

Kardiorenální problematika v experimentu, modely

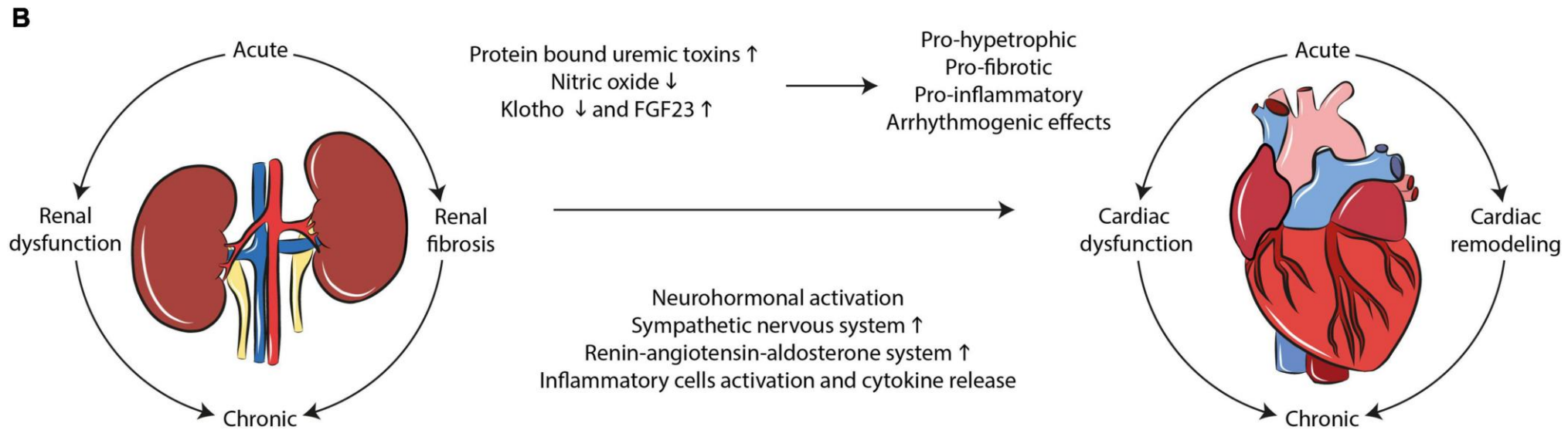
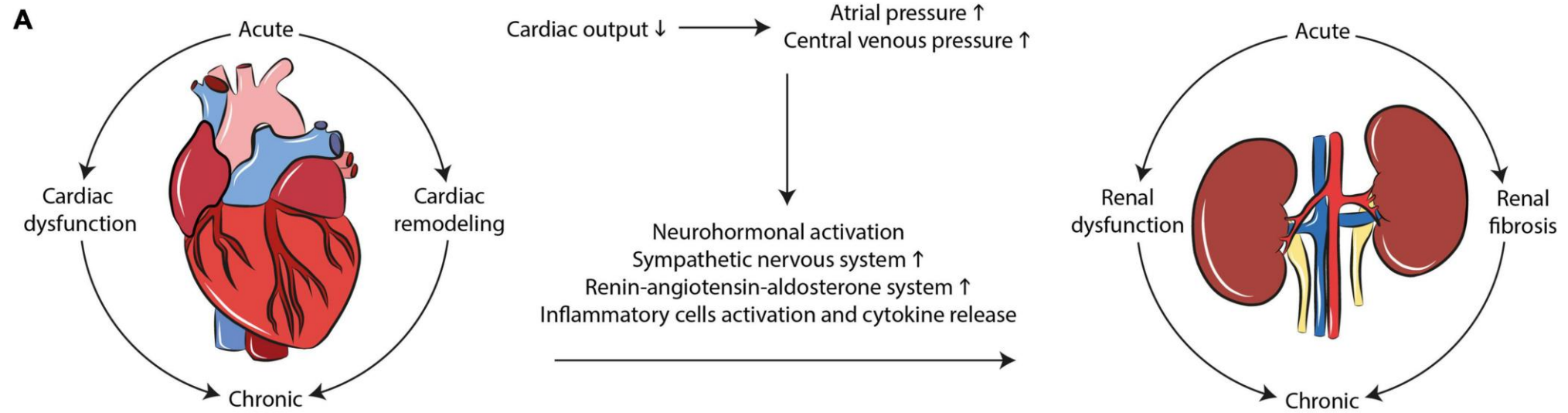


RNDr. Matúš Miklovič, PhD.

IKEM
CEM
LMEK



KLINICKÁ FYZIOLOGIE KARDIOVASKULÁRNÍHO A RENÁLNÍHO SYSTÉMU – OD TEORIE K PRAXI



CRS Type I (Acute cardiorenal syndrome)

Abrupt worsening of cardiac function leading to acute kidney injury

CRS Type II (Chronic cardiorenal syndrome)

Chronic abnormalities in cardiac function (e.g. chronic congestive heart failure) causing progressive and permanent chronic kidney disease

CRS Type III (Acute renocardiac syndrome)

Abrupt worsening of renal function (e.g. acute kidney ischaemia or glomerulonephritis) causing acute cardiac disorders (e.g. heart failure, arrhythmia, ischemia)

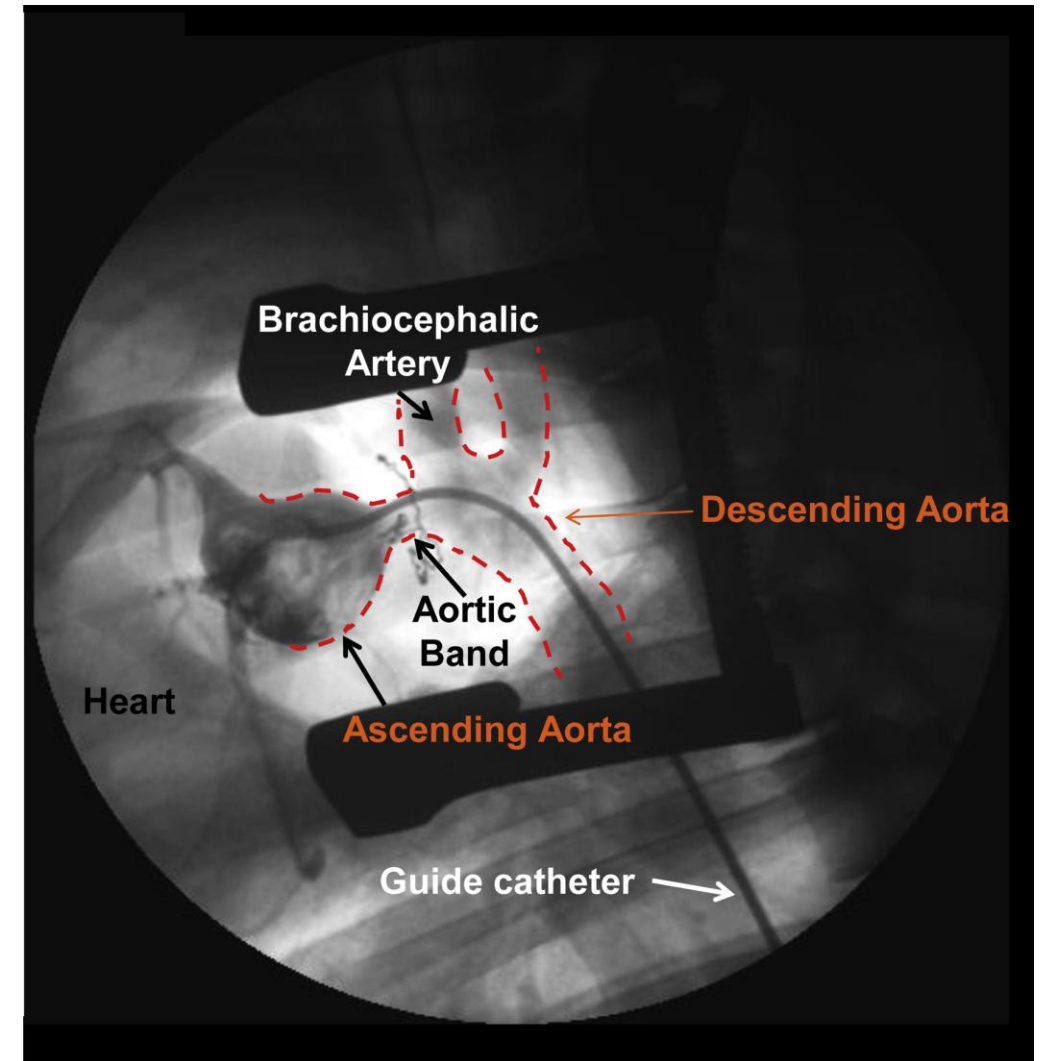
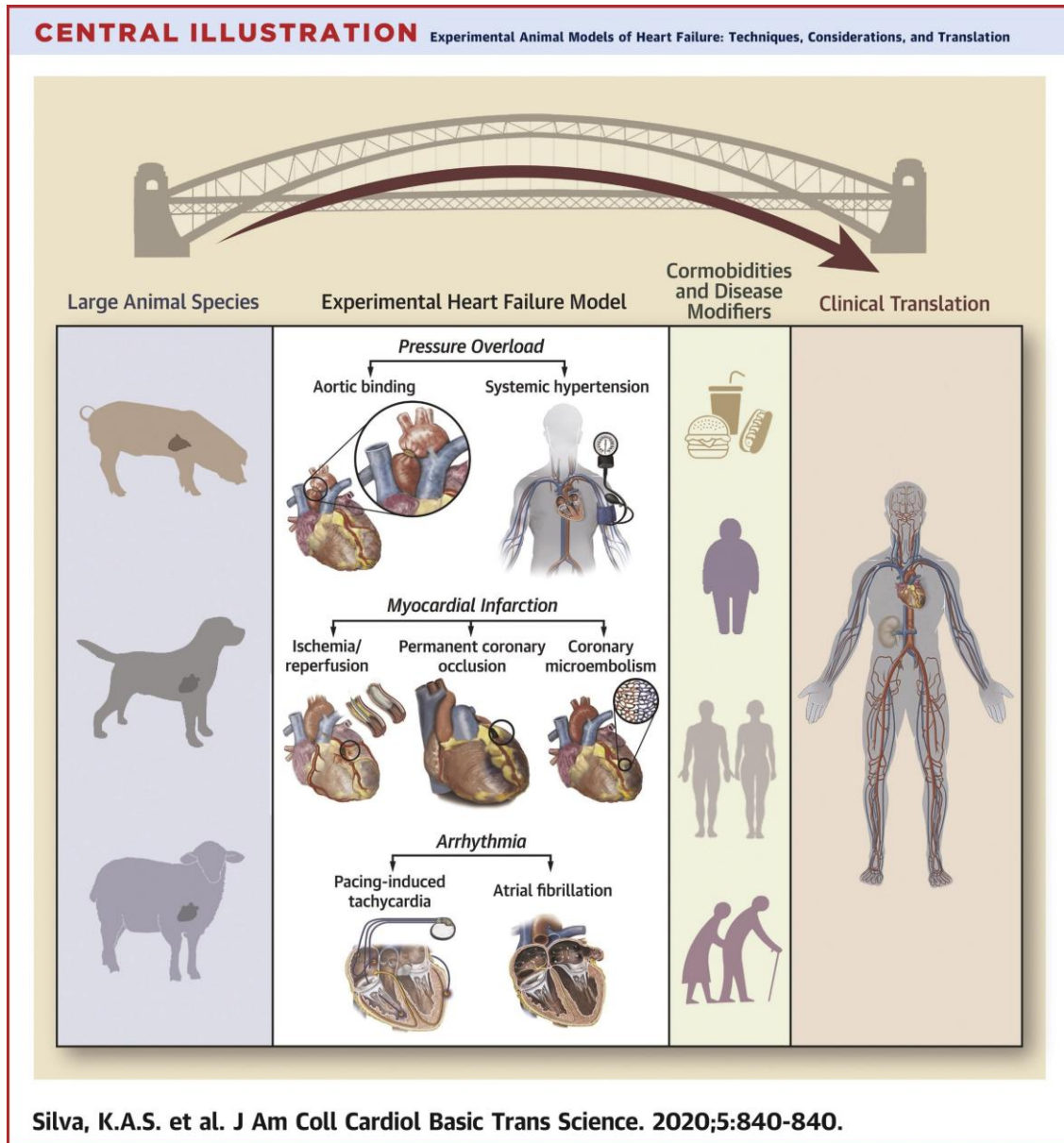
CRS Type IV (Chronic renocardiac syndrome)

Chronic kidney disease (e.g. chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events

CRS Type V (Secondary cardiorenal syndrome)

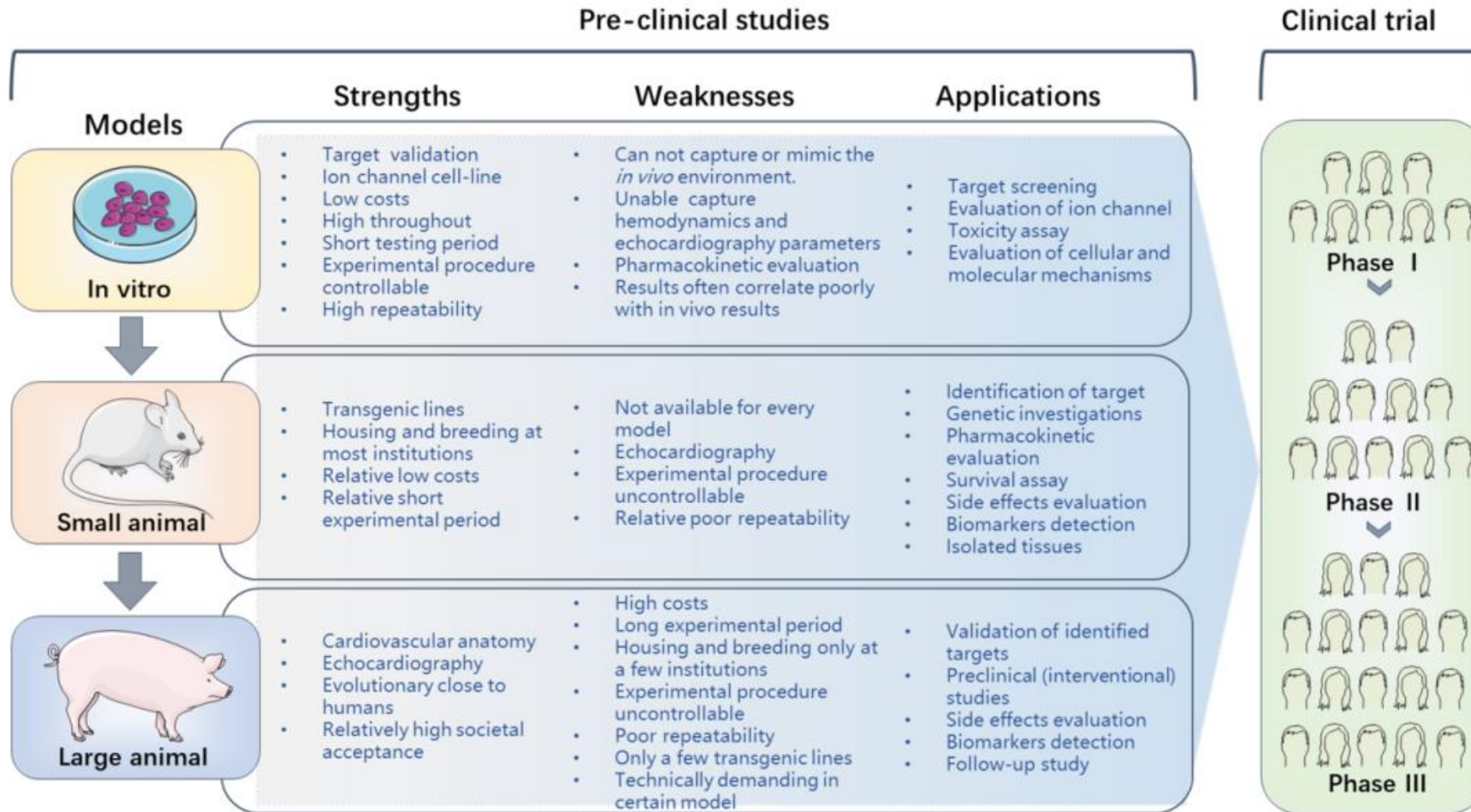
Systemic condition (e.g. DM, sepsis) causing both cardiac and renal dysfunction

Experimentálne modely a klinická translácia



Silva, K. A. S., & Emter, C. A. (2020). Large Animal Models of Heart Failure: A Translational Bridge to Clinical Success. *JACC. Basic to translational science*, 5(8), 840–856. <https://doi.org/10.1016/j.jacbts.2020.04.011>

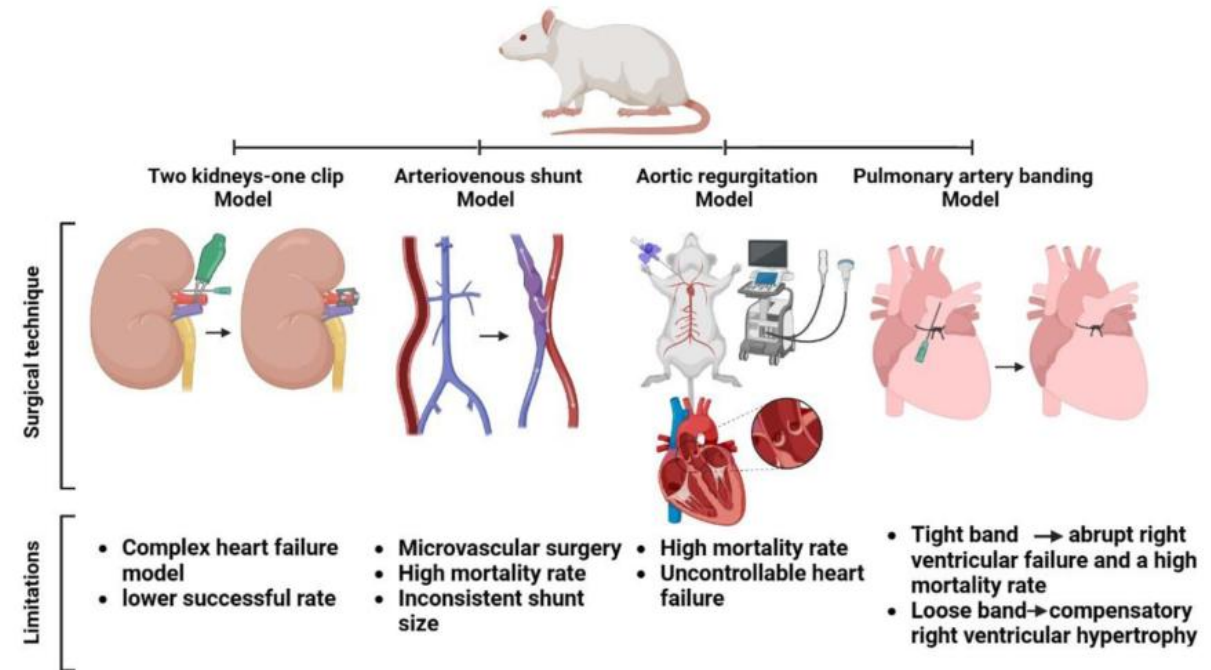
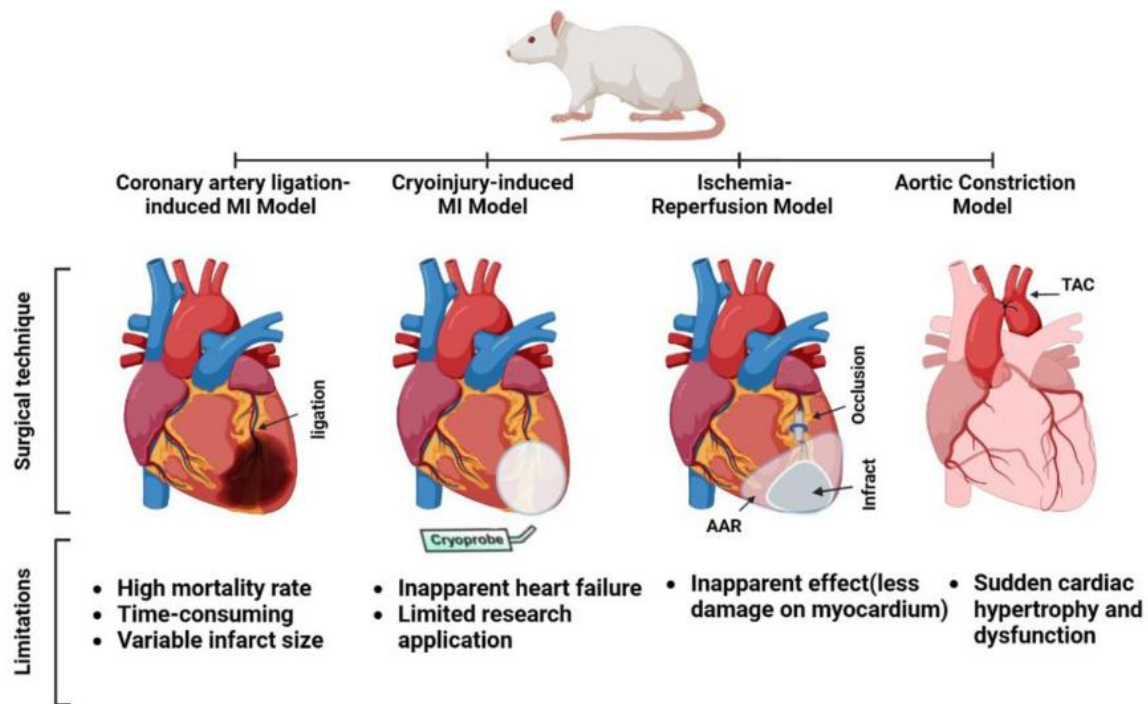
Výber vhodného experimentálneho modelu

