INTERNATIONAL CLINICAL RESEARCH CENTER

„CREATING THE FUTURE OF MEDICINE“

Transplantace srdce u AL amyloidózy

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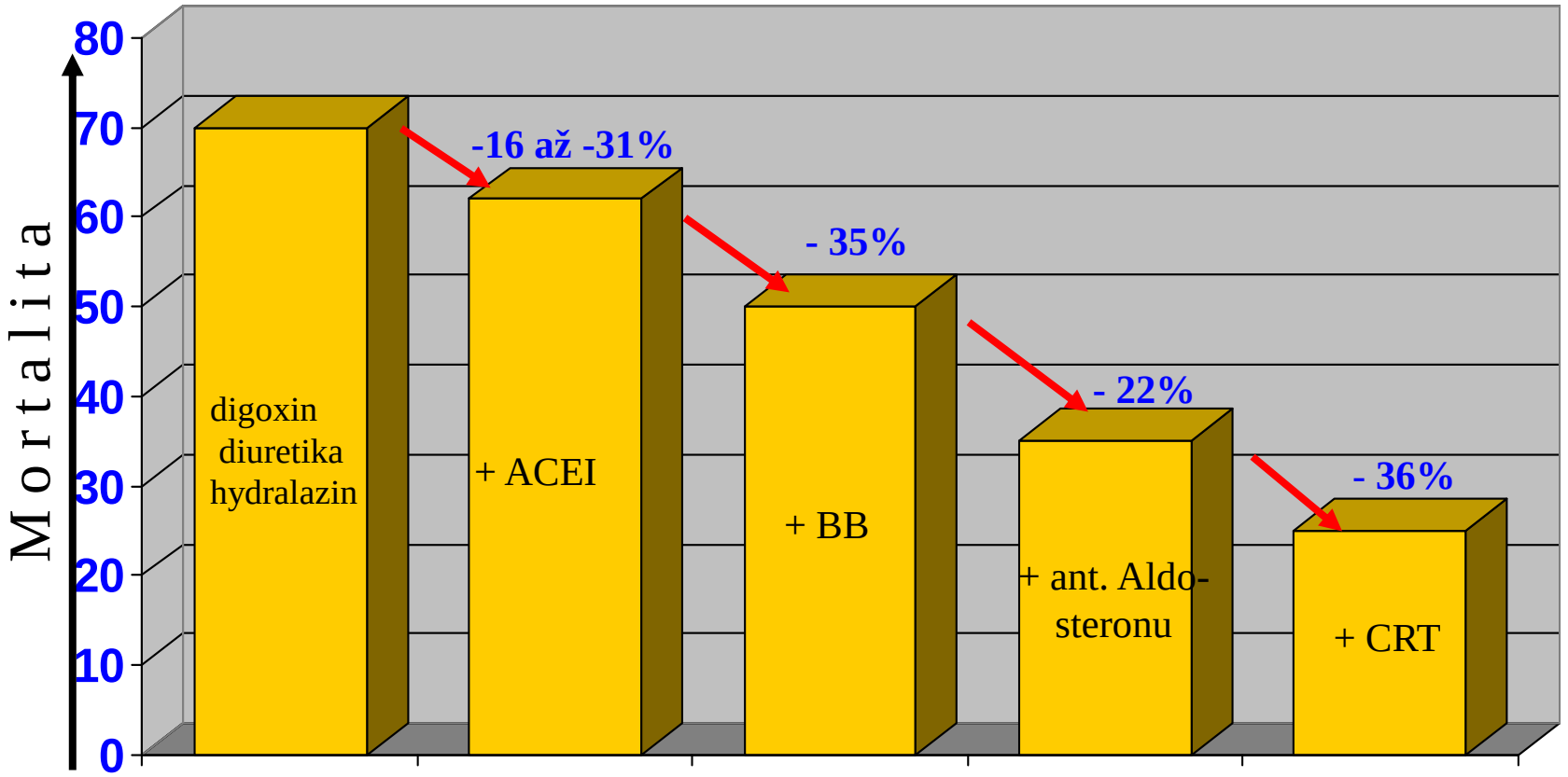
Vliv terapie na mortalitu srdečního selhání

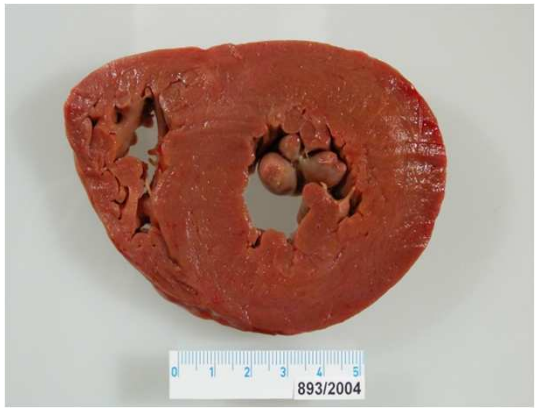


Ellenbogen KA et al. JACC 2005

Kardiomyopatie

- DKMP
- HKMP
- RKMP
- ARVC

→ **srdeční amyloidóza**



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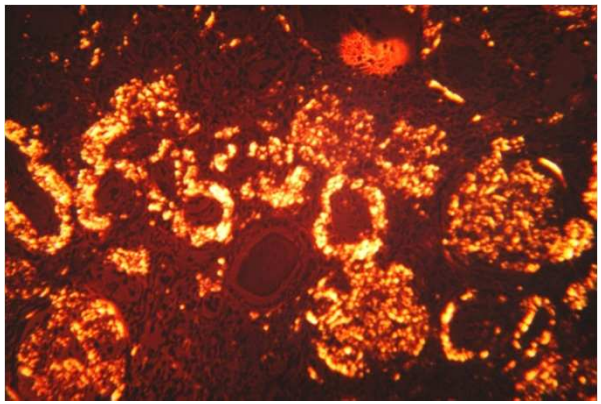
Amyloidóza

