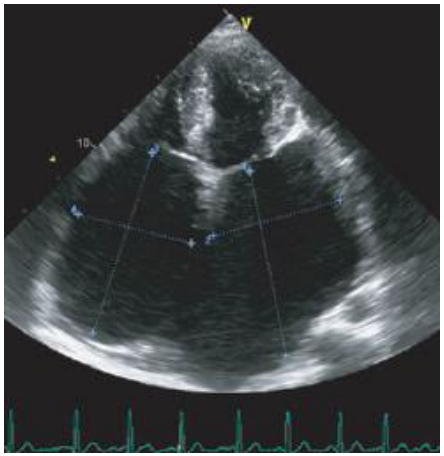
RESTRIKTIVNÍ KARDIOMYOPATIE

Jan Krejčí



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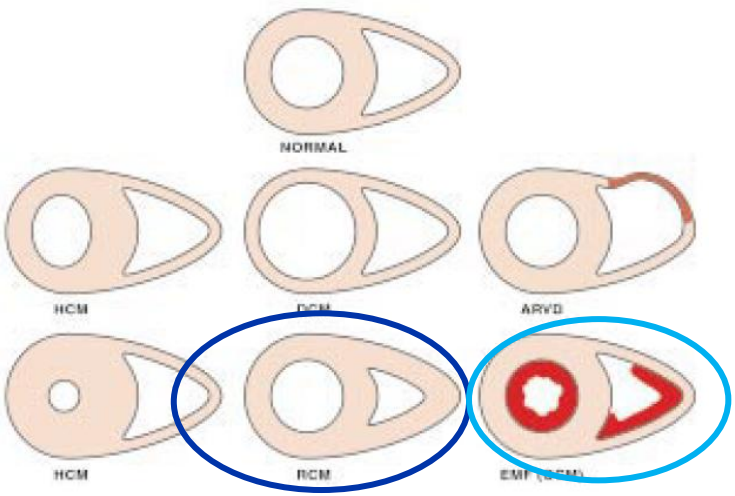
Restriktivní kardiomyopatie

CARDIOMYOPATHY

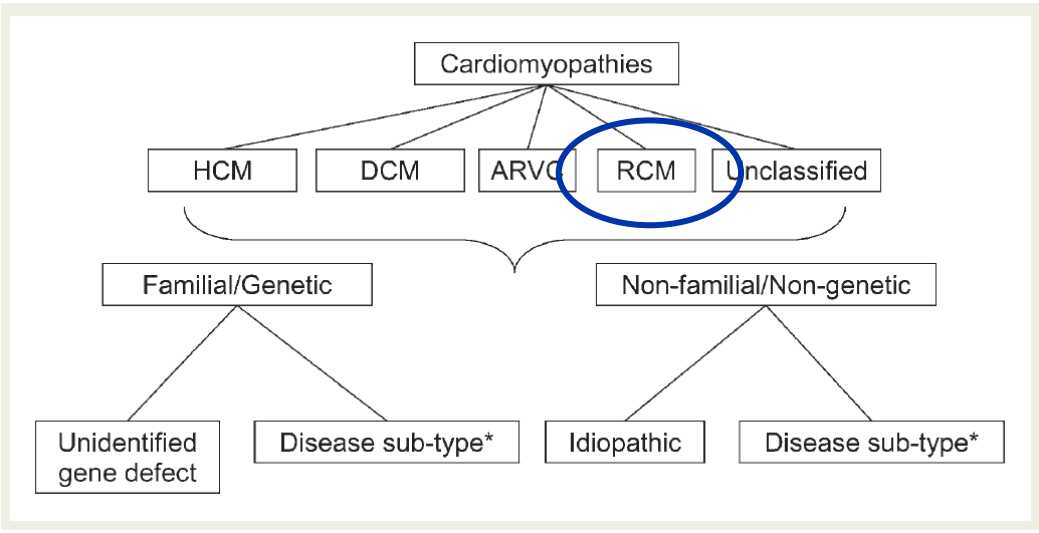
The cardiomyopathies: an overview

M J Davies
St George's Hospital Medical School, Histopathology Department, London, UK



Classification of the cardiomyopathies: a position statement from the european society of cardiology working group on myocardial and pericardial diseases

Perry Elliott, Bert Andersson, Eloisa Arbustini, Zofia Bilinska, Franco Cecchi, Philippe Charron, Olivier Dubourg, Uwe Kühl, Bernhard Maisch, William J. McKenna, Lorenzo Monserrat, Sabine Pankuweit, Claudio Rapezzi, Petar Seferovic, Luigi Tavazzi, and Andre Keren*



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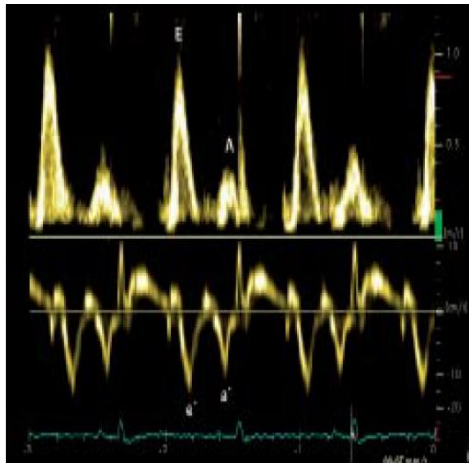
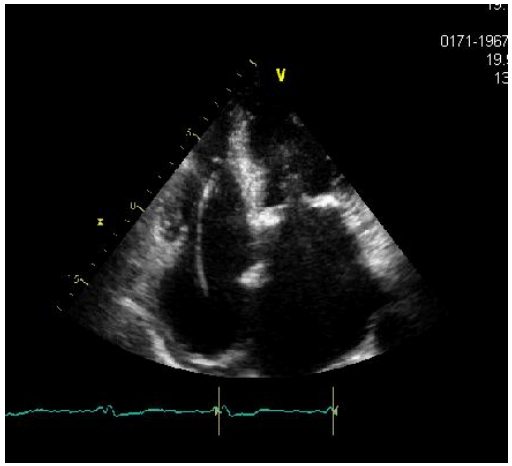
Restriktivní kardiomyopatie

- nejméně častá KMP
- je charakterizovaná restriktivní hemodynamikou
- typickým rysem je zvýšená tuhost myokardu (snížená kompliance), která může mít původ v myokardu, ale také v endokardu
- morfologicky jde o onemocnění s normální (či téměř normální) LVEF a normálními/sníženými objemy jedné nebo obou komor
- tloušťka stěn LK by neměla být zvýšená (?)





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Restriktivní kardiomyopatie

Table 1 Examples of different diseases that cause cardiomyopathies

	HCM	DCM	ARVC	RCM	Unclassified
Familial	Familial, unknown gene Sarcomeric protein mutations ß myosin heavy chain Cardiac myosin binding protein C Cardiac troponin I Troponin-T α-tropomyosin Essential myosin light chain Regulatory myosin light chain Cardiac actin α-myosin heavy chain Titin Troponin C Muscle LIM protein Glycogen storage disease (e.g. Pompe; PRKAG2, Forbes', Danon) Lysosomal storage diseases (e.g. Anderson–Fabry, Hurler's) Disorders of fatty acid metabolism Carnitine deficiency Phosphorylase B kinase deficiency Mitochondrial cytopathies Syndromic HCM Noonan's syndrome LEOPARD syndrome Friedreich's ataxia Beckwith–Wiedermann syndrome Swyer's syndrome Other Phospholamban promoter Familial amyloid	Familial, unknown gene Sarcomeric protein mutations (see HCM) Z-band Muscle LIM protein TCAP Cytoskeletal genes Dystrophin Desmin Metavinculin Sarcoglycan complex CRYAB Epicardin Nuclear membrane Lamin A/C Emerin Mildly dilated CM Intercalated disc protein mutations (see ARVC) Mitochondrial cytopathy	Familial, unknown gene Intercalated disc protein mutations Plakoglobin Desmoplakin Plakophilin 2 Desmoglein 2 Desmocollin 2 Cardiac ryanodine receptor (RyR2) Transforming growth factor-β3 (TGFβ3)	Familial, unknown gene Sarcomeric protein mutations Troponin I (RCM +/− HCM) Essential light chain of myosin Familial amyloidosis Transthyretin (RCM + neuropathy) Apolipoprotein (RCM + nephropathy) Desminopathy Pseuxanthoma elasticum Haemochromatosis Anderson–Fabry disease Glycogen storage disease	Left ventricular non-compaction Barth syndrome Lamin A/C ZASP α-dystrobrevin
Non-familial	Obesity Infants of diabetic mothers Athletic training Amyloid (AL/prealbumin)	Myocarditis (infective/toxic/immune) Kawasaki disease Eosinophilic (Churg Strauss syndrome) Viral persistence Drugs Pregnancy Endocrine Nutritional — thiamine, carnitine, selenium, hypophosphataemia, hypocalcaemia Alcohol Tachycardiomyopathy	Inflammation?	Amyloid (AL/prealbumin) Scleroderma Endomyocardial fibrosis Hypereosinophilic syndrome Idiopathic Chromosomal cause Drugs (serotonin, methysergide, ergotamine, mercurial agents, busulfan) Carcinoid heart disease Metastatic cancers Radiation Drugs (anthracyclines)	Tako Tsubo cardiomyopathy