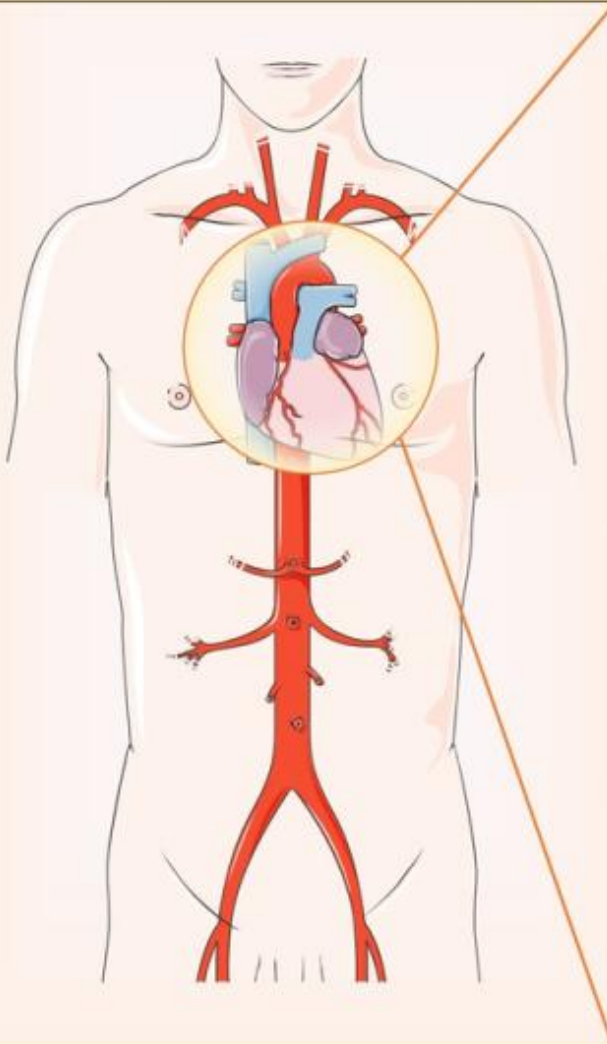


Rozdelenie modelov podľa spôsobu navodenia HF

- Operačný zákrok (ACF, IM, TAC, 2K1C, 5/6 nefraktómia)
- Injekčné podanie: cytotoxické antracyklínové ATB (doxorubicin), L-NAME
- Orálne podanie (L-NAME, adenín-CKD)
- Spontánne nadobudnuté (vrátane genetických modifikácií)
- Kombináciou (IM+ monocrotaline)

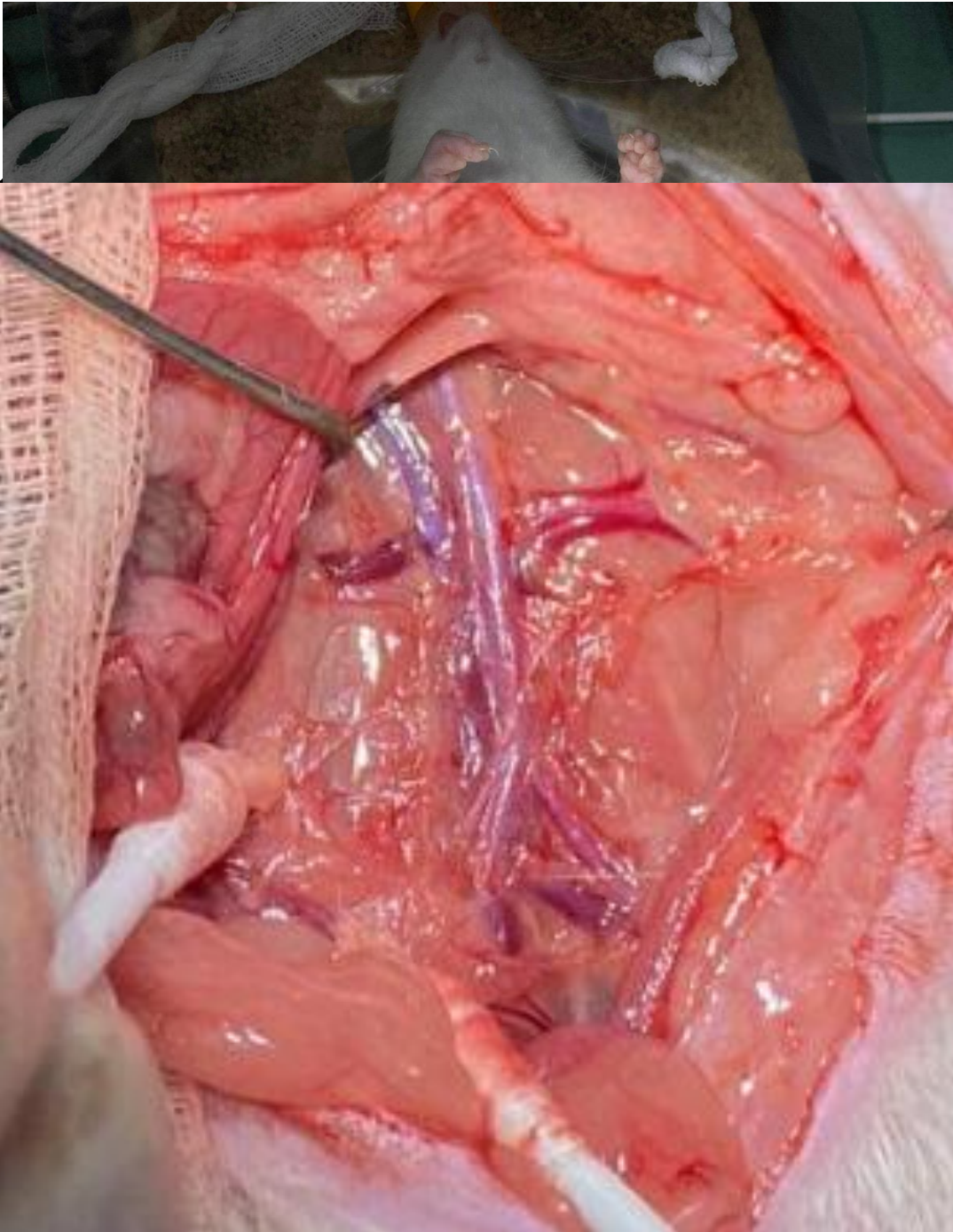
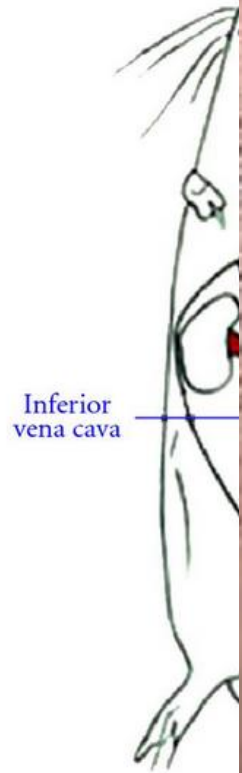
Modely HF a ich limitácie



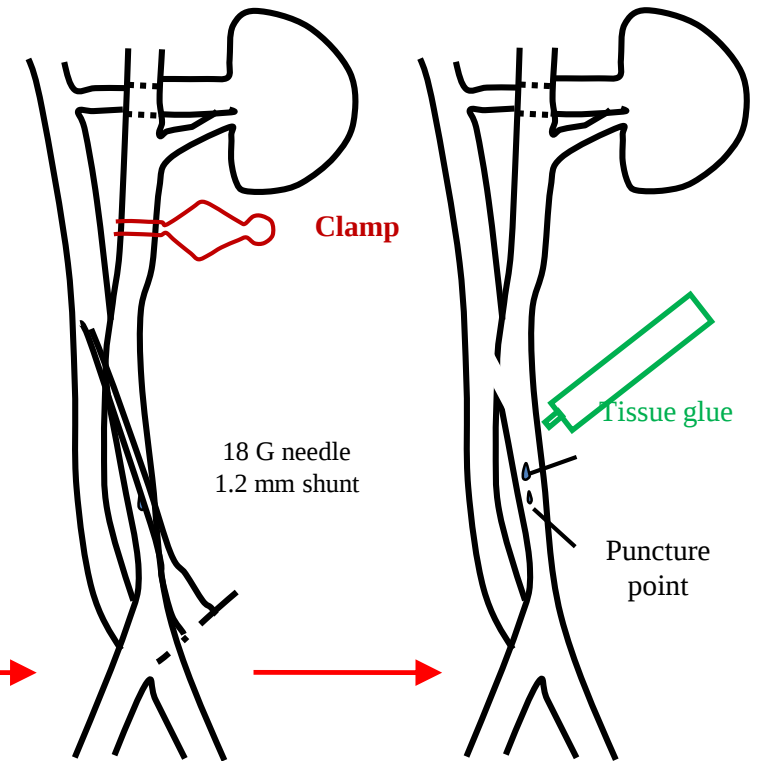
Major Causes of Heart Failure		Application of selected animal models for HF research					
		Heart Failure Stimulus					
	 Ischemia	Coronary artery occlusion	✓	✓	✓	✓	✓
		Ischemia-reperfusion	✓	✓	✓	✓	✓
		Coronary microembolization	✗	✗	✓	✓	✓
	 Hypertension	Transgenic animal	✓	✓	✗	✗	✗
		Renal artery stenosis	✓	✓	✓	✓	✓
		Pulmonary arterial hypertension	✓	✓	✓	✓	✓
	 DCM	Chemical induced	✓	✓	✓	✓	✓
		Rapid ventricular pacing	✗	✗	✓	✓	✓
		Transgenic animal	✓	✓	✗	✗	✗
	 Valve disease	Transverse aortic constriction	✓	✓	✓	✓	✓
		Chordae tendineae cutting	✗	✗	✓	✗	✓

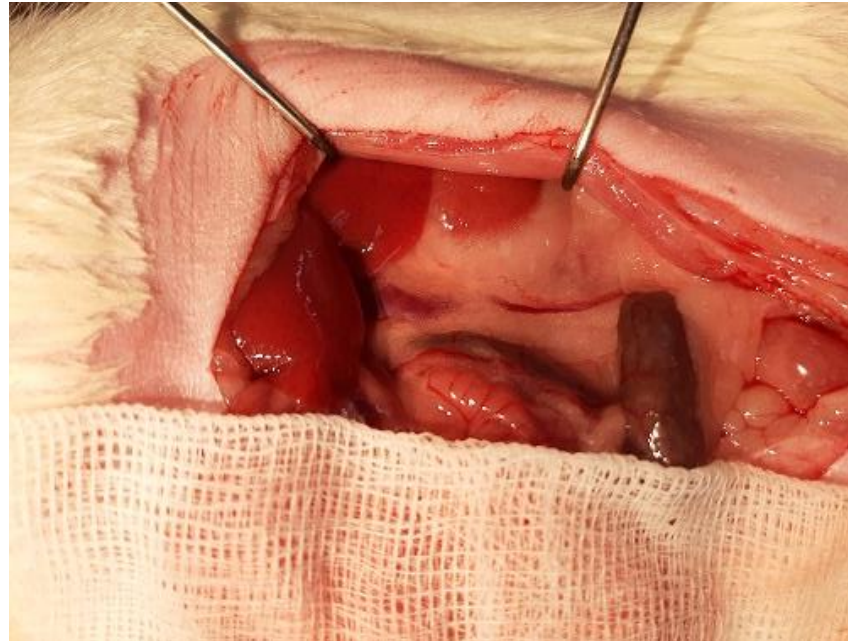
Volum

el

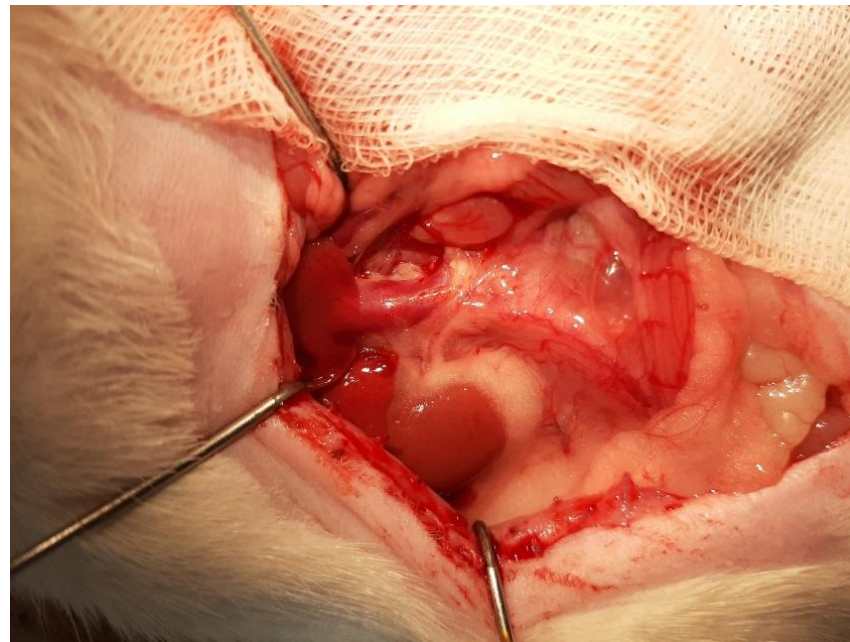


ey





**Sham-operated
rats**



**ACF rats
(1 week)**

Sham-operated HanSD

Heart weight (mg)/Body weight (g)
 2.97 ± 0.04



ACF HanSD

Heart weight (mg)/Body weight (g)
 3.86 ± 0.11



Sham-operated TGR

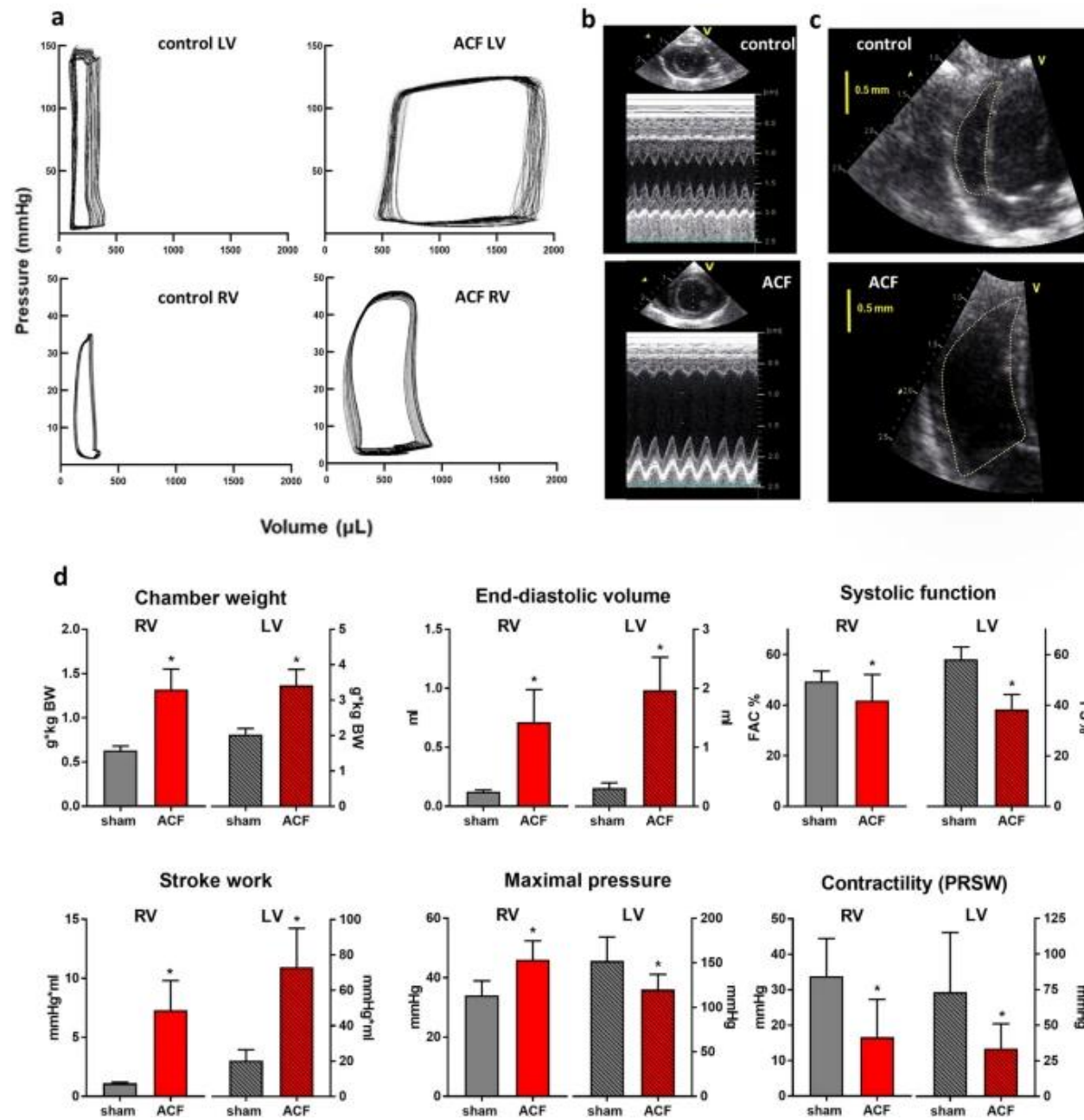
Heart weight (mg)/Body weight (g)
 3.68 ± 0.04

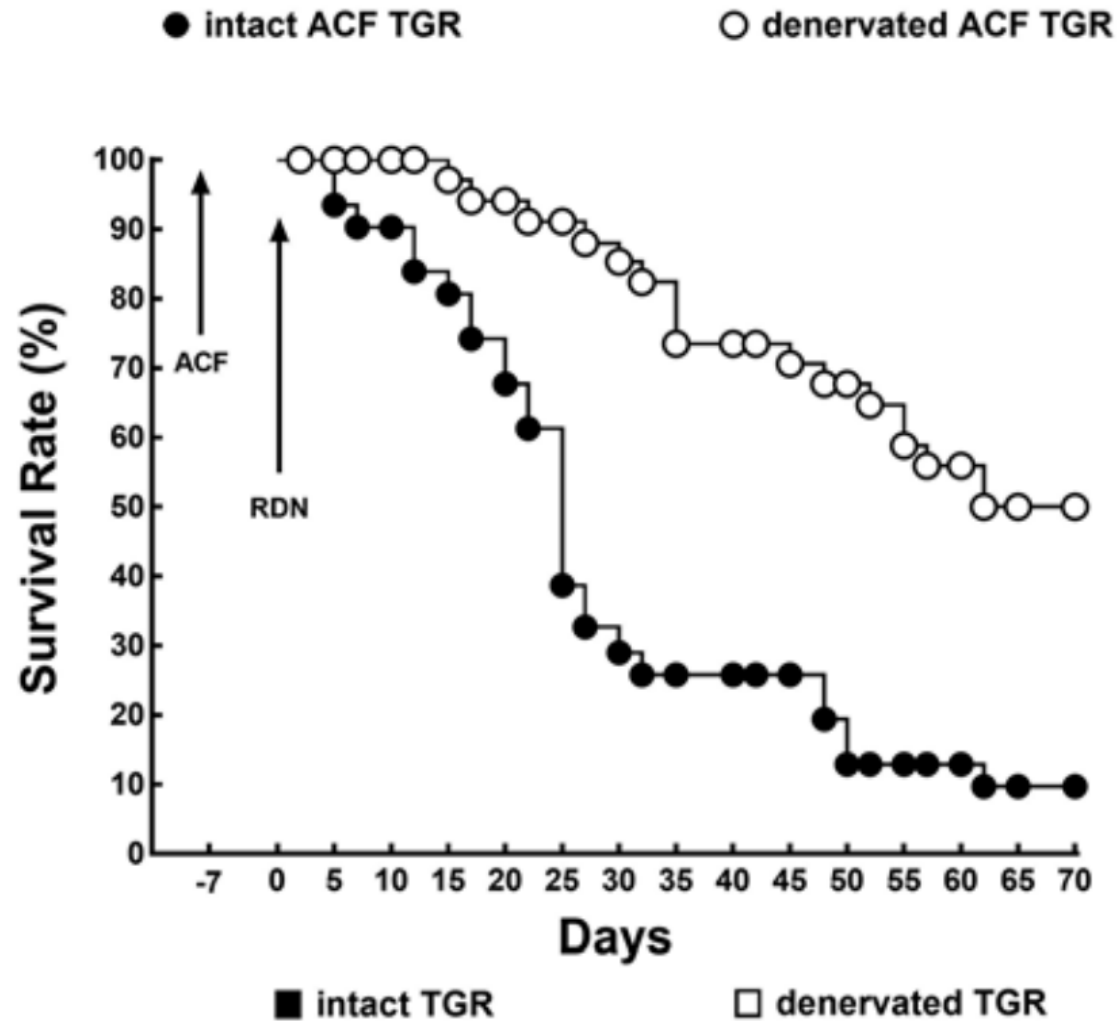


ACF TGR

Heart weight (mg)/Body weight (g)
 4.42 ± 0.07







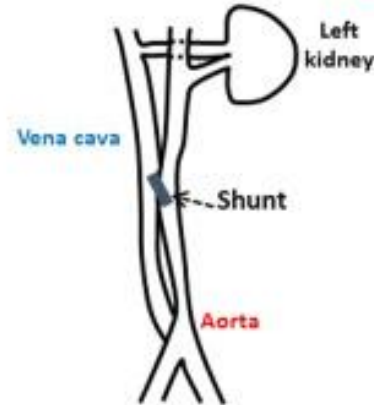
Honetschlagerová Z, et al. : Renal Sympathetic Denervation Attenuates Congestive Heart Failure in Angiotensin II-Dependent Hypertension: Studies with Ren-2 Transgenic Hypertensive Rats with Aortocaval Fistula. *Kidney Blood Press Res* 2021;46:95-113. doi: 10.1159/000513071

Ren-2 transgenic
hypertensive rats (TGR)



+

Aorto-caval fistula (ACF)



=

ACF TGR
model of combined
AGN II-dependent hypertension
+
heart failure

Basal values

1 week after ACF induction or sham-operation

ACF TGR vs. Sham-operated TGR

Renal Blood Flow (RBF)



Urine Flow (UF)



Absolute Sodium Excretion ($U_{Na}V$)