- **Incidence: 8-12/1.000 000**
- **extracelulární depozice amyloidních hmot**

- **AL amyloidóza - lehké řetězce IgG (nejčastěji lambda) – 85% srdečních amyloidóz**
- **Familiární amyloidóza – mutovaný transthyretin – 9%**
- **Senilní amyloidóza – transthyretin – 5%**
- **Sekundární amyloidóza – protein A – sporadicky**



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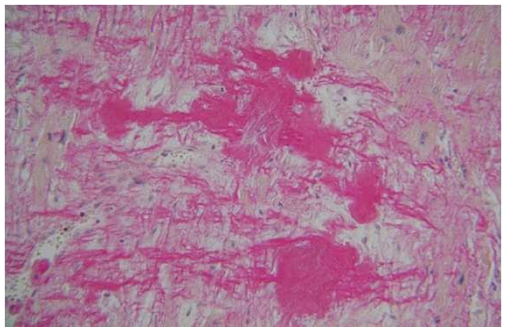
AL-A („primární A“)

- Amyloidogenním proteinem jsou nejčastěji lambda řetězce Ig – důsledek postižení plazmatických bb kostní dřeně
- postižení srdce v 60%
- manifestní srd. selhání v 25%
- multiorgánové postižení (ledviny, játra, GIT, plíce…neurovegetativní dysfunkce)



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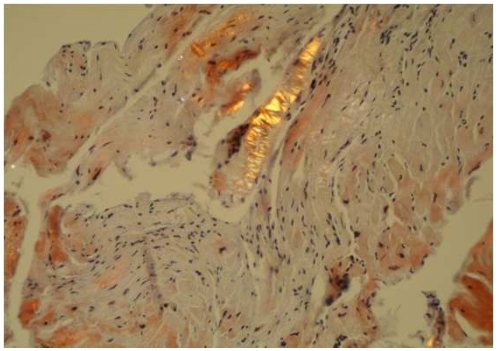
Prognóza amyloidózy

- **<u>nepříznivá u AL-A</u>**

  - v přítomnosti srdečního selhání medián přežití 5-6 měsíců !

  - 1/2 - 2/3 úmrtí mají kardiální příčinu

  (arytmická smrt - elektromechanická disociace, srdeční selhání)



- **Senilní A – medián 5 let**

- **Familiární A – až 15 let**

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Nepomohla by srdeční transplantace ?

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Izolovaná HTx

Heart Transplant. 1988 Mar-Apr;7(2):165-7.

Heart transplantation for cardiac amyloidosis: successful one-year outcome despite recurrence of the disease.

Conner R, Hosenpud JD, Norman DJ, Pantely GA, Cobanoglu A, Starr A.

Source

Cardiac Transplant Program, Oregon Health Sciences University, Portland 97201.

Abstract

Systemic amyloidosis has been considered a theoretical contraindication for heart transplantation because of the concern that amyloidosis is a systemic disease that could potentially recur in the allograft. To date, no patients have been reported to have undergone heart transplantation. One year ago a patient with amyloidosis had a transplantation at the Oregon Health Sciences University, Portland. Results of kidney, rectal, and bone marrow biopsies were normal; however, endomyocardial and gingival biopsies showed positive results for amyloidosis. Recurrence of amyloidosis was detected by electron microscopy 14 weeks after transplantation; however, light microscopy has not shown any amyloidosis at 1 year. No other organ involvement has been documented. The patient is New York Heart Association functional class I, with normal resting hemodynamic parameters 1 year after transplantation. Amyloid heart disease does not necessarily portend a poor early outcome.

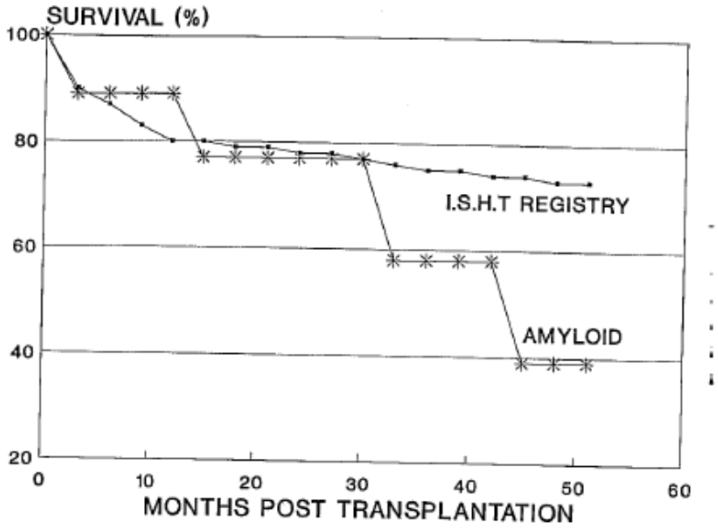
Izolovaná HTx

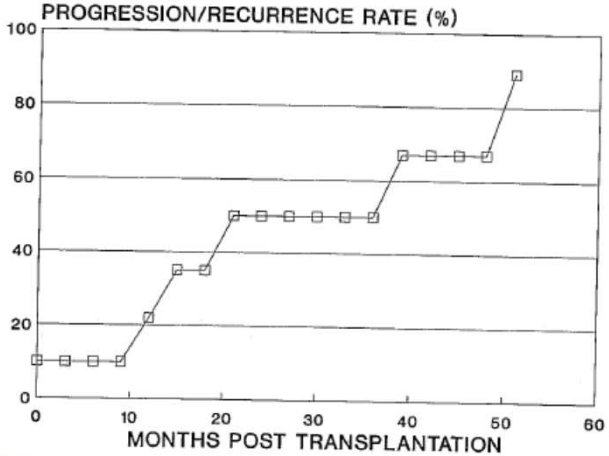
Progression of Systemic Disease and Reduced Long-term Survival in Patients With Cardiac Amyloidosis Undergoing Heart Transplantation

Follow-up Results of a Multicenter Survey

Jeffrey D. Hosenpud, MD; Teresa DeMarco, MD; O. Howard Frazier, MD; Bartley P. Griffith, MD; Barry F. Uretsky, MD; Alan H. Menkis, MD; John B. O'Connell, MD; Maria-Teresa Olivari, MD; and Hannah A. Valantine, MD

