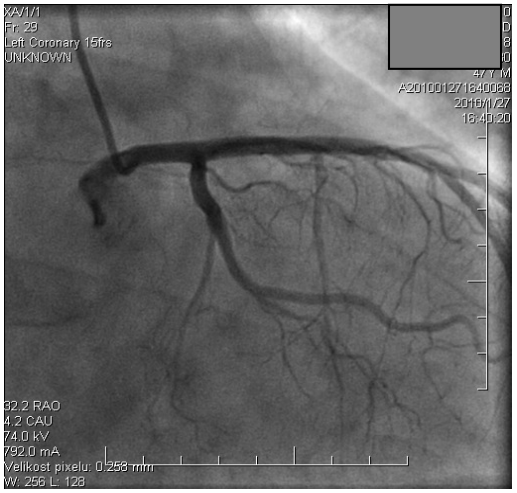
Klinický obraz

- anamnéza předchozího infektu (respirační či GIT) v asi 50-60%
- kardiální obtíže dny až týdny po infektu (dušnost, slabost, únavnost, tachykardie, palpitace, atypické bolesti na hrudi)
- cval, systolický šelest, perikard. třecí šelest
- nově vzniklá kardiomyopatie, komorové arytmie, synkopa
- EKG může imitovat AIM, elevace TnT/I, SKG s negativním nálezem



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European Heart Journal (2011) **32**, 897–903
doi:10.1093/eurheartj/ehq493

Virus serology in patients with suspected myocarditis: utility or futility?

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Received 20 July 2010; revised 25 October 2010; accepted 10 November 2010; online publish-ahead-of-print 8 January 2011

Aims Serological analyses of viral infection in suspected myocarditis are still widely used, although convincing evidence for their value is lacking. We determined prospectively the diagnostic value of virus serology in comparison with endomyocardial biopsy (EMB) including viral genome detection and immunohistochemistry in patients with clinically suspected myocarditis.

Methods and results Virus serology and state-of-the-art evaluation of EMB were performed in 124 patients (age 40 ± 15 years) with suspected myocarditis. Endomyocardial biopsy was studied for inflammation with histological and immunohistological criteria. The viral genome was detected in the myocardium by polymerase chain reaction. Acute viral infection with enterovirus, adenovirus, parvovirus B19, cytomegalovirus, human herpesvirus, and Epstein-Barr virus was diagnosed by IgM or IgA in the initial sample or IgG seroconversion in the follow-up sample. Immunohistological 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. Only in 5 out of 124 patients (4%), there was serological evidence of an infection with the same virus that was detected by EMB. Sensitivity and specificity of virus serology were 9 and 77%, respectively. The positive predictive value was 25% and the negative predictive value

Conclusions For patients with suspected myocarditis, virus serology has no relevance for the diagnosis of myocardial infection. Endomyocardial biopsy remains the gold standard in the diagnostic of viral myocarditis.

Keywords Myocarditis • Endomyocardial biopsy (EMB) • Virus serology

Myokarditidy

- „orgánově specifické“ autoimunitní onemocnění
- přítomnost autoprotilátek

  (IgG anti-alfa- a anti-beta- myosinovým těžkým řetězcům)

Patogeneza

1. fáze - přímé poškození myocytů inf. agens
2. fáze - buněčná či humorální imunitní reakce
3. fáze - dilatační kardiomyopatie

Liu PP, Mason JW. Advances in the understanding of myocarditis. Circulation 2001;104:1076-1082.

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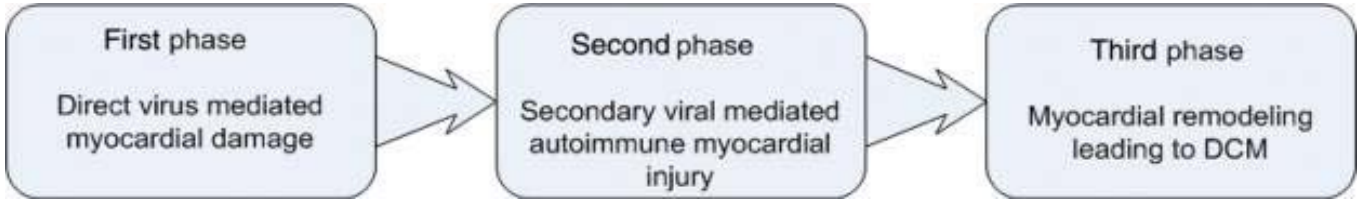
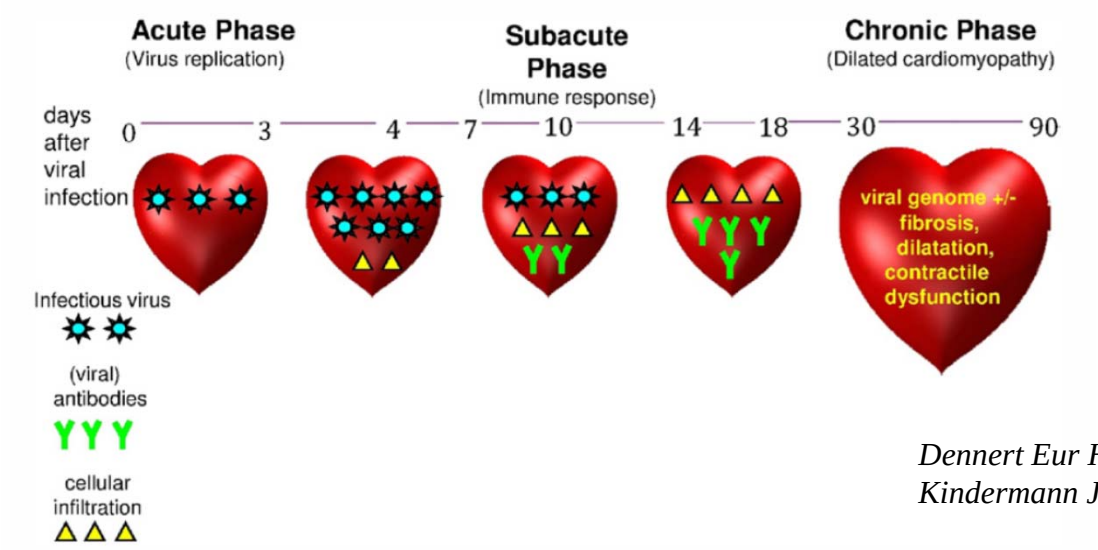
Patogenetické souvislosti

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





Dennert Eur Heart J 2008
Kindermann JACC 2012

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Myocarditis

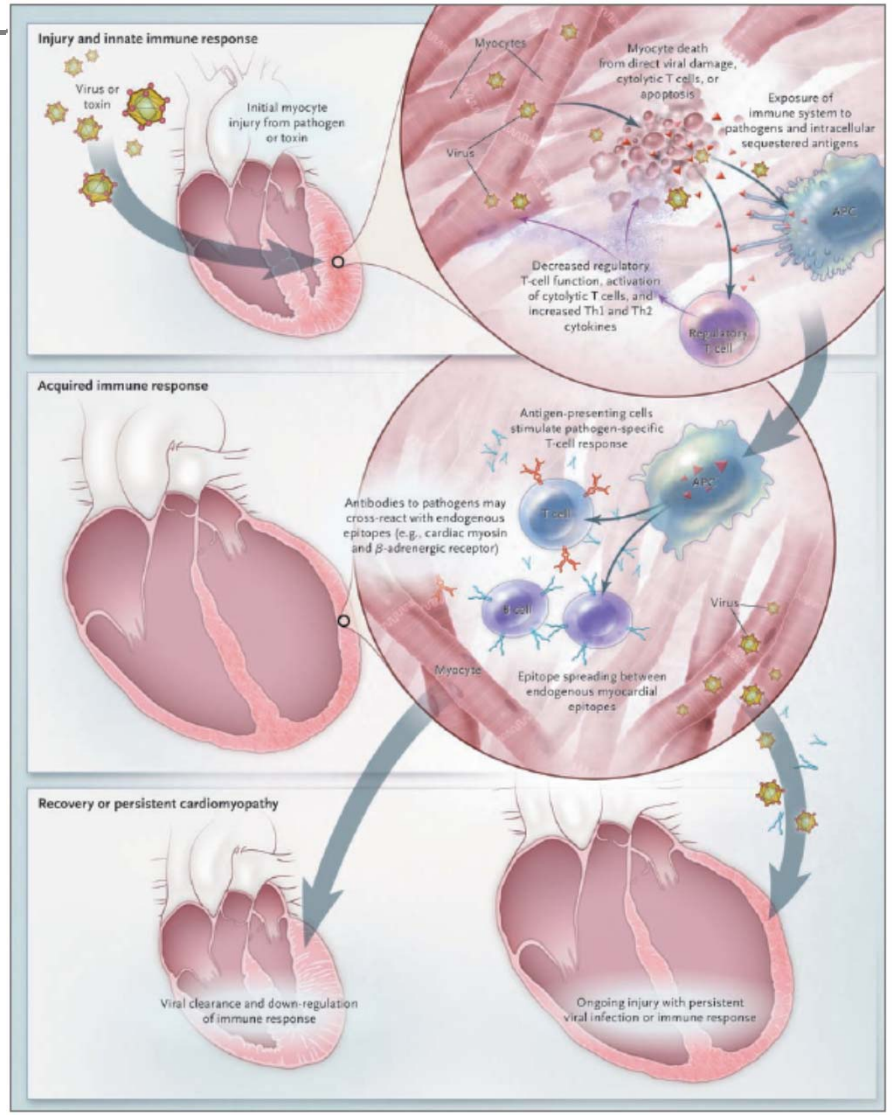
Leslie T. Cooper, Jr., M.D.

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



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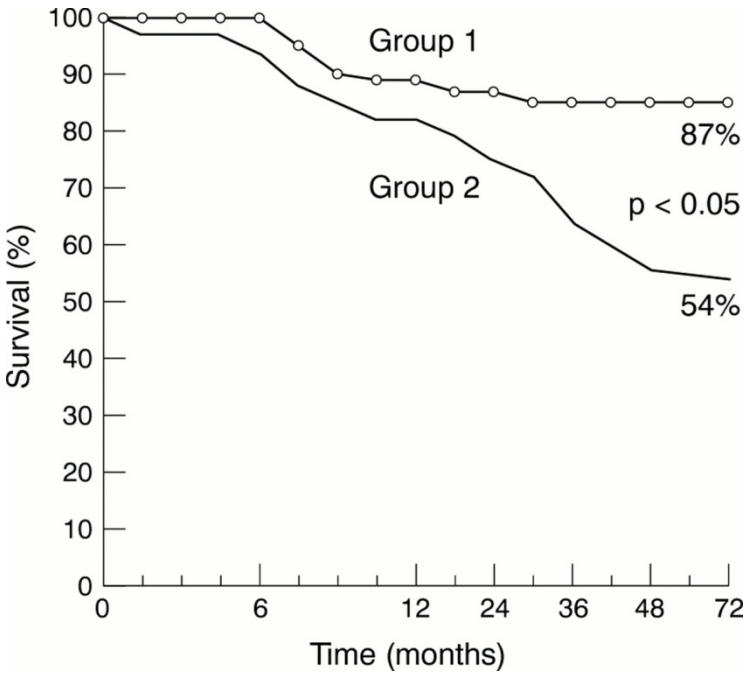
Prognóza

- **Spontánní úprava v 50-57%**
- **Rozvoj DKMP v 14-52%**
- **Prognóza – fulminantní myokarditida 11leté přežití 93%, nefulminantní 45%**
- **velkobuněčná myokarditida má horší prognózu (5-leté přežití bez OTS 10% x lymfocytární 50%)**
- **horší prognóza v dětském věku (75% mortalita u novorozenců)**



Skupina A arytmie + IM-like
Skupina B – srdeční selhání

D´Ambrosio A et al. The fate of acute myocarditis between spontaneous improvement and evolution to dilated cardiomyopathy: a review. Heart 2001;85:499-504.