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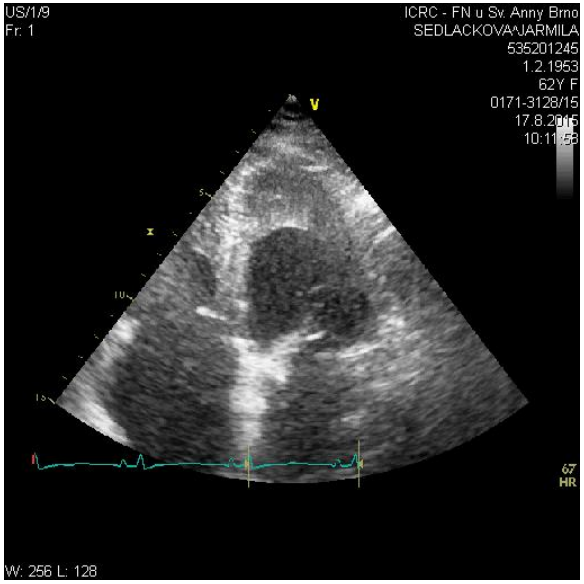
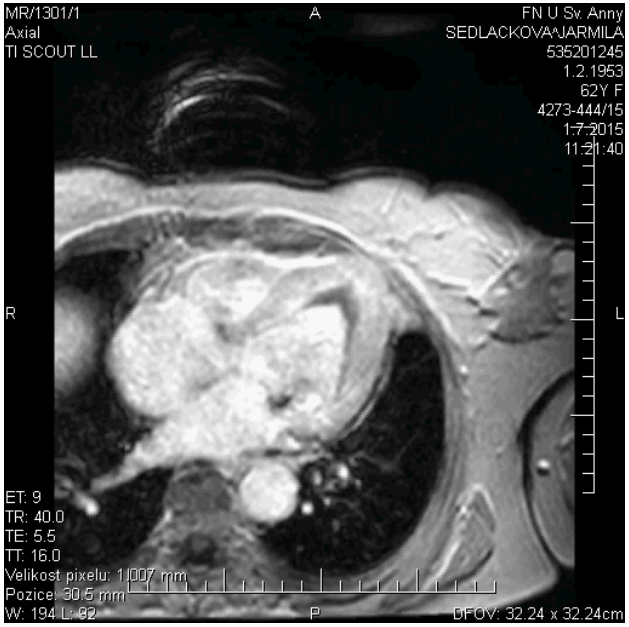
Vzácná příčina RKMP

Review article

Endomyocardial fibrosis: A form of endemic restrictive cardiomyopathy

Ana Olga Mocumbi*





Heart Transplantation in a Patient with Endomyocardial Fibrosis Due to Hypereosinophilic Syndrome

Dariusz Korczyk,[1,5] Graeme Taylor,[2] Hugh McAlistair,[3] Stephen May,[4] Arthur Coverdale,[2] Helen Gibbs,[1] and Peter Ruygrok[1]

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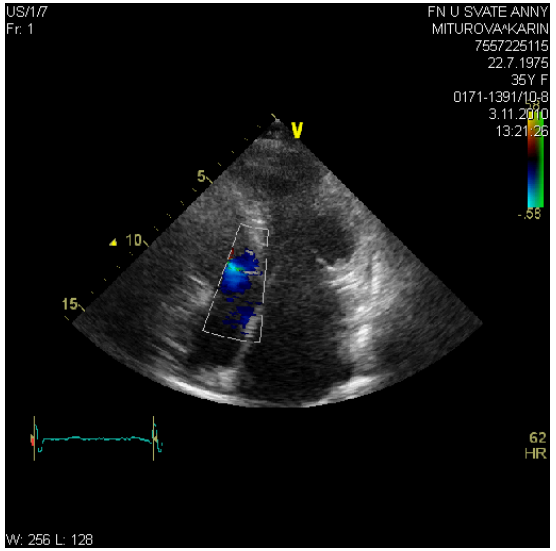
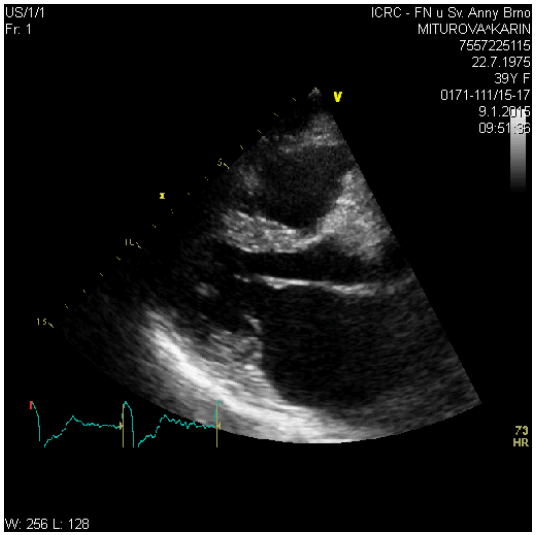
HKMP nebo RKMP

Prevalence, Clinical Significance, and Genetic Basis of Hypertrophic Cardiomyopathy With Restrictive Phenotype

Toru Kubo, MD,*† Juan R. Gimeno, MD,* Ajay Bahl, MD,* Ulla Steffensen,* Morten Steffensen,* Eyman Osman, BSc,* Rajesh Thaman, MD,* Jens Mogensen, MD, PhD,*‡ Perry M. Elliott, MD, FACC,* Yoshinori Doi, MD, FACC,† William J. McKenna, MD, FACC*



- sdílí řadu společných mutací
- vývoj HKMP do obrazu RKMP



Novel Phenotype–Genotype Correlations of Restrictive Cardiomyopathy With Myosin-Binding Protein C (*MYBPC3*) Gene Mutations Tested by Next-Generation Sequencing

Wei Wu, MD;* Chao-Xia Lu, PhD;* Yi-Ning Wang, MD; Fang Liu, MASc; Wei Chen, MD; Yong-Tai Liu, MD; Ye-Chen Han, MD; Jian Cao, MD; Shu-Yang Zhang, MD; Xue Zhang, PhD

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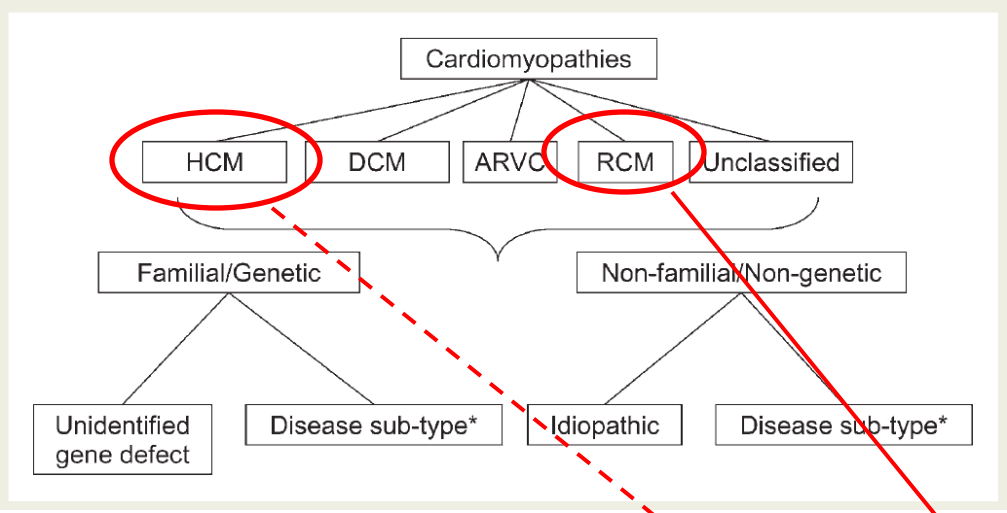
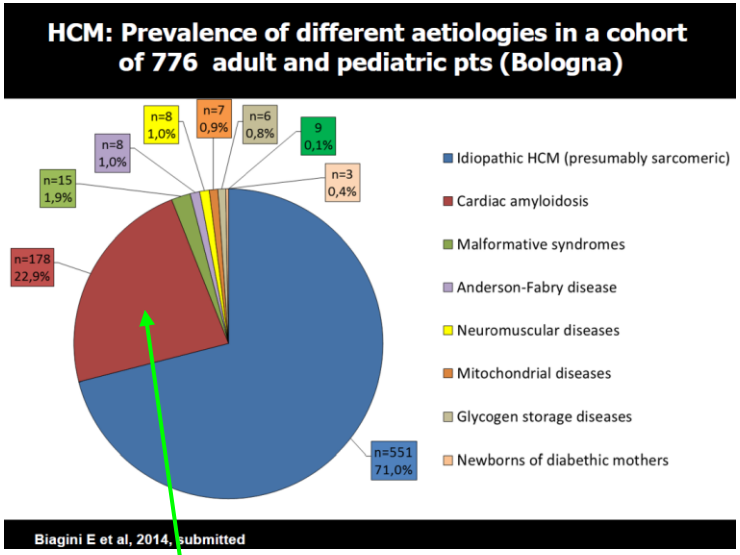
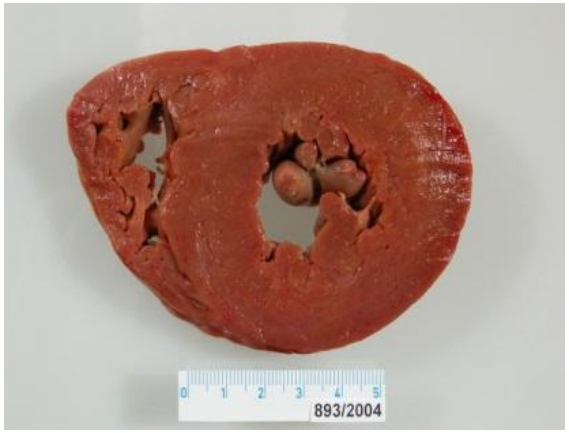
Srdeční amyloidóza jako příčina RKMP