Effects of stepwise changes in renal arterial pressure

Sham-operated TGR

ACF TGR

RBF



UF



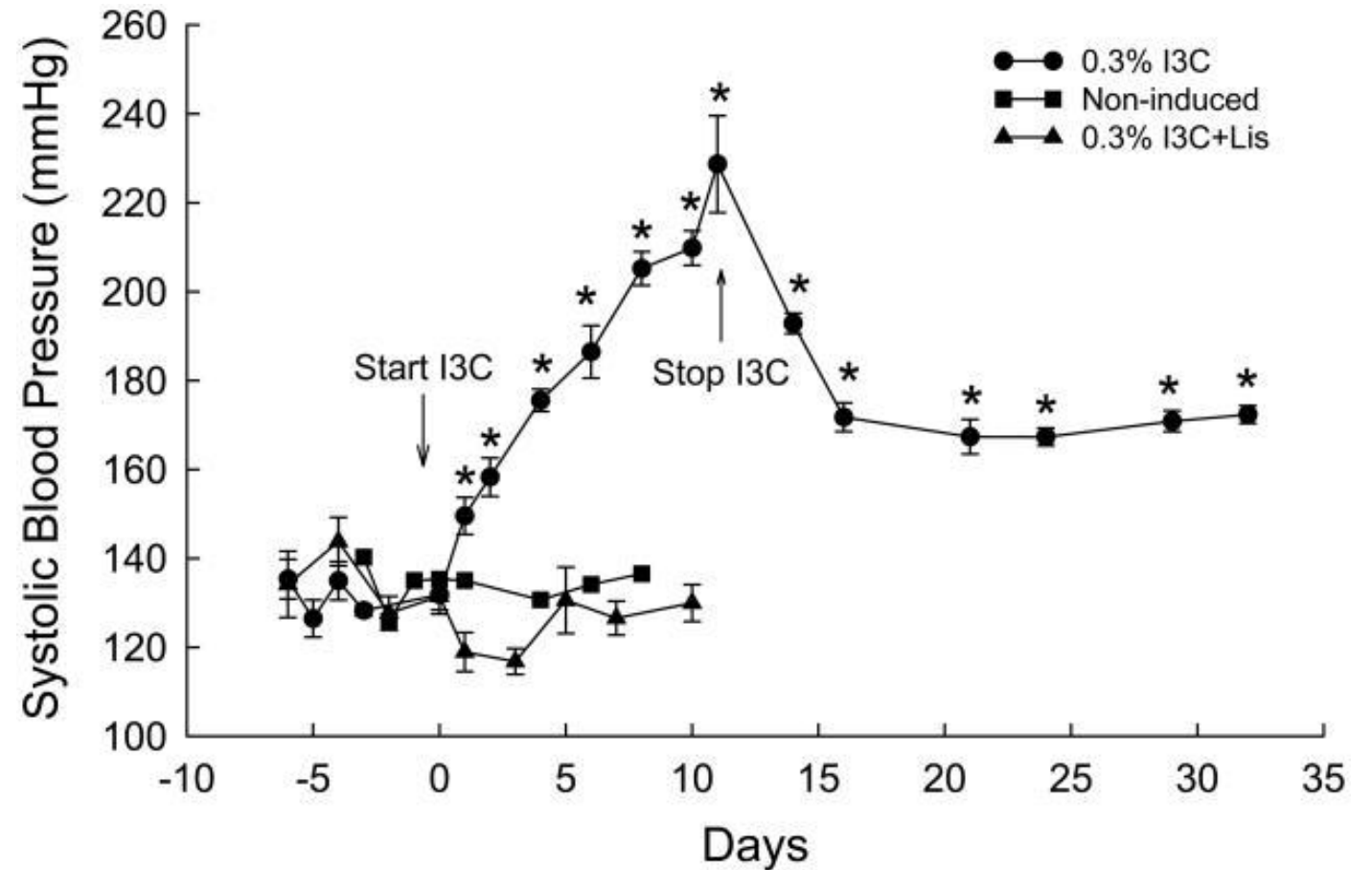
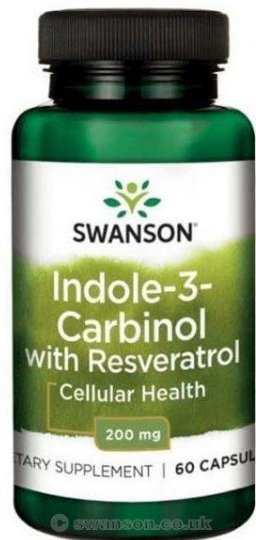
$U_{Na}V$



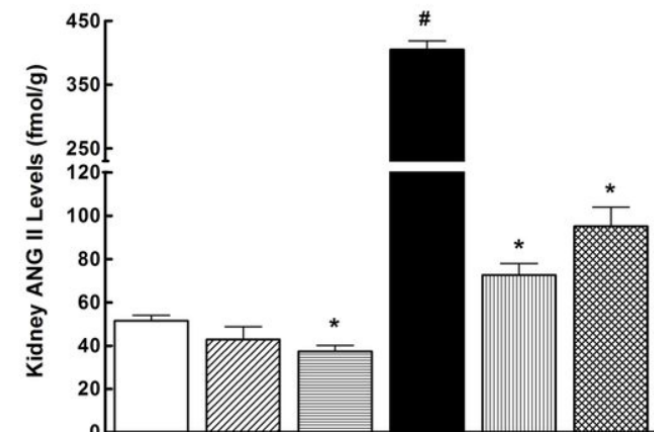
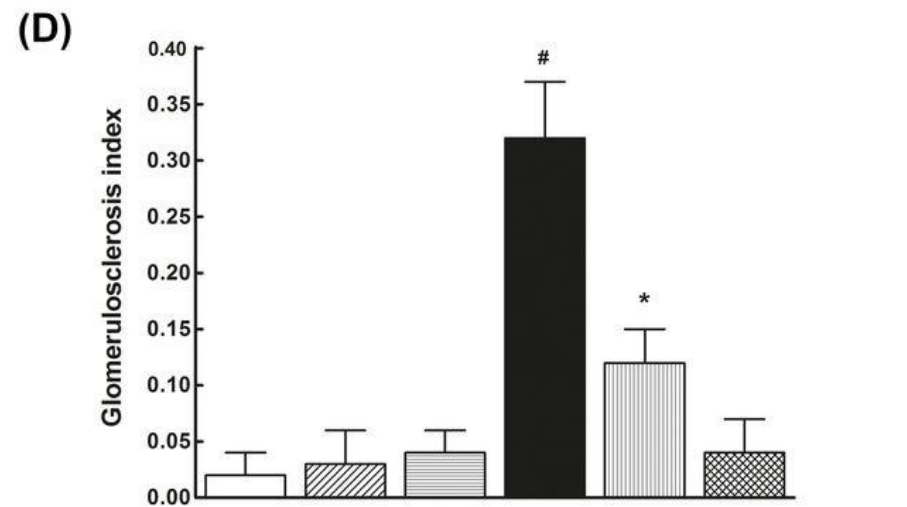
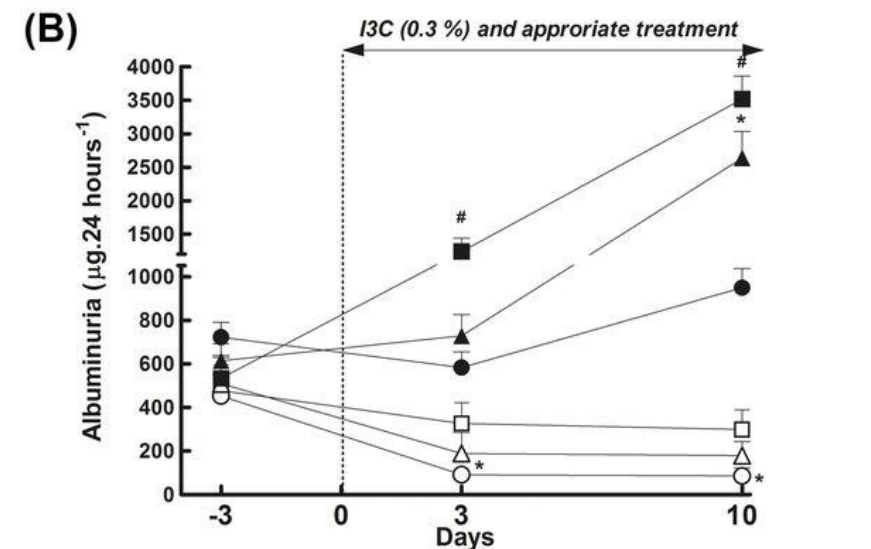
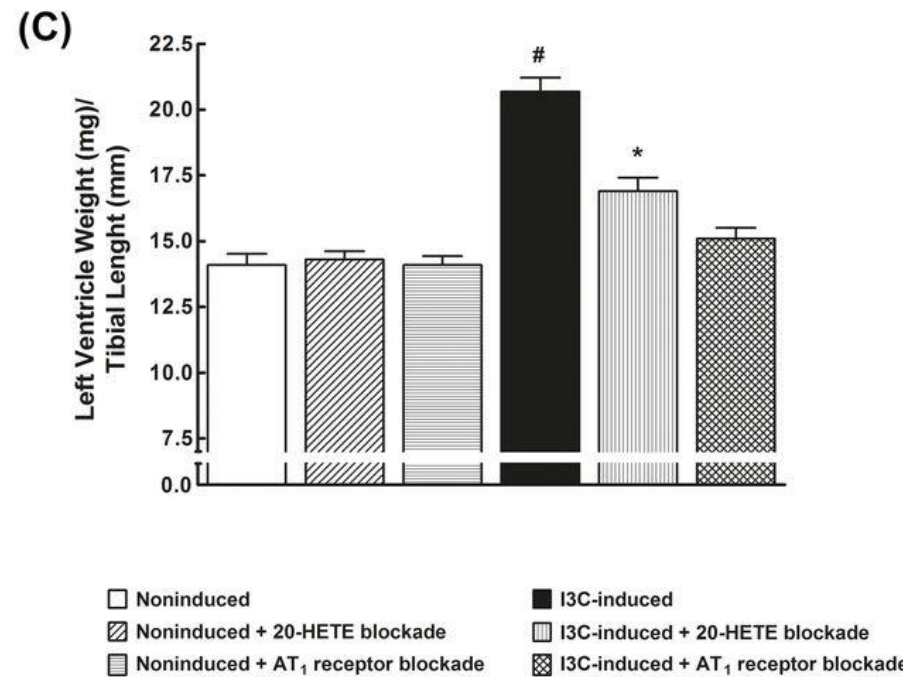
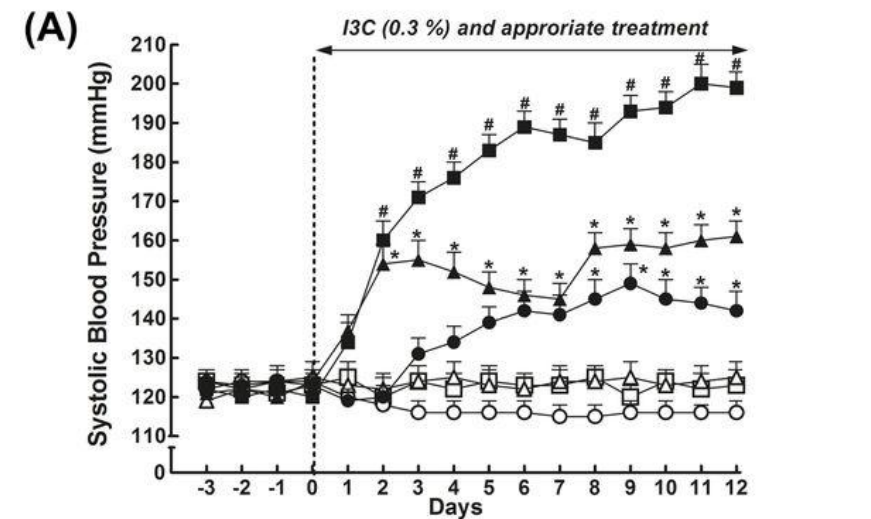
Conclusion: ACF TGR displayed well-maintained RBF autoregulatory capacity and better slope of the pressure-natriuresis relationship as compared with sham-operated TGR.

Pressure-overload model

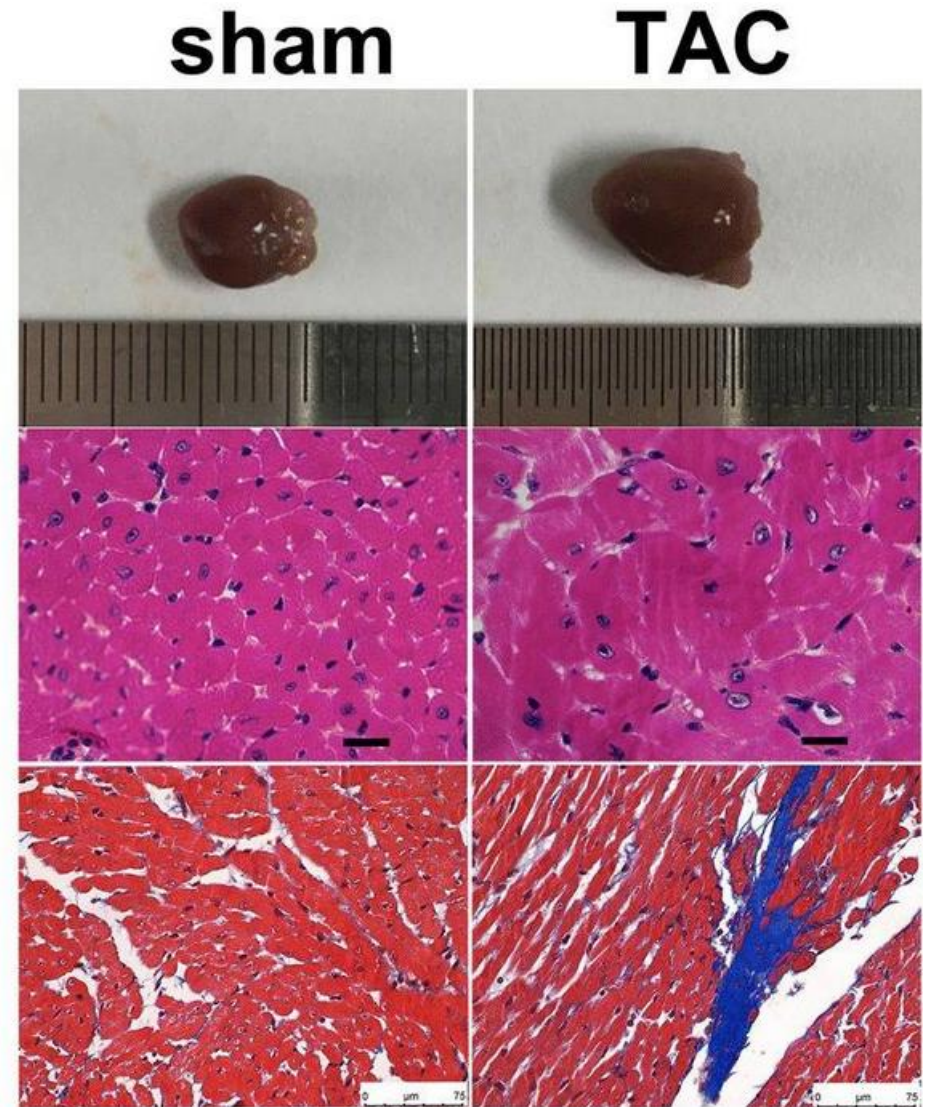
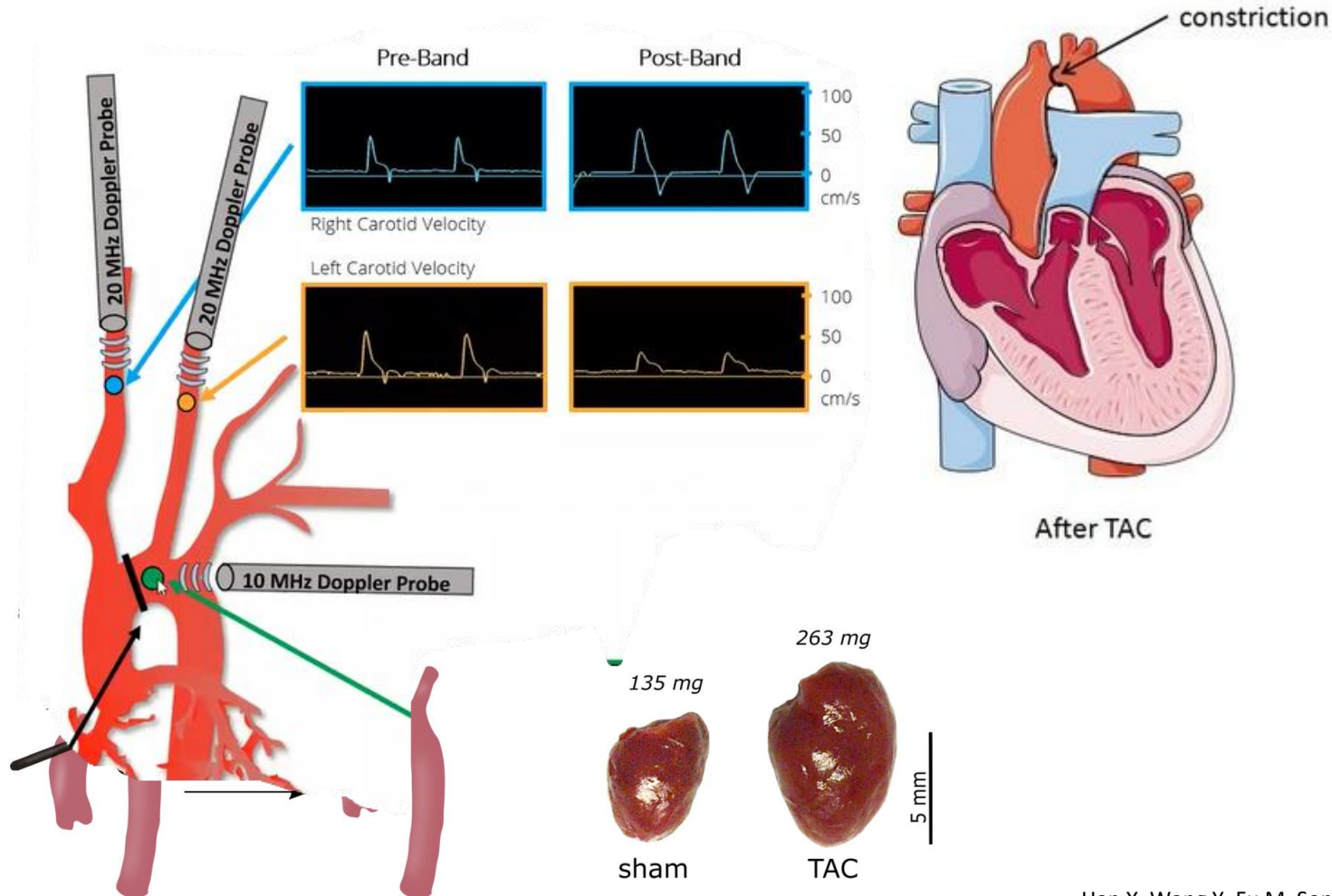
- Cyp1a1-Ren2 rats with I3C

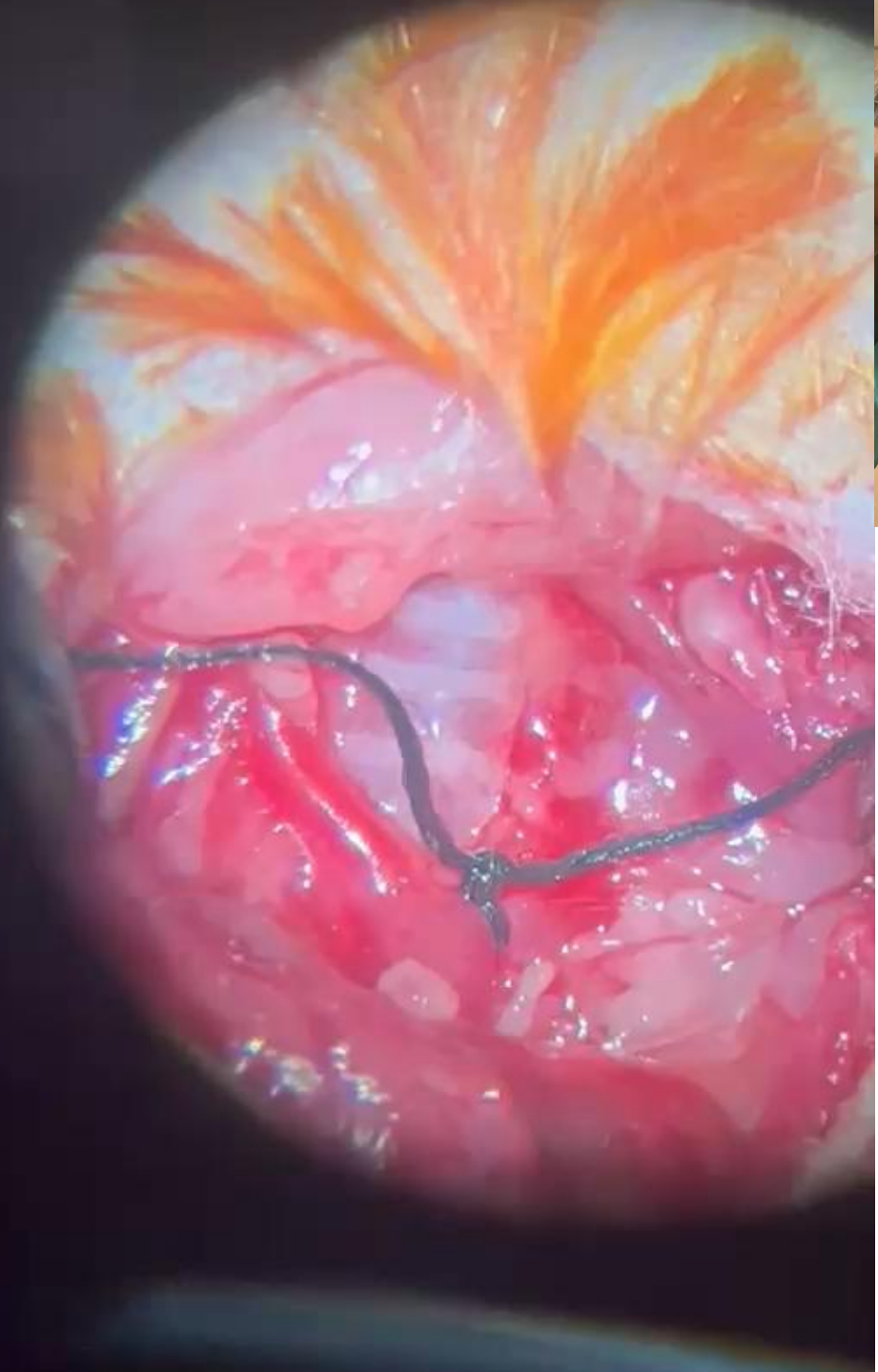
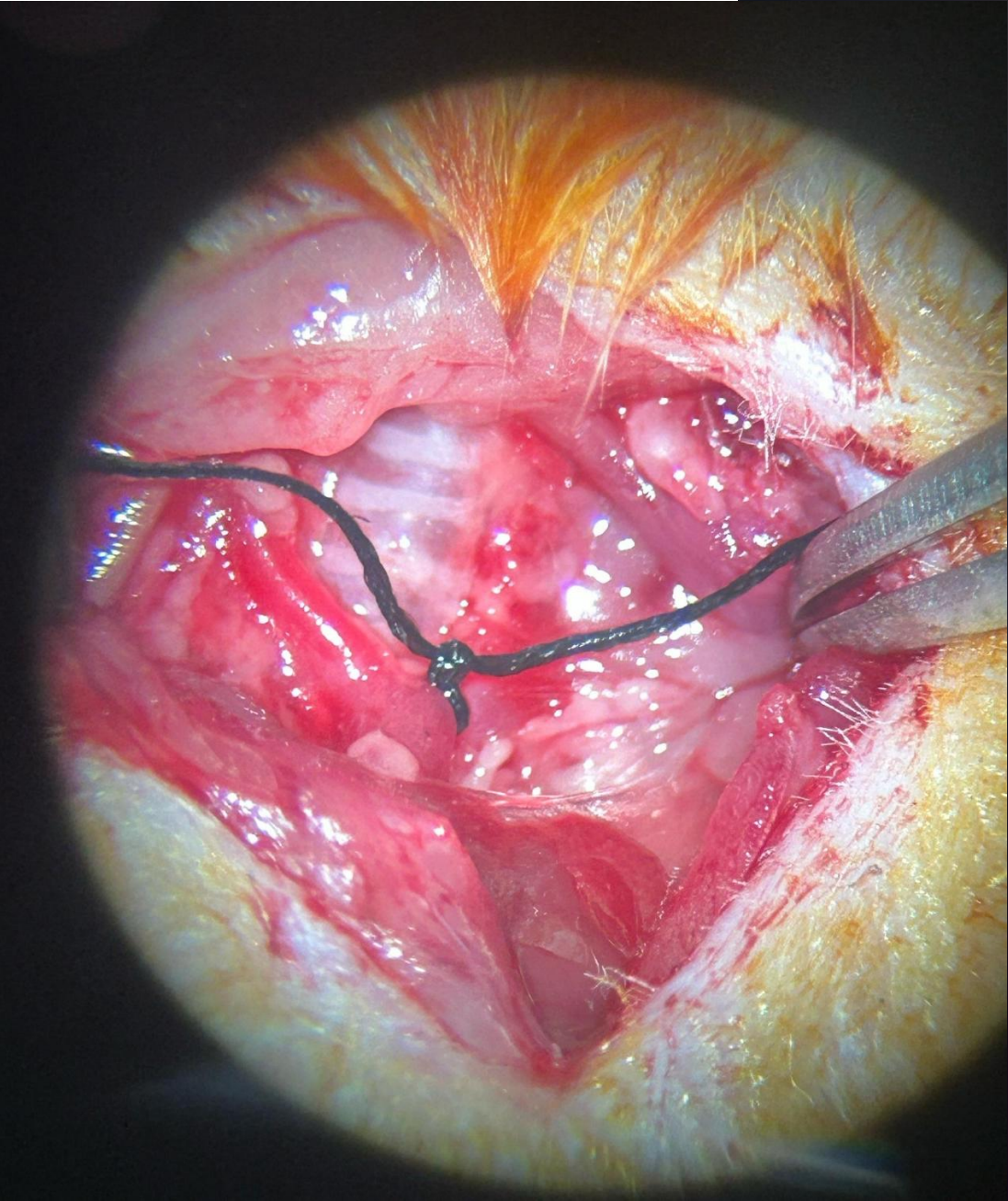