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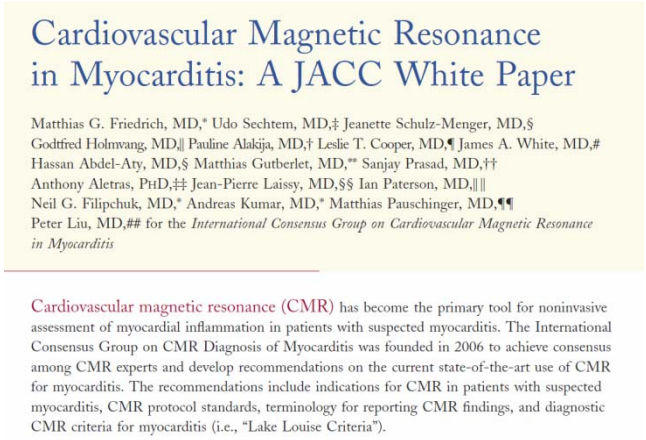
Diagnostika myokarditid

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

- **Magnetická rezonance**
  - **MR se stala jednou z nejdůležitějších diagnostických metod u myokarditid**



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").

  - **gadolinium late enhancement (LGE)**
  - **T2-weighted imaging**
  - **LGE ukazují ložiska poškozeného myokardu i edému, T2-weighted images ukazují intersticiální edém, který je při zánětu přítomen**

- **Endomyokardiální biopsie**

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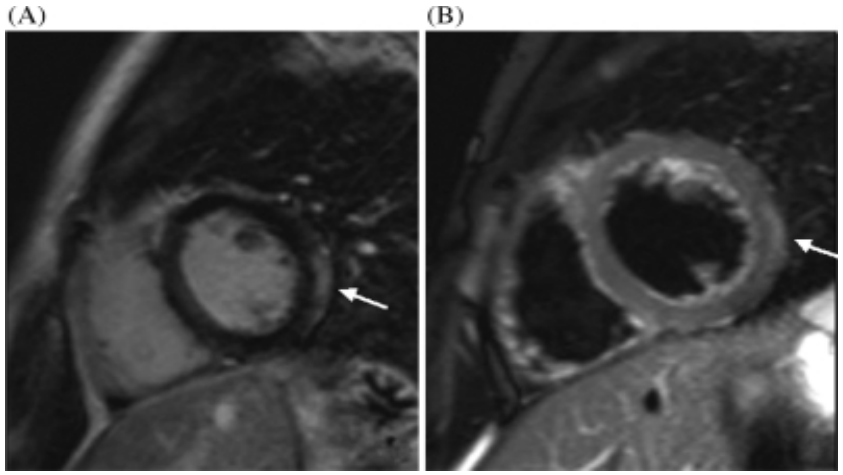
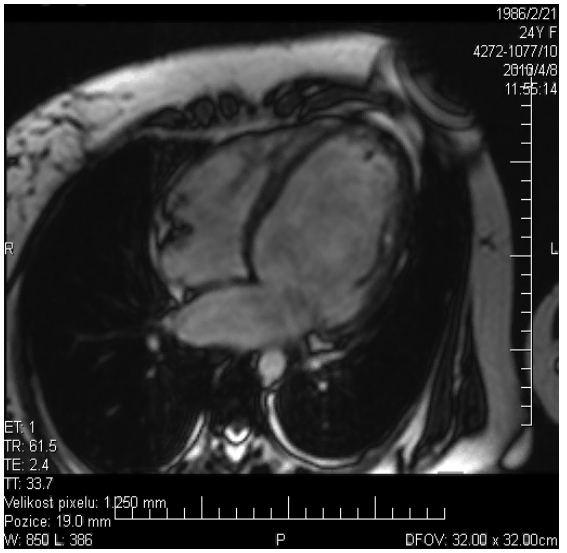
Magnetická rezonance

(A) T2-weighted image – zobrazuje subepikardiální edém laterální stěny levé komory

(B) Late enhancement – zvýšený signál ukazuje místa poškození myocytů, edému, reparativní fibrózy v tomtéž místě.





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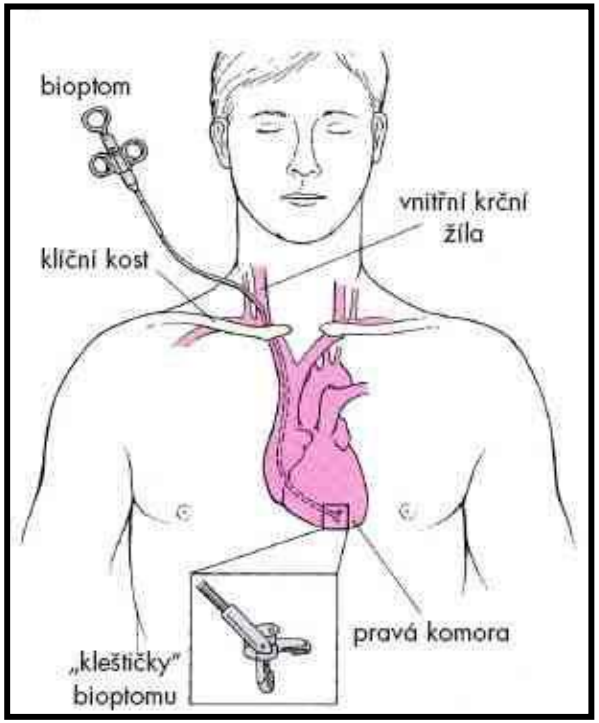
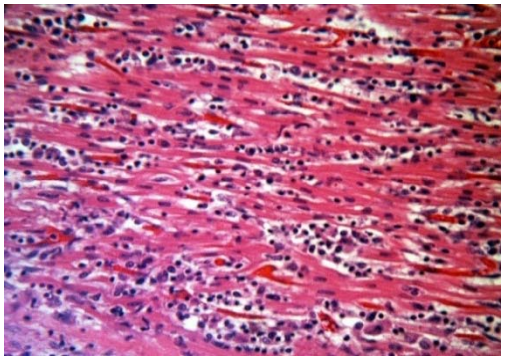
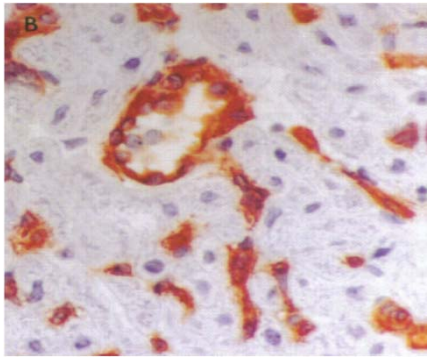
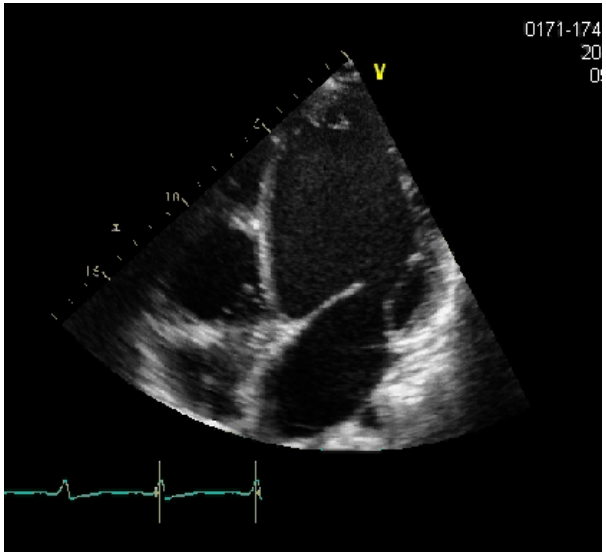
Endomyokardální biopsie

– „zlatý standard"









Význam EMB pro dg. ZKMP

- **v éře Dallaských kriterií (tzn. čistě histologického hodnocení) velmi malý!**

Aretz HT et al. Myocarditis: a histopatological definition and classification. Am J Cardiovasc Pathol. 1987;1:3-14.
Mason JW et al. A clinical trial of immunosupresive therapy for myocarditis. N Engl J Med. 1995;333:269-275

Baughman KL. Diagnosis of myocarditis. Death of Dallas Criteria. Circulation. 2006;113:593-595

V současnosti je EMB indikována pouze při dostupnosti imunohistologického a molekulárně genetického vyšetření

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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 densit were in the range 2–14 per high po field (HPF), equivalent to 7–50 per m of tissue. In 43 (89%) interstitial a endothelial immune activation demonstrated by MHC expression. In patients with T cell counts in the ra 1·5–2·0 per HPF, 80% also show endothelial activation. Lymphocyte d sity correlated with increased expres of MHC class I and II antigens and 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

accurately cellular infiltrates in myocardial biopsies and this study determines the frequency of increased lymphocytic infiltrates in DCM detected by these more specific techniques. The expression patterns of additional antigens which are expressed during an active immunological process within the myocardium (for example, HLA classes I and HLA-DR antigens, or adhesion molecules) were also analysed.