srdeční amyloidóza

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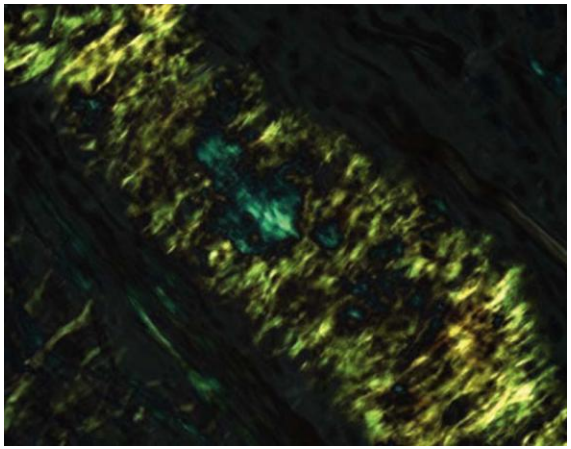
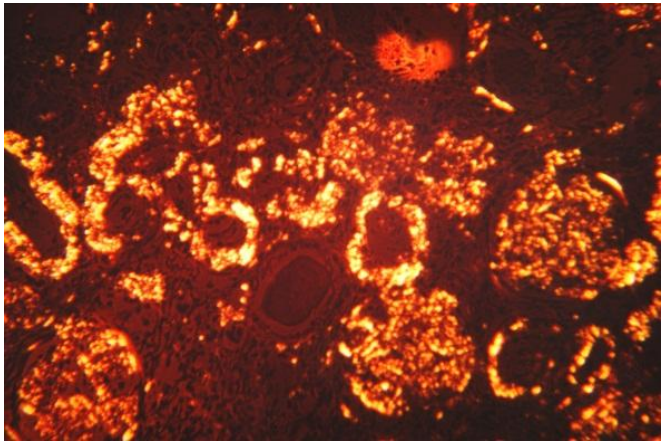
Amyloidóza

- skupina odlišných chorob, extracelulární depozice amyloidních hmot (fibrilární proteiny rezistentní k proteolýze)
- Incidence: 8-12/1.000 000

- AL amyloidóza - lehké řetězce IgG (nejčastěji lambda)
- Familiární amyloidóza – mutovaný transthyretin
- Senilní amyloidóza – transthyretin

- Sekundární amyloidóza – protein A – sporadicky





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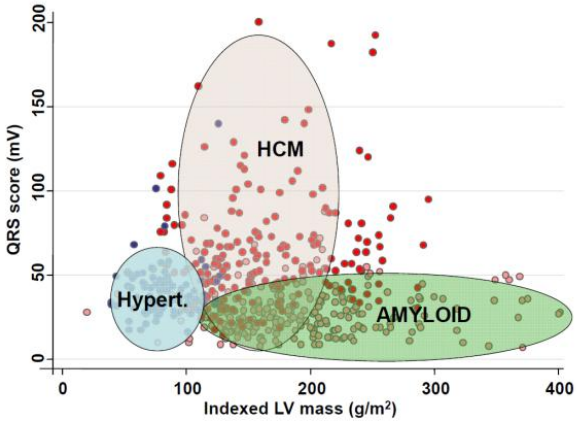
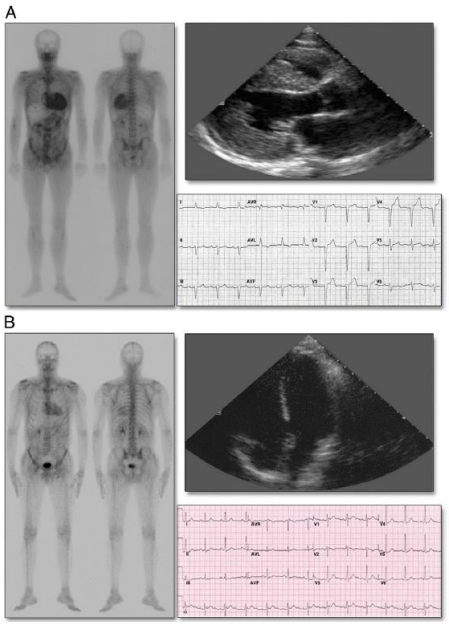
Diagnostika

- EKG
- ECHO srdce
- MRI
- DPD scintigrafie
- EMB

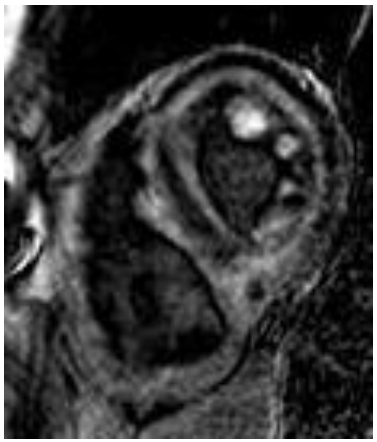


Quarta CC et al, Eur Heart J 2010 (abstr)

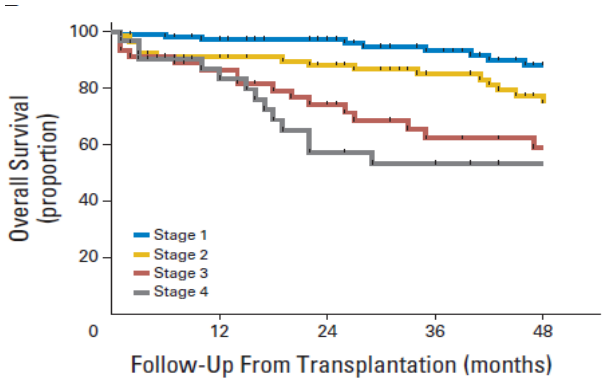


- Laboratorní vyš.:

  TnT/I, NTproBNP/BNP, FLC



Revised Prognostic Staging System for Light Chain Amyloidosis Incorporating Cardiac Biomarkers and Serum Free Light Chain Measurements



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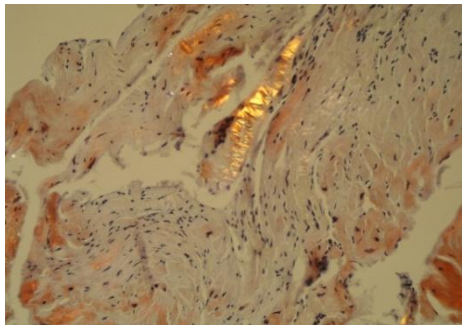
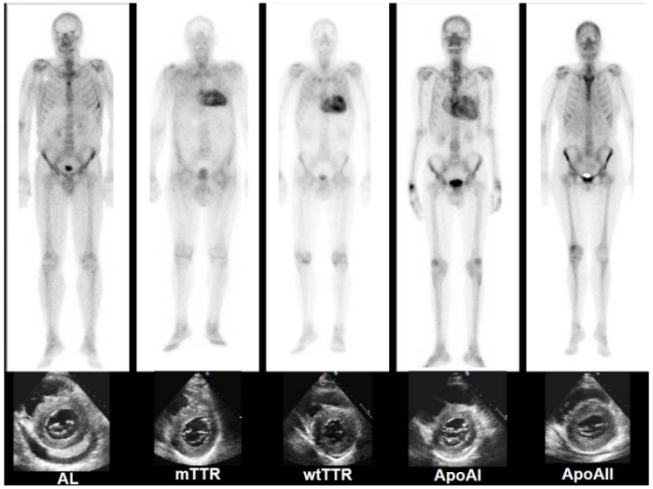
Dif. dg srdeční amyloidózy (AL vs ATTR)

- postižení dalších orgánů
- laboratorní diagnostika – FLC (pozit AL)
- genetické vyšetření (diff. dg mATTR vs wtATTR)
- DPD scinti (pozit u ATTR)
- Imunofluorescence EMB vzorků
  (typizace amyloidogenního proteinu)
- Hmotnostní spektrometrie EMB vzorků
  (typizace amyloidogenního proteinu)



ZÁSADNÍ VÝZNAM PRO TERAPII I PROGNÓZU!