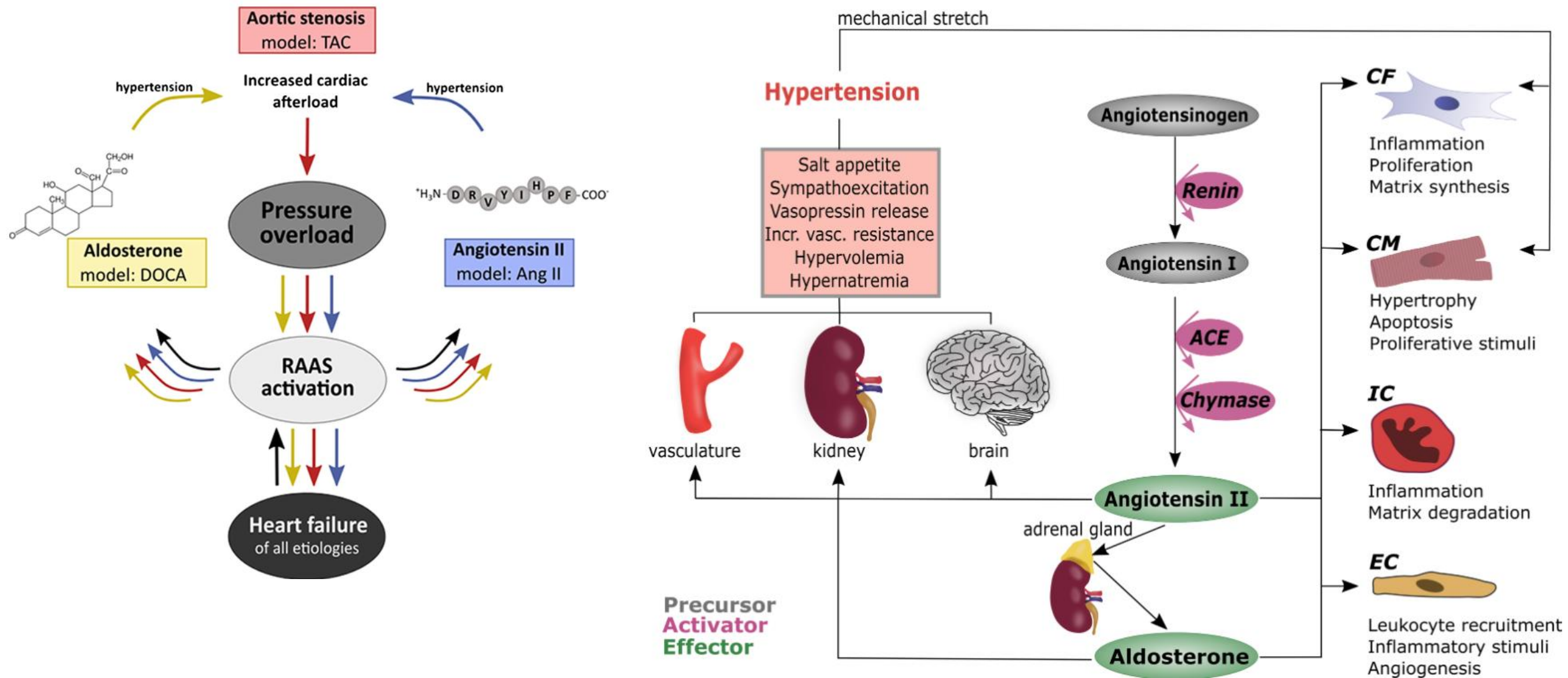
Effects of early treatment



Pressure-overload model HF



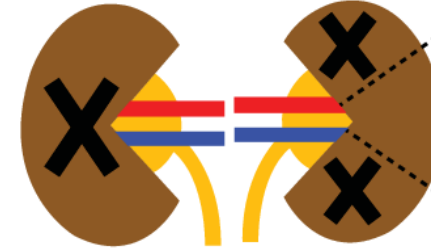




Pressure-overload model HF

- 5/6 nephrectomy model of HF

①



Sub-total (5/6)
nephrectomy

②



Unilateral ureteral
obstruction

Comparison of the Surgical Resection and Infarct 5/6 Nephrectomy Rat Models of Chronic Kidney Disease

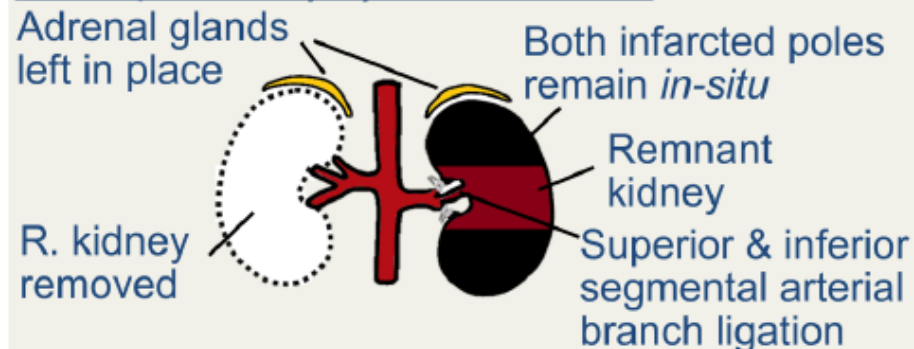
Rabe, Michael and Franz Schaefer. "Non-Transgenic Mouse Models of Kidney Disease." *Nephron* 133 (2016): 53 - 61.

METHODS

5/6 Nephrectomy by Surgical Pole Removal



5/6 Nephrectomy by Pole Infarction



OUTCOME

Phenotypic Similarities Between Models

- Loss of nephrons upon surgery
- Compensatory remodeling
- Uremia, fibrosis and glomerular injury
- Ultimately develop renal failure

Phenotypic Differences Between Models

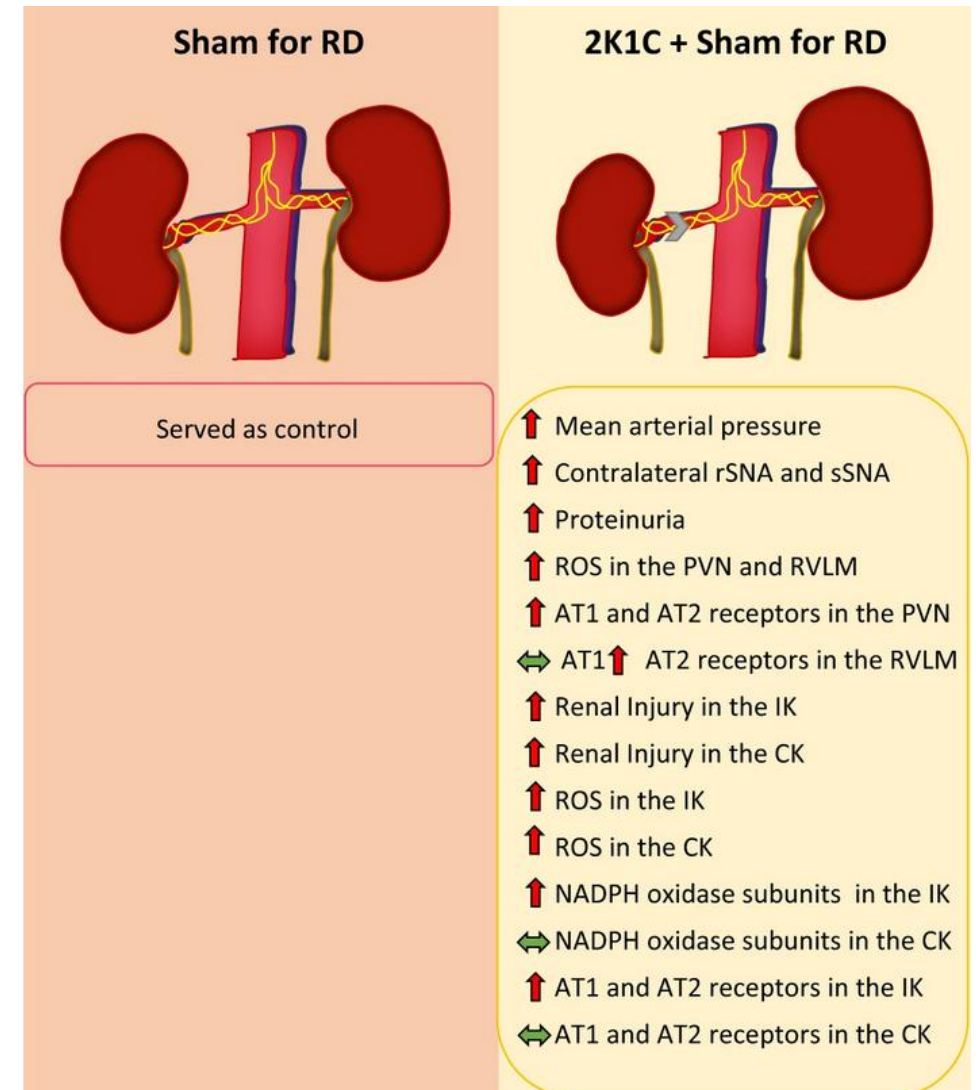
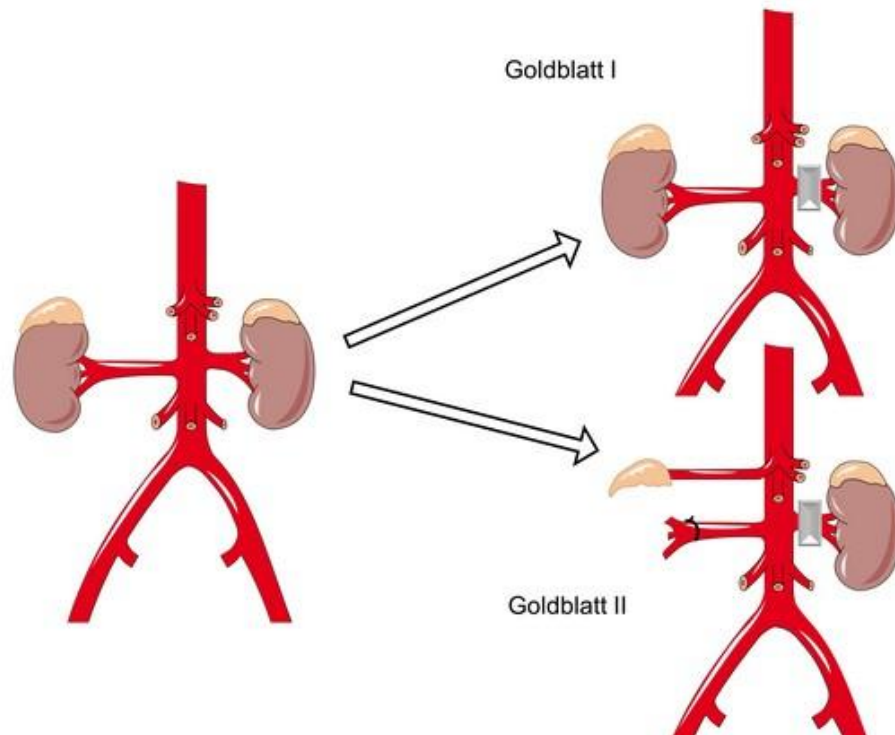
- Infarction model has relatively more RAAS activation.
- Infarction model spontaneously develops greater increases in mean arterial pressure.

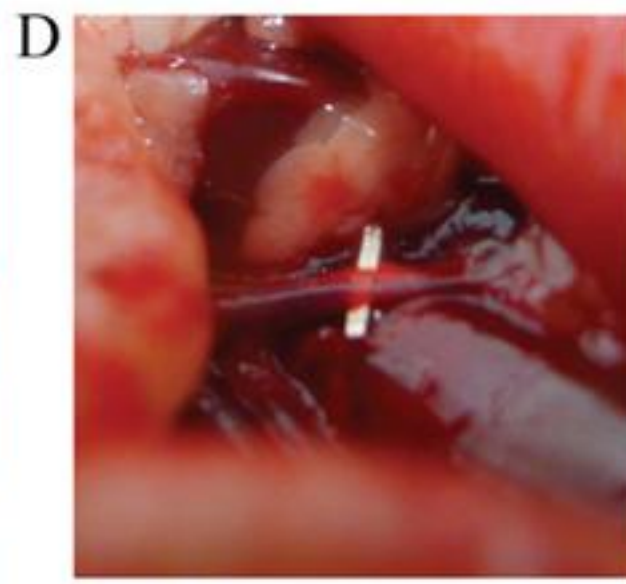
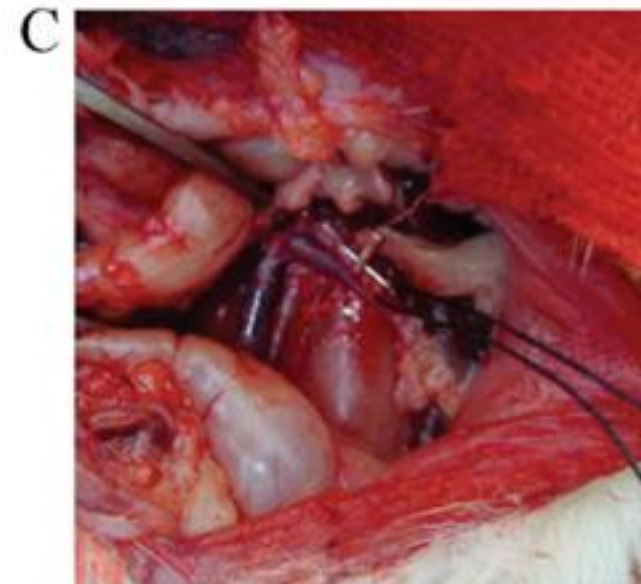
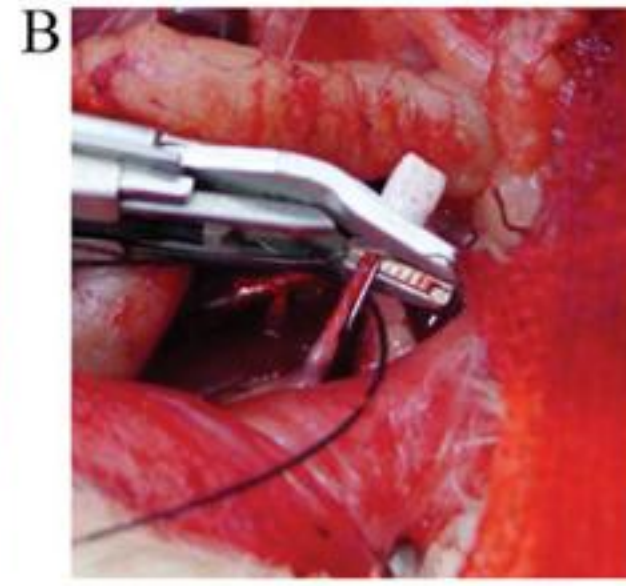
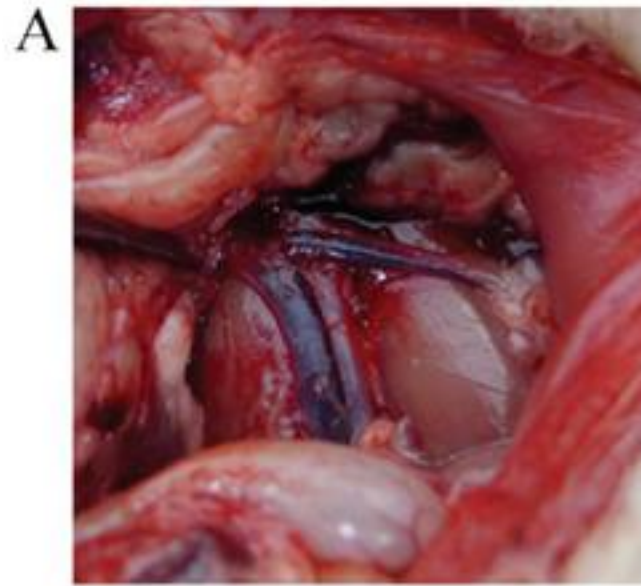
CONCLUSION These models have much in common but also have significant differences and thereby model unique aspects of human CKD.