Patients and methods

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

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

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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

Received 11 February 2009; revised 8 May 2009; accepted 29 May 2009; online publish-ahead-of-print 25 June 2009

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 immunosuppres

Conclusion These data co response in 12 not susceptible

Keywords Inflammatory c

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

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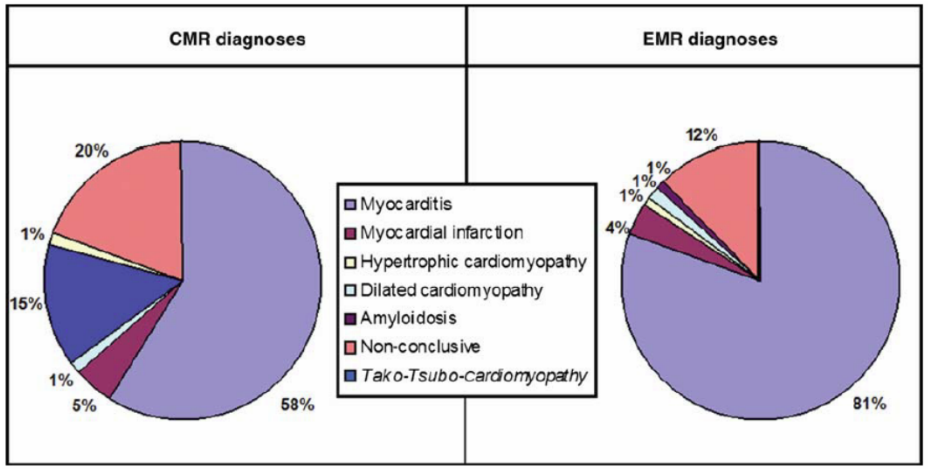
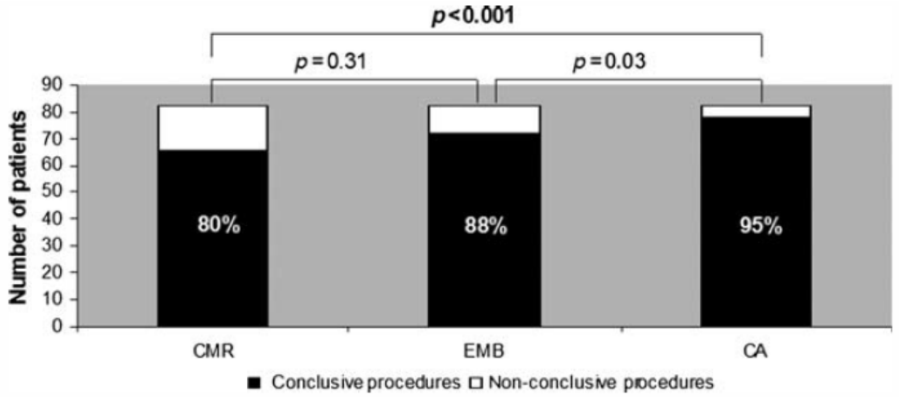
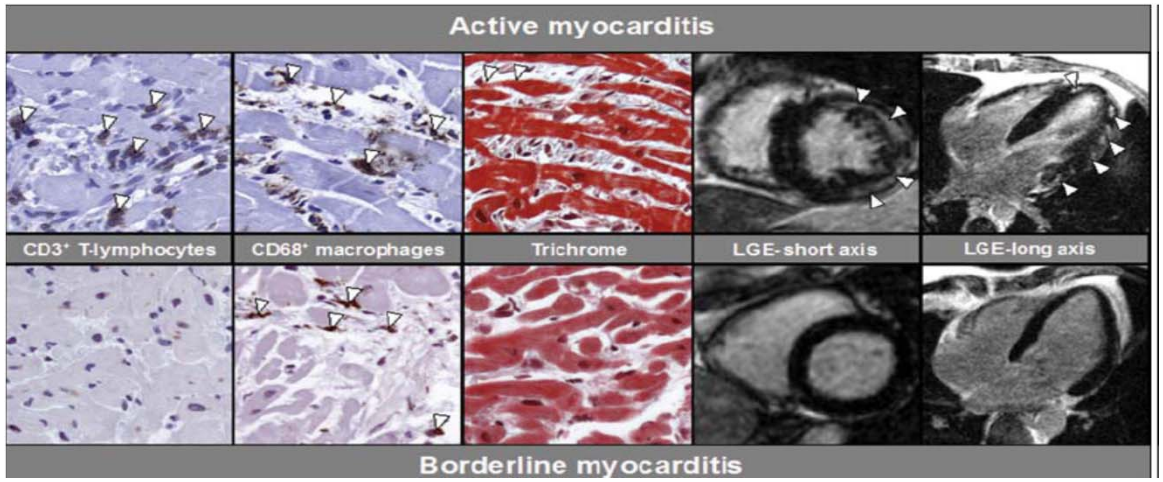
Diagnostic synergy of non-invasive cardiovascular magnetic resonance and invasive endomyocardial biopsy in troponin-positive patients without coronary artery disease

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]*







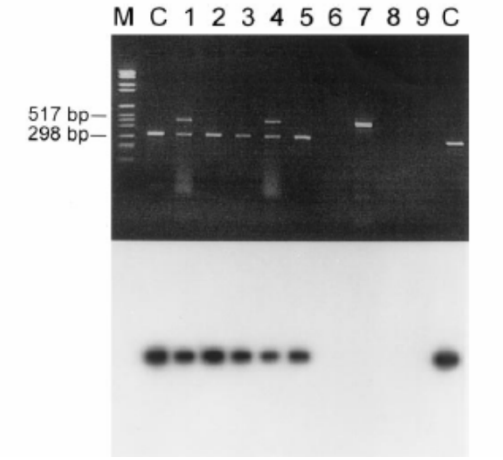
„Naše“ hodnocení EMB

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



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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*)

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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.**)

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Léčba - imunosupresivní

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.**)

TABLE 2. Results of Secondary End Point

	Baseline				3-Month Follow-Up				6-Month Follow-Up			
	n	Mean±SD	95% CI	*P*	n	Mean±SD	95% CI	*P*	n	Mean±SD	95% CI	*P*
LV EF, %												
Placebo	43	24.9±7.3	−2.33–4.64	0.51	43	27.2±10.1	4.20–13.12	<0.001	35	30.2±12.4	3.79–14.83	0.001
IT group	41	23.8±8.6			39	35.9±10.0			35	39.5±10.7		
LV EDV, mL												
Placebo	43	233.2±58.9	−1.94–56.92	0.085	43	219.1±58.8	17.12–68.76	0.001	35	208.4±63.9	17.22–74.25	0.002
IT group	41	213.6±53.5			39	176.1±58.5			35	162.7±55.4		
LV ESV, mL												
Placebo	43	181.7±54.1	−3.11–47.93	0.088	43	169.1±59.4	24.03–71.42	<0.001	35	158.3±63.2	20.73–72.80	0.001
IT group	41	160.8±52.8			39	121.4±46.9			35	111.6±44.3		
LV EDD, mm												
Placebo	43	68.5±8.0	−0.14–7.33	0.059	43	66.6±8.1	2.30–10.59	0.003	35	65.9±9.9	3.04–12.21	0.001
IT group	41	65.6±8.6			39	60.1±10.7			35	58.2±9.3		

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

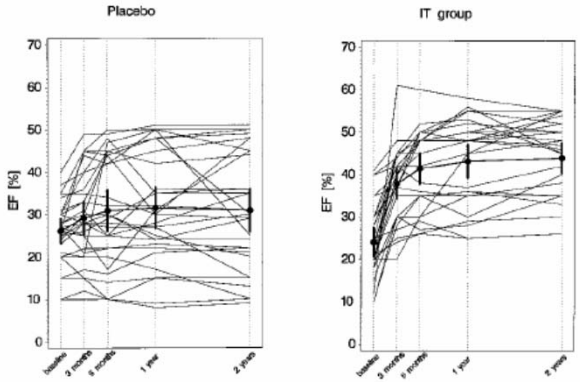

Figure 2. Serial EF in 58 patients from placebo (n=30) and immunosuppression groups (n=28) who completed 2 years of follow-up. ● and lines show mean±SD.

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Léčba - imunosupresivní

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

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Léčba - imunosupresivní

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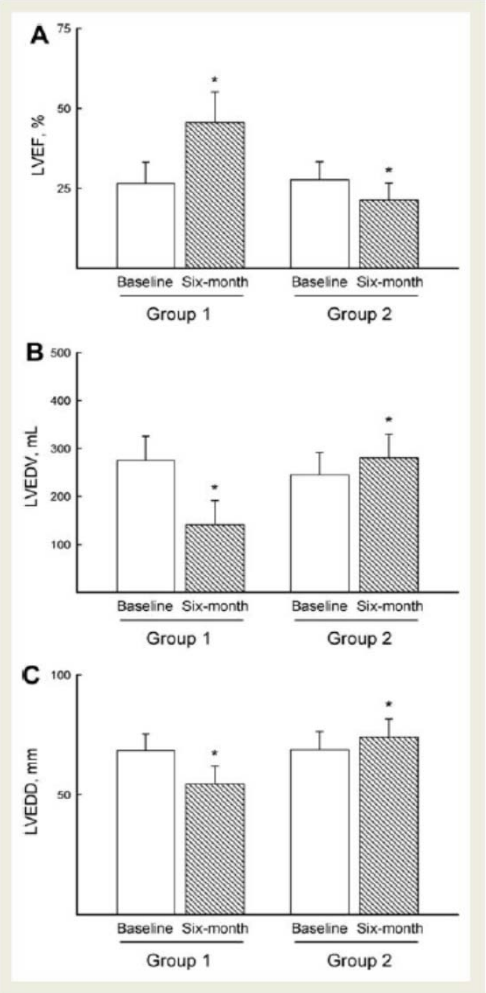
Table 2 Comparison of characteristics between baseline and 6 month treatment in the two groups of patients

Variables	Group 1 ($n = 43$)	*P*-value	Group 2 ($n = 42$)	*P*-value
Ejection fraction, %		<0.001		<0.001
Baseline	26.5 ± 6.7		27.7 ± 5.6	
Six month	45.6 ± 9.6		21.3 ± 5.3	
LVEDV, mL		<0.001		<0.001
Baseline	257.3 ± 50.1		245.4 ± 46.3	
Six month	140.7 ± 50.6		280.6 ± 48.9	
LVESV, mL		<0.001		<0.001
Baseline	188.8 ± 38.3		176.9 ± 34.1	
Six month	79.7 ± 43.9		223.4 ± 43.3	
LVEDD, mm		<0.001		<0.001
Baseline	68.4 ± 7.0		68.8 ± 7.5	
Six month	54.4 ± 7.4		74.0 ± 7.6	
NYHA class III/IV, *n* (%)		0.008		0.010
Baseline	21 (49)		16 (38)	
Six month	9 (21)		28 (67)	

Data are presented as mean ± SD unless stated otherwise.
LV, left ventricular; ESV, end-systolic volume; EDV, end-diastolic volume; EDD, end-diastolic diameter; NYHA, New York Heart Association.



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Léčba arytmií

The 2006 American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) guidelines for the management of ventricular arrhythmias and the prevention of sudden cardiac death included recommendations for the management of arrhythmias associated with myocarditis

Arrhythmias — Patients with myocarditis can develop both tachy- and bradyarrhythmias. Because these arrhythmias often resolve after the acute phase of myocarditis, therapy is generally supportive.

- **Sustained ventricular arrhythmias should be treated with urgent cardioversion, and recurrent arrhythmias should be treated with antiarrhythmic drugs.**
- **Symptomatic nonsustained ventricular tachycardia can be treated with antiarrhythmic drugs.**
- **ICD implantation can be beneficial in patients with life-threatening ventricular arrhythmias who are not in the acute phase of myocarditis**...
- **Complete heart block and/or symptomatic bradycardia are indications for pacing during the acute phase of myocarditis. This conduction abnormality is often transient; as a result, use of a temporary pacemaker should be the first step.**

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Shrnutí - diagnostika

- význam EMB pro diagnostiku ZKMP je zásadní (zlatý standard)
- význam EMB pro výběr specifické léčebné strategie je rovněž zásadní, zatím ale méně podložený daty
- MRI je důležitá dg metoda, mimo jiné i u nemocných bez indikace EMB

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Závěr

- **Myokarditida často vede k ZKMP a ta často přechází do DKMP**
- **½ „idiopatických“ chronických DKMP jsou vlastně ZKMP**
- **DKMP je nejčastější dg. vedoucí k HTx (53%)**

Včasná diagnostika a léčba myokarditid by mohla zásadním způsobem ovlivnit průběh a prognózu onemocnění !