Amyloid heart disease has been considered a contraindication for cardiac transplant based on the hypothesis that it is a systemic disease and that amyloid deposition would occur in the cardiac allograft. A survey was sent to all of the US centers and a limited number of Canadian and European centers listed with the International Registry. Twenty-four centers responded, and data were ultimately provided for a total of 10 patients (3 men, 7 women, mean age 48 years, range 30–60 years) who were transplanted for cardiac amyloid. The diagnosis of cardiac amyloidosis was made histologically on endomyocardial biopsy and/or examination of the explanted heart. Additional documented organ involvement included liver (two of 10), rectal (three of 10), renal (two of 10), gingiva (two of 10), and tongue (one of 10), although invasive biopsies were not performed in a majority of patients. A specific amyloid protein was identified in eight patients (seven λ, one κ immunoglobulin light chain). Although four of the surviving nine patients (one perioperative death) developed recurrent amyloid deposition in the allograft, it was detected solely by electron microscopy in two of these and had no clinical significance. There was, however, a progressive risk of major organ involvement with organ function impairment in this group (22% at 12 months, 50% at 24 months, 66% at 48 months). Although the immediate and early postoperative outcomes were not dissimilar between this group and patients undergoing transplantation for other cardiac diseases, late survival was reduced (39% at 48 months) compared with the larger population, but differences were not statistically significant due to the small amyloid sample size (p=0.16). The majority of deaths were secondary to progressive amyloidosis. These data demonstrate that patients transplanted for systemic amyloidosis have ongoing progression of the systemic disease in other organs, despite the fact that the allograft is infrequently importantly involved. Furthermore, the data suggest that current immunosuppressive protocols do not appear to alter the progression of systemic amyloid deposition, and we currently consider systemic amyloidosis to be a contraindication to cardiac transplantation. (*Circulation* 1991;84[suppl III]:III-338–III-343)





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Izolovaná HTx

Long term results of heart transplantation in patients with amyloid heart disease

S W Dubrey, M M Burke, A Khaghani, P N Hawkins, M H Yacoub, N R Banner

Abstract

Objective—To determine the outcome of heart transplantation for end stage amyloid heart disease in patients treated at a single centre.

Design—Records of all patients with amyloid heart disease who underwent heart transplantation were examined to determine survival, graft involvement by amyloid, the course of systemic amyloid disease, and the cause of death.

Patients—10 patients, mean (SD) age 54 (8) years, received transplants in the 13 year period 1984 to 1997.

Results—Two patients, both with AL amyloid (primary systemic amyloidosis), died perioperatively. Mean follow up in the remaining eight patients was 49.9 (39.5) months (range 3–116 months). Amyloid deposits in the grafts became evident histologically in five patients with AL amyloid at 5, 11, 12, 28, and 30 months after transplantation, and in one patient with familial amyloid at 60 months. Echocardiography showed no evidence of left ventricular systolic impairment at the time of recurrence. Seven patients died, at 3, 11, 26, 32, 49, 85, and 116 months after transplantation; four of these deaths were related to amyloidosis. Actuarial survival at one and two years was 60% and at five years, 30%.

Conclusions—Heart transplantation for amyloid heart disease remains controversial because of the scarcity of hearts for transplantation, the systemic nature of amyloidosis, and the potential for amyloid deposition in the graft. Postoperative mortality was high (20%), reflecting extracardiac amyloid. Heart transplantation for end stage cardiac amyloidosis is feasible but, without treatment of the underlying process, it is a palliative procedure.

(*Heart* 2001;85:202–207)

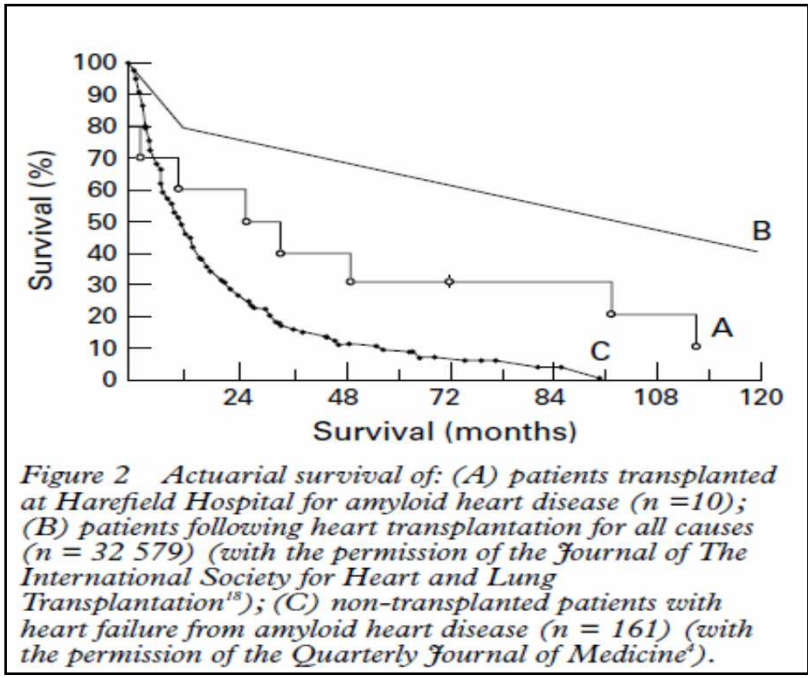


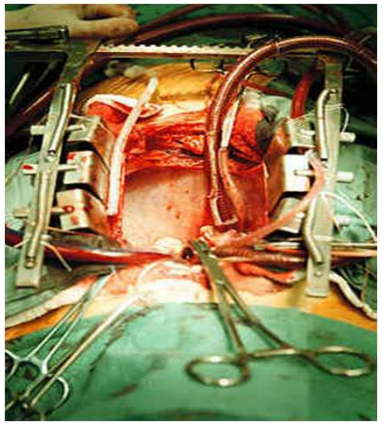
Figure 2 Actuarial survival of: (A) patients transplanted at Harefield Hospital for amyloid heart disease (n =10); (B) patients following heart transplantation for all causes (n = 32 579) (with the permission of the Journal of The International Society for Heart and Lung Transplantation[18]); (C) non-transplanted patients with heart failure from amyloid heart disease (n = 161) (with the permission of the Quarterly Journal of Medicine[4]).