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Prognóza amyloidózy

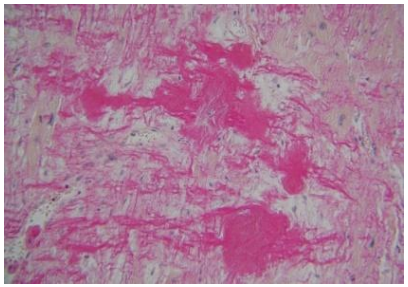
- nepříznivá u AL-A
- v přítomnosti srdečního selhání medián přežití neléčených jedinců 5-6 měsíců
- méně než 20% přežije 2 roky!
- 1/2 - 2/3 úmrtí mají kardiální příčinu

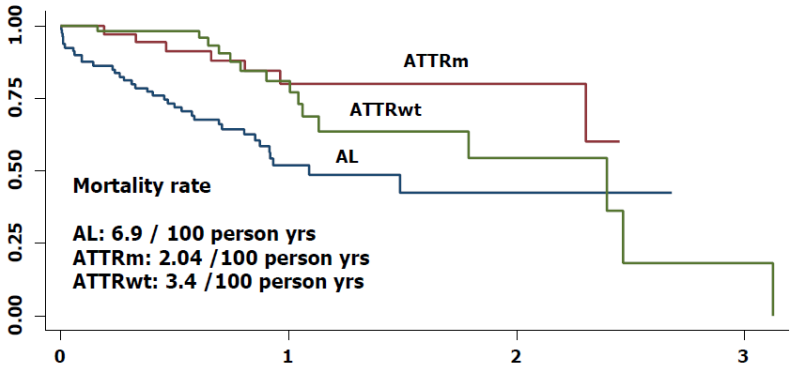
- mATTR (familiární) - až 15 let

Cardiomyopathy Disease Overview

Claudio Rapezzi, M.D.
Director, School of Cardiovascular Diseases
University of Bologna, Italy

Overall survival in patients with cardiac amyloidosis





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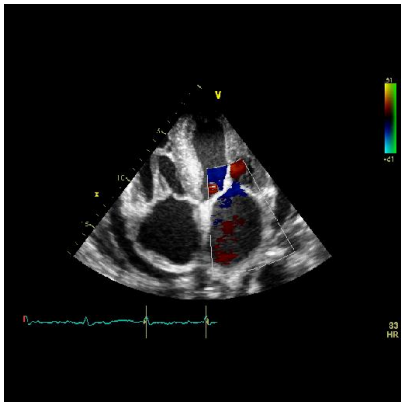
Jak se liší AL a ATTR amyloidózy?

Clinical Investigations

Echocardiographic and Biohumoral Characteristics in Patients With AL and TTR Amyloidosis at Diagnosis

Francesco Cappelli, MD; Samuele Baldasseroni, MD; Franco Bergesio, MD; Stefano Perlini, MD; Francesco Salinaro, MD; Luigi Padeletti, MD; Paola Attanà, MD; Alessandro Paoletti Perini, MD; Alberto Moggi Pignone, MD; Elisa Grifoni, MD; Alessia Fabbri, MD; Niccolò Marchionni, MD; Gian Franco Gensini, MD; Federico Perfetto, MD



- Výraznější infiltrace amyloidem u ATTR
- Ale v případech ATTR menší symptomy, nižší hladiny NTproBNP
- pomalejší progrese

- AL multiorgánové postižení
- rychlá progrese
- „light chain toxicity“

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Echokardiografie u srdeční amyloidózy

Clinical Investigations

Echocardiographic and Biohumoral Characteristics in Patients With AL and TTR Amyloidosis at Diagnosis

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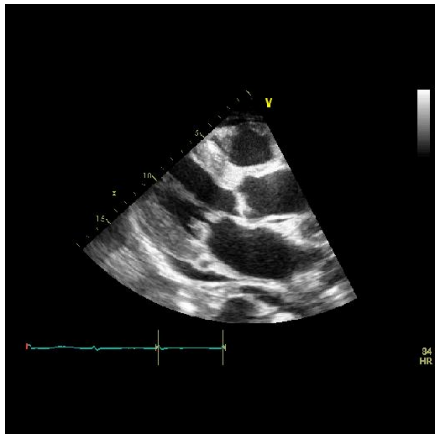
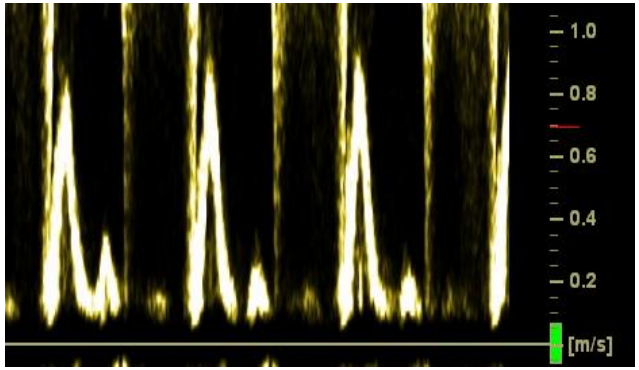
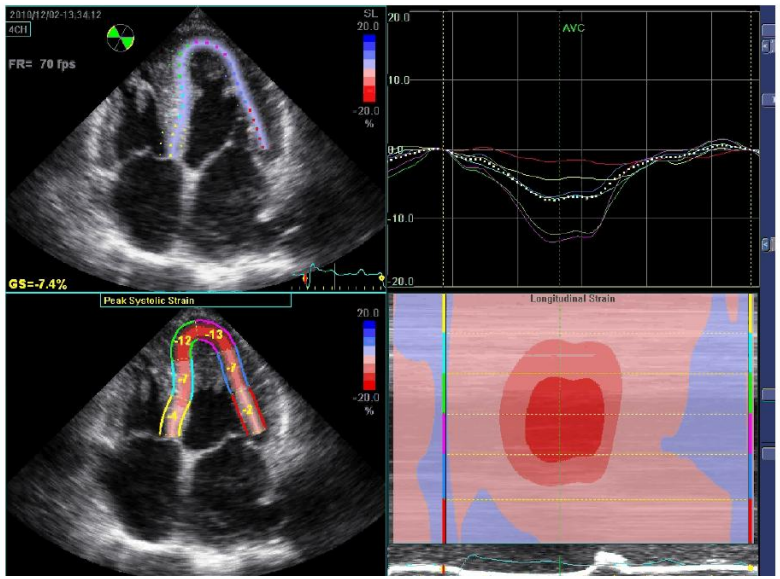




- koncentrická hypertrofie obou komor
- časné postižení longitudinální kontraktility
- těžká diastolická dysfunkce
- zesílení IAS, perikardiální výpotek
- typický nález při vyš. strainu

Amyloid strain



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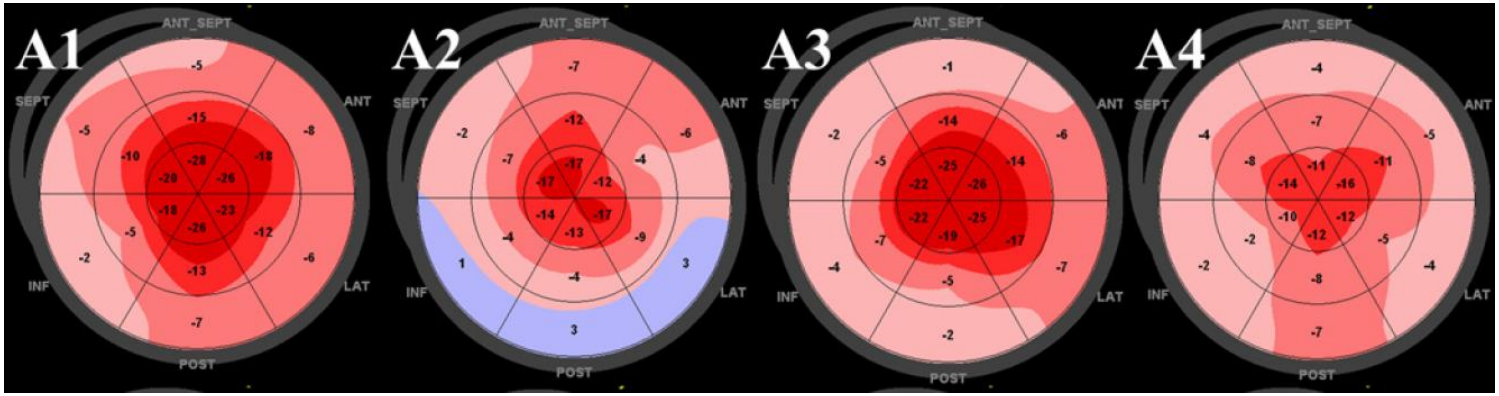
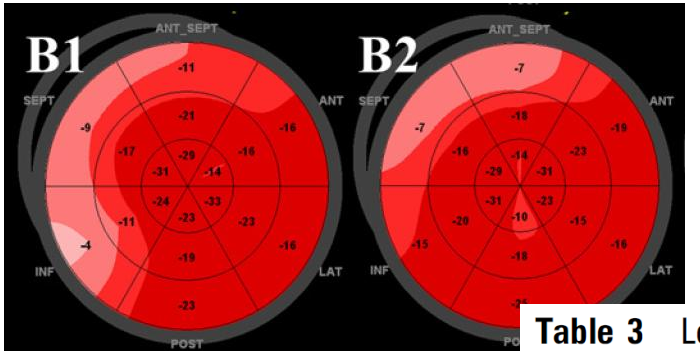
Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis