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ARYTMOGENNÍ KARDIOMYOPATIE

(PRAVÉ KOMORY)

Jan Krejčí
FN u sv. Anny –ICRC, Brno

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Terminologie

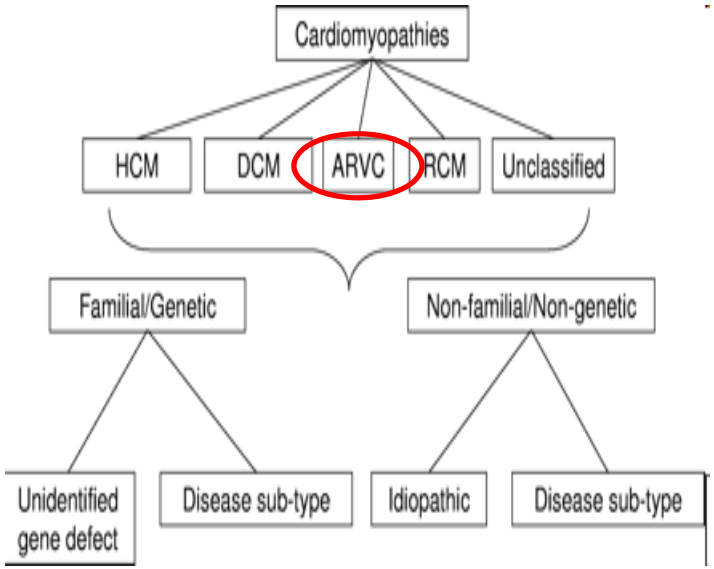
- **Arytmogenní dysplazie pravé komory (ARVD)**
- **Arytmogenní kardiomyopatie pravé komory (ARVC)**

- **Arytmogenní kardiomyopatie * (ACMP)**

* *Sen-Chowdhry S, Syrris P, Prasat SK, et al. Left-Dominant Arrhythmogenic Cardiomyopathy.J Am Coll Cardiol 2008;52:2175-87.*

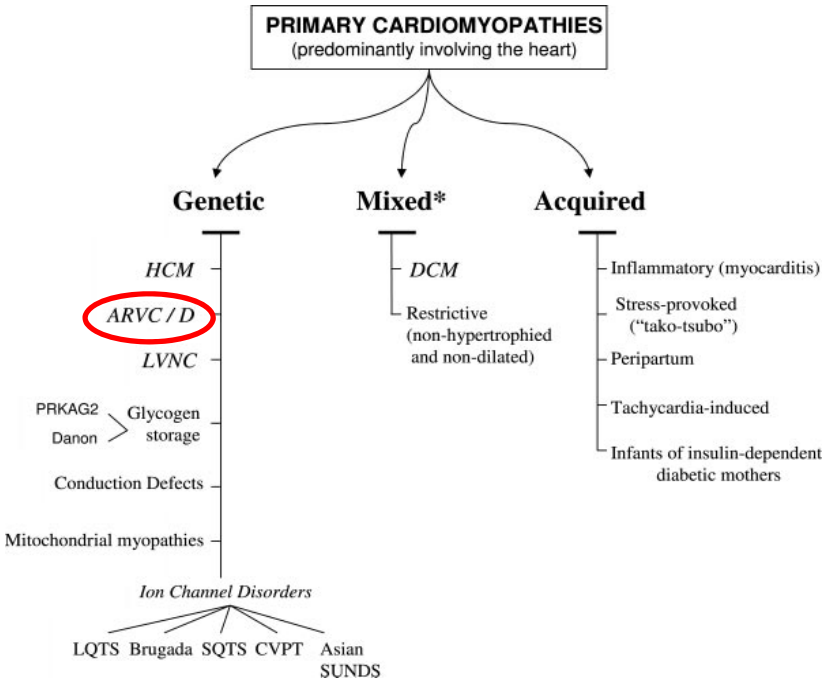
Klasifikace kardiomyopatií

ESC



Eur Heart J. 2008; 29: 270–276

AHA



Circulation 2006;113:1807-1816

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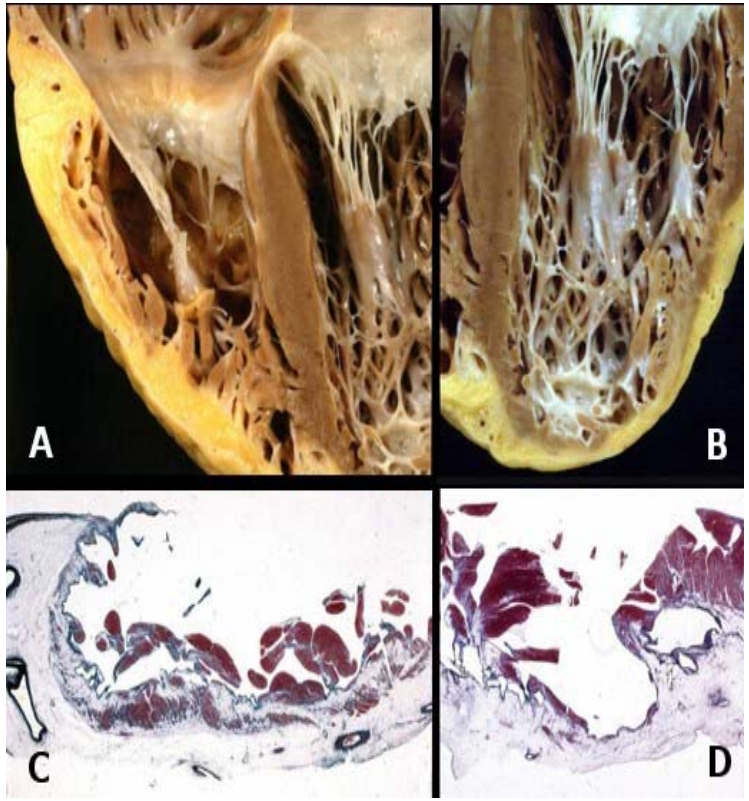
ACMP

- onemocnění charakterizované progresivní náhradou svaloviny (nejčastěji pravé komory) tukovou a vazivovou tkání
- je spojeno s komorovými arytmiemi typicky s morfologií BLRTw
- biventrikulární postižení až ve 25%
- „left-dominant arrhythmogenic cardiomyopathy"



Sen-Chowdhry S, Syrris P, Prasat SK, et al. Left-Dominant Arrhythmogenic Cardiomyopathy. J Am Coll Cardiol 2008;52:2175-87.

Historie

- G.M. Lancisi 1736
- palpitace, srdeční selhávání, dilatace a aneurysmata pravé komory a výskyt náhlé smrti
- výskyt ve 4 generacích jedné rodiny

- 70./80. léta 20. století

Lancisi GM. De Motu Cordis et Aneurysmatibus. Naples 1736.

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Prevalence ACMP

- 0,02 – 0,1 % (1:5000)
- endemický výskyt (ostrov Naxos, regiony Benátek a Padovy) s prevalencí 0,4 - 0,8 %.
- postihuje častěji muže v poměru 2,7:1
- muži více ohroženi náhlou smrtí (relativní riziko 6,8)

Anderson EL. Arrhythmogenic Right Ventricular Dysplasia. Am Fam Physician 2006;73:1391-8.
McNally E, MacLeold H, Dellefave L. Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy. GeneReviews 2008.

Genetika ACMP

- **„desmosomální kardiomyopatie“ – převažují mutace v genech pro desmosomální proteiny**

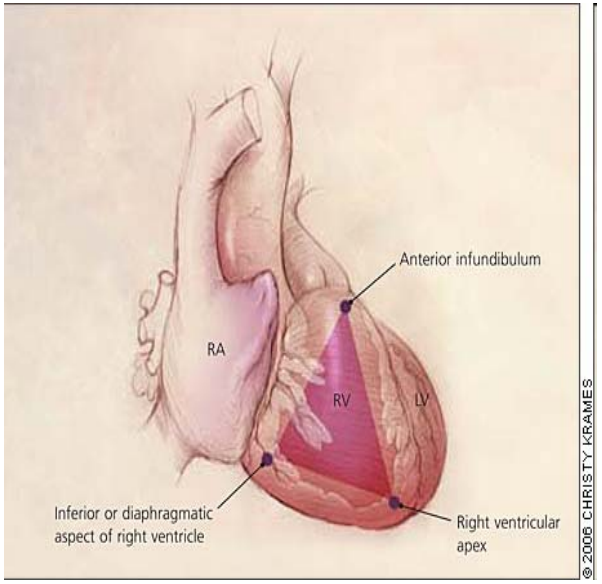
(Plakophilin-2, desmoplakin, desmocollin-2, plakoglobin, TGFB3, desmoglein)

- **autozomálně dominantní dědičnost**
- **autozomálně recesivní podtypy (Naxos disease, Carvajal syndrom)**
- **rodinný výskyt ve 30-80%**
- **variabilní penetrance**
- **polymorfní fenotyp**

Vatta M, Marcus F, Towbin JA. Arrhythmogenic Right Ventricular Cardiomyopathy: a ‘final common pathway‘ that defines clinical phenotype. Eur Heart J 2007;28:529-30
McNally E, MacLeold H, Dellefave L. Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy. GeneReviews 2008.

Patofyziologie

- postižení myokardu nejčastěji PK
- náhrada myocytů tukovou a fibrózní tkání (arytmogenní substrát)
- dilatace PK, systolická dysfunkce PK – typicky ložisková (aneurysmata), méně často difúzní
- nejčastější postižení je v oblasti tzv. trojúhelníku dysplazie
- postupně postižení dalších oblastí pravé (popř. i levé) komory
- mezikomorové septum bývá postiženo až v pokročilých stádiích nemoci
- nejprve subepikardiální postižení



Anderson EL. Arrhythmogenic Right Ventricular Dysplasia. Am Fam Physician 2006;73:1391-8.