Conclusions—Heart transplantation for amyloid heart disease remains controversial because of the scarcity of hearts for transplantation, the systemic nature of amyloidosis, and the potential for amyloid deposition in the graft. Postoperative mortality was high (20%), reflecting extracardiac amyloid. Heart transplantation for end stage cardiac amyloidosis is feasible but, without treatment of the underlying process, it is a palliative procedure.

HTx s následnou léčbou AL-A

➢ HTx + ASCT

- při EF LK pod 40% a NYHA III-IV je ASCT kontraindikována pro vysokou periprocedurální mortalitu
- selektovaným nemocným s izolovaně (dominantně) kardiálním postižením můžeme HTx umožnit podstoupit potenciálně kurativní léčbu AL-A



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HTx + ASCT

Brief report

Sequential heart and autologous stem cell transplantation for systemic AL amyloidosis

Julian D. Gillmore, Hugh J. Goodman, Helen J. Lachmann, Mark Offer, Ashutosh D. Wechalekar, Jayshree Joshi, Mark B. Pepys, and Philip N. Hawkins

Extensive cardiac amyloid deposition in systemic AL amyloidosis is associated with a grave prognosis. Heart transplantation is rarely performed because of the systemic and progressive nature of the disease. Patients with severe cardiac amyloid infiltration are ineligible for the preferred treatment of melphalan chemotherapy with stem cell transplantation (SCT) rescue because of the high risk for treatment-related mortality. Heart transplantation followed by SCT was performed in 5 patients with AL amyloidosis and predominant cardiomyopathy. Patients were followed up for a median of 95 months (range, 37-118 months) from diagnosis. At censor, 3 of 5 patients were well without evidence of intracardiac or extracardiac amyloid accumulation, and median overall survival by Kaplan-Meier estimate was not reached. Two patients died of progressive amyloidosis 33 and 90 months after heart transplantation after relapse of their underlying plasma cell dyscrasia. Heart transplantation followed by SCT is feasible in selected patients with cardiac AL amyloidosis and may confer substantial survival benefit. (Blood. 2006;107:1227-1229)

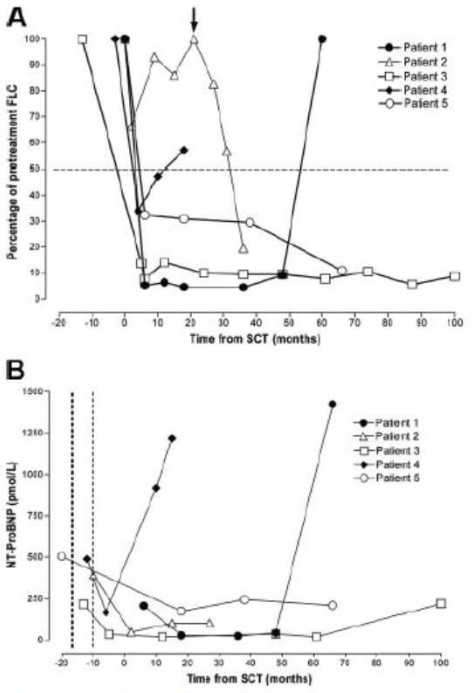

Figure 1. Serial serum FLC and NT-ProBNP concentration. Each line represents a single patient. Open symbols represent patients alive at censor; filled symbols, patients who had died. (A) Response of the FLC concentration to chemotherapy. FLC concentration decreased after SCT to less than 50% of pretreatment levels in 4 patients. Patient 3 experienced a decrease in FLC concentration after heart transplantation and before SCT that was further consolidated by SCT. Patient 2 had a poor initial FLC response to SCT and then had a relapse but responded to high-dose dexamethasone therapy (arrow). Patients 1 and 4 experienced FLC relapse associated with progressive intracardiac and extracardiac amyloid accumulation and died. (B) Serial serum NT-proBNP concentration decreased after heart transplantation (timing indicated between the dotted vertical lines) in the 4 patients in whom it was measured. Relapse of the plasma cell dyscrasia and accumulation of amyloid in the cardiac allograft and major viscera in 2 patients were associated with a marked increase in NT-ProBNP concentration and patient death.

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HTx + ASCT

Cardiac Transplantation Using Extended-Donor Criteria Organs for Systemic Amyloidosis Complicated by Heart Failure

Mathew S. Maurer, Amresh Raina, Charles Hesdorffer, Rachel Bijou, Paolo Colombo, Mario Deng, Ronald Drusin, Jennifer Haythe, Evelyn Horn, Sun Hi Lee, Charles Marboe, Yoshifumi Naka, Larry Schulman, Brian Scully, Peter Shapiro, Kenneth Prager, Jai Radhakrishnan, Susan Restaino, and Donna Mancini

Background. Systemic amyloidosis complicated by heart failure is associated with high cardiovascular morbidity and mortality. Heart transplantation for patients with systemic amyloidosis is controversial due to recurrence of disease in the transplanted organ or progression of disease in other organs.

Methods. All patients with systemic amyloidosis and heart failure referred for heart transplant evaluation from 1997 to 2004 were included in this retrospective cohort analysis. An interdisciplinary protocol for cardiac transplantation using extended-donor criteria organs, followed in 6 months by either high-dose chemotherapy and stem cell transplantation for patients with primary (AL) or by orthotopic liver transplantation for familial (ATTR) amyloidosis, was developed. Survival of the transplanted amyloid cohort was compared to survival of those amyloid patients not transplanted and to patients transplanted for other indications.

