Myocardial involvement in patients with systemic scleroderma (SSc)

(prospective observational study)

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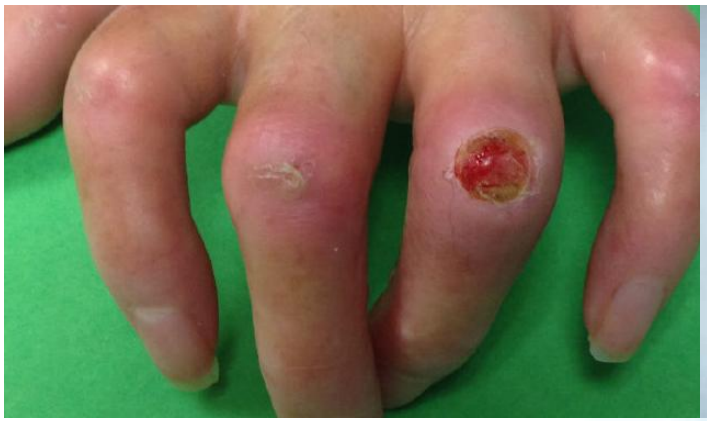
Scleroderma

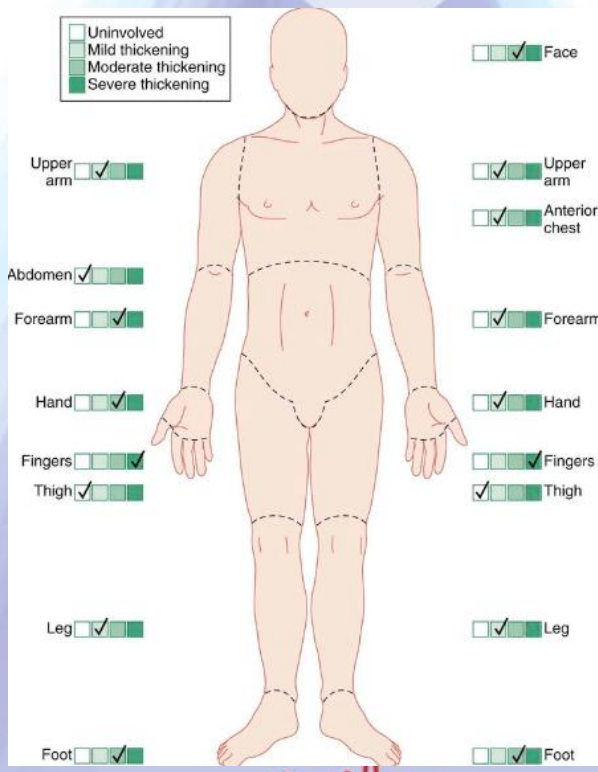
- chronic connective tissue disease
- extracellular matrix deposition
- fibrotic sclerosis of peripheral and visceral arteries
- Raynaud's phenomenon with trophic changes, stiffening of the skin and involvement of the GIT, lungs, heart and kidneys



Modified Rodnan skin score (mRSS)

- the gold standard for the clinical assessment of skin fibrosis in SSc patients
- based on a palpation method that assesses skin thickness in combination with skin tethering at 17 anatomical sites on the body
- clasification from 0-3

mRSS	
0	uninvolved/normal skin
1	skin is harder to grasp, when grasped, a skin fold is formed, mild thickening
2	skin forms the skin fold, when grasped, but is definitely thicker
3	severe thickening of the skin, skin does not form a skinfold



Cardiac complications of SSc

- low prevalence, but negative prognostic impact
- mortality from cardiac causes approx. 26%
- PAH prevalence 12%
- pericarditis 7-20%
- conduction disorders
- myocardial fibrosis not corresponding to typical coronary artery localization
- recurrent ischemia with subsequent reperfusion abnormalities → cardiac insufficiency

Study 2015

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Myocardial fibrosis detected by magnetic resonance in systemic sclerosis patients – Relationship with biochemical and echocardiography parameters