Klinický obraz

- příznaky se objevují na počátku dospělosti
- diagnóza je nejčastěji stanovena kolem 30. roku věku
- typické příznaky: palpitace, slabost, synkopy či závratě
- náhlá smrt
- méně často známky pravostranného selhávání (otoky, hepatomegalie, ascites)
- při biventrikulárním postižení se přidávají dušnost, únavnost, nevýkonnost

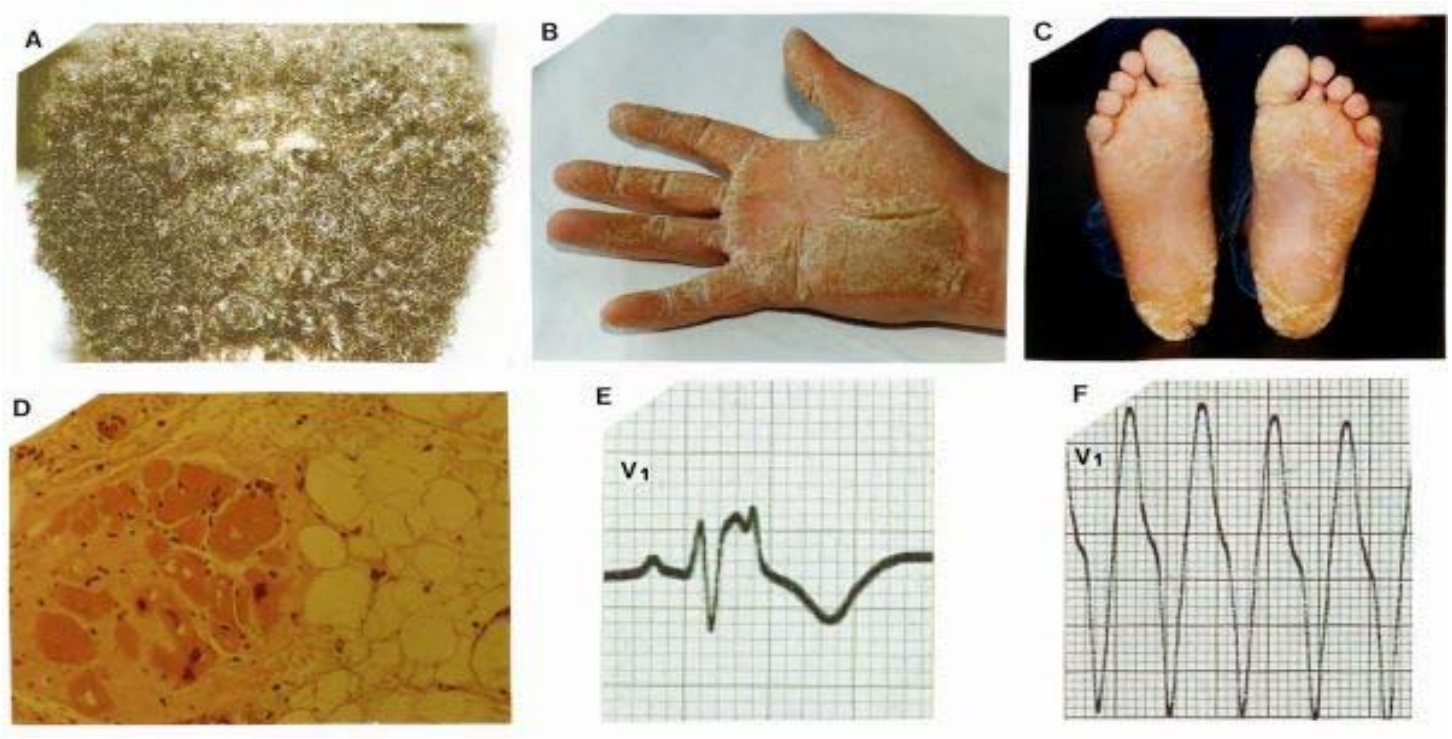
Thiene G, Corrado D, Basso C. Arrhythmogenic right ventricular cardiomyopathy/dysplasia. Orphanet Journal of Rare Diseases 2007;2:45.

Klinický obraz

- **<u>první stádium</u> - subklinické postižení (náhlá smrt bez předchozích prodromů)**
- **<u>druhé stádium</u> - projevy elektrické nestability (palpitace či synkopy často vázané na fyzickou zátěž, arytmie zprvu izolované, postupně až setrvalé komorové tachykardie s morfologií BLRTw)**
- **<u>třetí stádium</u> - selhávání pravé komory**
- **<u>čtvrté stádium</u> - biventrikulární postižení s projevy bilaterálního srdečního selhávání, s morfologickým obrazem podobným dilatační kardiomyopatii, výskyt polymorfních komorových arytmií**

Thiene G, Corrado D, Basso C. Arrhythmogenic right ventricular cardiomyopathy/dysplasia. Orphanet Journal of Rare Diseases 2007;2:45.

Naxos disease
(kardiokutánní syndrom)



Protonotarios N, Tsatsopoulou A. Naxos disease. Indian Pacing and Electrophysiology Journal 2005;5(2):76-80.

MINISTRY OF EDUCATION, YOUTH AND SPORTS
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Diagnostika (ARVC)

Br Heart J 1994;71:215–218

CRITERIA

Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy

William J McKenna, Gaetano Thiene, Andrea Nava, Fabrice Fontaliran, Carina Blomstrom-Lundqvist, Guy Fontaine, Fulvio Camerini on behalf of the Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology, supported by the Schoepfer Association

- ✓ 2 velká kritéria
- ✓ 1 velké a 2 malá
- ✓ 4 malá

Criteria for diagnosis of right ventricular dysplasia

I Global and/or regional dysfunction and structural alterations[17–23]*

MAJOR
Severe dilatation and reduction of right ventricular ejection fraction with no (or only mild) LV impairment
Localised right ventricular aneurysms (akinetic or dyskinetic areas with diastolic bulging)
Severe segmental dilatation of the right ventricle

MINOR
Mild global right ventricular dilatation and/or ejection fraction reduction with normal left ventricle
Mild segmental dilatation of the right ventricle
Regional right ventricular hypokinesia

II Tissue characterisation of walls

MAJOR
Fibrofatty replacement of myocardium on endomyocardial biopsy

III Repolarisation abnormalities

MINOR
Inverted T waves in right precordial leads (V2 and V3) (people aged more than 12 yr; in absence of right bundle branch block)

IV Depolarisation/conduction abnormalities

MAJOR
Epsilon waves or localised prolongation (>110 ms) of the QRS complex in right precordial leads (V1–V3)

MINOR
Late potentials (signal averaged ECG)

V Arrhythmias

MINOR
Left bundle branch block type ventricular tachycardia (sustained and non-sustained) (ECG, Holter, exercise testing).
Frequent ventricular extrasystoles (more than 1000/24 h) (Holter)

VI Family history

MAJOR
Familial disease confirmed at necropsy or surgery

MINOR
Familial history of premature sudden death (<35 yr) due to suspected right ventricular dysplasia.
Familial history (clinical diagnosis based on present criteria)

*Detected by echocardiography, angiography, magnetic resonance imaging, or radionuclide scintigraphy. ECG, electrocardiogram; LV, left ventricle.

European Heart Journal (2010) **31**, 806–814
doi:10.1093/eurheartj/ehq025

SPECIAL REPORT

Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia

Proposed Modification of the Task Force Criteria

Frank I. Marcus[1]* Chair, … Sherrill[1], Cristina Basso[3], Barbara … lkins[5] Domenico Corrado[3], M… Kathleen Gear[1], Richard… Nikos Protonotarios[13], … Jonathan S. Steinberg[9], … Adalena Tsatsopoulou[13]

Table 1 Comparison of original and revised task force criteria

Original task force criteria	Revised task force criteria
I. Global or regional dysfunction and structural alterations*	
Major	
	By 2D echo:
• Severe dilatation and reduction of RV ejection fraction with no (or only mild) LV impairment • Localized RV aneurysms (akinetic or dyskinetic areas with diastolic bulging) • Severe segmental dilatation of the RV	• Regional RV akinesia, dyskinesia, or aneurysm • *and* 1 of the following (end diastole): — PLAX RVOT ≥ 32 mm (corrected for body size [PLAX/BSA] ≥ 19 mm/m^2) — PSAX RVOT ≥ 36 mm (corrected for body size [PSAX/BSA] ≥21 mm/m^2) — or fractional area change ≤33%
	By MRI:
	• Regional RV akinesia or dyskinesia or dyssynchronous RV contraction • *and* 1 of the following: — Ratio of RV end-diastolic volume to BSA ≥110 mL/m^2 (male) or ≥ 100 mL/m^2 (female) — or RV ejection fraction ≤40%
	By RV angiography:
	• Regional RV akinesia, dyskinesia, or aneurysm
Minor	
	By 2D echo:
• Mild global RV dilatation and/or ejection fraction reduction with normal LV • Mild segmental dilatation of the RV • Regional RV hypokinesia	• Regional RV akinesia or dyskinesia • *and* 1 of the following (end diastole): — PLAX RVOT ≥29 to <32 mm (corrected for body size [PLAX/BSA] ≥ 16 to <19 mm/m^2) — PSAX RVOT ≥ 32 to <36 mm (corrected for body size [PSAX/BSA] ≥ 18 to <21 mm/m^2) — or fractional area change >33% to ≤40%
	By MRI:
	• Regional RV akinesia or dyskinesia or dyssynchronous RV contraction • *and* 1 of the following: — Ratio of RV end-diastolic volume to BSA ≥ 100 to < 110 mL/m^2 (male) or ≥90 to <100 mL/m^2 (female) — or RV ejection fraction >40% to ≤45%
II. Tissue characterization of wall	
Major	
• Fibrofatty replacement of myocardium on endomyocardial biopsy	• Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
Minor	• Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥ 1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
III. Repolarization abnormalities	
Major	• Inverted T waves in right precordial leads (V_1, V_2, and V_3) or beyond in individuals >14 years of age (in the absence of complete right bundle-branch block QRS ≥120 ms)
Minor	
• Inverted T waves in right precordial leads (V_2 and V_3) (people age >12 years, in absence of right bundle-branch block)	• Inverted T waves in leads V_1 and V_2 in individuals > 14 years of age (in the absence of complete right bundle-branch block) or in V_4, V_5, or V_6 • Inverted T waves in leads V_1, V_2, V_3, and V_4 in individuals >14 years of age in the presence of complete right bundle-branch block

Table 1 *Continued*

Original task force criteria	Revised task force criteria
IV. Depolarization/conduction abnormalities	
Major	
• Epsilon waves or localized prolongation (>110 ms) of the QRS complex in right precordial leads (V_1 to V_3)	• Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V_1 to V_3)
Minor	
• Late potentials (SAECG)	• Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS duration of ≥110 ms on the standard ECG • Filtered QRS duration (fQRS) ≥114 ms • Duration of terminal QRS < 40 μV (low-amplitude signal duration) ≥ 38 ms • Root-mean-square voltage of terminal 40 ms ≤20 μV • Terminal activation duration of QRS ≥ 55 ms measured from the nadir of the S wave to the end of the QRS, including R′, in V_1, V_2, or V_3, in the absence of complete right bundle-branch block
V. Arrhythmias	
Major	
	• Nonsustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)
Minor	
• Left bundle-branch block-type ventricular tachycardia (sustained and nonsustained) (ECG, Holter, exercise) • Frequent ventricular extrasystoles (>1000 per 24 hours) (Holter)	• Nonsustained or sustained ventricular tachycardia of RV outflow configuration, left bundle-branch block morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis • > 500 ventricular extrasystoles per 24 hours (Holter)
VI. Family history	
Major	
• Familial disease confirmed at necropsy or surgery	• ARVC/D confirmed in a first-degree relative who meets current Task Force criteria • ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative • Identification of a pathogenic mutation† categorized as associated or probably associated with ARVC/D in the patient under evaluation
Minor	
• Family history of premature sudden death (<35 years of age) due to suspected ARVC/D • Familial history (clinical diagnosis based on present criteria)	• History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria • Premature sudden death (< 35 years of age) due to suspected ARVC/D in a first-degree relative • ARVC/D confirmed pathologically or by current Task Force Criteria in second-degree relative

Arytmogenní kardiomyopatie

Jan Krejčí

I. interní kardioangiologická klinika, Fakultní nemocnice u sv. Anny a Lékařská fakulta Masarykovy univerzity, Brno, Česká republika

Krejčí J. **Arytmogenní kardiomyopatie.** *Cor Vasa 2010;52:405–408.*

- ✓ **2 velká kritéria**
- ✓ **1 velké a 2 malá**
- ✓ **4 malá**

Tabulka 1 **Diagnostická kritéria**

I. Globální anebo regionální porucha funkce či struktury PK

Velké kritérium

Echokardiografické vyšetření

- regionální porucha kinetiky PK (akineze, dyskineze, aneurysma)
- + jedno z následujících:
  - rozměr RVOT v PLAX ≥ 32 mm nebo ≥ 19 mm/m²
  - rozměr RVOT v PSAX ≥ 36 mm nebo ≥ 21 mm/m²
  - frakční změna plochy PK ≤ 33 %