Adam, R. J., Williams, A. C., & Kriegel, A. J. (2022). Comparison of the surgical resection and infarct 5/6 nephrectomy rat models of chronic kidney disease. *American journal of physiology. Renal physiology*, 322(6), F639–F654. <https://doi.org/10.1152/ajprenal.00398.2021>

Pressure-overload model HF

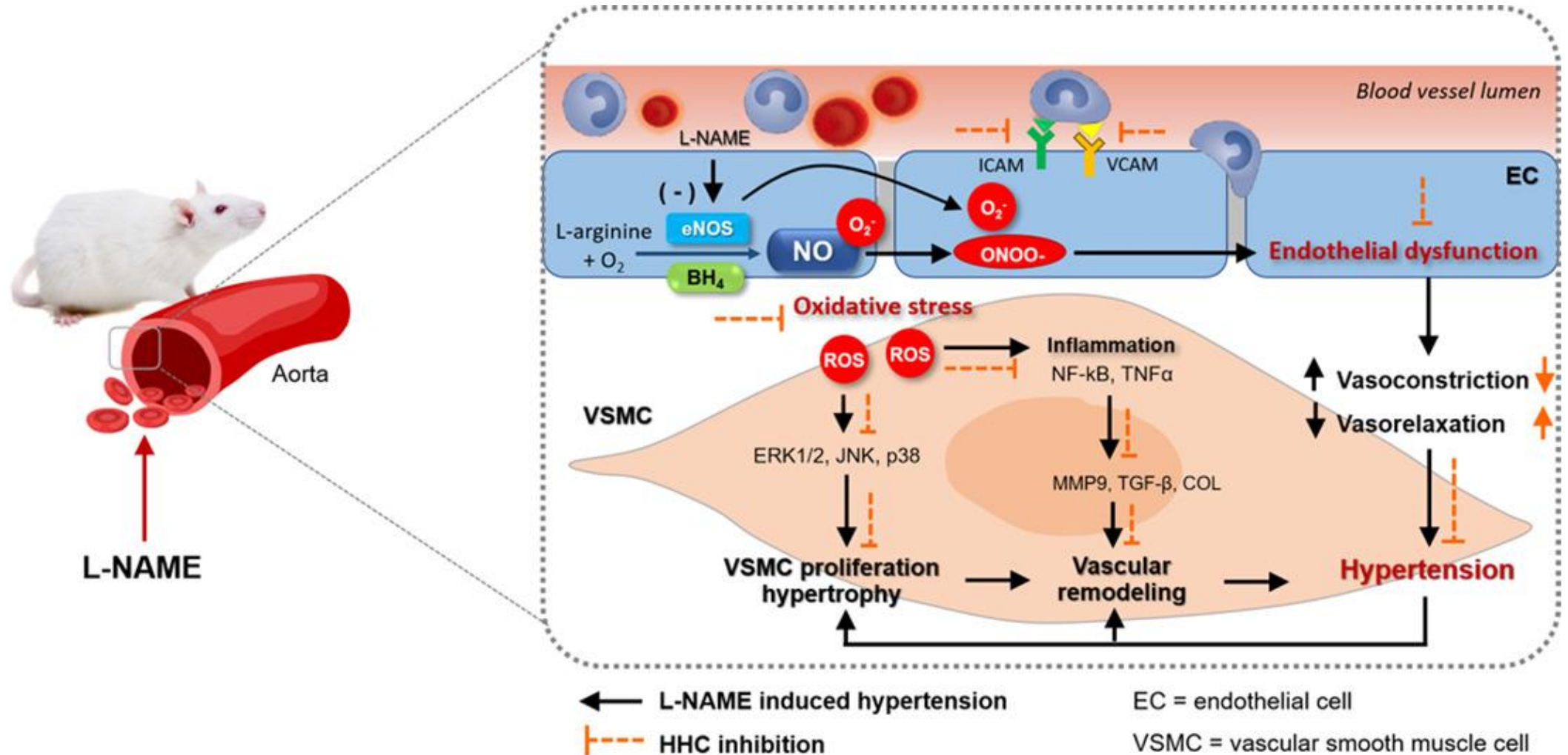
- 2K1C a 1K1C





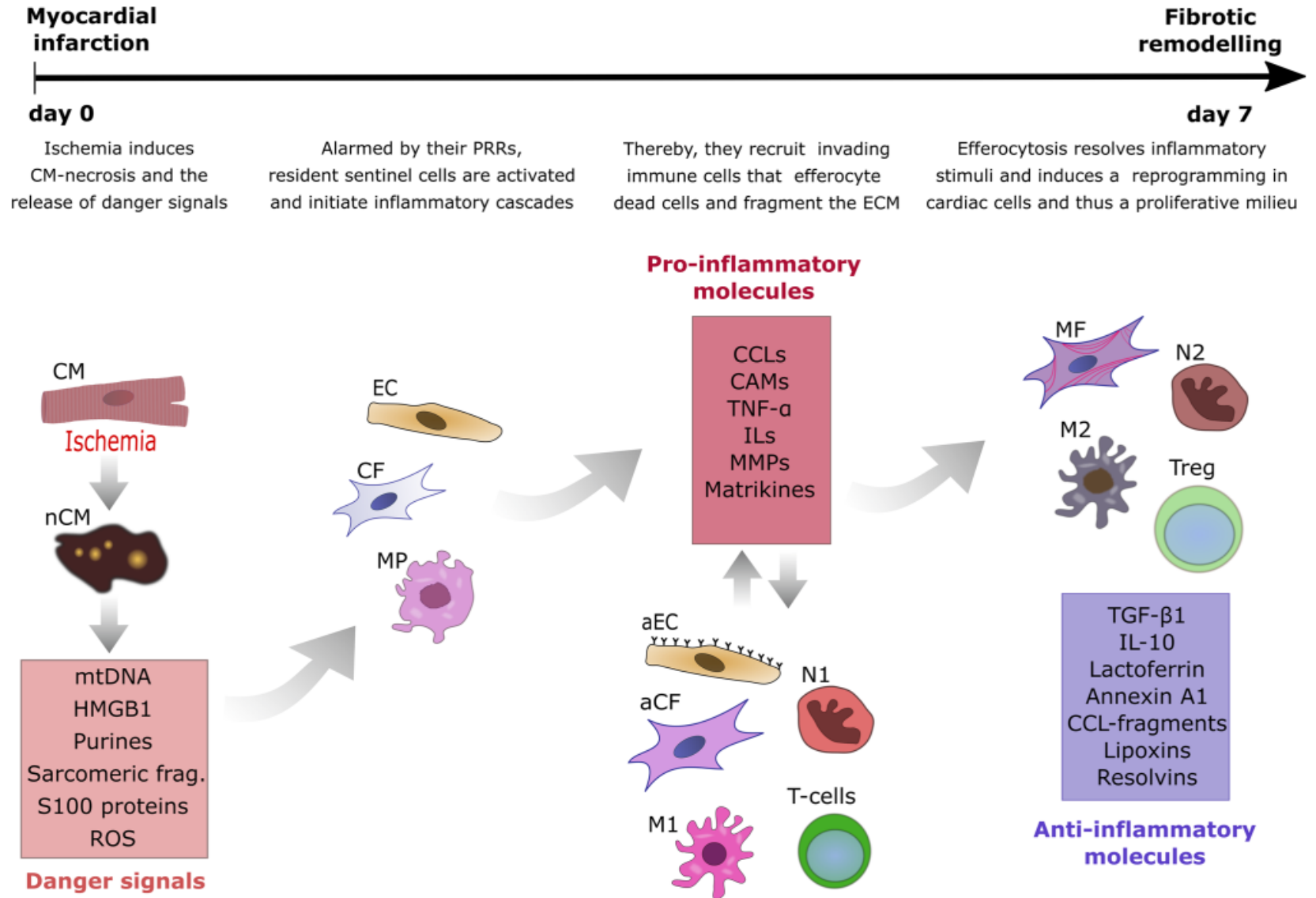
Pressure-overload model HF

- L-NAME

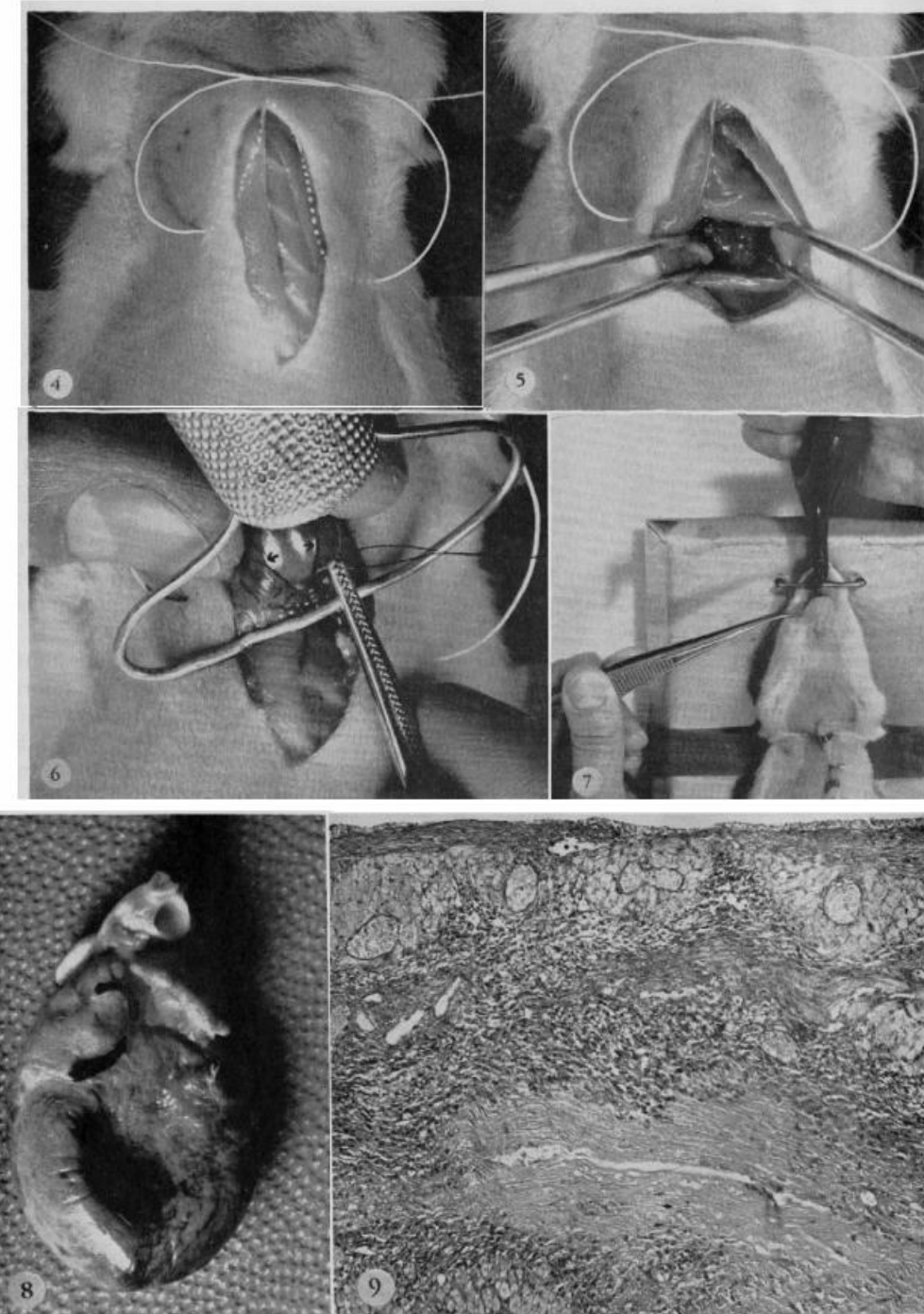
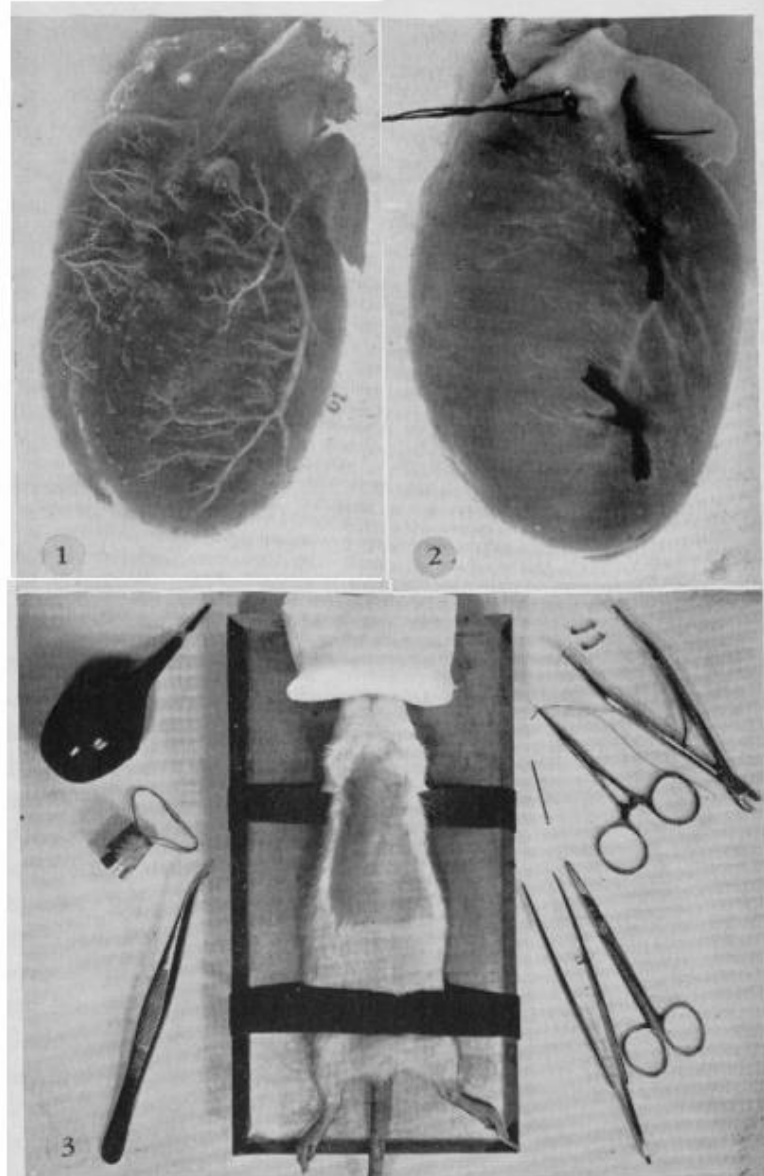


Infarktový model HF

- IM/R
- IM
- IM+sugen
- IM+monocrotaline/hypoxia

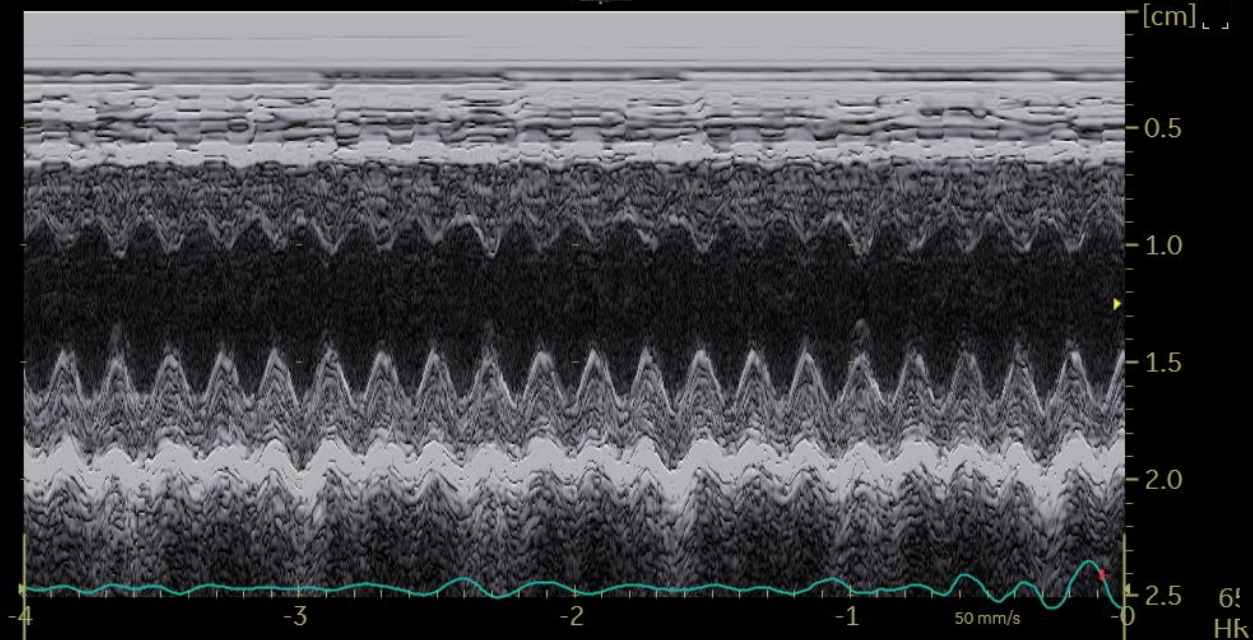
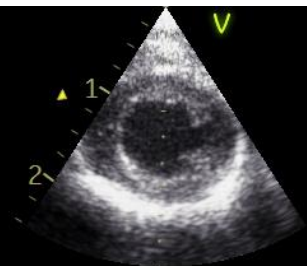


Infarktový model HF

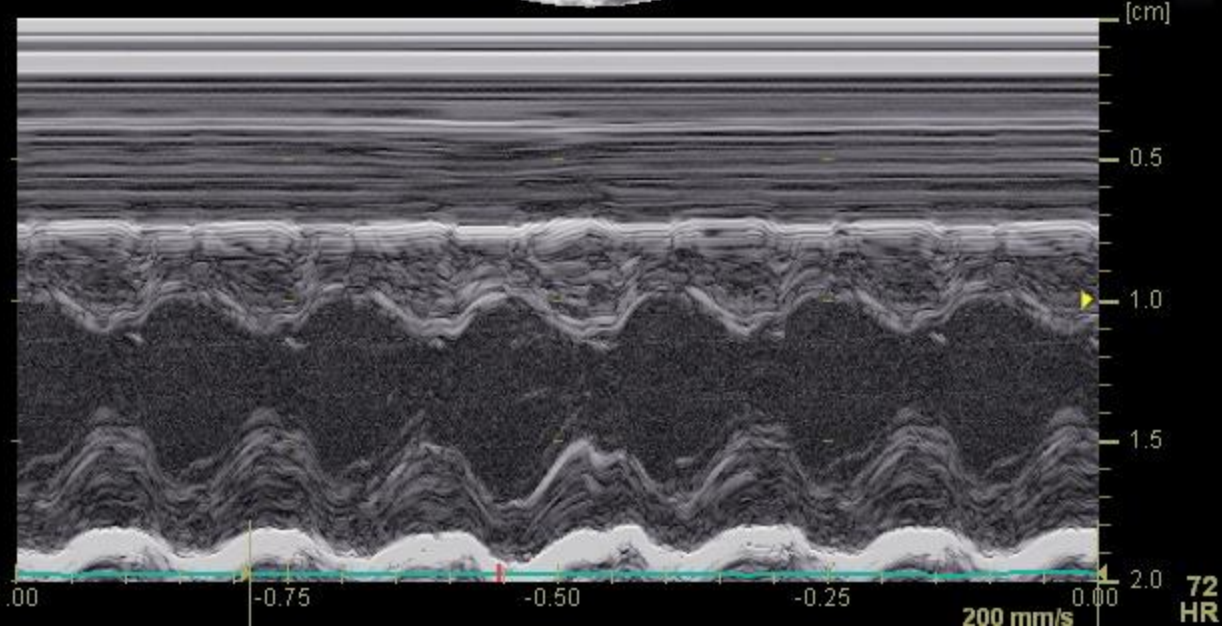
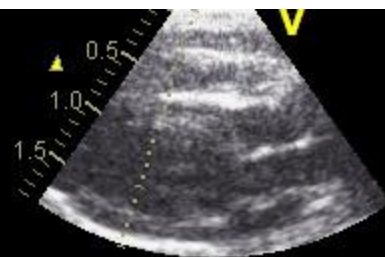


Selye H, Bajusz E, Grasso S, Mendell P.
Simple Techniques for the Surgical
Occlusion of Coronary Vessels in the
Rat. *Angiology*. 1960;11(5):398-407.
doi:[10.1177/000331976001100505](https://doi.org/10.1177/000331976001100505)