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ABSTRACT

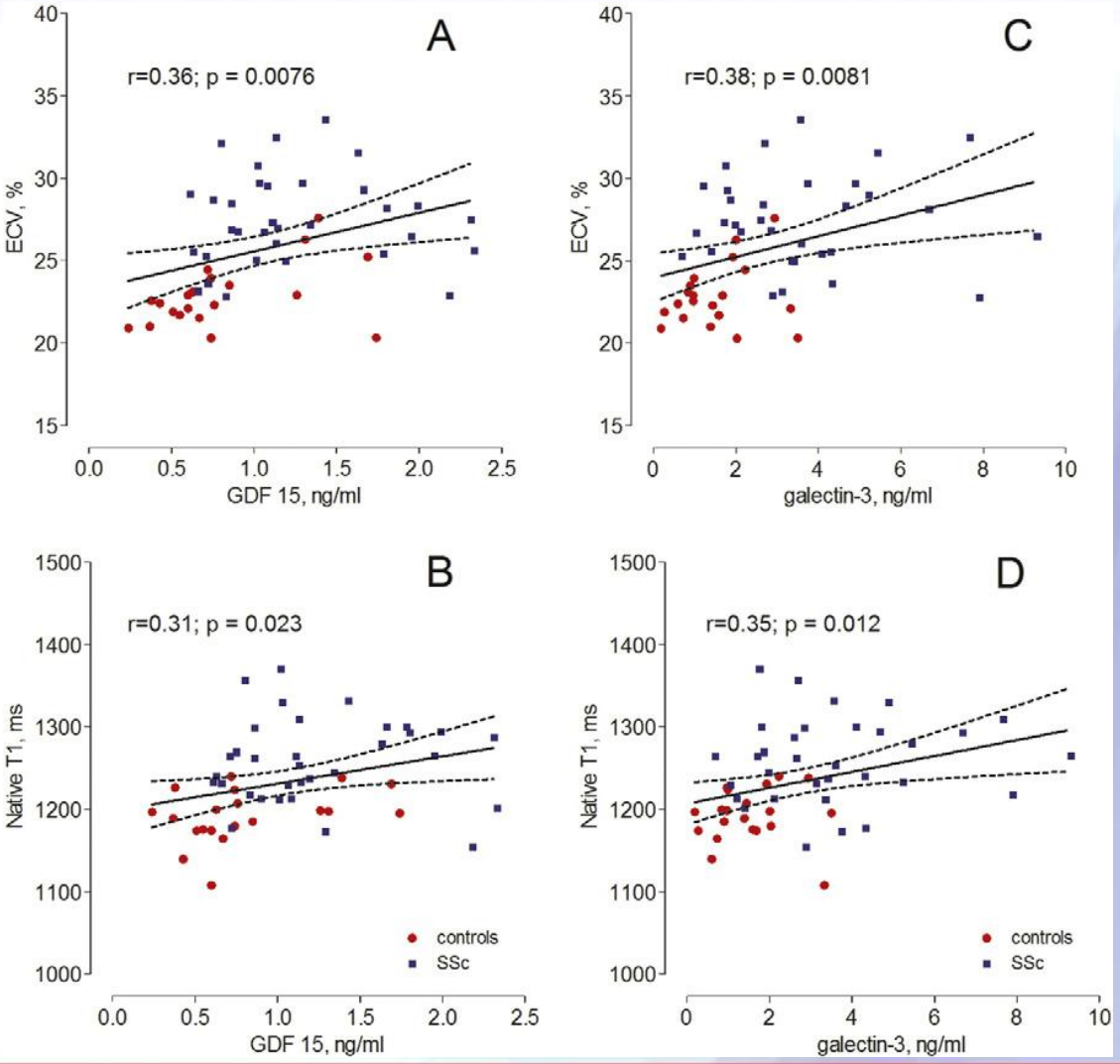
Objectives: Systemic scleroderma (SSc) is a rare connective tissue disease presenting with fibrosis affecting skin and internal organs. Cardiovascular magnetic resonance (CMR) with quantification of extracellular volume (ECV) and T1 mapping might help to detect heart involvement. We aimed to evaluate whether myocardial involvement correlates with functional and laboratory parameters.

Methods: Thirty-three asymptomatic SSc patients (29 women, aged 56.6 ± 12.2 years) and 20 controls (10 women, 53.7 ± 13.1 years) were examined using CMR, echocardiography, functional pulmonary test and laboratory assessment.