Dermot Phelan, Patrick Collier, Paaladinesh Thavendiranathan, Zoran B Popović, Mazen Hanna, Juan Carlos Plana, Thomas H Marwick, James D Thomas



CA



HKMP

Table 3 Longitudinal strain parameters in cardiac amyloidosis

	AL amyloidosis (n = 27)	TTR amyloidosis (n = 26)	p Value
Mean basal strain (%)	−4.6 ± 3.8	−3.3 ± 3.3	0.20
Mean mid-strain (%)	−8.7 ± 4.1	−7.0 ± 3.5	0.12
Mean apical strain (%)	−17.5 ± 5.2	−14.5 ± 4.8	0.03
Mean global strain (%)	−9.9 ± 3.9	−7.9 ± 3.5	0.07
Mean relative strain	1.9 ± 2.1	2.0 ± 1.4	0.90

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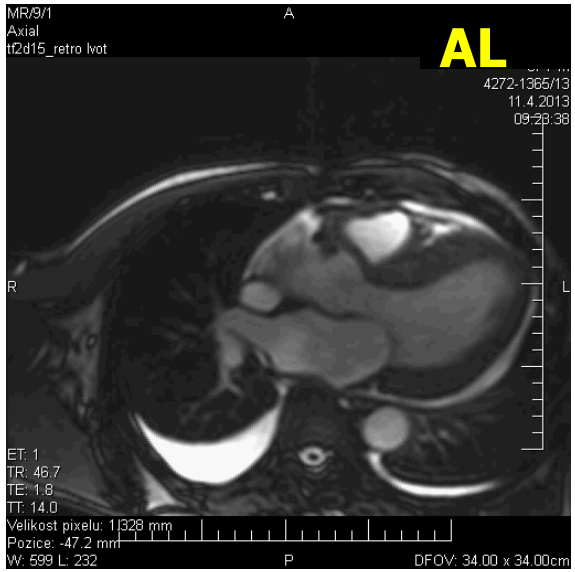
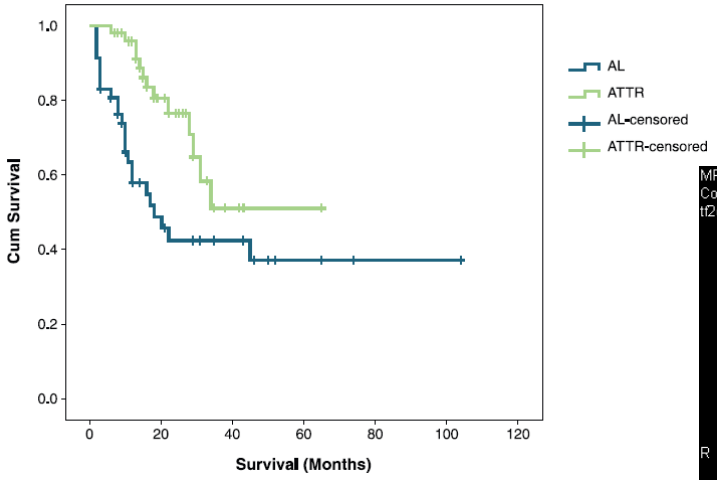
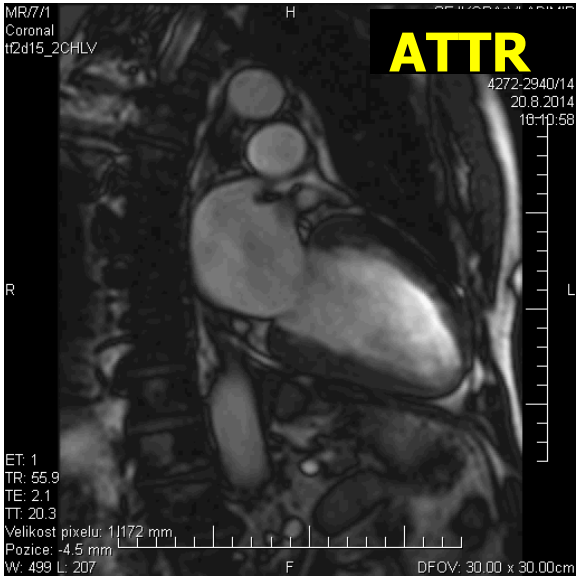
CMR-Based Differentiation of AL and ATTR Cardiac Amyloidosis

Jason N. Dungu, MBBS, BSc,*† Oswaldo Valencia, MSc, MD,† Jennifer H. Pinney, BM, BS,*
Simon D. J. Gibbs, MBBS,* Dorota Rowczenio, MSc,* Janet A. Gilbertson, CSci,*
Helen J. Lachmann, MD,* Ashutosh Wechalekar, MD,* Julian D. Gillmore, MD, PhD,*
Carol J. Whelan, MD,* Philip N. Hawkins, PhD,* Lisa J. Anderson, MD†
London, United Kingdom

- **Medián přežití u AL 18 měsíců, u ATTR 45 měsíců**
- **ATTR častěji muži (88% vs 59%), starší (74 vs 63 let)**







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CMR-Based Differentiation of AL and ATTR Cardiac Amyloidosis

Jason N. Dungu, MBBS, BSc,*† Oswaldo Valencia, MSc, MD,† Jennifer H. Pinney, BM, BS,* Simon D. J. Gibbs, MBBS,* Dorota Rowczenio, MSc,* Janet A. Gilbertson, CSci,* Helen J. Lachmann, MD,* Ashutosh Wechalekar, MD,* Julian D. Gillmore, MD, PhD,* Carol J. Whelan, MD,* Philip N. Hawkins, PhD,* Lisa J. Anderson, MD†

London, United Kingdom

- **výraznější postižení myokardu amyloidem u ATTR**

Table 3. Comparison of AL and ATTR Amyloidosis (LGE)

	Cardiac AL Amyloidosis (n = 46)	Cardiac ATTR (n = 51)	p Value
LV LGE	45 (98)	51 (100)	0.47
RV LGE	33 (72)	51 (100)	<0.001
Global subendocardial LGE	18 (39)	6 (12)	0.002
Global transmural LGE	2 (4)	11 (22)	0.01
Any transmural LGE	17 (37)	46 (90)	<0.001
Base-apex gradient	19 (41)	36 (71)	0.004
Atrial LGE	34 (74)	47 (92)	0.02

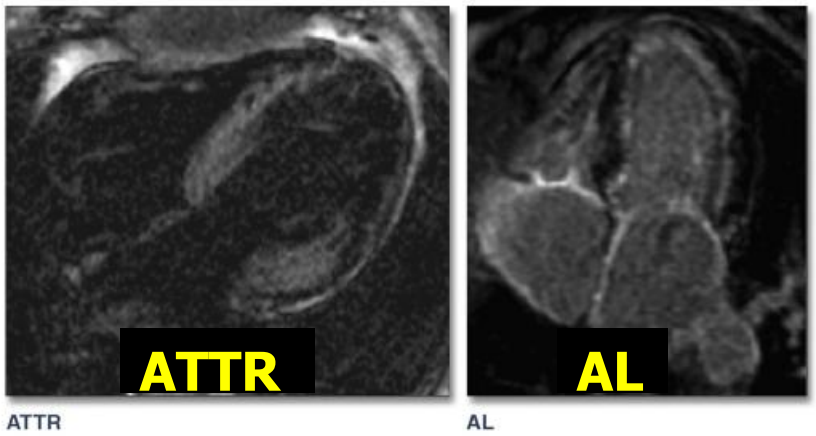
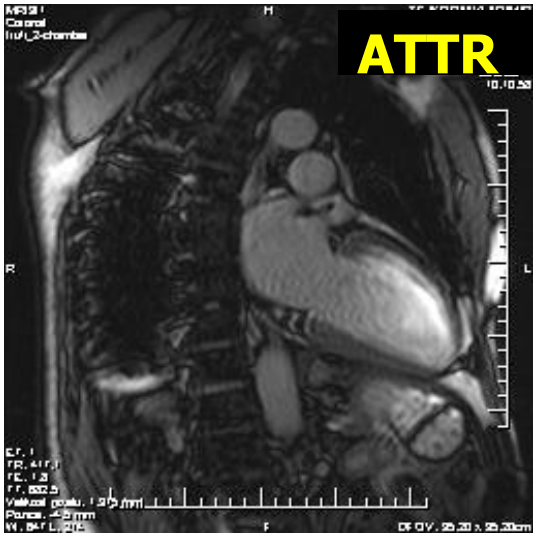