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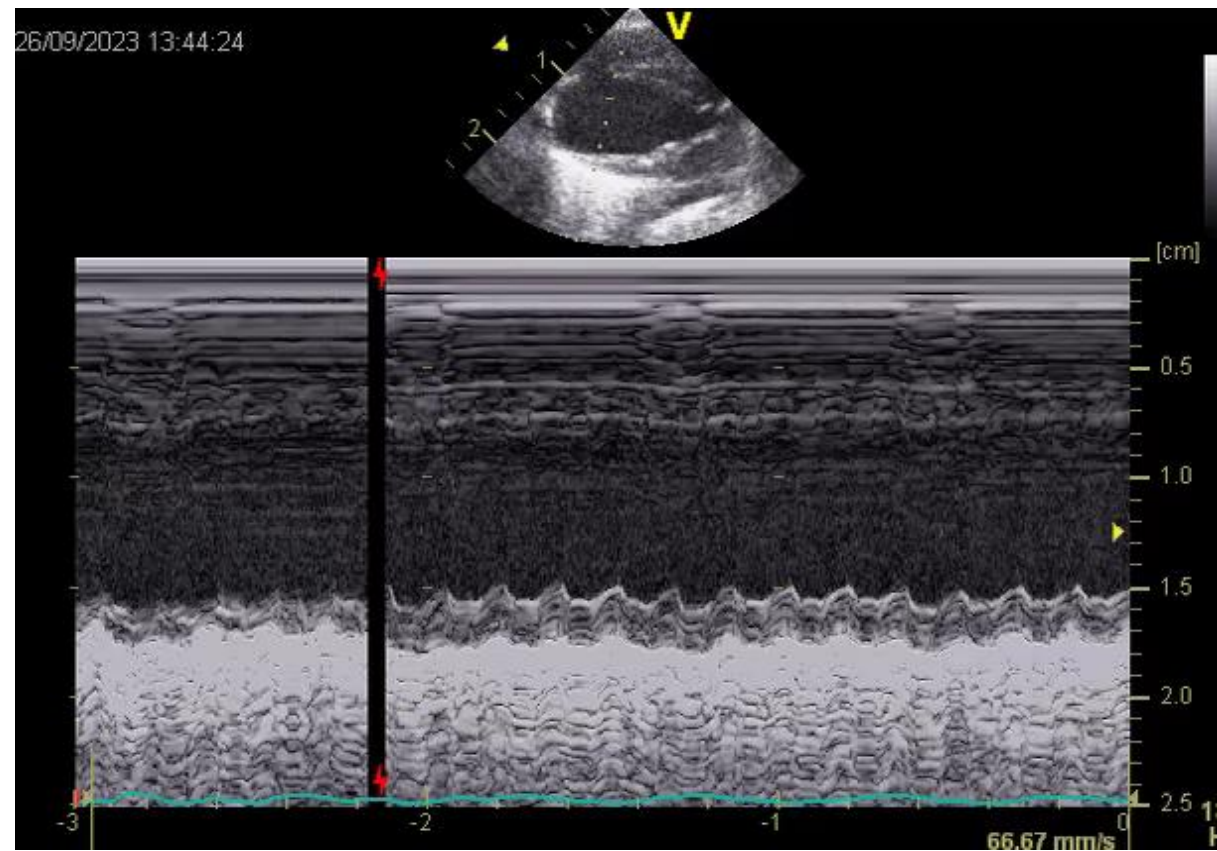
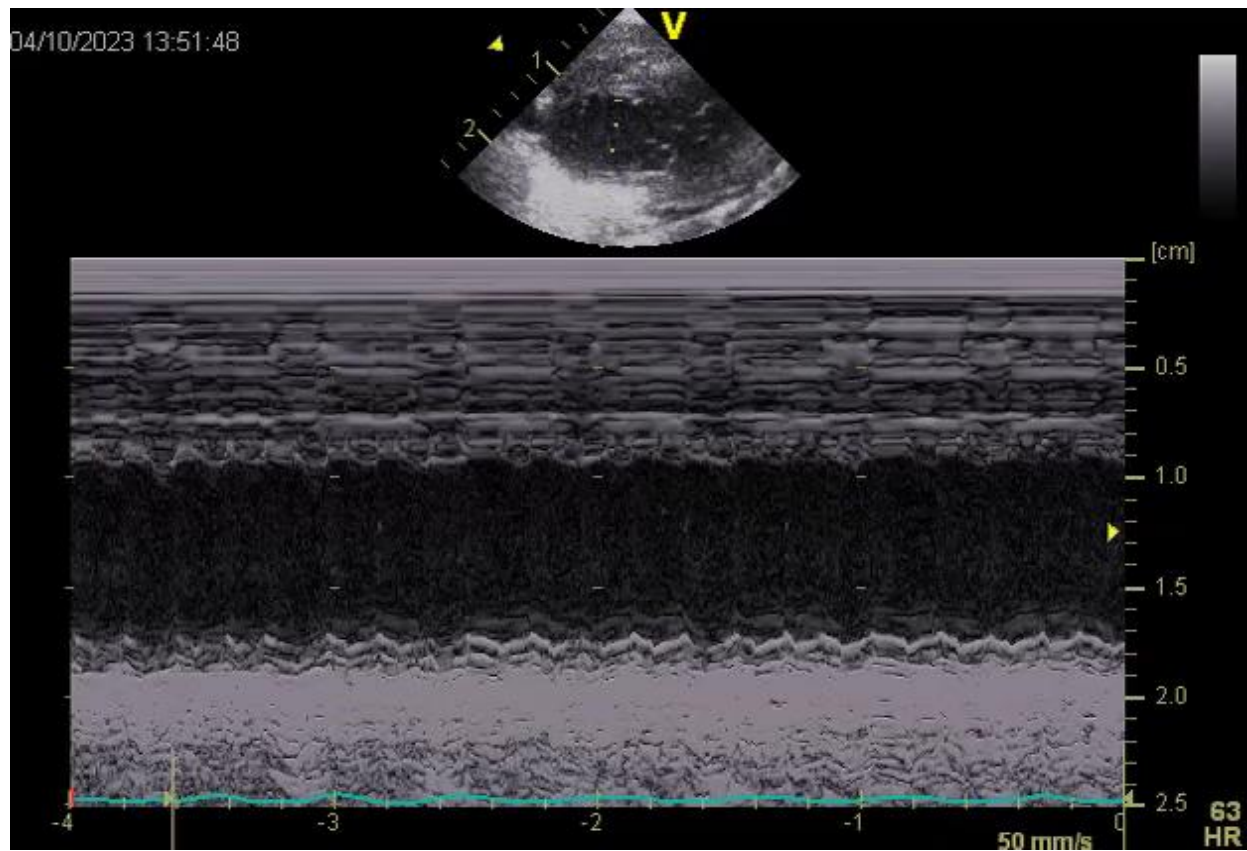
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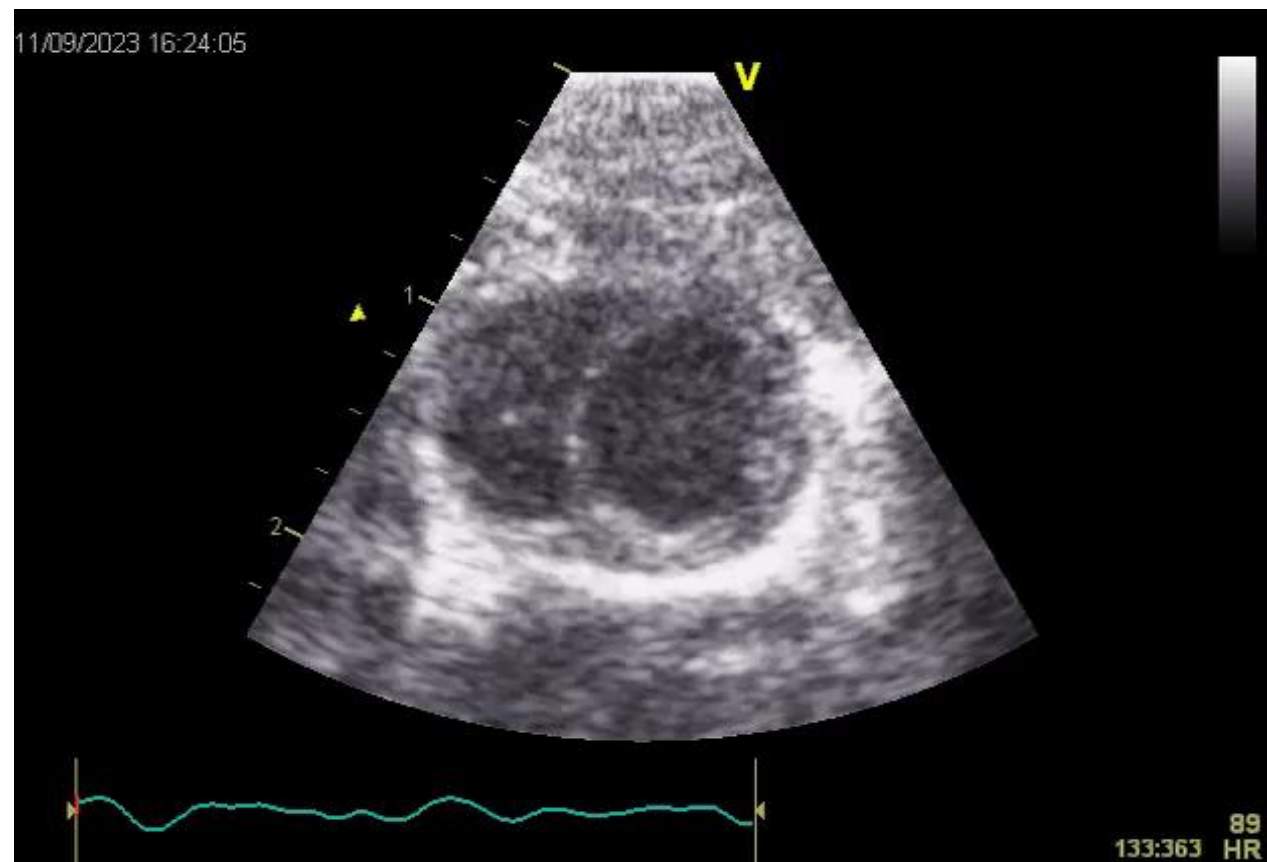
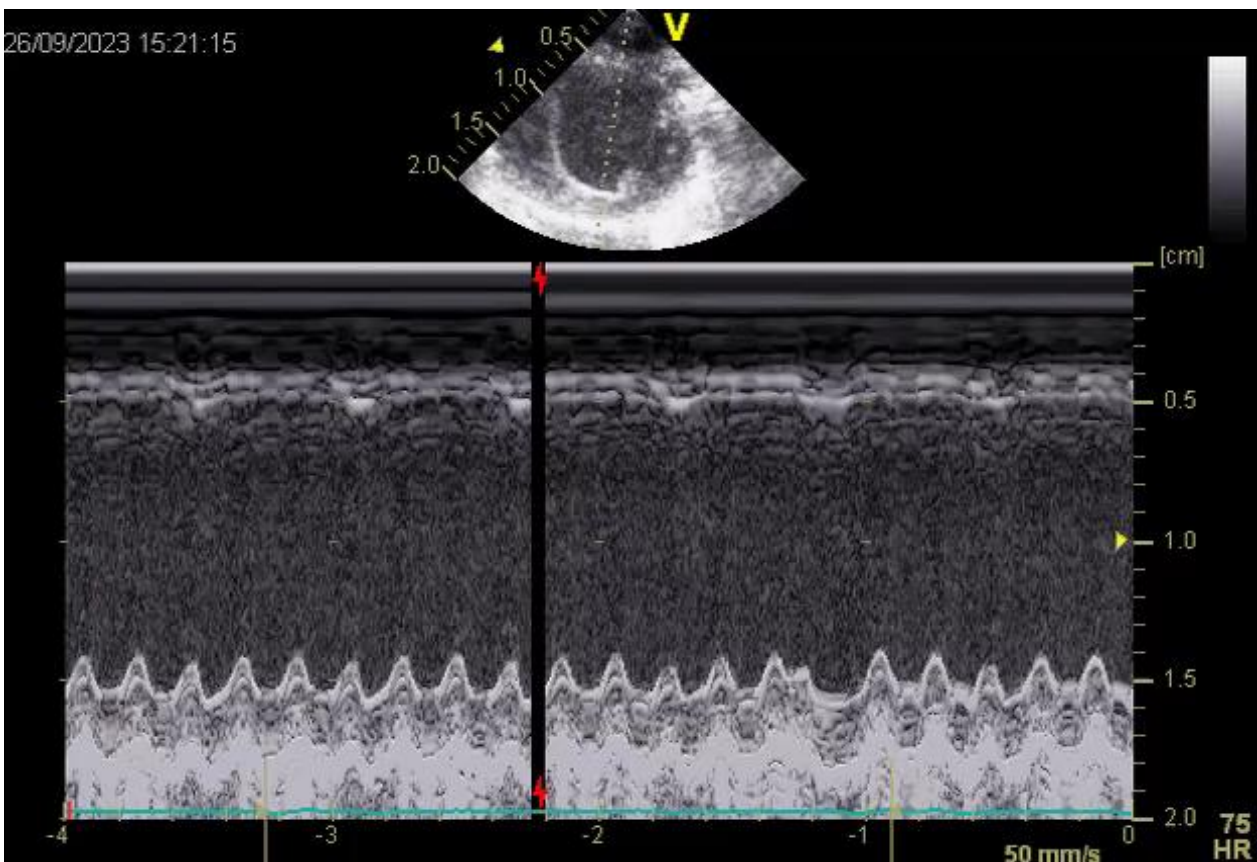
61 HR

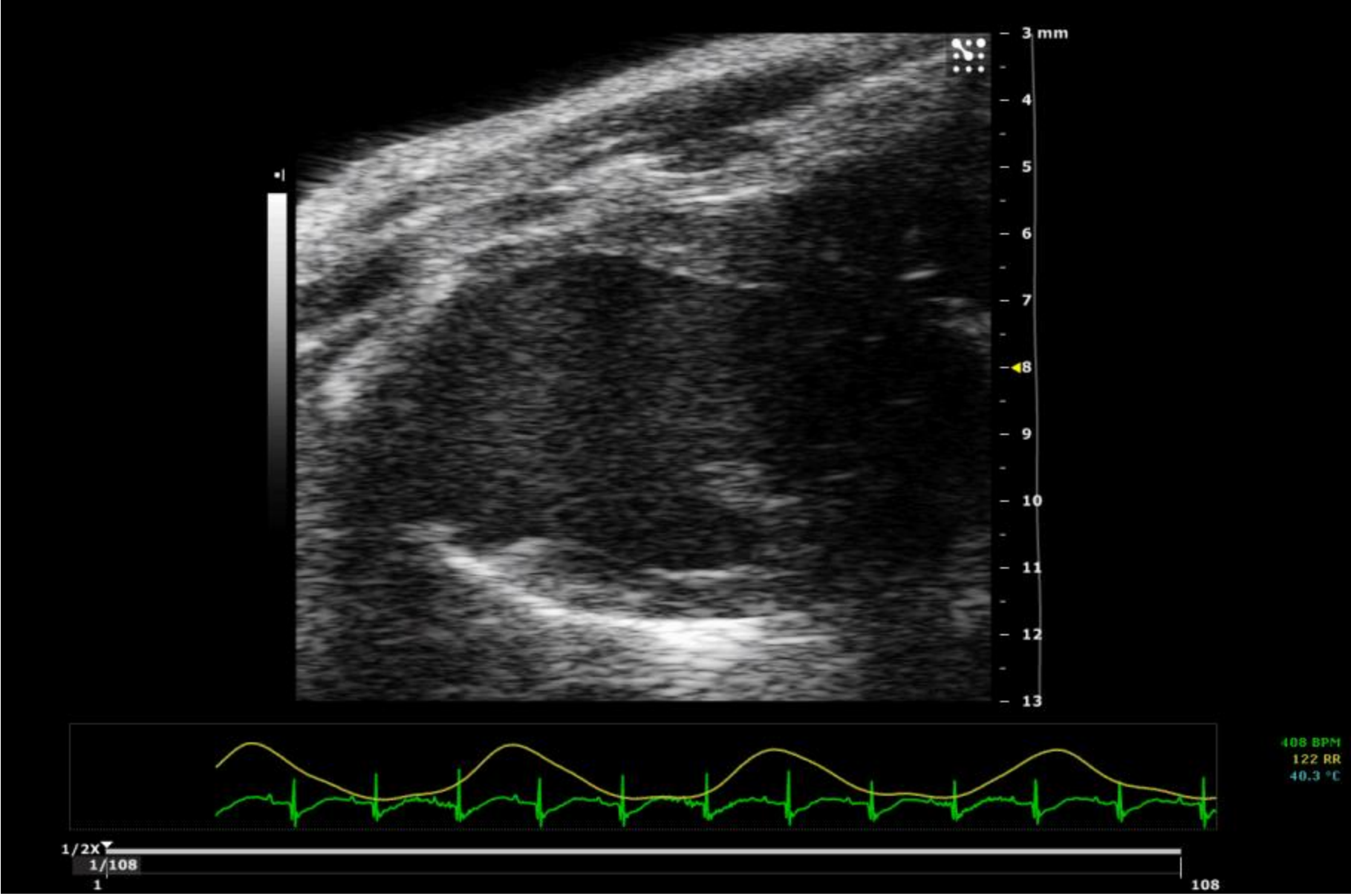
72 HR

2weeks after IM

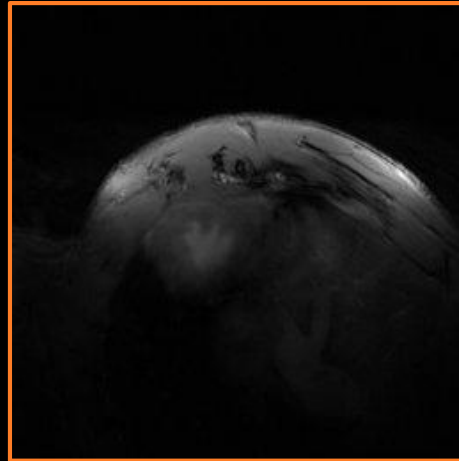
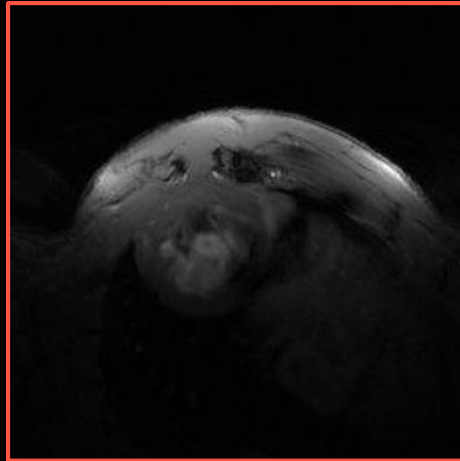
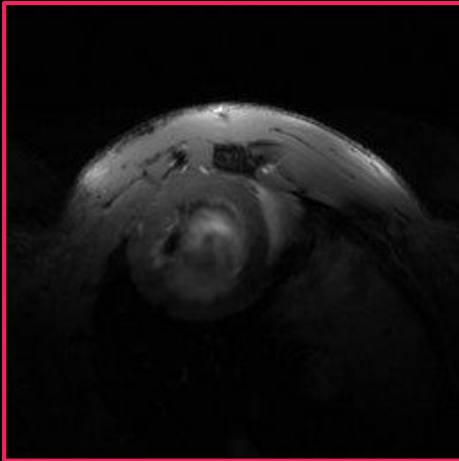
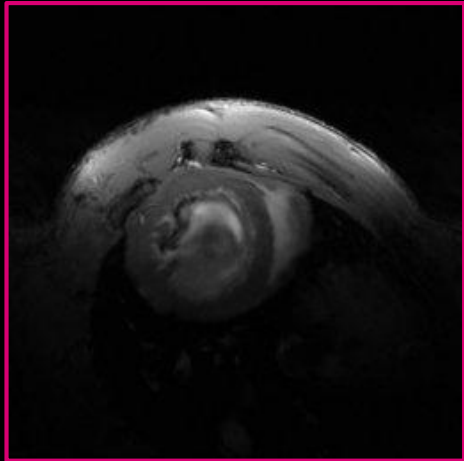
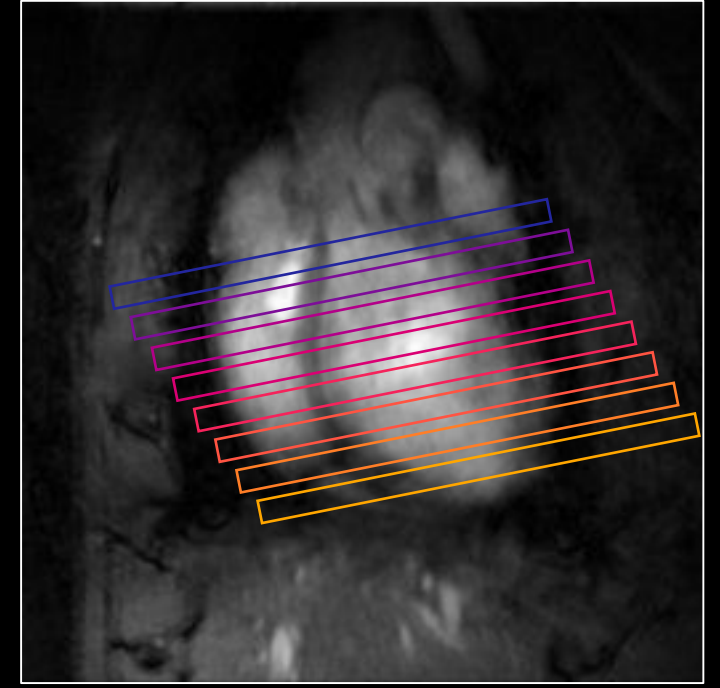
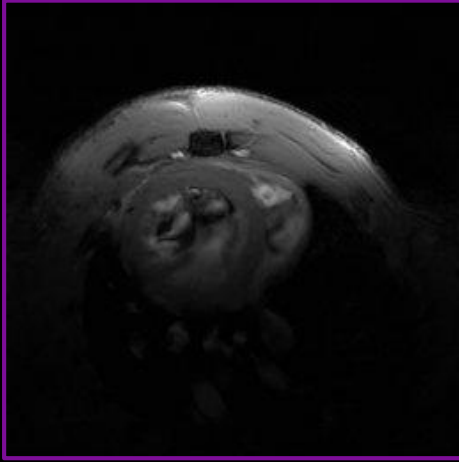
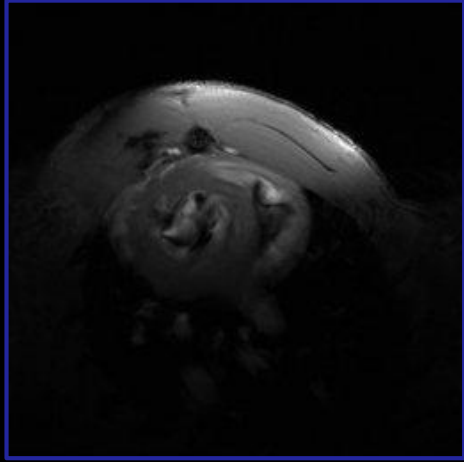


2weeks after IM



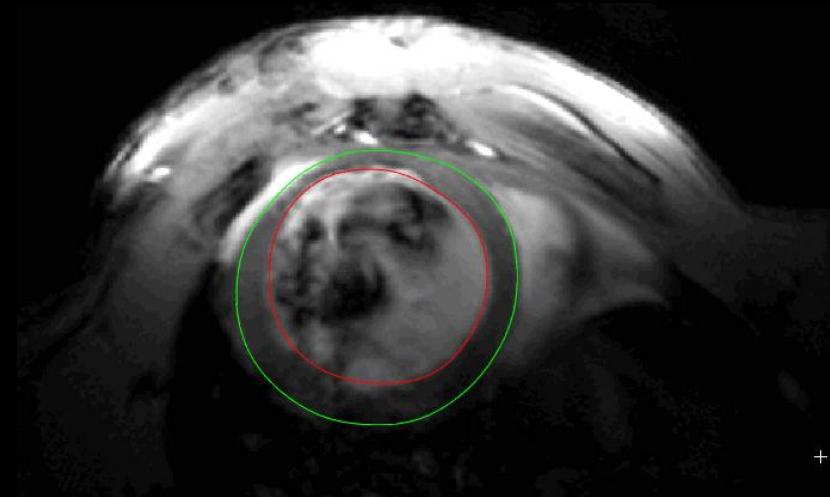


SHAM 2 (control)



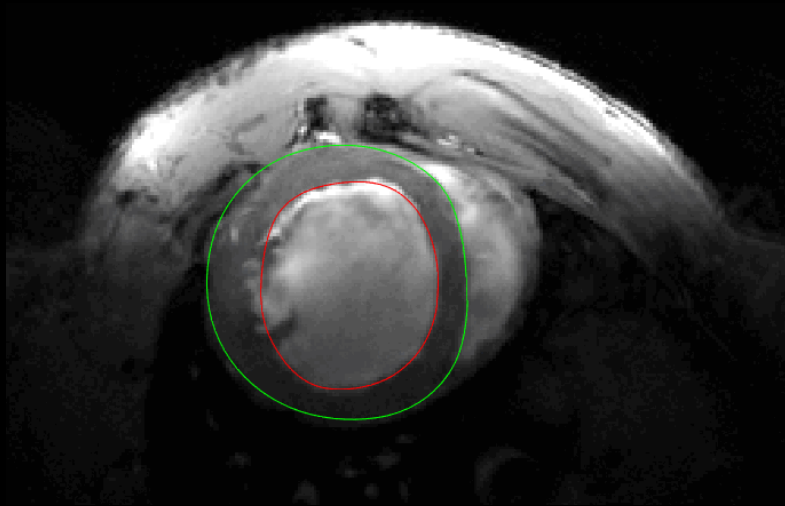
IM 1

- **Ejection fraction: 31 %**
- Evaluated from end-systole and end-diastole from all slices
- Software: Segment Medviso