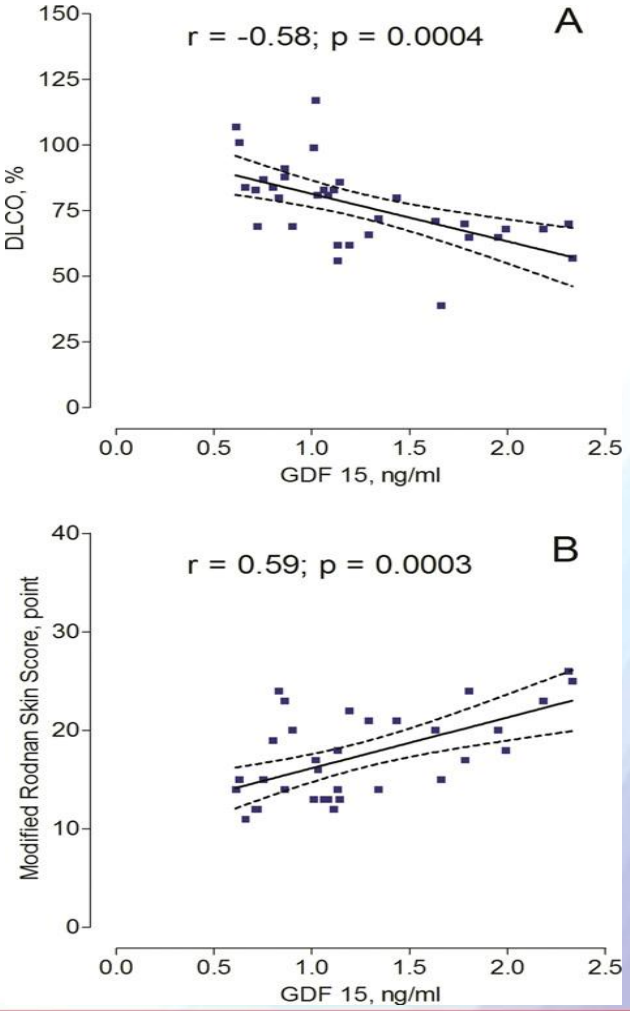
Results: SSc patients had higher ECV (27.5 ± 2.8 vs. 22.8 ± 1.9%, P < 0.0001) and native T1 values (1258.9 ± 51.2 vs. 1192.2 ± 32.6, P < 0.0001) compared to controls. Plasma level of growth differentiation factor 15 (GDF-15) and galectin-3 correlated with ECV (r = 0.35; P = 0.0076 and r = 0.38; P = 0.0081) and native T1 (r = 0.31; P = 0.023 and r = 0.35; P = 0.012). GDF-15 was also negatively correlated with diffusing capacity of the lung for carbon monoxide (r = −0.58; P = 0.0004) and positively correlated with modified Rodnan skin score (r = 0.59; P = 0.0003). Conventional echocardiography parameters were similar in SSc patients and controls. However, the global longitudinal peak systolic strain (GLPS) was lower in SSc patients compared to controls (18.6 ± 1.6 vs. 21.1 ± 1.2%; P < 0.0001). GLPS also negatively correlated with native T1 (r = −0.35; P = 0.0097), ECV (r = −0.33; P = 0.014), GDF 15 (r = −0.31; P = 0.022), and galectin-3 (r = −0.37; P = 0.0076).

Conclusions: Asymptomatic heart involvement is common in SSc patients and includes focal and diffuse myocardial fibrosis. GDF-15 and galectin-3 were positively correlated with myocardial fibrosis parameters. Future outcome studies must show whether measurement of GDF-15 and galectin-3 in SSC patients might be may be useful in clinical practice.

GDF-15, galectin-3 a ECV, nativ T1



GDF-15 a DLCO, Rodnan Skin Score



Clinical outcome

- patients with SSc had higher values of ECV and T1 nativ
- correlation of MR parameters with the degree of skin involvement
- correlation of MR parameters with levels of GDF 15 and galectin-3
- GDF-15 corelated with with the degree of skin involvement and DLCO

- Screening testing for GDF 15 a galectin-3 ?
- trend of the disease ?