Figure 2. Examples of LGE Patterns in ATTR and AL Amyloidosis



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AL-A (imunoglobulinová, light-chains A)

- nejčastější forma srdeční amyloidózy, multiorgánové postižení
- důsledek postižení plazmatických bb kostní dřeně
- hematologická léčba (ASCT, Mel + Dex, bortezomib)
- při EF LK pod 40% a NYHA III-IV je ASCT kontraindikována pro vysokou periprocedurální mortalitu
- transplantace srdce s následnou léčbou AL-A (tedy ASCT) u nemocných s izolovaně (dominantně) kardiálním postižením

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ATTR (transthyretinová A)

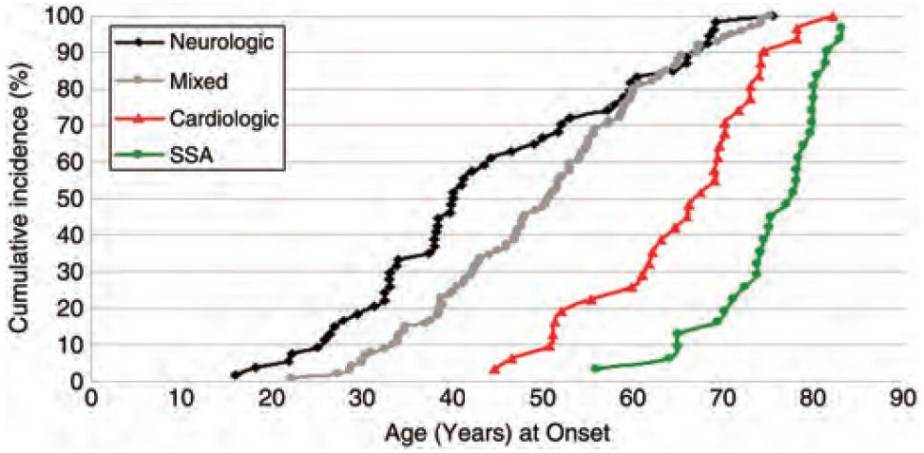
- **mutovaný transthyretin mATTR (familiární A)**

  - dřívější manifestace, endemické oblasti, izolovaně kardiální postižení méně časté (systémové onemocnění)

- **nemutovaný transthyretin wtATTR (senilní A)**

  - starší nemocní (> 65 let), muži, izolované kardiální postižení

Se stárnutím populace a zlepšením diagnostiky (MRI) narůstá výskyt ATTR !



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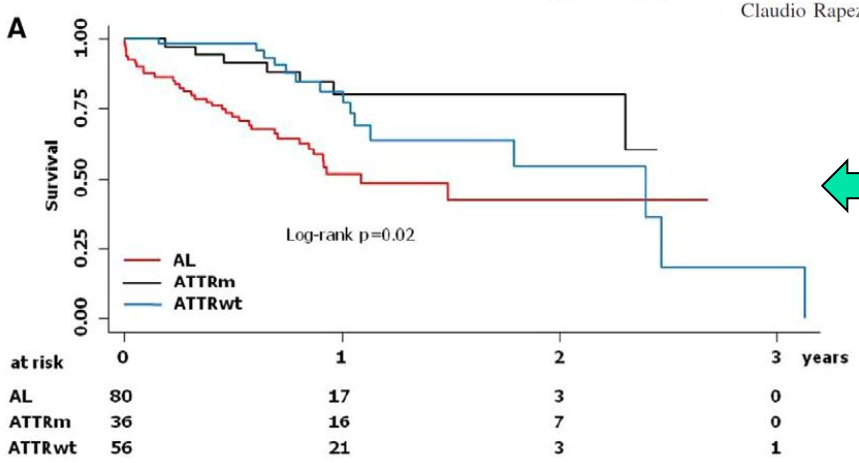
ATTR (transthyretinová A)

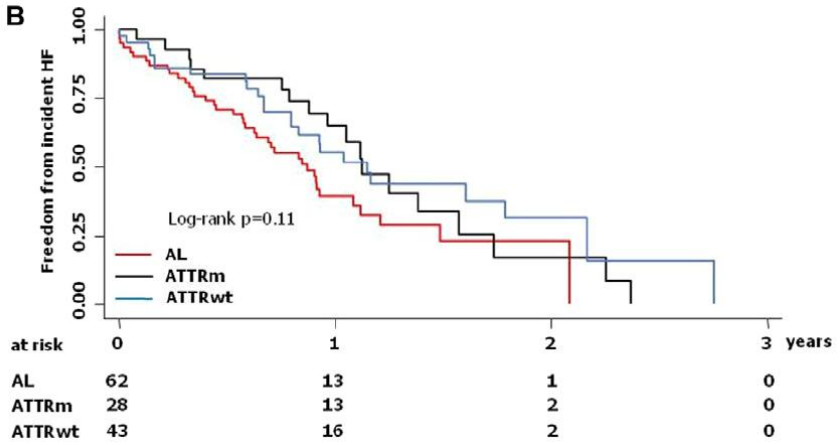
Left Ventricular Structure and Function in Transthyretin-Related Versus Light-Chain Cardiac Amyloidosis

Candida Cristina Quarta, MD; Scott D. Solomon, MD; Imran Uraizee, BS; Jenna Kruger, BS; Simone Longhi, MD; Marinella Ferlito, MD; Christian Gagliardi, MD; Agnese Milandri, MD; Claudio Rapezzi, MD; Rodney H. Falk, MD

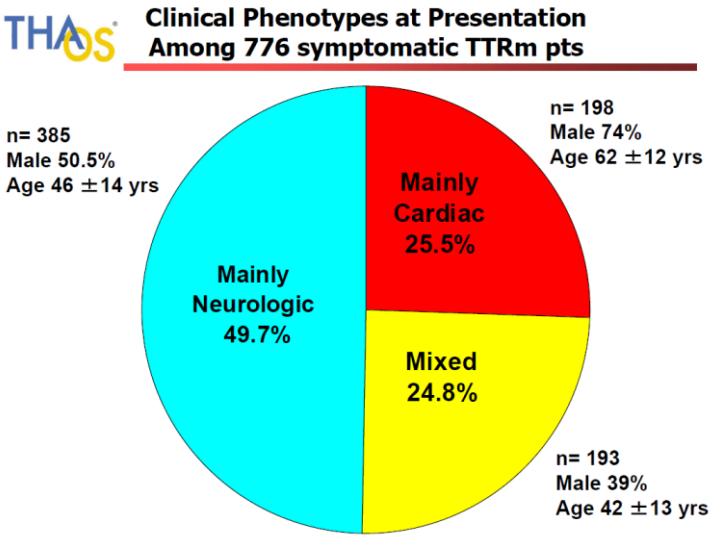


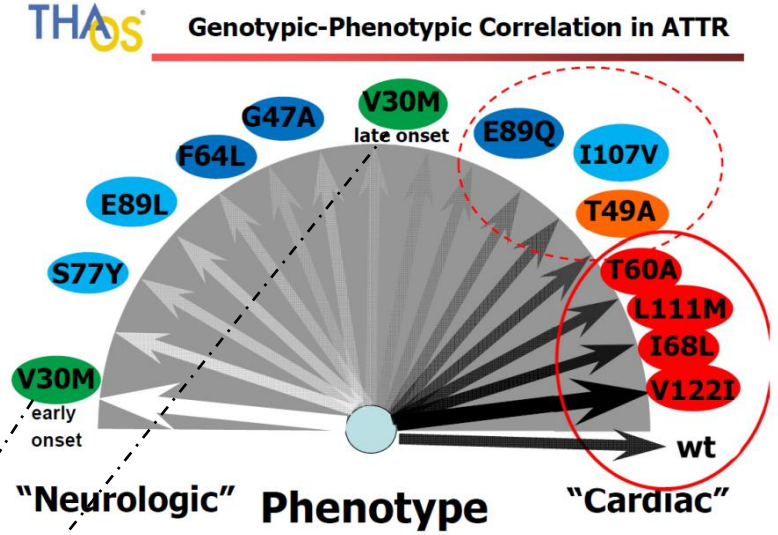
Prognóza ATTR je sice lepší než u AL, ale…