Results. A total of 25 patients with systemic amyloidosis and heart failure were included in the study; 12 patients received heart transplants. Amyloid heart transplant recipients were more likely female (58% vs. 8%, $P=0.02$) and had lower serum creatinine (1.3±0.5 vs. 2.0±0.7 mg/dL, $P=0.01$) than nontransplanted amyloid patients. Survival at 1-year after heart transplant evaluation was higher among transplanted patients (75% vs. 23%) compared to patients not transplanted ($P=0.001$). Short-term survival posttransplant did not differ between transplanted amyloid patients and contemporaneous standard and extended-donor criteria heart transplant patients ($P=0.65$).

Conclusions. Cardiac transplantation for amyloid patients with extended-donor criteria organs followed by either stem cell or liver transplantation is associated with improved survival compared to patients not transplanted. Short- to intermediate-term survival is similar to patients receiving heart transplantation for other indications. This clinical management strategy provides cardiac amyloid patients a novel therapeutic option.

Keywords: Cardiac transplantation, Amyloid, Extended donor criteria, Stem cell transplantation.

(*Transplantation* 2007;83: 539–545)

Cardiac Transplantation Using Extended-Donor Criteria Organs for Systemic Amyloidosis Complicated by Heart Failure

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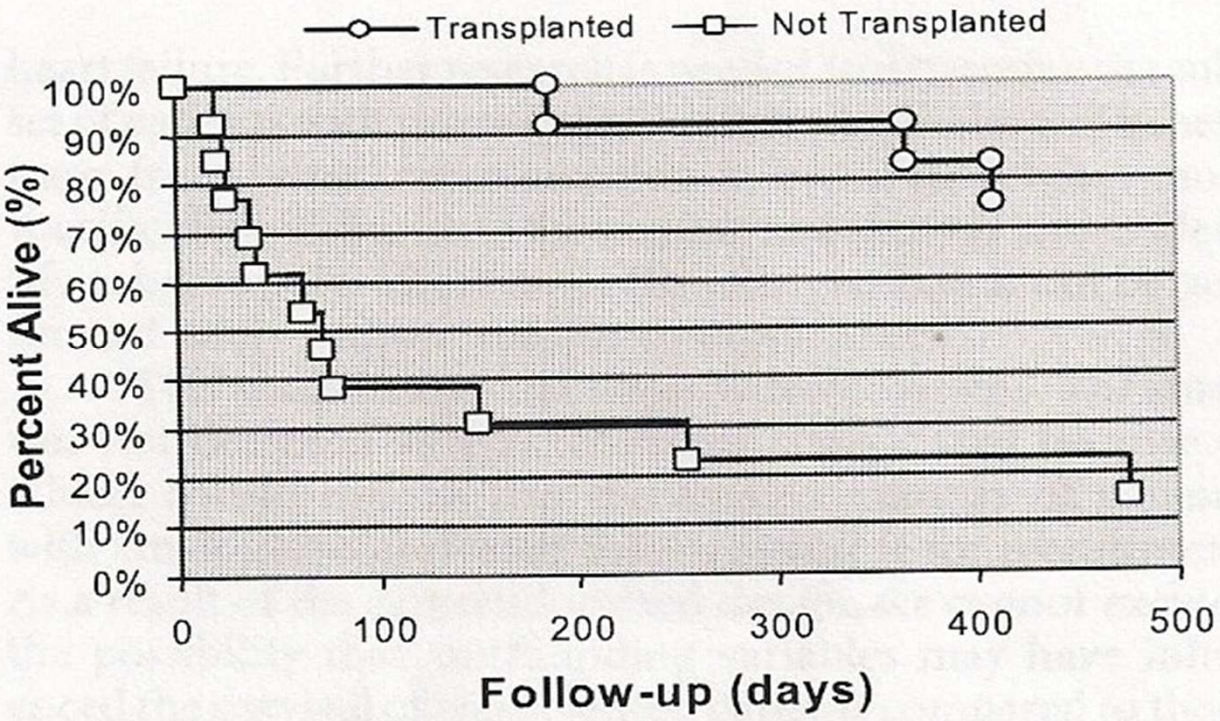

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Autologous Stem Cell Transplant after Heart Transplant for Light Chain (AL) Amyloid Cardiomyopathy

Martha Q. Lacy, MD,[a] Angela Dispenzieri, MD,[a] Suzanne R. Hayman, MD,[a] Shaji Kumar, MD,[a] Robert A. Kyle, MD,[a] S. Vincent Rajkumar, MD,[a] Brooks S. Edwards, MD,[b] Richard J. Rodeheffer, MD,[b] Robert P. Frantz, MD,[b] Sudhir S. Kushwaha, MD,[b] Alfredo L. Clavell, MD,[b] Joseph A. Dearani, MD,[c] Thoralf M. Sundt, MD,[c] Richard C. Daly, MD,[c] Christopher G. A. McGregor, MD,[c] Dennis A. Gastineau, MD,[a] Mark R. Litzow, MD,[a] and Morie A. Gertz, MD[a]

Background: Historically, patients with AL amyloidosis and overt congestive heart failure have had an ominous prognosis with median survival of approximately 6 months.

Methods: Between 1994 and 2005, 11 patients underwent sequential orthotopic heart transplantation (HT) followed by autologous peripheral blood stem cell transplantation (SCT) for treatment of AL amyloidosis. Patients were accepted for this approach if they had heart-dominant AL with minimal/no other organ impairment and no evidence of multiple myeloma. Conditioning chemotherapy consisted of melphalan 200 mg/m^2 (6 patients) or melphalan 140 mg/m^2 (5 patients).

Results: Two patients died of complications from the SCT (18% transplant-related mortality). Nine patients survived both the HT and the SCT. Three patients subsequently died from progressive amyloidosis at 66, 56.7 and 55 months after SCT. The 1- and 5-year survival for HT was 82% and 65%. The median survival was 76 months from HT and 57 months from SCT.

Conclusions: These data suggest that aggressive treatment of the underlying plasma cell clone after HT may improve long-term outcomes in patients with cardiac amyloid. HT followed by SCT is feasible and offers the possibility of remission for carefully selected patients with cardiac amyloidosis. J Heart Lung Transplant 2008;27:823–9.