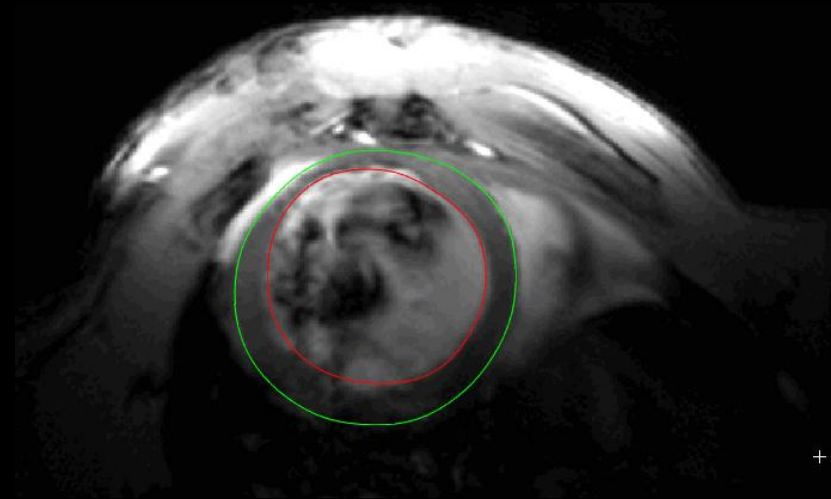
Comparison

SHAM 2



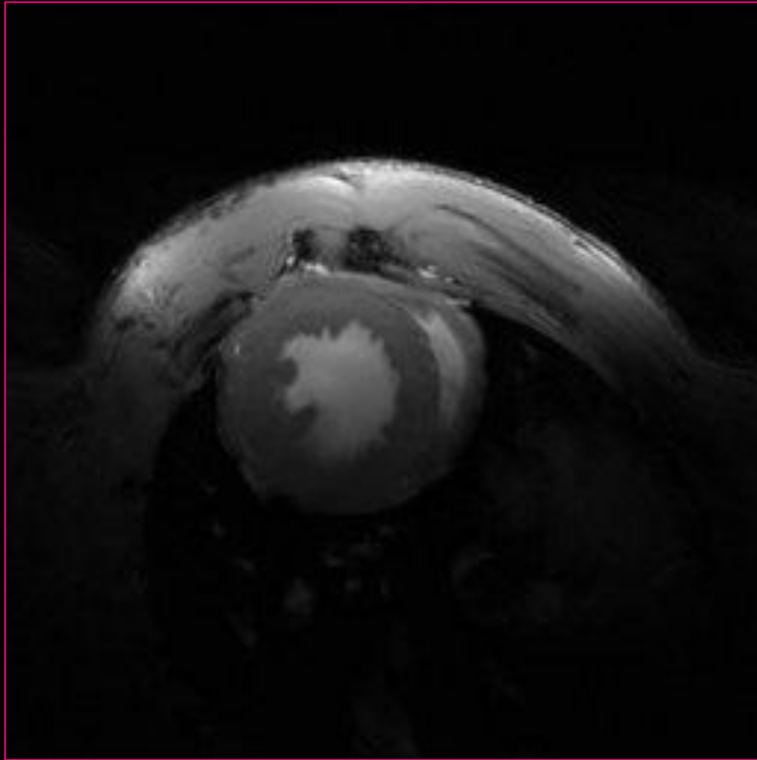
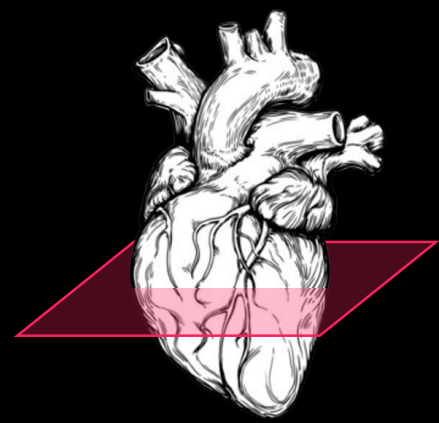
EF: 67 %

IM 1

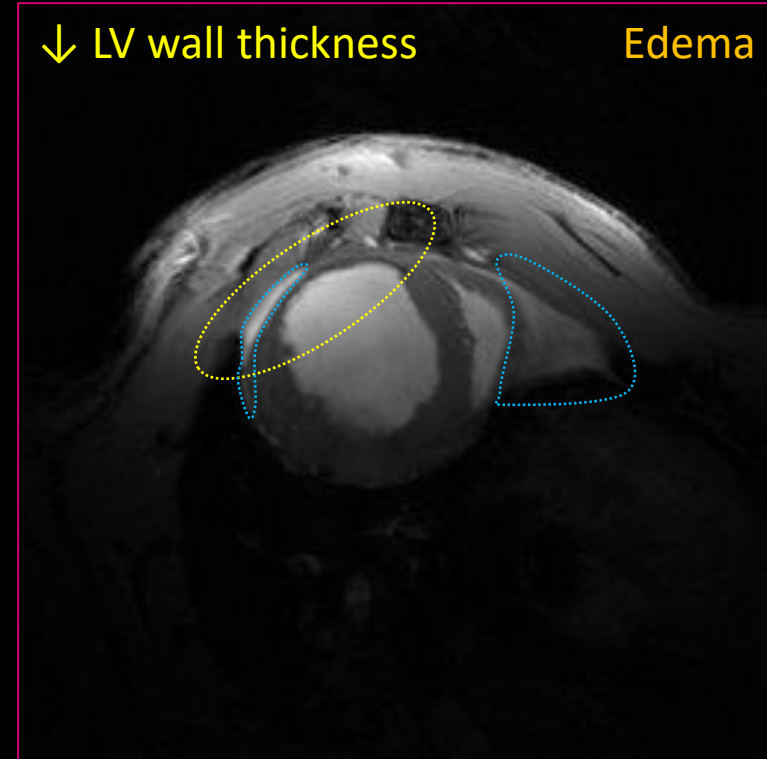


EF: 31 %

Comparison ES



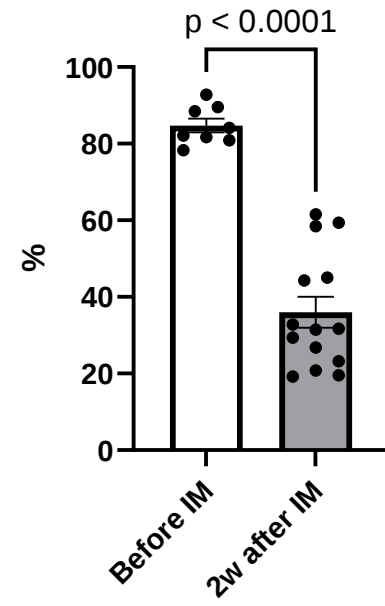
SHAM 2
EF: 67 %



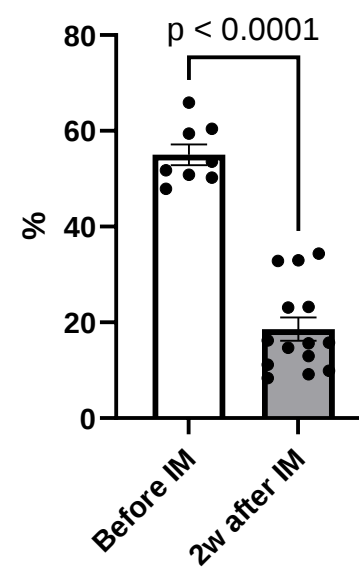
IM 1
EF: 31 %

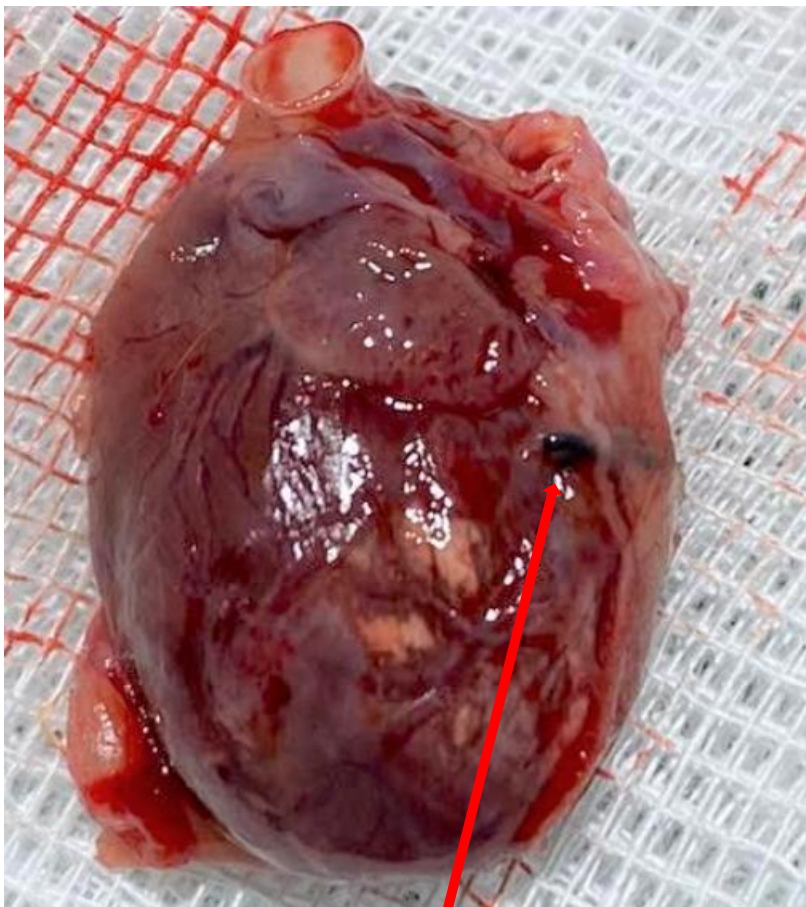


Ejection fraction LV

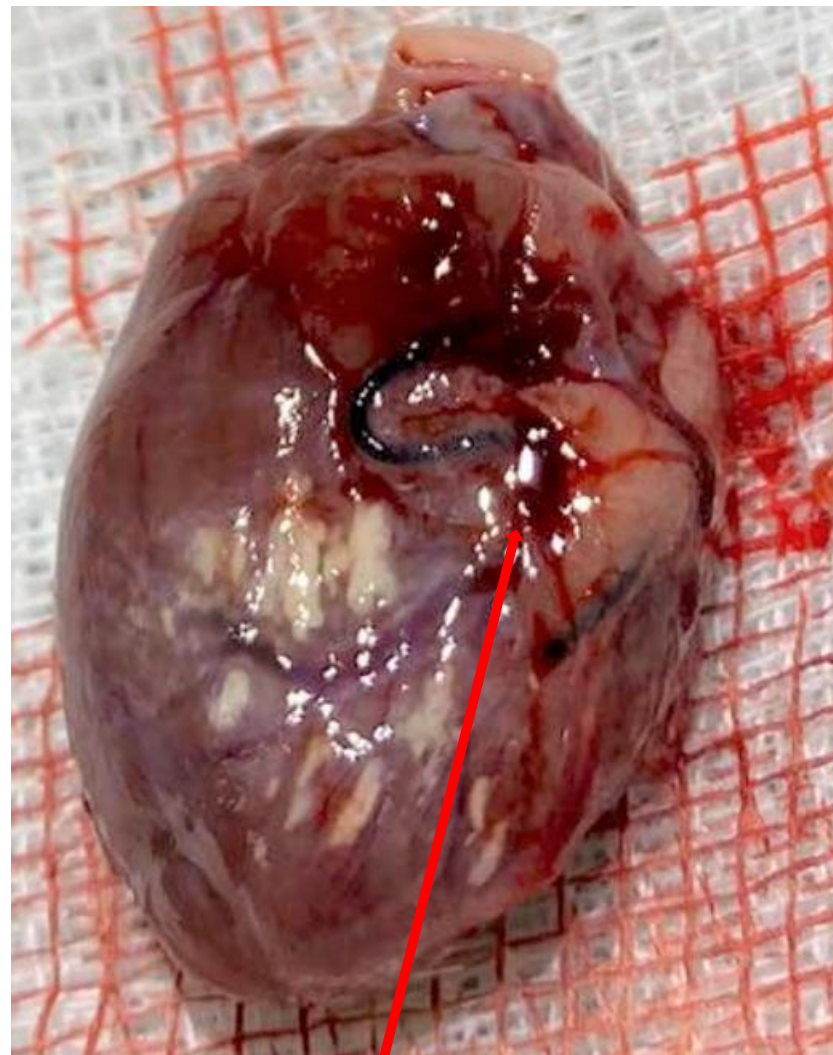


Fractional shortening LV



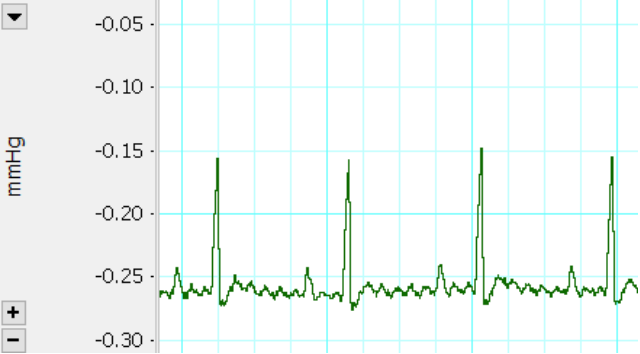


Podváz

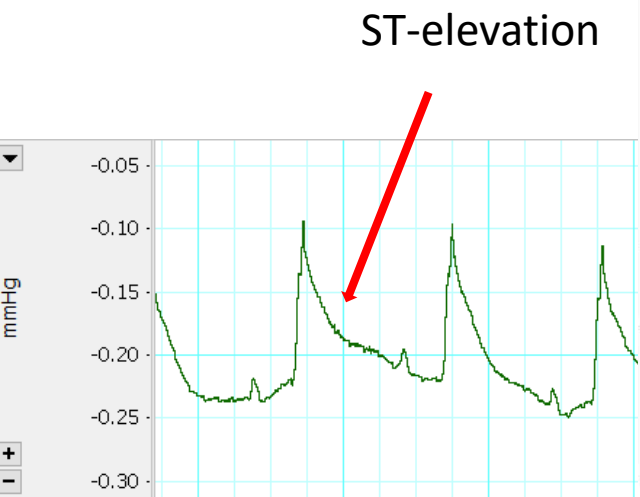
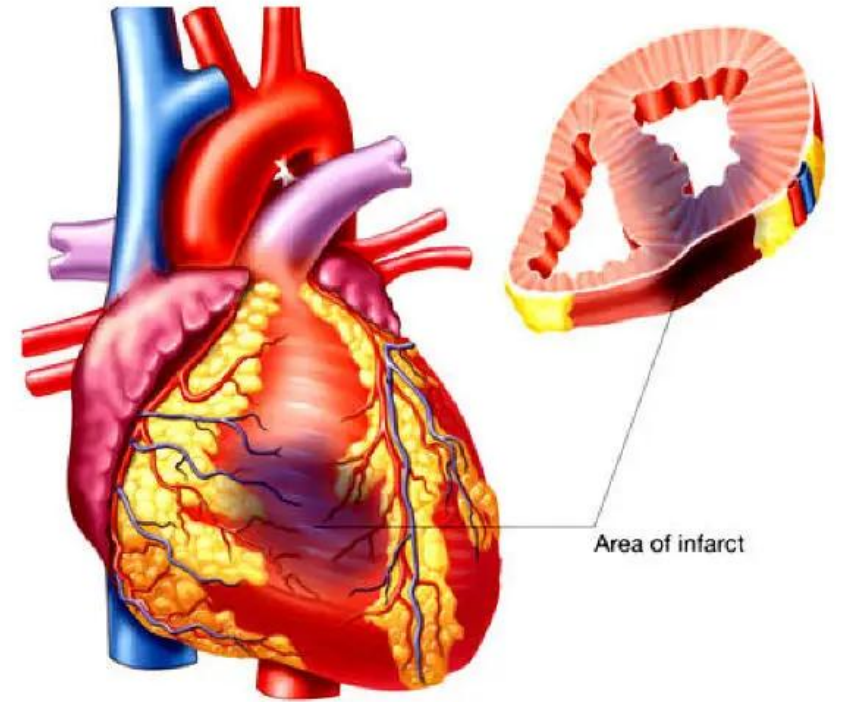
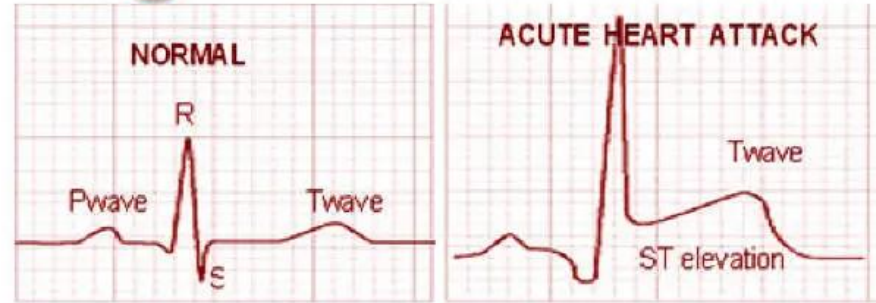


Podváz

Ecg and heart attack, the classic signs



Before IM



Cardiac cycle	Minutes after heart attack starts	Hours later	1-2 days	Several days	Weeks after the attack
Normal	ST shifted	- ST shifted - R dropping - Q appears to be noticeable	- T inverted - Q goes lower	- ST normal - T inverted	- ST and T normal - Q no change