Goal of the study

- assessment of the trend of myocardial damage by MRI with a 5-year interval
- correlation with biomarkers: hsTnI, NT-proBNP, galectin-3, sST2, GDF-15
- Echocardiography
- pulmonary function tests including DLCO *(Diffusing Capacity of Lung for Carbon Monoxide)*

Surveyed cohort

- 25/33 patients with SSc diagnosis according to American College of Rheumatology who underwent a baseline study in 2015
- 8 patients could not be reevaluated
- Reasons for exclusions: pregnancy (1 patient), death due to malignancy (2 pts), stroke (1pt.), imobility (1pt.), refusal to follow-up (3 pts)

Exclusion criteria

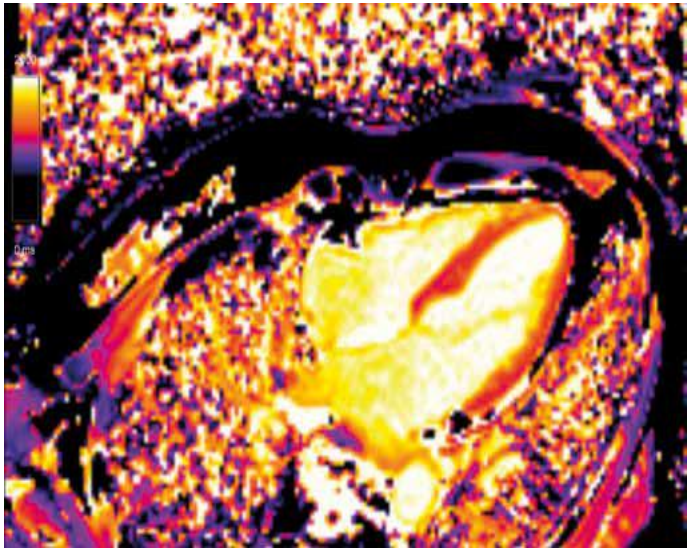
- current or past cardiac disease
- PAH
- contraindications to perform MRI
- contraindications for administration of Gd contrast agent
- renal dysfunction with GF < 30ml/min
- pregnancy or brest feeding

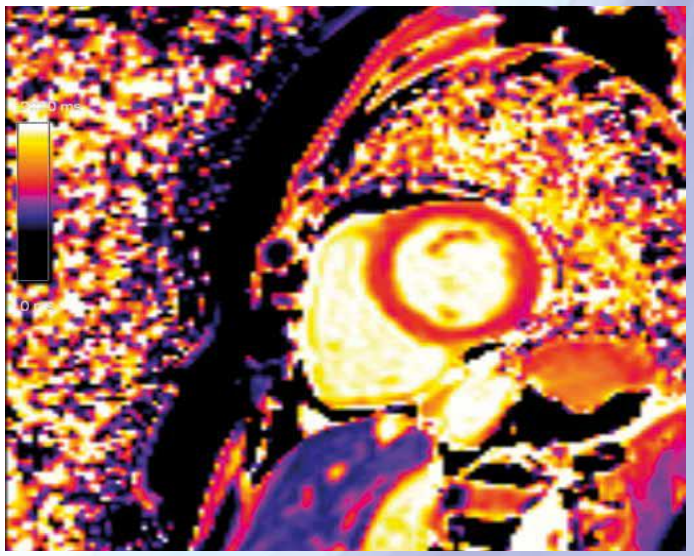
MRI

- 3 T MR device (MAGENTOM Skyra, Siemens Healtcare, Forcheheim, Germany)..32 element surface coil for thorax and body
- T1 mapping using MOLLLI (Modified Look-Locker Inversion Recovery)
- Four-chamber projection and short axis from base to apex before and after Gd administration (12 min apart)

T1 mapping technique

- colour maps of T1 relaxation time (ms)
- pixel-based parametric imaging
- higher values for edema and connective tissue transformation