Autologous Stem Cell Transplant after Heart Transplant for Light Chain (AL) Amyloid Cardiomyopathy

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Table 1. Cardiac Transplantation: pre-transplant evaluation of AL amyloid patients

Routine cardiac transplantation evaluation with the following additional studies:	• Serum protein electrophoresis • Urine protein electrophoresis (24-hour urine) • Factor X and thrombin time (special coagulation studies) • Bone marrow biopsy with aspirate, labeling index and smear • Labeling index in peripheral blood with number of circulating plasma cells • Serum carotene • β_2-microglobulin • C-reactive protein • 24-hour urine creatinine clearance • 48-hour stool collection for fat • Subcutaneous fat aspirate • Metastatic bone survey with single views of humeri and femurs
Pulmonary assessment will proceed as follows:	Recurrent pleural effusions, refractory to treatment will necessitate: • Chest CT • Possible lung biopsy dependent on CT findings
Liver assessment will proceed as follows:	• If alkaline phosphatase <1.5-fold upper limit of normal (350), then proceed with transplant evaluation • If alkaline phosphatase 1.5- to 3-fold upper limit of normal, then proceed to liver biopsy: 1. If there is portal tract amyloid deposition, then there is an absolute contraindication 2. If vascular amyloid only, then proceed with transplant evaluation • If alkaline phosphatase is ≥3.0-fold upper limit of normal (750), absolute then there is an contraindication to HT
Renal assessment will proceed as follows:	Lothalamate clearance should exceed 50 ml/min/1.73 m^2 • If urinary albumin is <250 mg/24 hours, then proceed with transplant evaluation • If urinary albumin is 250 to 1,000 mg/24 hours, then proceed to renal biopsy 1. If vascular amyloid only, is present then proceed with transplant evaluation 2. If interstitial or glomerular amyloid is present, then there is an absolute contraindication to cardiac transplant
Blood/marrow plasma cell labeling index assessment will proceed as follows:	Plasma cell labeling index • If plasma cell labeling index is ≥2%, then exclude from consideration for transplant evaluation • If plasma cell labeling index is ≥1%, then proceed to metastatic bone survey to exclude myeloma-associated bony lesions • If plasma cell labeling index is <1%, then proceed with transplant evaluation Peripheral blood labeling index • If peripheral blood plasma cell labeling index is >1%, then absolute contraindication to cardiac transplant Plasmacytosis • If plasma cell differential on marrow aspirate is <10%, then proceed with transplant evaluation • If plasma cell differential on marrow aspirate is 10% to 20%, then do metastatic bone survey to exclude myeloma-associated bony lesions • If plasma cell differential on marrow aspirate, marrow biopsy or cytoplasmic immunoglobulin–positive plasma cells are ≥20%, then contraindication to there is an absolute cardiac transplant
Intestinal assessment will proceed as follows:	• 48-hour stool collection for fecal fat to rule out malabsorption • Serum carotene if low level could indicate malabsorption • Endoscopic and flexible sigmoidoscopic evaluation with biopsy 1. If vascular amyloid deposition only, then proceed with transplant evaluation 2. If mucosal amyloid deposition, then there is an absolute contraindication to cardiac transplantation

HTx + ACST

European Journal of Heart Failure (2009) **11**, 1014–1020
doi:10.1093/eurjhf/hfp121

Staged heart transplantation and chemotherapy as a treatment option in patients with severe cardiac light-chain amyloidosis

Arnt V. Kristen[1]*, Falk-Udo Sack[2], Stefan O. Schonland[3], Ute Hegenbart[3], Burkhard M. Helmke[4], Achim Koch[2], Philipp A. Schnabel[4], Christoph Röcken[5], Stefan Hardt[1], Andrew Remppis[1], Hartmut Goldschmidt[3], Matthias Karck[2], Anthony D. Ho[3], Hugo A. Katus[1], and Thomas J. Dengler[1]

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Received 24 June 2009; revised and accepted 27 July 2009

Aims The prognosis of advanced cardiac light-chain amyloidosis is poor. Heart transplantation might enable causative therapy and ultimately improve prognosis.

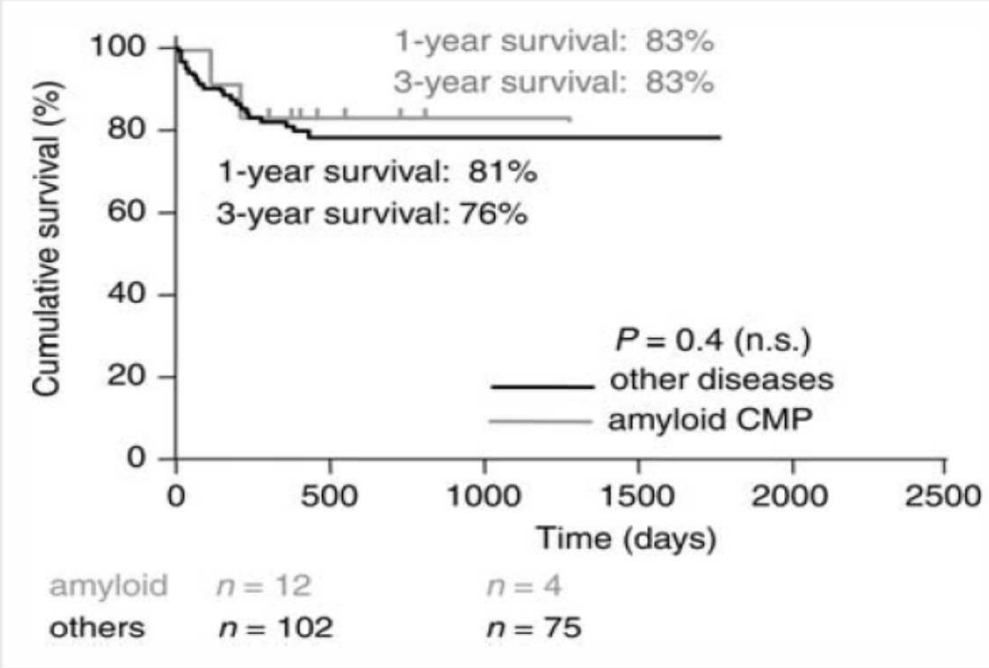
Methods and results Nineteen patients with cardiac amyloidosis but no obvious involvement of other organs were scheduled for heart transplantation. Four to 6 months later, high-dose melphalan chemotherapy and autologous stem cell transplantation (HDM–ASCT) was planned in patients not in complete remission. Seven of nineteen patients died while waiting for heart transplantation. The remaining 12 patients (complete remission, $n = 4$) underwent surgery. Chemotherapy in patients not in complete remission consisted of HDM–ASCT ($n = 5/12$; subsequent complete remission, $n = 2$; partial remission, $n = 3$) or melphalan–prednisolone (partial remission, $n = 1$). Two of twelve patients were ineligible for any chemotherapy. Three of twelve patients died [423.5 (105–2131) days] from progressive disease, relapse, or sepsis. The 1- and 3-year survival rates were 83 and 83%, respectively, similar to those of patients undergoing heart transplantation for standard indications. Corresponding survival rates stratified by haematological response were 100 and 100% for complete remission (partial remission, 100 and 100%; progressive disease, 0 and 0%).