MR

- regionální porucha kinetiky PK nebo asynchronie kontrakce PK
- + jedno z následujících:
  - end-diastolický objem PK ≥ 110 ml/m² (muži), resp. ≥ 100 ml/m² (ženy)
  - ejekční frakce PK ≤ 40 %

PK ventrikulografie

- regionální porucha kinetiky PK (akineze, dyskineze, aneurysma)

Malé kritérium

Echokardiografické vyšetření:

- regionální porucha kinetiky PK (akineze, dyskineze)
- + jedno z následujících:
  - RVOT v PLAX ≥ 29 a < 32 mm nebo ≥ 16 a < 19 mm/m²
  - RVOT v PSAX ≥ 32 a < 36 mm nebo ≥ 18 a < 21 mm/m²
  - frakční změna plochy PK > 33 % a ≤ 40 %

MR

- regionální porucha kinetiky PK nebo asynchronie kontrakce PK
- + jedno z následujících:
  - end-diastolický objem PK ≥ 100 a < 110 ml/m² (muži), resp. ≥ 90 a < 100 ml/m² (ženy)
  - ejekční frakce PK > 40 % a ≤ 45 %

II. Charakteristika stěny pravé komory

Velké kritérium

- reziduální počet myocytů < 60 % morfometricky (resp. < 50 % odhadem) s fibrotickou náhradou myocytů ve ≥ 1 vzorku z volné stěny PK, s tukovou tkání nebo bez ní

Malé kritérium

- reziduální počet myocytů ≥ 60 % a < 75 % morfometricky (resp. ≥ 50 %, < 60 % odhadem) s fibrotickou náhradou myocytů ve ≥ 1 vzorku z volné stěny PK, s tukovou tkání nebo bez ní

III. Abnormality repolarizační fáze

Velké kritérium

- negativní T-vlny ve svodech V_1–V_3 u osob starších 14 let v nepřítomnosti RBBB

Malé kritérium

- negativní T-vlny ve svodech V_1 a V_2 nebo V_4–V_6 u osob starších 14 let v nepřítomnosti RBBB
- negativní T vlny ve svodech V_1–V_4 u osob starších 14 let při kompletní RBBB

IV. Abnormality depolarizace a vedení

Velké kritérium

- přítomnost vlny ε ve svodech V_1–V_3

Malé kritérium

- přítomnost pozdních komorových potenciálů na signálově zprůměrovaném EKG v nepřítomnosti trvání QRS ≥ 110 ms na standardním EKG (pozitivita minimálně jeden z následujících parametrů):
  - trvání filtrovaného QRS ≥ 114 ms
  - trvání terminálního nízkoamplitudového signálu (< 40 μV) ≥ 38 ms
  - „root-mean-square" (střední kvadratická) voltáž terminálních 40 ms ≤ 20 μV
- trvání terminální aktivace QRS ≥ 55 ms ve svodech V_1–V_3 v nepřítomnosti RBBB

V. Poruchy srdečního rytmu

Velké kritérium

- nesetrvalé či setrvalé komorové tachykardie morfologie LBBB s „horní osou" (negativní QRS ve II, III a aVF, pozitivní v aVL)

Malé kritérium

- nesetrvalé či setrvalé komorové tachykardie morfologie LBBB z výtokového traktu PK (s „dolní osou" – pozitivní QRS ve II, III a aVF, negativní v aVL) nebo s neznámou osou
- četné komorové arytmie (> 500/24 h) při holterovském monitorování EKG

VI. Rodinná anamnéza

Velké kritérium

- ARVC u příbuzného prvního stupně stanovená podle těchto kritérií
  - nekropticky nebo chirurgicky potvrzená ARVC u příbuzného prvního stupně
  - záchyt mutace asociované s ARVC u vyšetřovaného pacienta

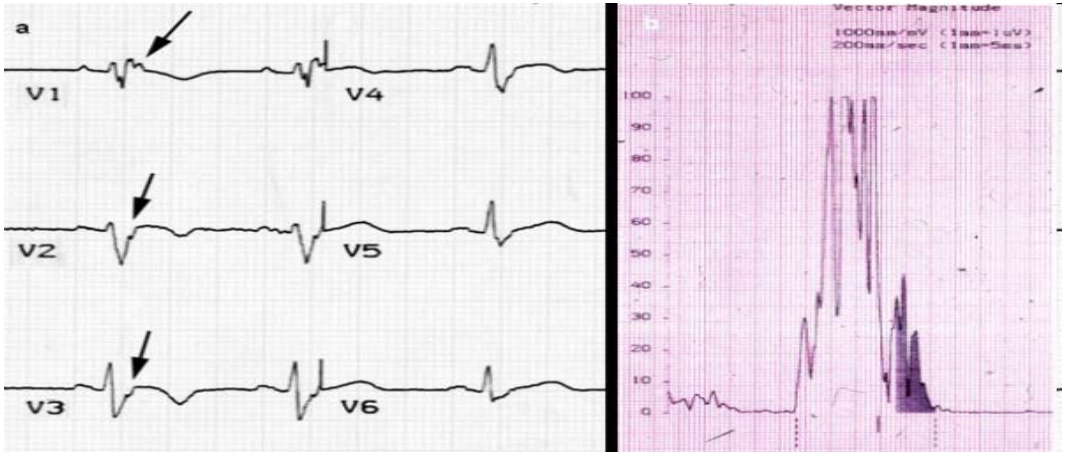
Malé kritérium

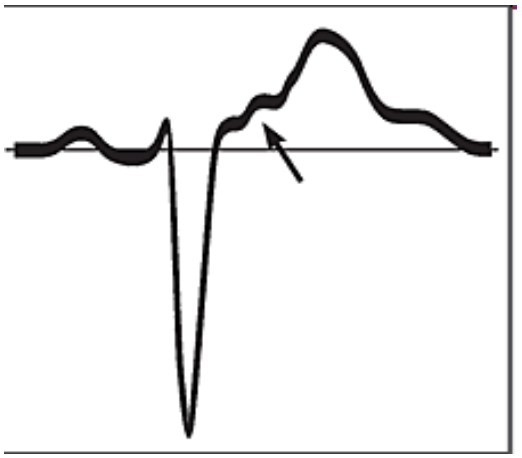
- ARVC u příbuzného prvního stupně v případě, že není možné potvrdit diagnózu podle současných kritérií
- anamnéza náhlé smrti ve věku < 35 let u příbuzného prvního stupně při suspektní ARVC
- ARVC potvrzená nekropticky či chirurgicky nebo podle současných kritérií u příbuzného druhého stupně

Diagnostika (ARVC)

EKG + SA-EKG

- inverze T vln v pravých prekordiálních svodech (V2 a V3) v nepřítomnosti BPRTw
- iBPRTw
- vlna epsilon (elektrický potenciál na konci QRS)
- prodloužení QRS ve svodech V1-V3 nad 110ms

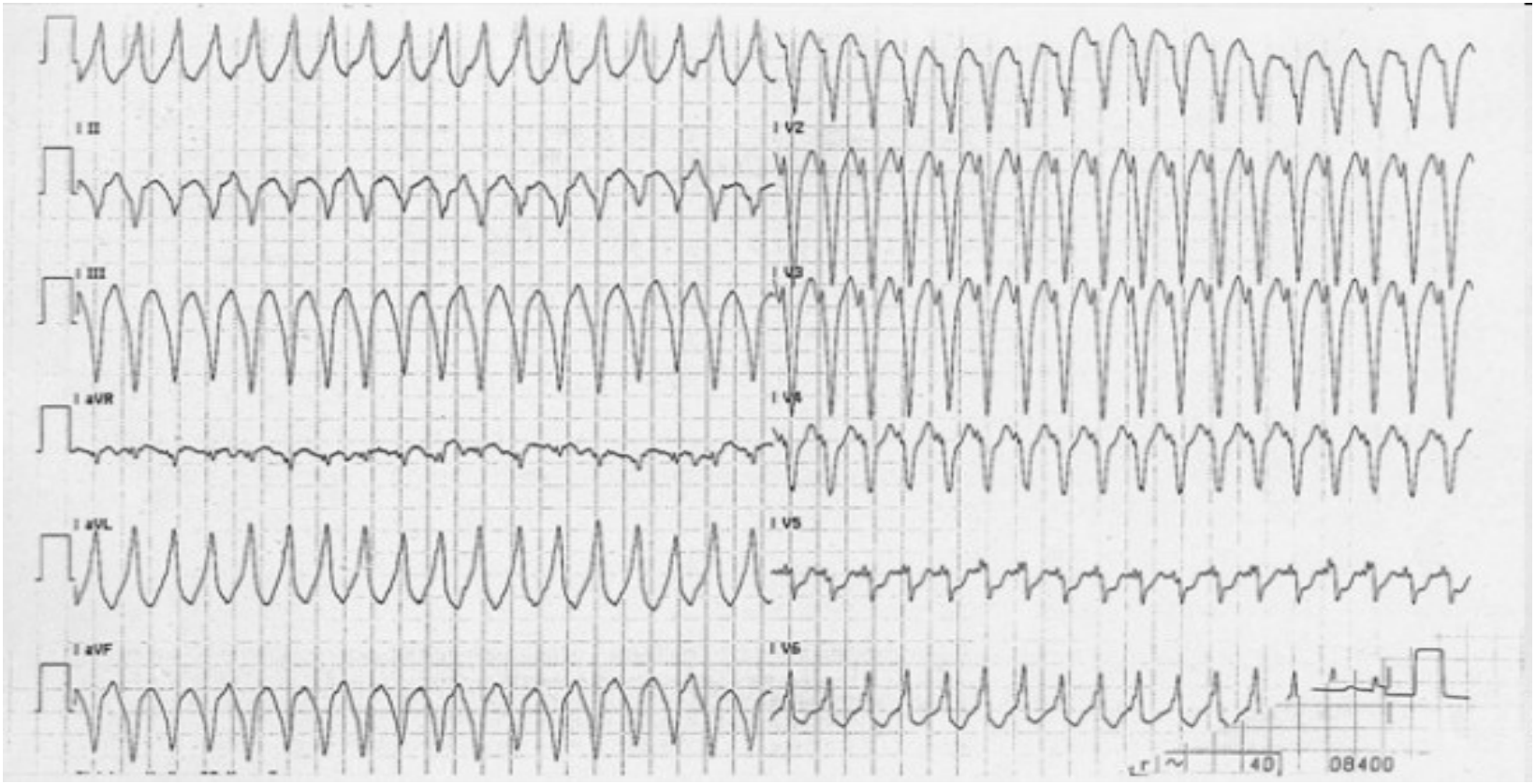




Thiene G, Corrado D, Basso C. Arrhythmogenic right ventricular cardiomyopathy/dysplasia. Orphanet Journal of Rare Diseases 2007;2:45.