Source: prof. MUDr. J.Baxa, Ph.D., University Hospital Pilsen

Measurement of T1 relaxation time before and after Gd

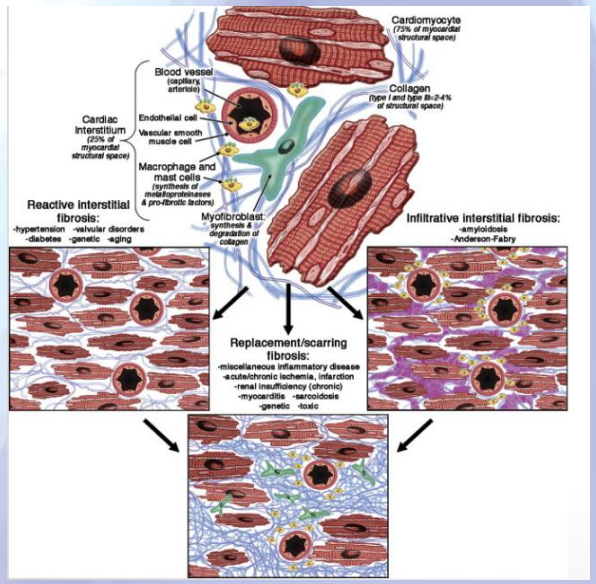
- using a region of interest (ROI)
- ROI placed manually in the intramyocardial part of the LV septum, main values from basal, mid-ventricular and apical

Source: prof. MUDr. J.Baxa, Ph.D., University Hospital Pilsen

Extracelular volume

- increase in ECV (%) during fibrotic transformation
- calculation from T1 maps (before and after contrast + HCT)

$$\text{ECV (\%)} = \frac{(1-HTK)\ x\ \left(\frac{1}{T1\ (Gd)} - \frac{1}{T1\ (nat)}\right)}{\frac{1}{T1\ (Gd)} - \frac{1}{T1\ (nat)}}$$



Cohort of patients

	Baseline	Follow-up	P
Systolic blood pressure, mm Hg	134.8 ± 17.4	135.6 ± 14.8	0.6800
Diastolic blood pressure, mm Hg	82.6 ± 9.5	82.0 ± 9.3	0.7200
BMI, kg/m^2	26.1 ± 4.4	26.7 ± 4.5	0.0090
Medication			
Use of RAAS blockers	0 (0.0)	12 (48.0)	**<0.001**
Corticosteroids	16 (64.0)	16 (64.0)	1.0000
Anti-rheumatic drugs	13 (52.0)	14 (56.0)	0.9870
Disease severity markers			
mRSS, points	17.3 ± 4.3	17.9 ± 4.4	**0.0020**
DL_{CO}, %	80.7 ± 15.1	77.7 ± 13.9	**0.0043**
CMR			
Native T1, ms	1253.4 ± 56.8	1251.5 ± 64.6	0.9500
ECV, %	0.28 ± 0.03	0.29 ± 0.04	0.0730
ECHO			
LVEF, %	63.1 ± 2.1	62.8 ± 2.5	0.5790
E/e´	9.26 ± 3.1	10.24 ± 4.8	0.3098
Biomarkers			
hsTnI, ng/l	3.0 (2.0–5.8)	2.8 (2.2–8.7)	0.4800
NT-proBNP, ng/l	141.88 ± 102.87	194.12 ± 218.46	0.6567
Galectin-3, ng/ml	3.45 ± 1.88	3.51 ± 1.80	0.7000
sST2, ng/ml	1358.6 ± 410.2	1645.8 ± 725.0	**0.0078**
GDF 15, pg/ml	1042 (791–1525)	1299 (1061–1843)	**0.0046**

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Change trends after 5 years

Changes in	Native T1	ECV	DL_{CO}	mRSS
hsTnI P	0.14 0.52	0.05 0.83	-0.11 0.60	0.15 0.48
Galectin-3 P	0.56 **0.0050**	0.71 **0.0001**	-0.12 0.57	0.06 0.77
sST2 P	0.05 0.83	0.07 0.75	-0.09 0.68	0.14 0.51
GDF 15 P	0.23 0.29	0.25 0.24	-0.51 **0.011**	0.63 **0.0009**
NT-proBNP P	-0.0739 0.73	0.0569 0.79	-0.1005 0.63	0.3819 0.059