Conclusion Heart transplantation in advanced cardiac amyloidosis is a promising approach to interrupting the vicious circle of ineligibility for potential curative chemotherapeutic treatment and extremely poor prognosis of cardiac amyloidosis without chemotherapy. Highly urgent heart transplantation combined with subsequent HDM–ASCT appears to offer a successful treatment option to improve the poor outcome of cardiac amyloidosis. However, it should be restricted to highly selected patients in specialized centres.

Keywords Amyloidosis • Autologous stem cell transplantation • Heart transplantation • Survival

Staged heart transplantation and chemotherapy as a treatment option in patients with severe cardiac light-chain amyloidosis

Arnt V. Kristen[1]*, Falk-Udo Sack[2], Stefan O. Schonland[3], Ute Hegenbart[3], Burkhard M. Helmke[4], Achim Koch[2], Philipp A. Schnabel[4], Christoph Röcken[5], Stefan Hardt[1], Andrew Remppis[1], Hartmut Goldschmidt[3], Matthias Karck[2], Anthony D. Ho[3], Hugo A. Katus[1], and Thomas J. Dengler[1]



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Cardiac Transplantation Followed by Dose-Intensive Melphalan and Autologous Stem-Cell Transplantation for Light Chain Amyloidosis and Heart Failure

Bimalangshu R. Dey,[1] Stephen S. Chung,[1] Thomas R. Spitzer,[1] Hui Zheng,[2] Thomas E. MacGillivray,[3] David C. Seldin,[4] Steven McAfee,[1] Karen Ballen,[1] Eyal Attar,[1] Thomas Wang,[5] Jordan Shin,[5] Christopher Newton-Cheh,[5] Stephanie Moore,[5] Vaishali Sanchorawala,[4] Martha Skinner,[4] Joren C. Madsen,[3] and Marc J. Semigran[5,6]

Background. Patients with light chain (AL) amyloidosis who present with severe heart failure due to cardiac involvement rarely survive more than 6 months. Survival after cardiac transplantation is markedly reduced due to the progression of amyloidosis. Autologous stem-cell transplantation (ASCT) has become a common therapy for AL amyloidosis, but there is an exceedingly high treatment-related mortality in patients with heart failure.

Methods. We developed a treatment strategy of cardiac transplant followed by ASCT. Twenty-six patients were evaluated, and of 18 eligible patients, nine patients underwent cardiac transplantation. Eight of these patients subsequently received an ASCT.

Results. Six of seven evaluable patients achieved a complete hematologic remission, and one achieved a partial remission. At a median follow-up of 56 months from cardiac transplant, five of seven patients are alive without recurrent amyloidosis. Their survival is comparable with 17,389 patients who received heart transplants for nonamyloid heart disease: 64% in nonamyloid vs. 60% in amyloid patients at 7 years (P=0.83). Seven of eight transplanted patients have had no evidence of amyloid in their cardiac allograft.

Conclusions. This demonstrates that cardiac transplantation followed by ASCT is feasible in selected patients with AL amyloidosis and heart failure, and that such a strategy may lead to improved overall survival.

Keywords: Amyloid, Cardiac amyloidosis, Stem-cell transplantation.

(*Transplantation* 2010;90: 905–911)

Cardiac Transplantation Followed by Dose-Intensive Melphalan and Autologous Stem-Cell Transplantation for Light Chain Amyloidosis and Heart Failure

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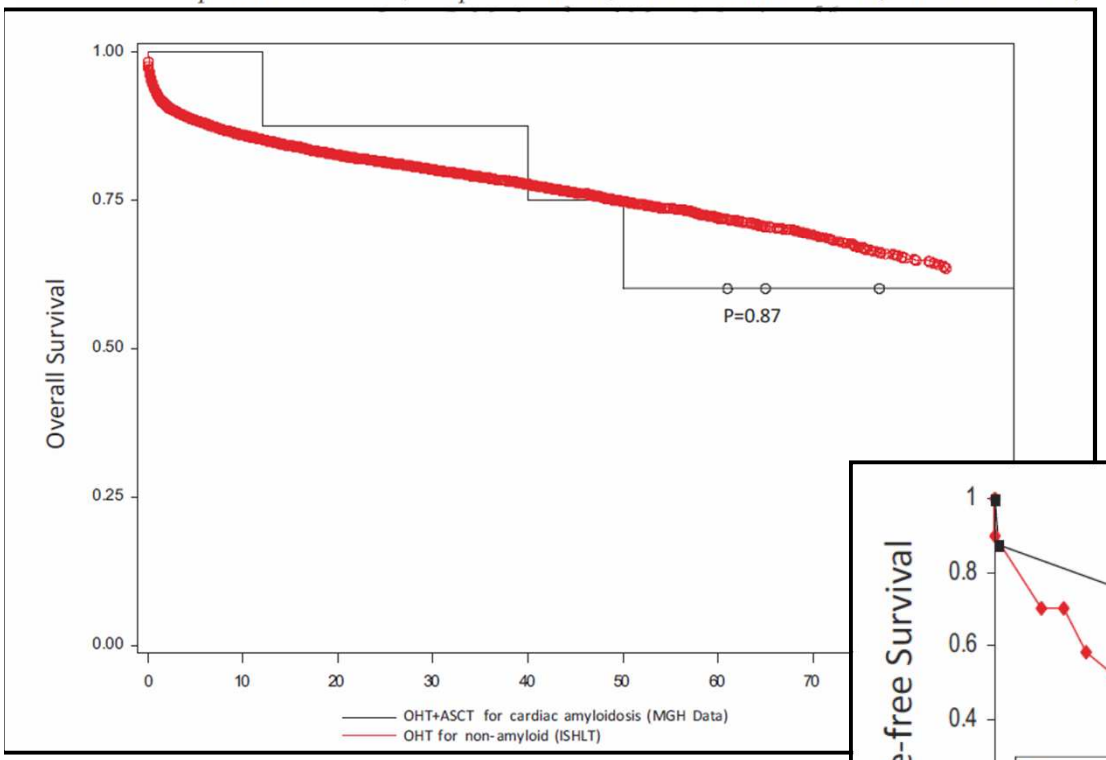