Diagnostika (ARVC)

Holterovo monitorování, zátěž. testy

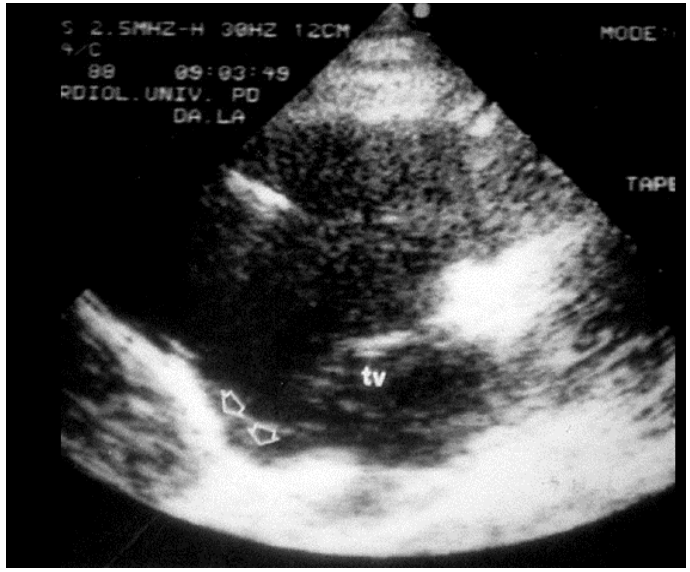


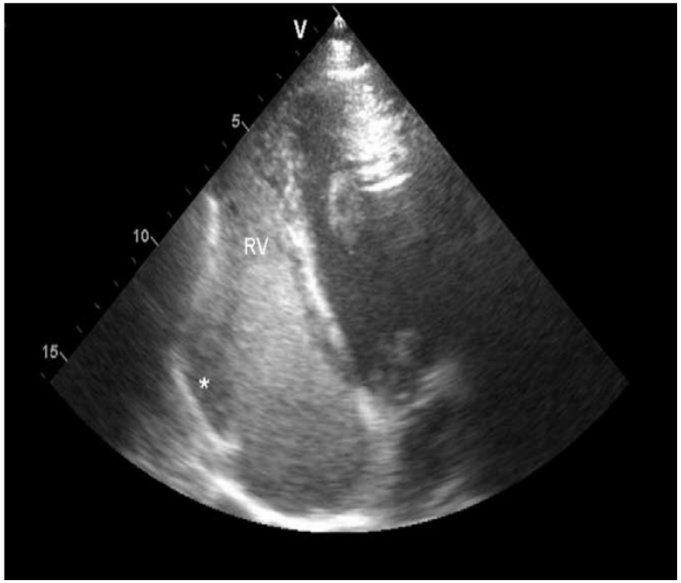
Thiene G, Corrado D, Basso C. Arrhythmogenic right ventricular cardiomyopathy/dysplasia. Orphanet Journal of Rare Diseases 2007;2:45.

Diagnostika

Echokardiografie

- konvenční
- kontrastní
- TDI, strain, 3D

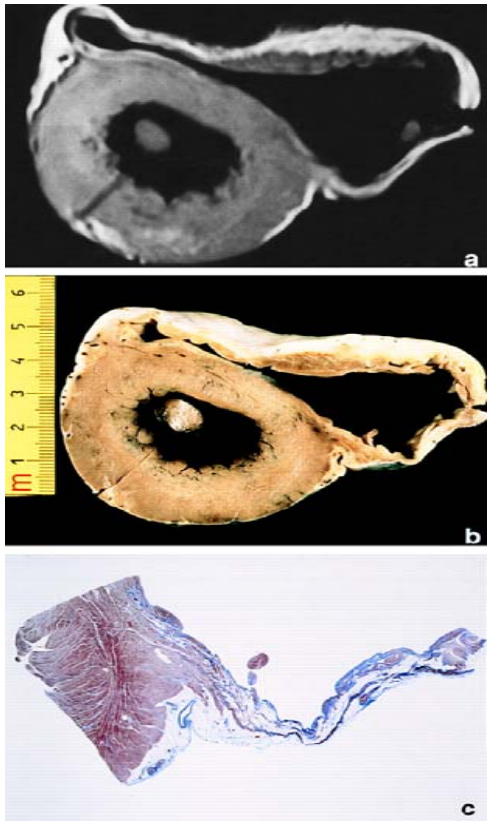


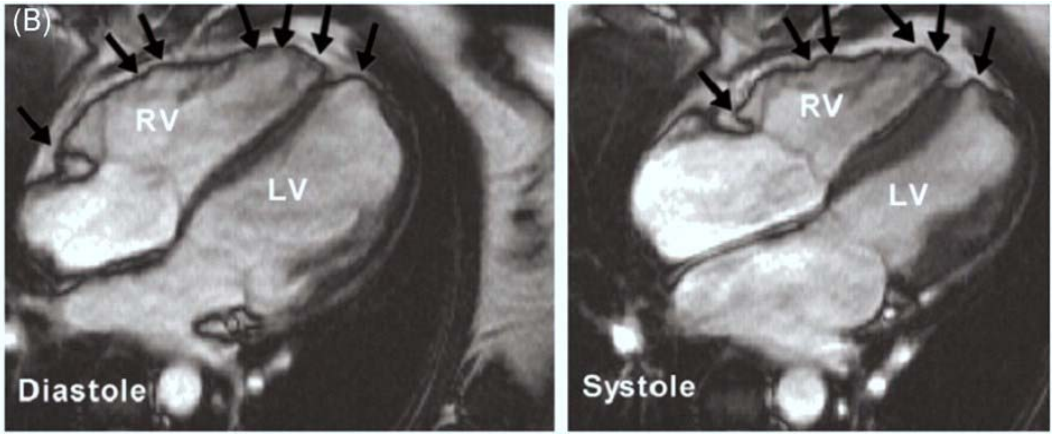


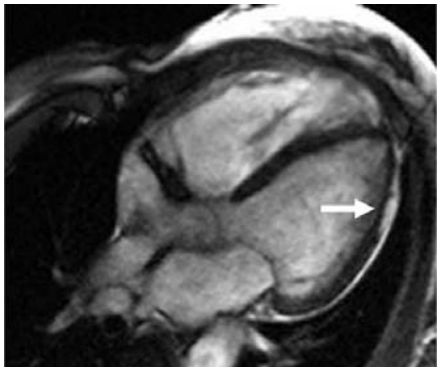
Kiès P, Bootsma M, Bax J, et al. Arrhythmogenic right ventricular dysplasia/cardiomyopathy: Screening, diagnosis, and Treatment. Heart Rhythm 2006;3:225–234.

Diagnostika

Nukleární magnetická rezonance



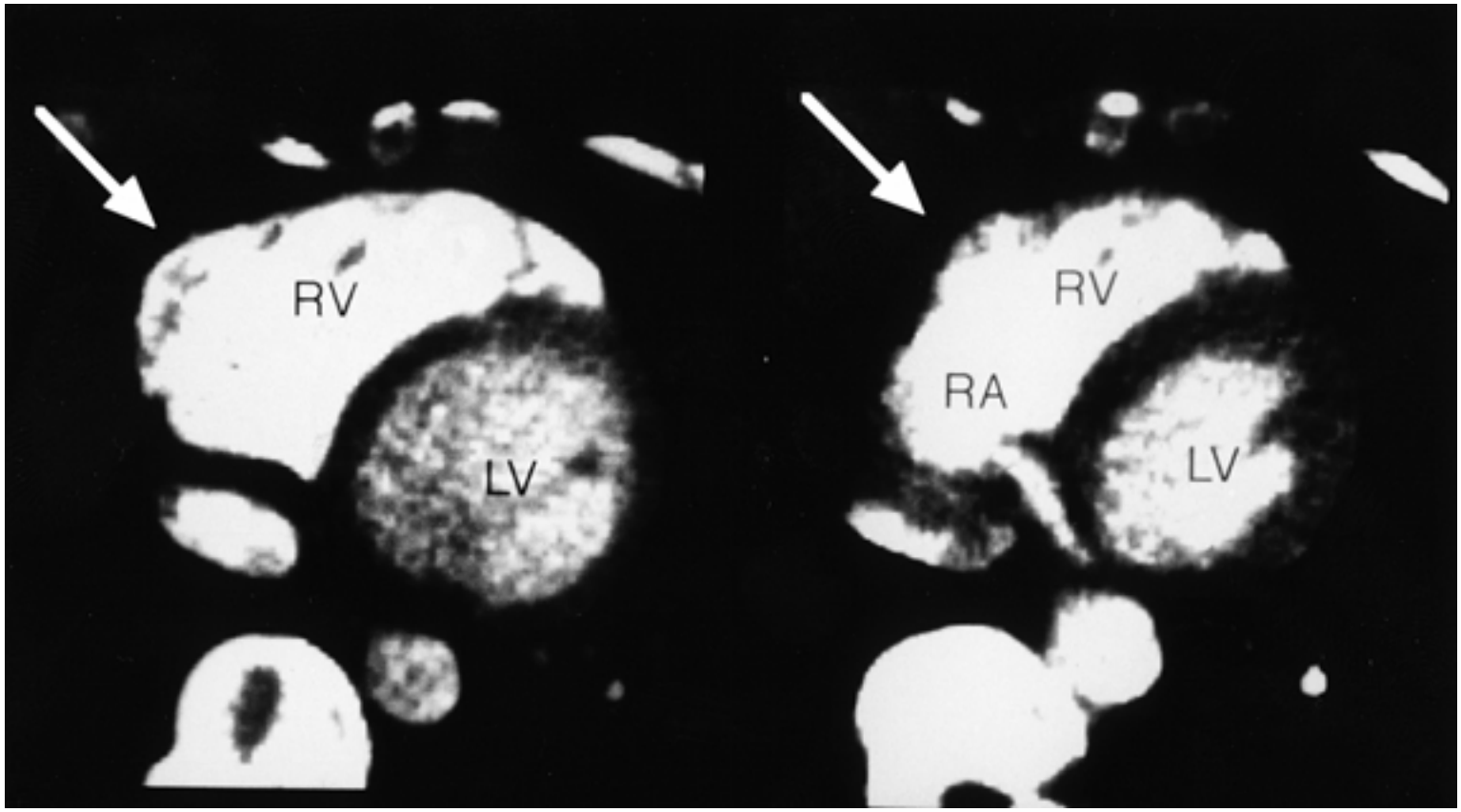




Jain A, Tandri H, Calkins H, Bluemke DA. Role of cardiovascular magnetic resonance imaging in arrhythmogenic right ventricular dysplasia. J Cardiovasc Magn Reson 2008;10:32

Diagnostika

Počítačová tomografie



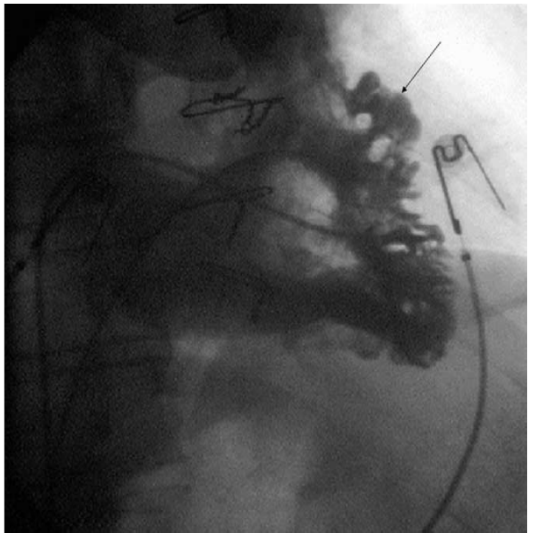
M. Takagi, N. Aihara, S. Kuribayashi, et al. Localized right ventricular morphological abnormalities detected by electron-beam computed tomography represent arrhythmogenic substrates in patients with the Brugada syndrome European Heart Journal (2001) 22, 1032–1041.