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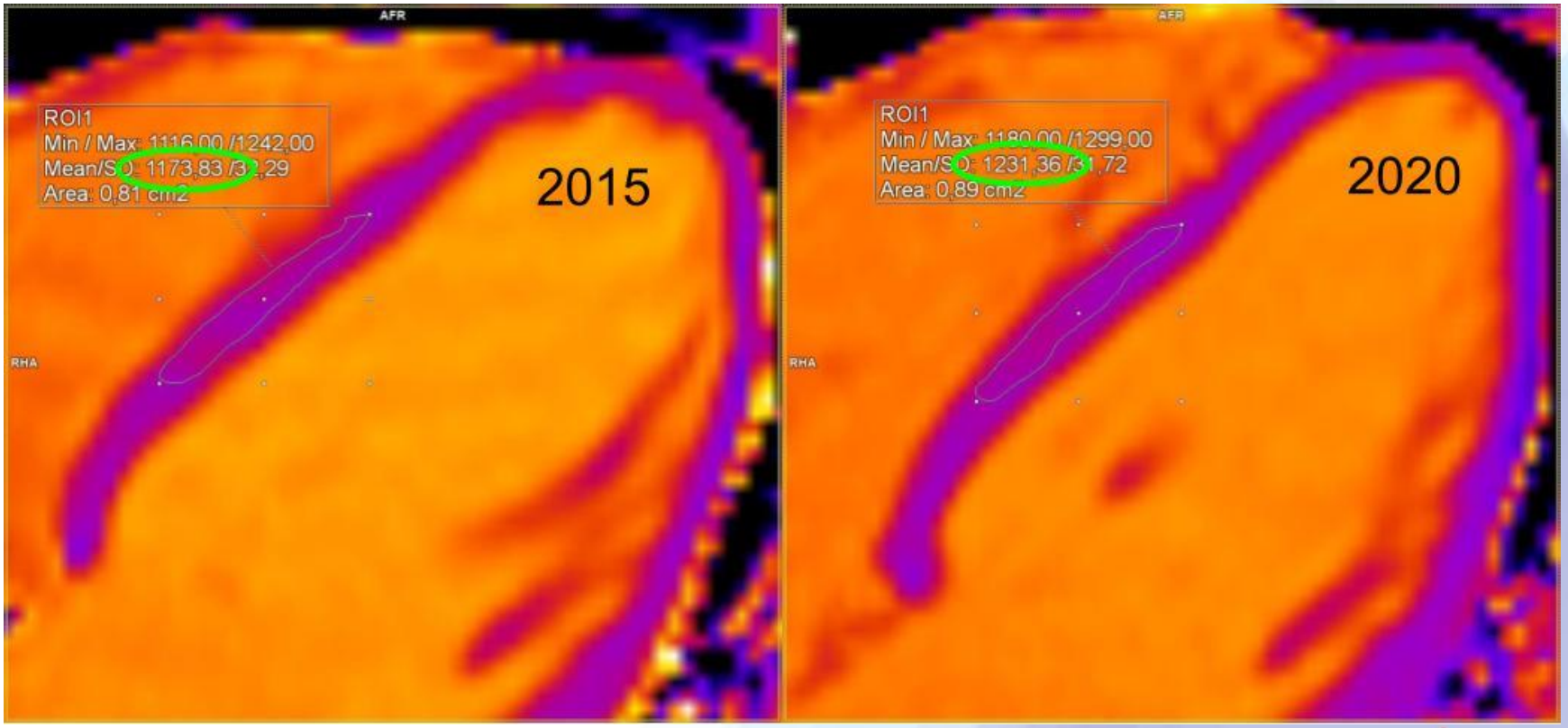
T1 mapping



zdroj prof. MUDr. J.Baxa, Ph.D FN Plzeň

Therapy with RAAS blocators

Changes in	RAAS blockers 0 n = 13	RAAS blockers 1 n = 12	P
native T1, ms	4.28 ± 36.5	-8.47 ± 46.8	0.30
ECV, %	0.023 ± 0.025	0.005 ± 0.043	0.073
galectin-3, ng/ml	1.35 ± 1.90	-1.31 ± 2.07	**0.0068**
GDF 15, ng/ml	522.8 ± 718.5	221.0 ± 518.8	0.30
sST2, ng/ml	492.37 ± 459.75	82.16 ± 484.61	**0.015**
hsTnI, ng/l	-2.20 ± 30.73	-3.71 ± 11.01	**0.023**
NT-proBNP, ng/l	130.30 ± 268.95	32.67 ± 135.25	0.16