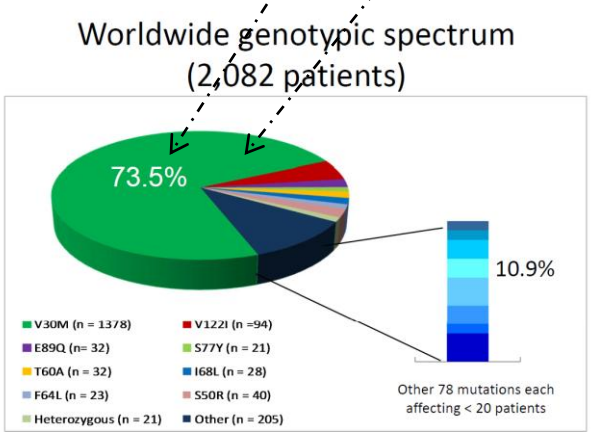
…symptomy jsou srovnatelné!



mutovaný transthyretin mATTR (familiární A)







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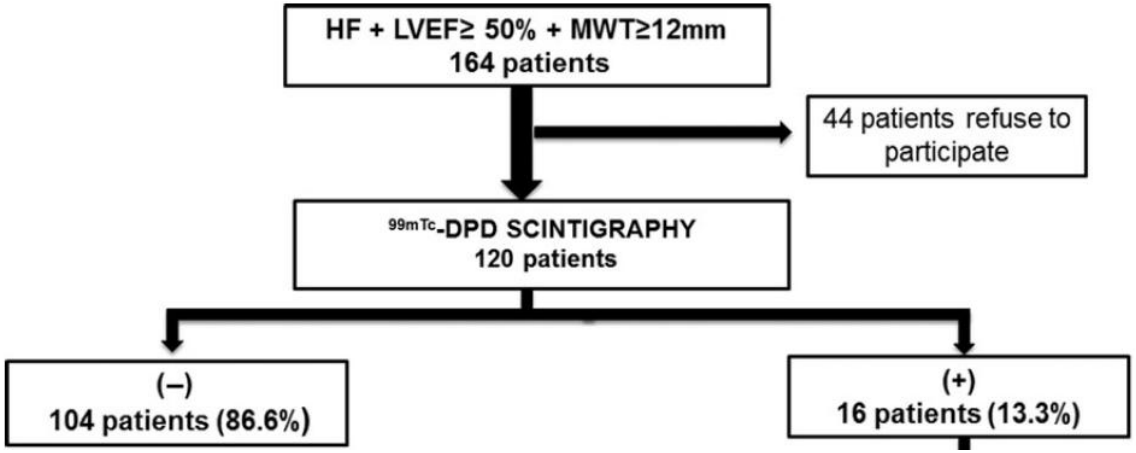
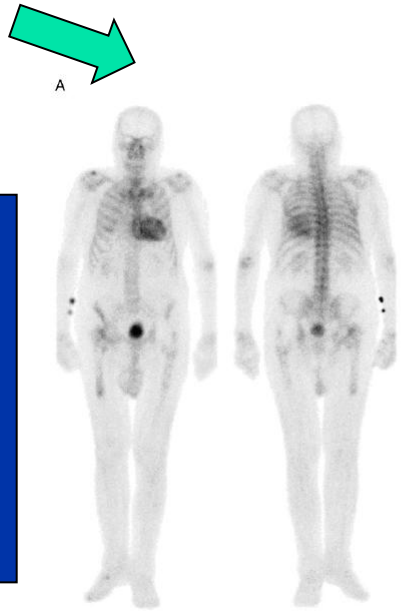
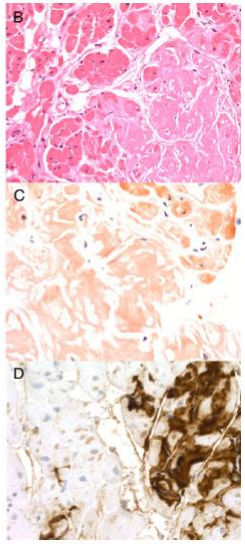
- **nemutovaný transthyretin wtATTR (senilní A)**

Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction

Esther González-López[1], Maria Gallego-Delgado[1], Gonzalo Guzzo-Merello[1], F. Javier de Haro-del Moral[2], Marta Cobo-Marcos[1], Carolina Robles[1], Belén Bornstein[3,4,5], Clara Salas[6], Enrique Lara-Pezzi[7], Luis Alonso-Pulpon[1], and Pablo Garcia-Pavia[1,7]*







- Senilní amyloidóza (wtATTR) může být častou příčinou HFpEF u starších jedinců
- Vyskytovala se u 13% nad 60 let
- **Pod-diagnostikovaná v populaci!**

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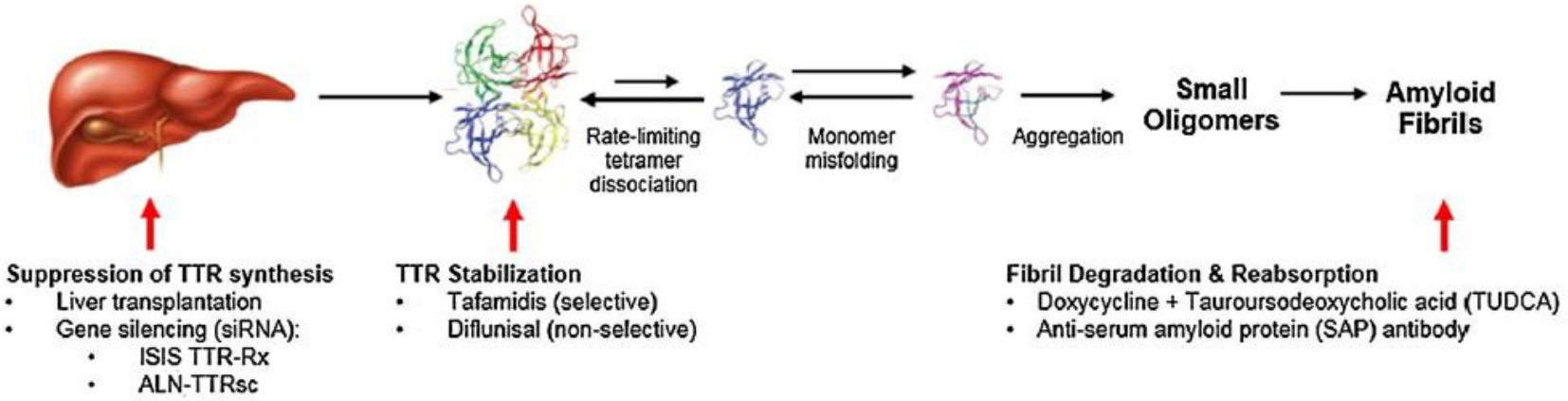
Terapie ATTR

- aktuálně pouze podpůrná léčba SS
- nové terapeutické koncepty ve fázi klinického testování

Natural history and therapy of TTR-cardiac amyloidosis: emerging disease-modifying therapies from organ transplantation to stabilizer and silencer drugs

Adam Castaño · Brian M. Drachman · Daniel Judge · Mathew S. Maurer

Heart Fail Rev (2015) 20:163–178



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Terapie ATTR

B3461028

ATTR-ACT

TRANSTHERETIN AMYLOID CARDIOMYOPATHY
TAFAMIDIS STUDY

- Tafamidis se osvědčil v léčbě TTR neuropatie
- stabilizuje tetramerickou strukturu transthyretinu, čímž zabraňuje tvorbě amyloidních fibril
- bude účinný i u ATTR-CMP ?
- …možnost kauzální terapie ATTR-CMP!

Clinical Study Outline

A Multicenter, International, Phase 3, Double-Blind, Placebo-Controlled, Randomized Study to Evaluate the Efficacy, Safety, and Tolerability of Daily Oral Dosing of Tafamidis Meglumine (PF-06291826) 20 mg or 80 mg in Comparison to Placebo in Subjects Diagnosed With Transthyretin Cardiomyopathy (TTR-CM)

Candidate Project Short Description	Tafamidis for Transthyretin Cardiomyopathy (TTR-CM)
Study Number/Name	B3461028
Phase of Development	Phase 3
Projected Timeline	Start (First Subject First Visit) : 9 December 2013 End (Last Subject Last Visit) : 5 September 2017

Study Objective(s)

The objective of this study is to determine the efficacy, safety, and tolerability of tafamidis in subjects with transthyretin cardiomyopathy.

The primary objective is to assess the efficacy, safety, and tolerability of an oral dose of 20 mg or 80 mg tafamidis meglumine soft gel capsules in comparison to placebo and given once daily, in addition to standard of care, for 30 months in subjects diagnosed with either a TTR variant or wild-type TTR-CM. The study is designed to assess the potential for benefit from treatment with tafamidis relative to placebo based on all-cause mortality and frequency of cardiovascular-related hospitalizations (including heart failure, arrhythmia, myocardial infarction, and stroke as well as other cardiovascular-related events)..