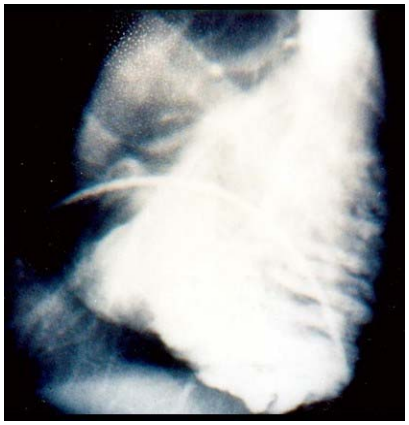
Diagnostika (ARVC)

Izotopová pravokomorová ventrikulografie

Kontrastní ventrikulografie

- **ložiskové poruchy kinetiky PK**
- **dilatace PK**





Kiès P, Bootsma M, Bax J, et al. Arrhythmogenic right ventricular dysplasia/cardiomyopathy: Screening, diagnosis, and Treatment. Heart Rhythm 2006;3:225–234.
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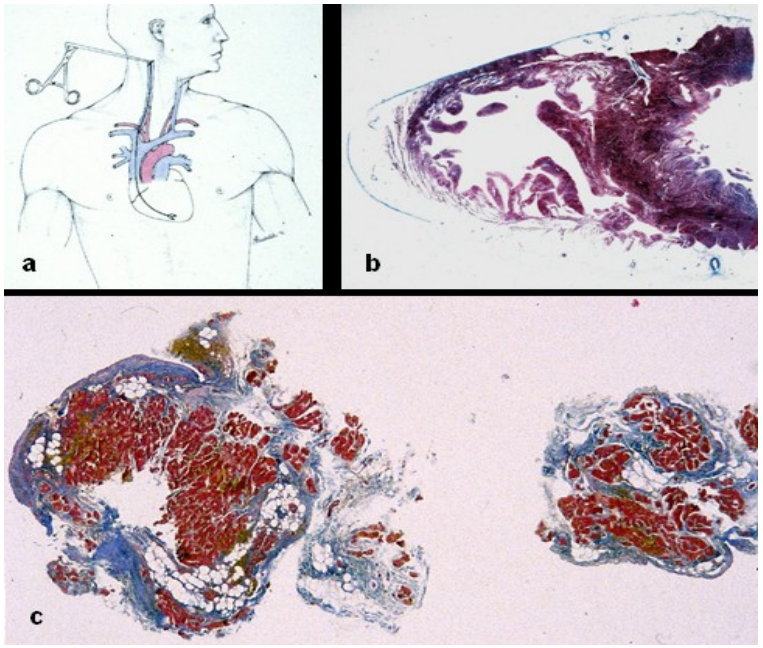
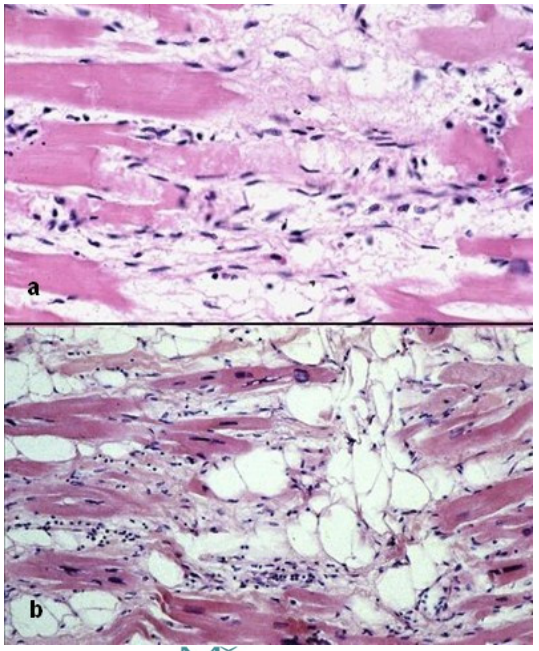
Diagnostika

Endomyokardiální biopsie

- fibrózně-tuková přestavba stěny PK spojená s relativním poklesem počtu myocytů pod 60 %
- atrofie myocytů a zvýšené relat. množství vaziva (tento nález je diagnosticky cennější, než samotný průkaz tuku)



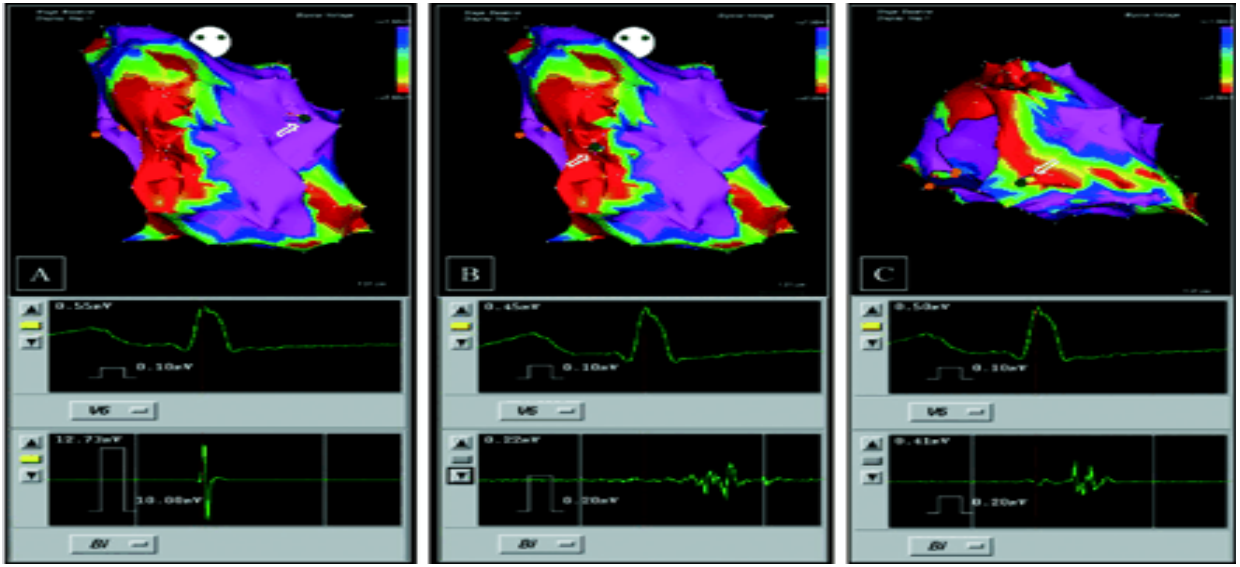


Thiene G, Corrado D, Basso C. Arrhythmogenic right ventricular cardiomyopathy/dysplasia. Orphanet Journal of Rare Diseases 2007;2:45.

Diagnostika (ARVC)

Elektrofyziologické vyšetření

- snadná vyvolatelnost setrvalých komorových arytmií
- záchyt oblastí myokardu s nízkou voltáží při elektroanatomickém mapování



Corrado D, Basso C, Leoni L, et al. Three-Dimensional Electroanatomic Voltage Mapping Increases Accuracy of Diagnosing Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia. Circulation. 2005;111:3042-3050.)

Prognóza

- **ACMP je progresivní onemocnění, které si žádá pravidelné přehodnocování stavu**
- **celková mortalita 2,5 % za rok**
- **ve Spojených státech 5 % náhlých úmrtí u osob mladších 35 let, v některých oblastech Itálie (region Benátek) až 25 %**
- **nejčastější příčinou smrti obvykle bývá arytmická smrt, méně často srd. selhání**
- **prediktory špatné prognózy: mladý věk v době stanovení diagnózy, rodinná anamnéza náhlé smrti, anamnéza synkopy či oběhové zástavy, záchyt KT a postižení LK.**

Thiene G, Corrado D, Basso C. Arrhythmogenic right ventricular cardiomyopathy/dysplasia. Orphanet Journal of Rare Diseases 2007;2:45.

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Terapie

- empirická data
- režimová opatření (zákaz sportovních a fyzicky náročných aktivit)
- u asymptomatických nemocných není pravděpodobně léčba indikovaná
- u pacientů s nízkým rizikem nebo jako první krok farmakologická léčba (sot, BB, amio)
- u pacientů s vysokým rizikem ICD
- radiofrekvenční ablace
- chirurgie - HTx nebo ventrikulotomie

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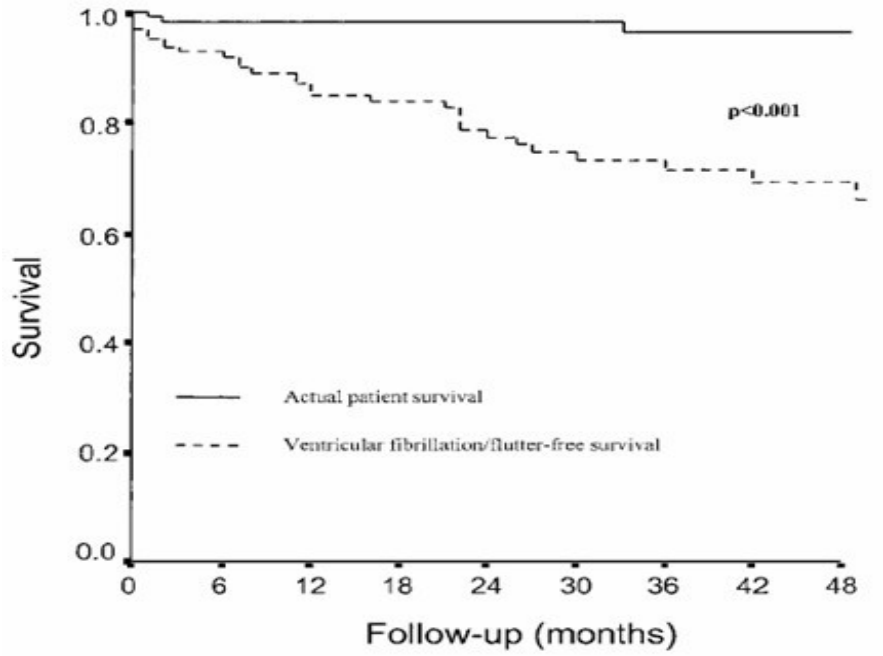
Terapie

- **ICD (v sekundární prevenci terapie u 94%, v primární u 39% implantovaných)**



Thiene G, Corrado D, Basso C. Arrhythmogenic right ventricular cardiomyopathy/dysplasia. Orphanet Journal of Rare Diseases 2007;2:45.

Závěr

- ACMP je vzácné onemocnění s potenciálně nepříznivou prognózou
- kurativní léčebný postup není k dispozici (vyjma HTx)
- léčba arytmií dramaticky zlepšuje prognózu (ICD)
- nadějí je genetická diagnostika a léčba

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