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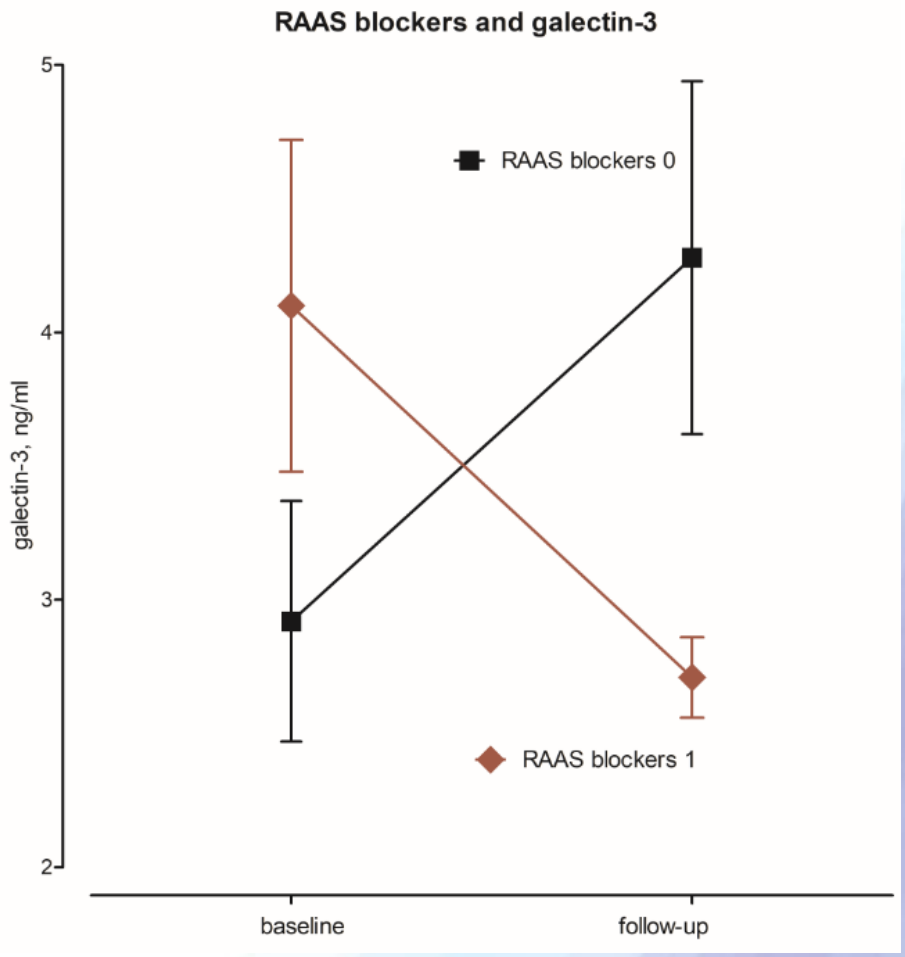
RAAS blocators and galectin-3