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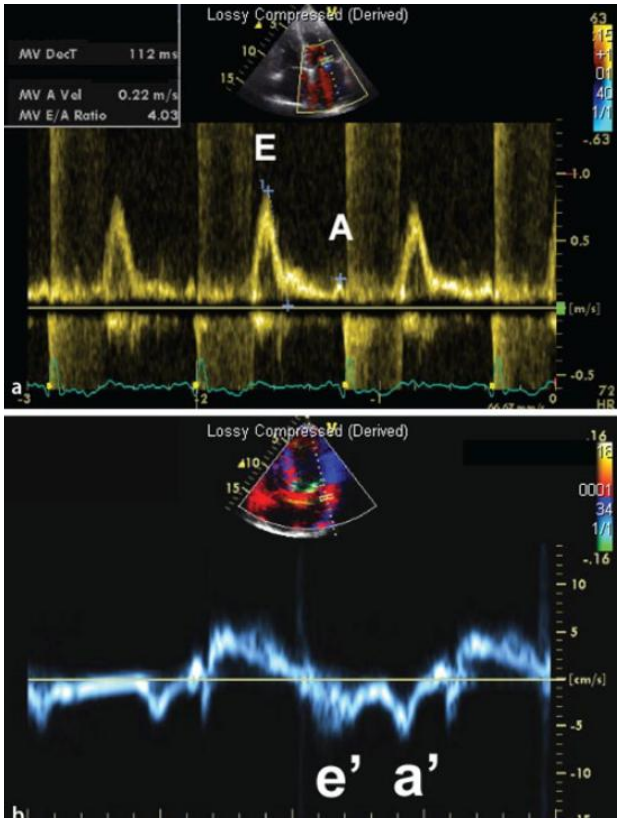
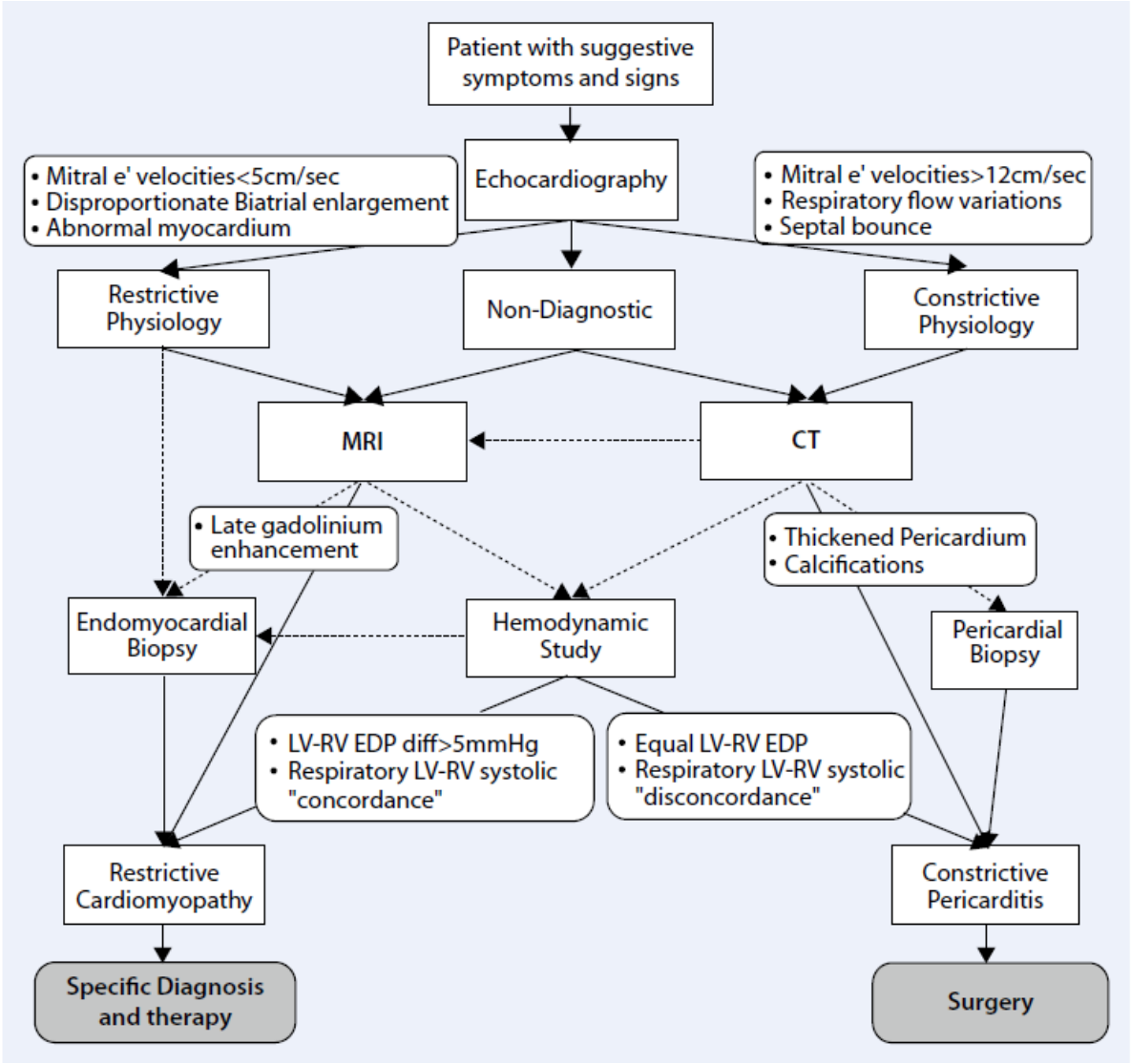
Dif. dg. RKMP a konstriktivní perikarditidy

D.R. Zwas · I. Gotsman · D. Admon · A. Keren
Heart Failure Center, Heart Institute, Hadassah University Hospital, Jerusalem

Advances in the differentiation of constrictive pericarditis and restrictive cardiomyopathy





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Dif. dg. RKMP a konstriktivní perikarditidy

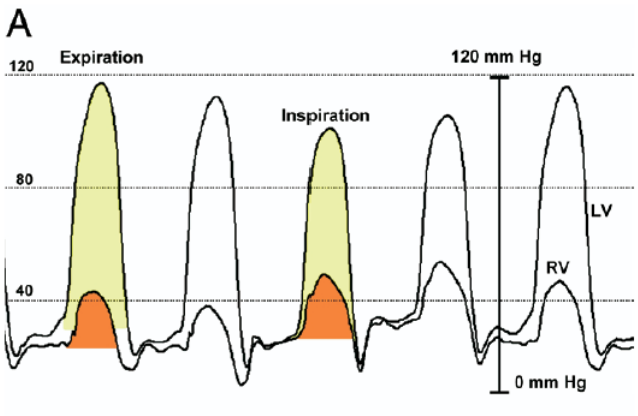
Constrictive Pericarditis in the Modern Era

Novel Criteria for Diagnosis in the Cardiac Catheterization Laboratory

Deepak R. Talreja, MD, FACC, Rick A. Nishimura, MD, FACC, Jae K. Oh, MD, FACC, David R. Holmes, MD, FACC

Rochester, Minnesota

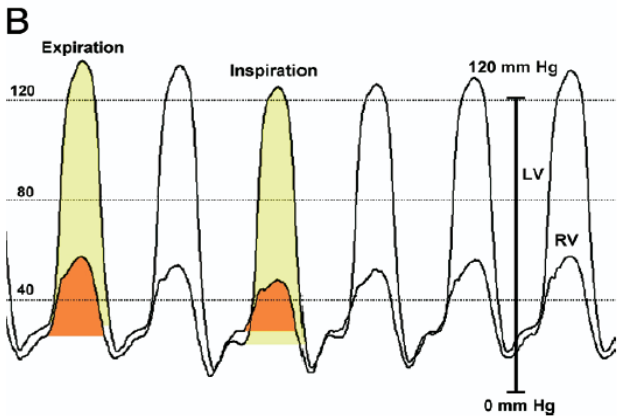
Konstriktivní perikarditis



Diskordance systolických komorových tlaků

Zvýrazněná interventrikulární dependence

Restriktivní kardiomyopatie



Konkordance systolických komorových tlaků

(J Am Coll Cardiol 2008;51:315–9)

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Závěry

- RKMP je nejméně častou KMP
- geneticky je „příbuzná“ s HKMP, v některých případech může jít o vývojovou fázi HKMP
- RKMP ≠ srdeční amyloidóza
- ta je ale nejčastější příčinou RKMP, a její výskyt (zejména wtATTR) narůstá
- AL a ATTR jsou odlišné nemoci s odlišnou léčbou – zásadní význam diferenciální diagnostiky srdečních amyloidóz
- na obzoru jsou nové terapeutické možnosti ATTR-CMP
- Dif. dg konstriktivní perikarditidy a RKMP