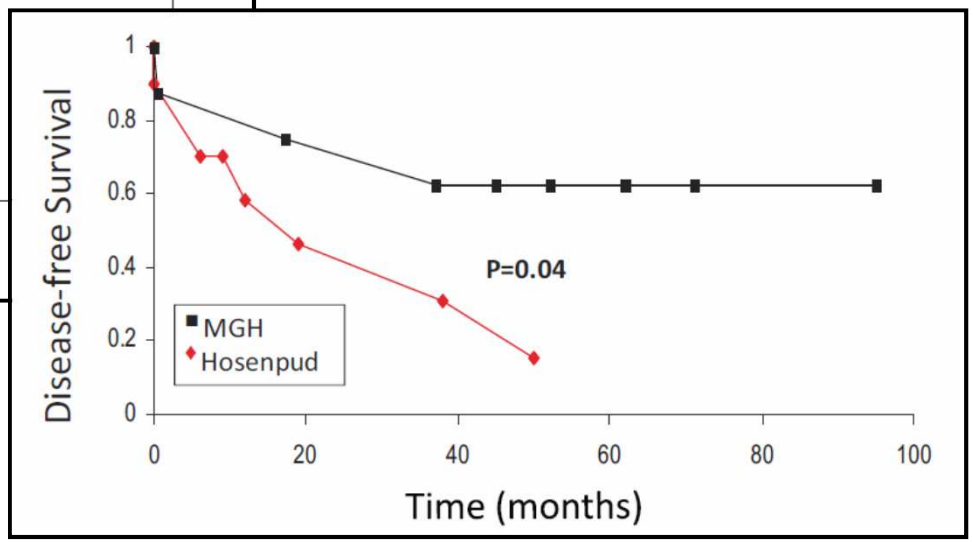

Conclusions. This demonstrates that cardiac transplantation followed by ASCT is feasible in selected patients with AL amyloidosis and heart failure, and that such a strategy may lead to improved overall survival.

Transplantace srdce a následná léčba AL-amyloidózy

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Závěry 1

- **Srdeční amyloidóza (nejčastěji AL-A) je onemocnění s extrémně nepříznivou prognózou**
- **Potencionálně kurativní léčbou je ASCT**

- **při EF LK pod 40% a NYHA III-IV je ASCT kontraindikována pro vysokou periprocedurální mortalitu**
- **jedinou možností jak umožnit radikální léčbu AL-A je předchozí HTx**
- **pečlivá selekce kandidátů – KI jsou nemocní s MM**
- **vysoká mortalita na WL**

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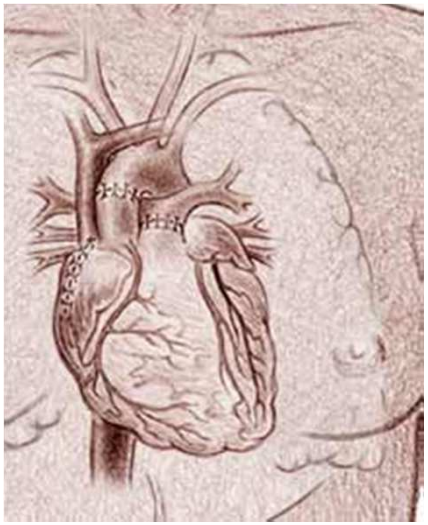
Závěry 2

- **výjimečná indikace, která ale přináší nemocnému výrazný prognostický profit**
- **nezbytná mezioborová spolupráce**
- **o dlouhodobé prognóze rozhoduje úspěch hematologické léčby, remise dosaženo v 40-60% případů**



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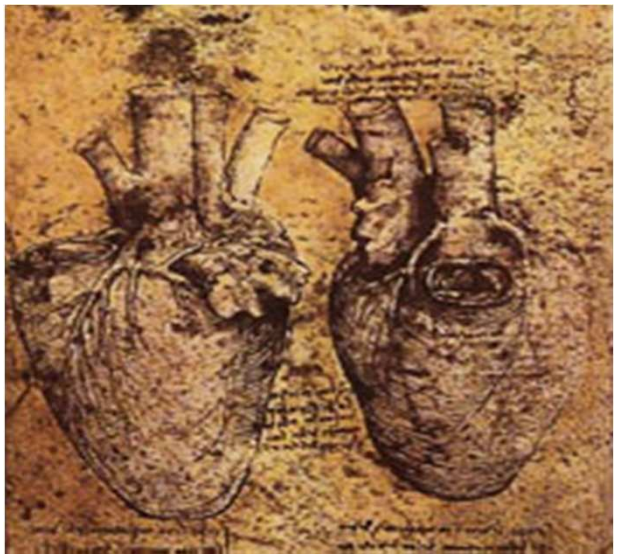

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