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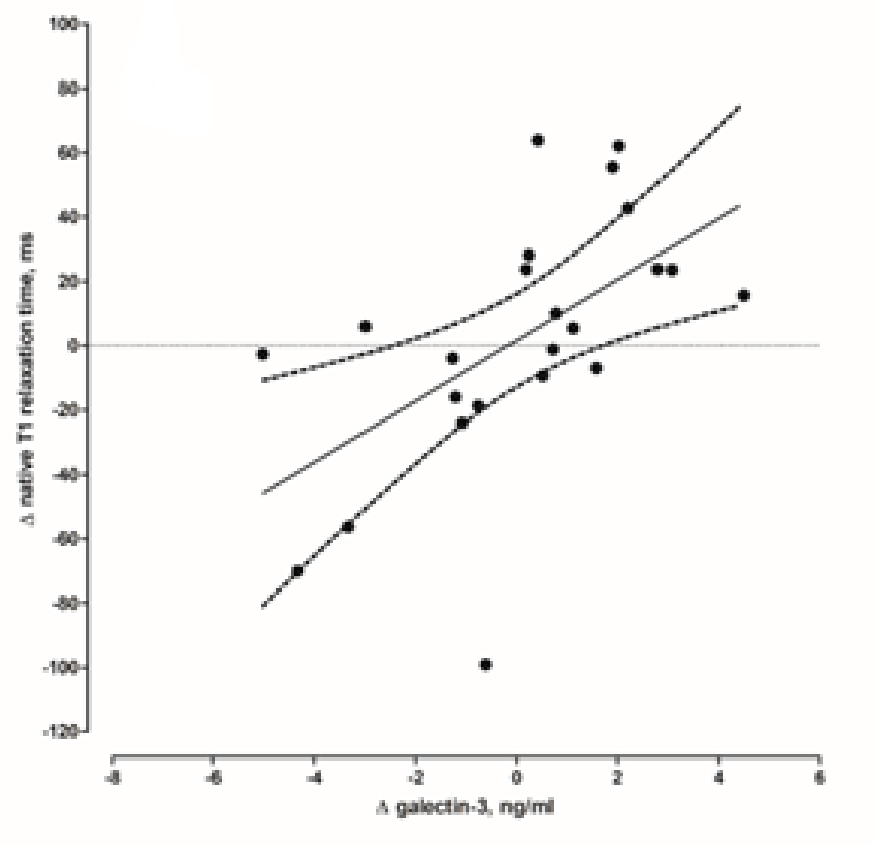
Δ galectinu-3 and T1-mapping



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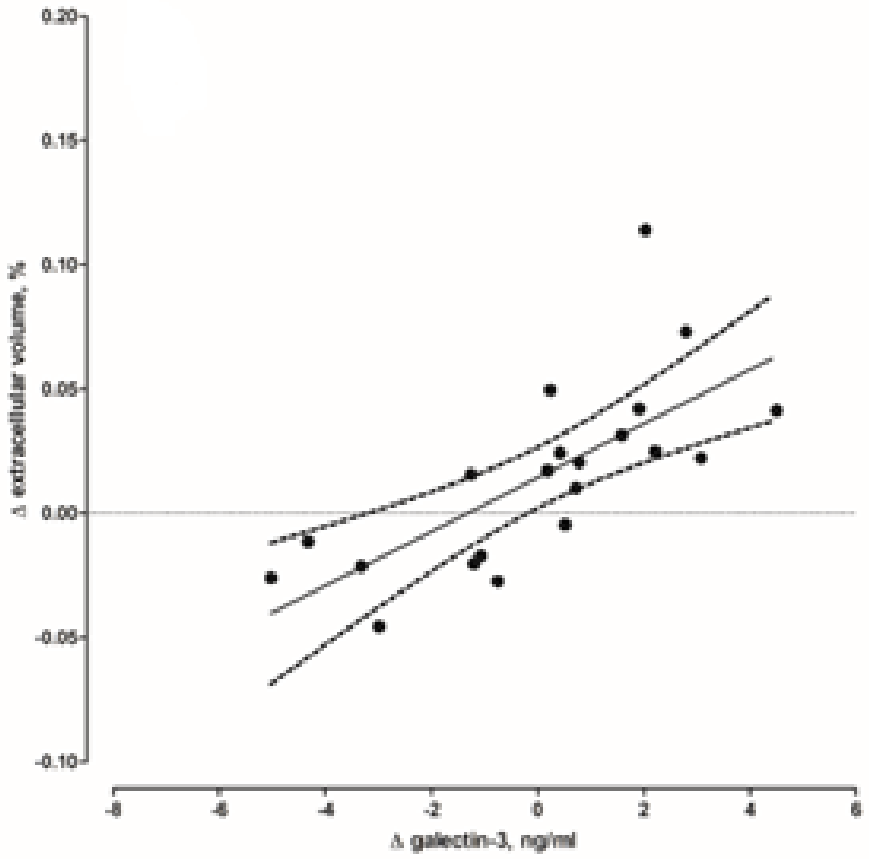
Δ galectinu-3 and ECV



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Conclusion

- Progression of subclinical myocardial fibrosis significantly correlates with galectin-3 elevation
- GDF-15 is associated with progression of skin involvement and decrease in DLCO
- RAAS inhibitor treatment correlates with galectin-3, hsTnI and sST2 levels
- Modulation of the fibrotic process by RAAS blockers ?

Thank you for your attention