Waves of cardiac injury



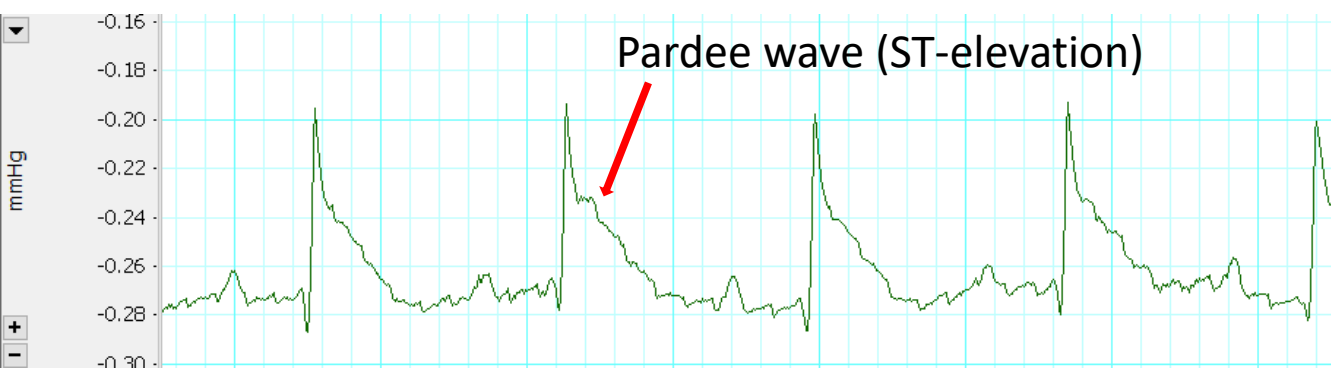
T NEGATIVE

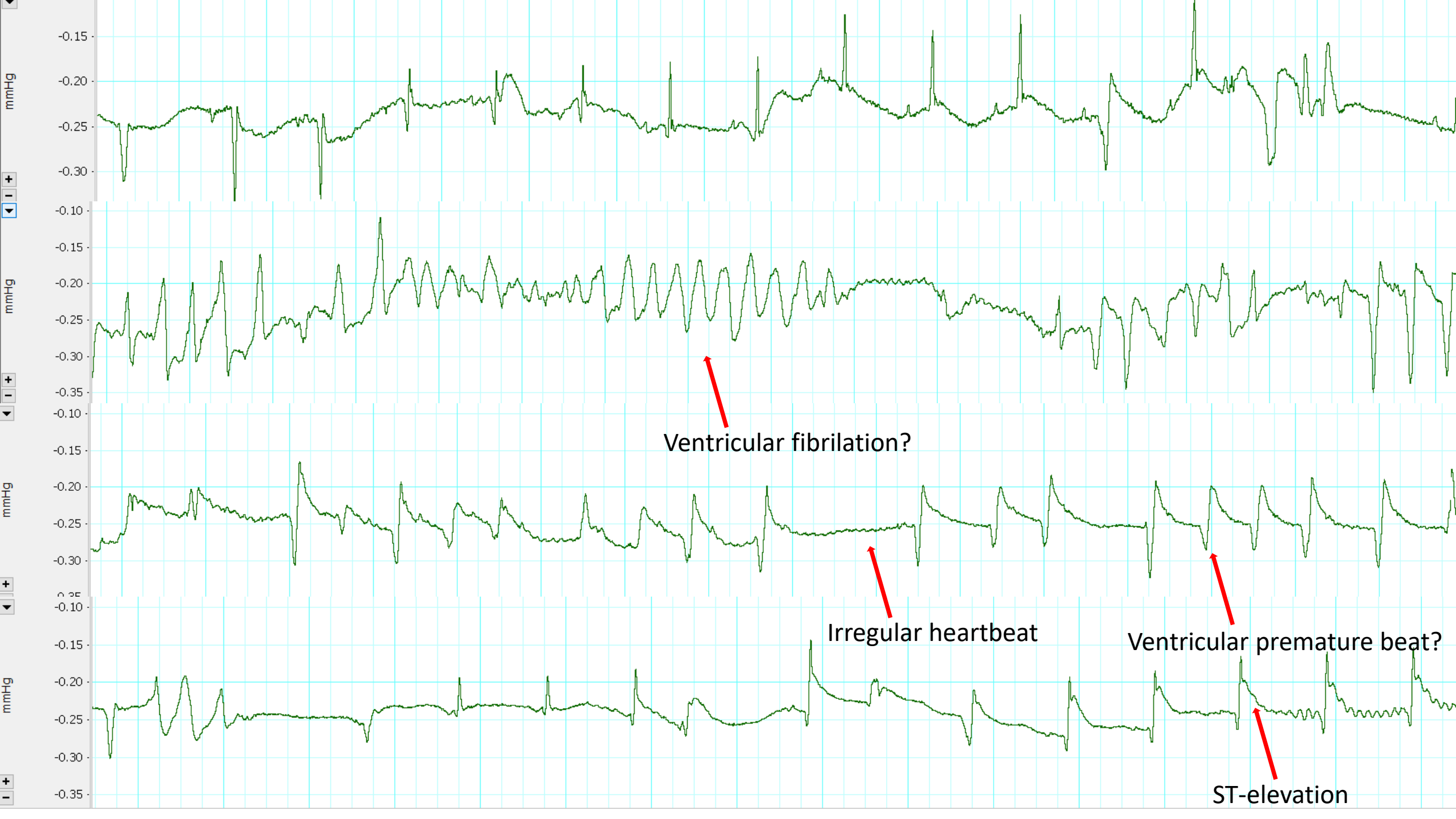
Subendocardial
ischemia wave



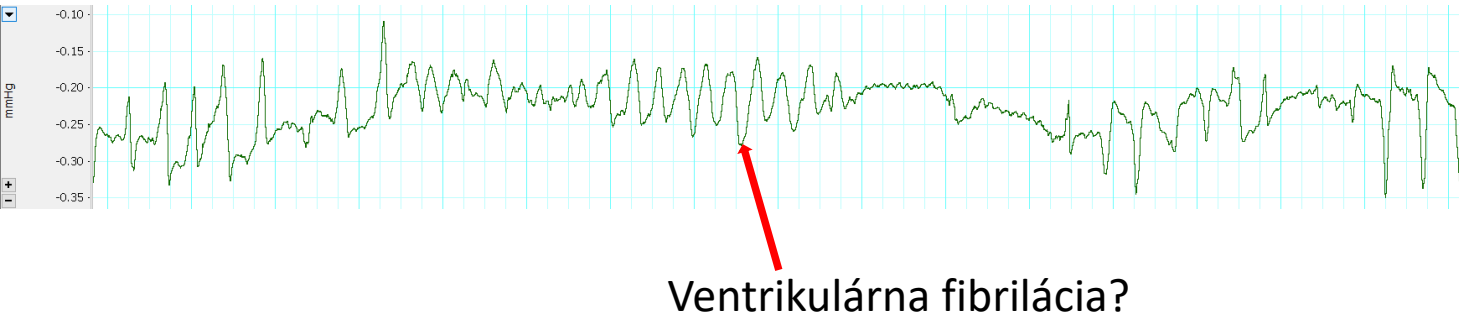
Pardee
wave

Transmural
ischemia wave





Prototyp defibrilátoru na potkany



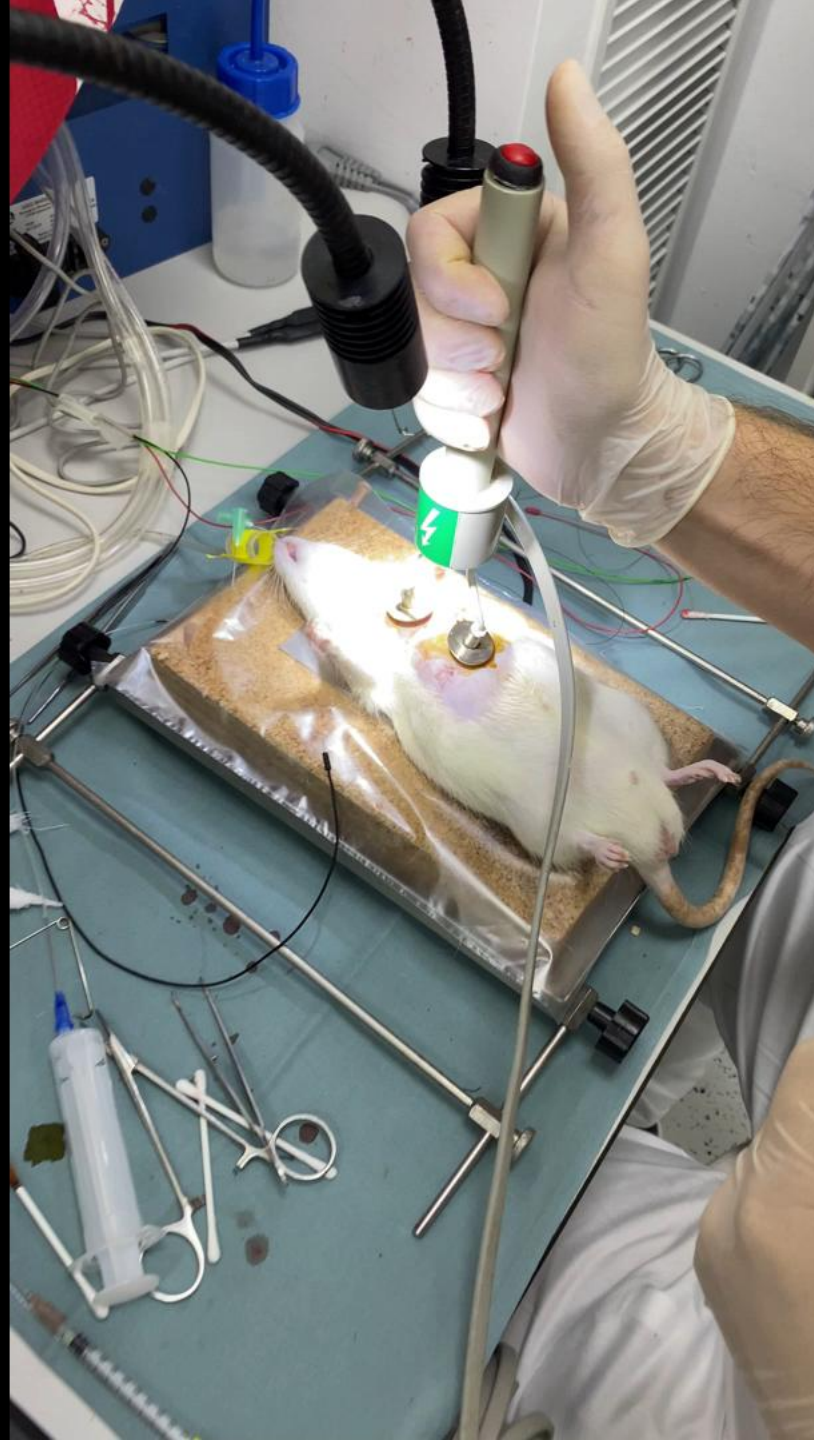
- Približne 20% potkanov umrie pri fibrilácii
- Potreba defibrilátoru pre zníženie mortality
- Žiadny defibrilátor na trhu, ktorý by sa dal reálne objednať a kúpiť
- Vytvorenie defibrilátoru technikmi na IKEM



Oddělení zdravotnické techniky a investic do ZT ÚIIV

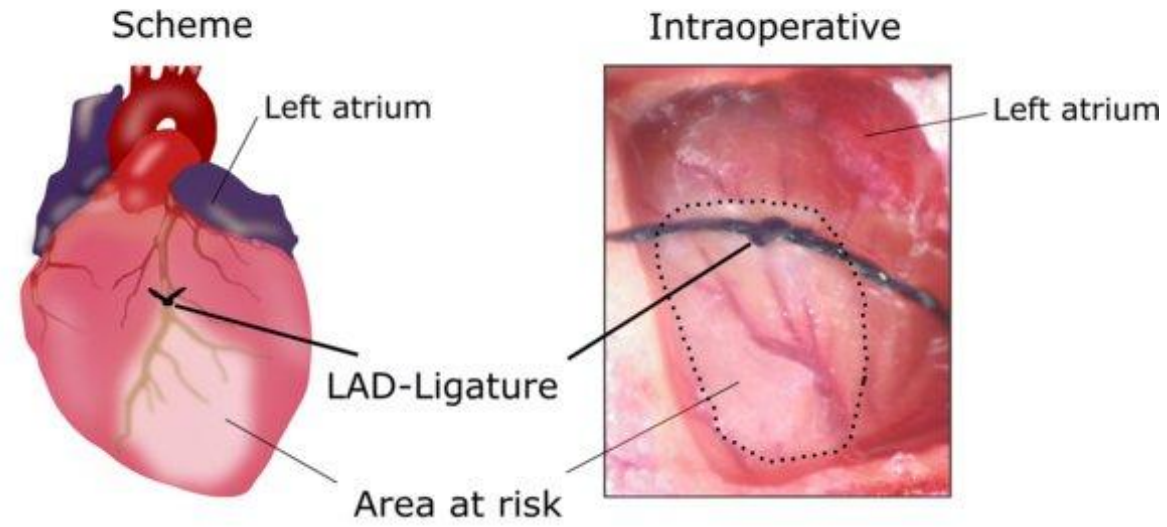
IKEM

Ing. Petr Moravec
Ing. Ondřej Švagr



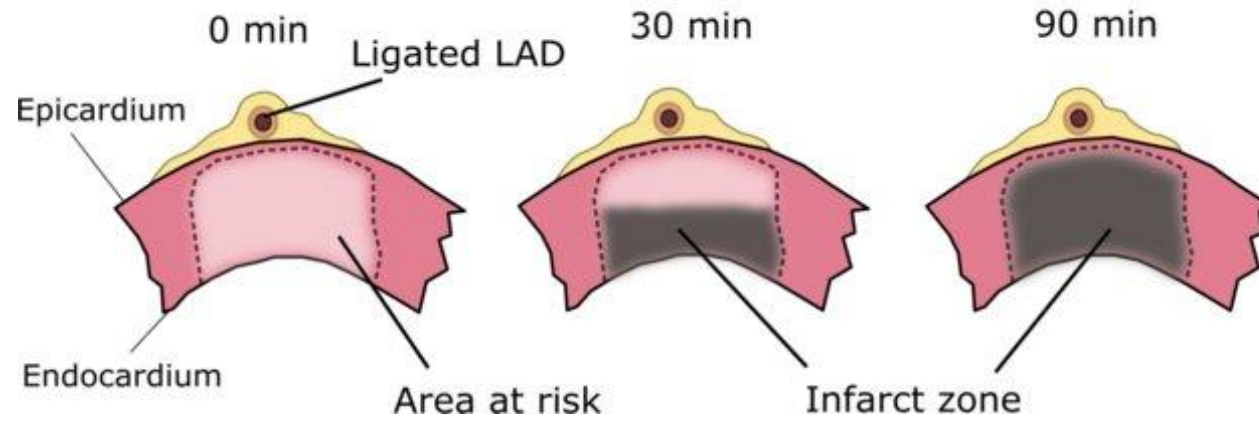
a

Induction of MI

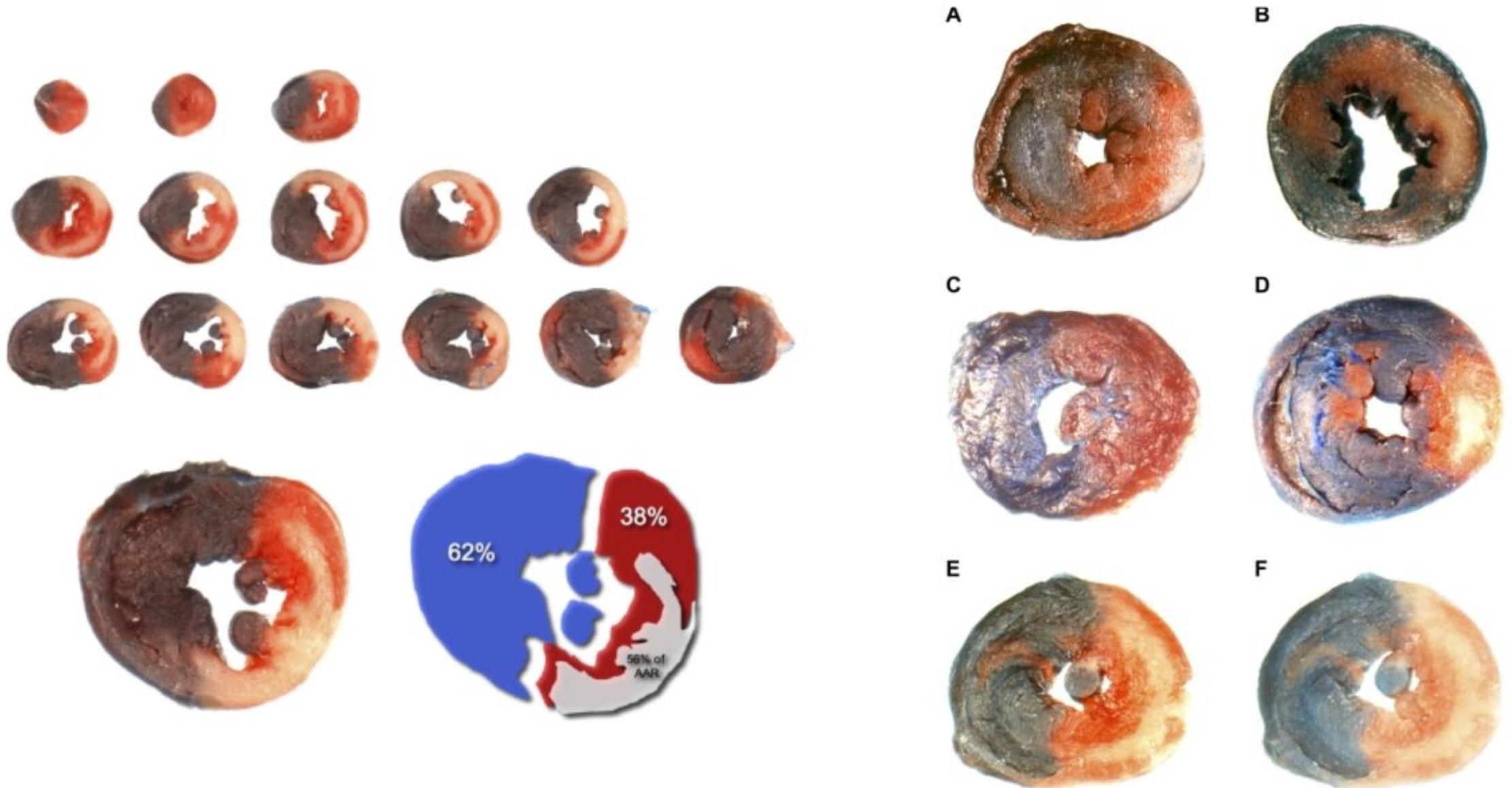


b

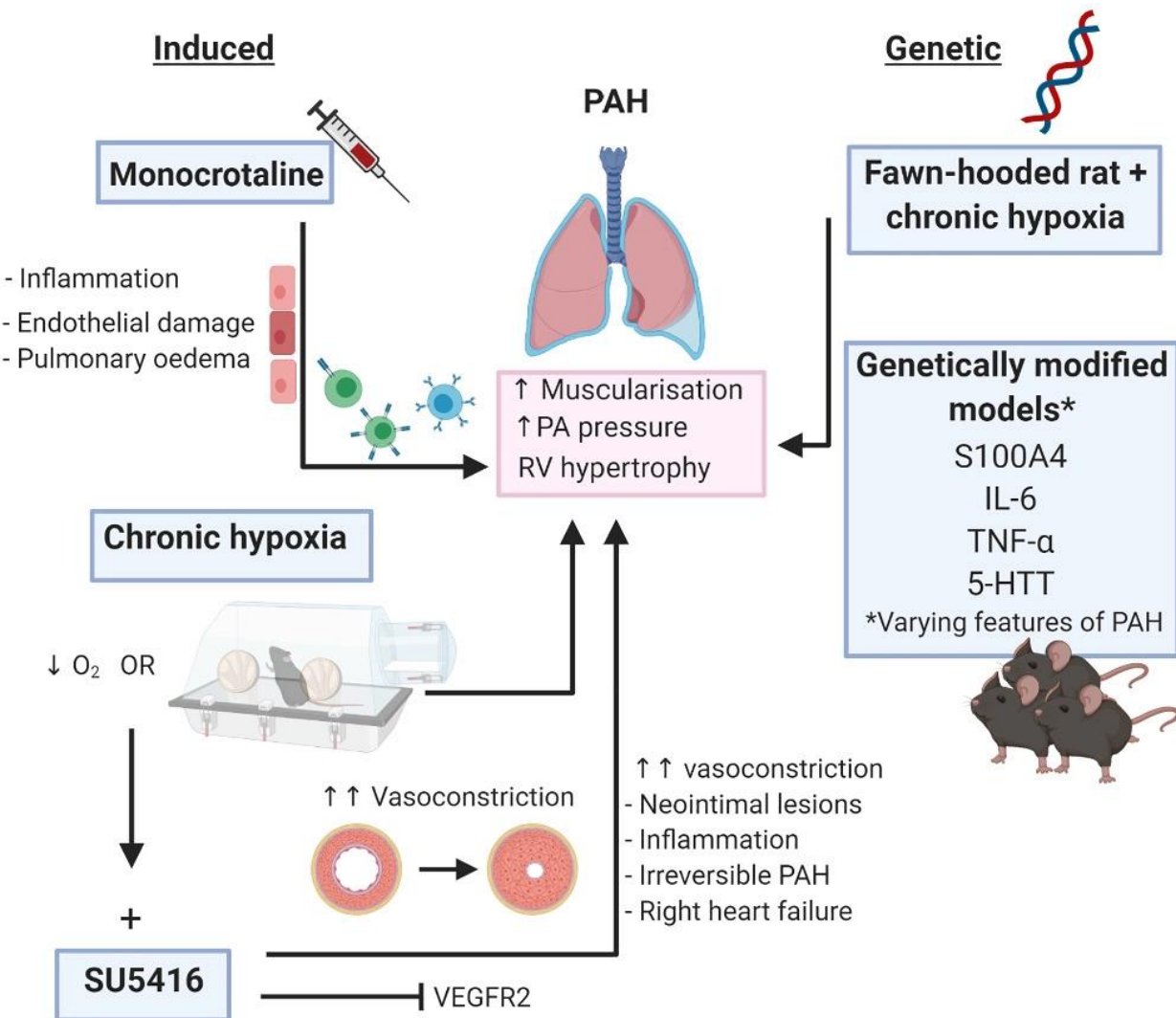
Wave front progression of the infarct zone



IM area evaluation (evans blue dye perfusion with subsequent triphenyltetrazolium chloride immersion)



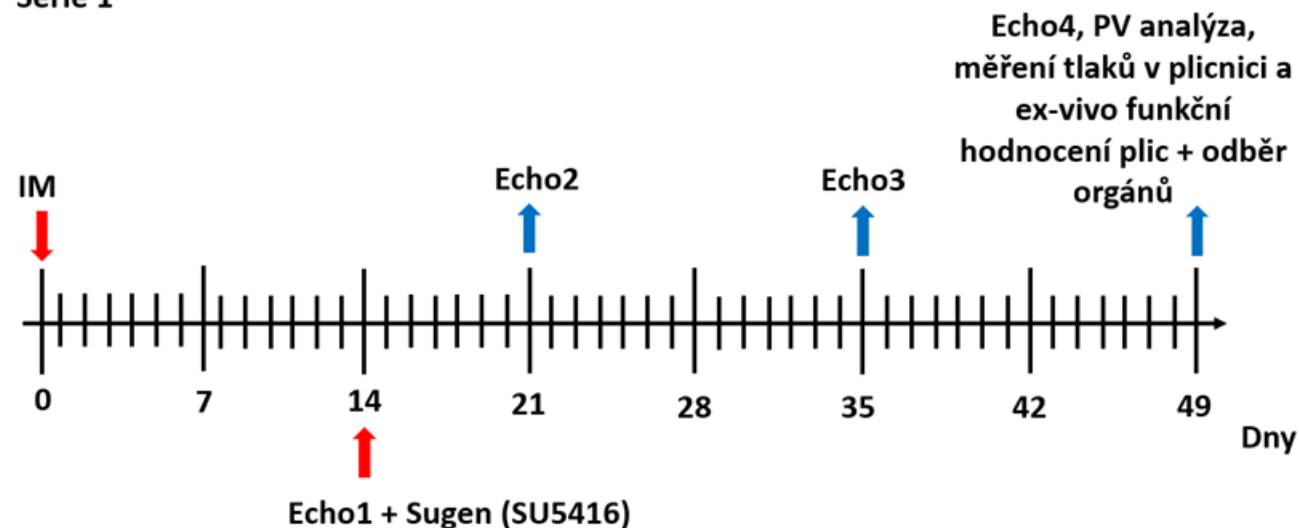
Model obojkomorového srdcového zlyhania



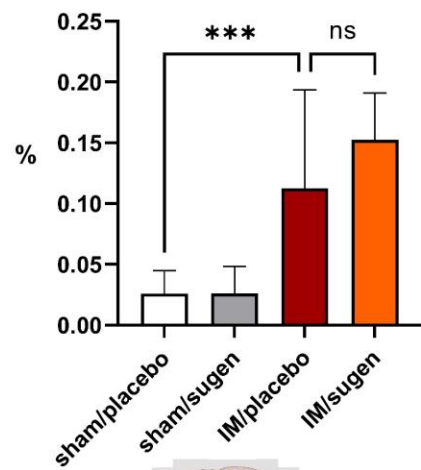
Část 1: optimalizace experimentálního modelu srdečního selhání s plicní vaskulopatií

1. Sham HanSD/placebo
2. IM HanSD/placebo
3. IM HanSD/SU5416

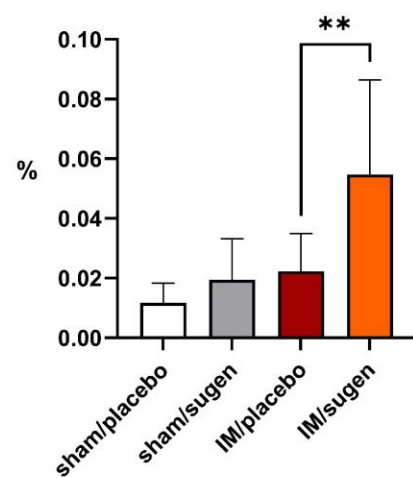
Série 1



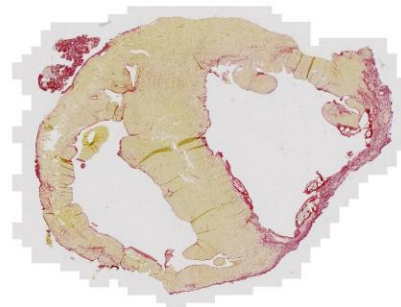
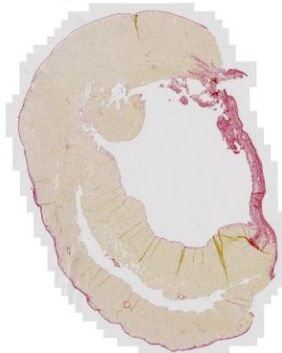
a) Collagen composition in LV



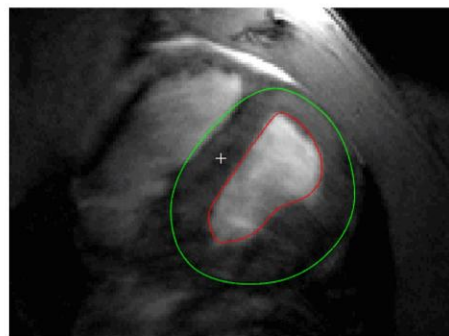
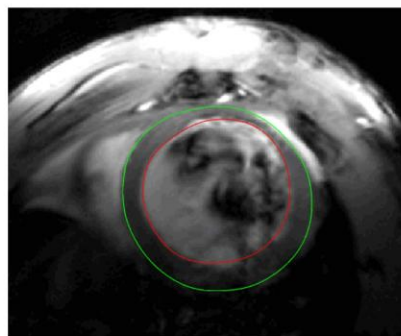
Collagen composition in RV



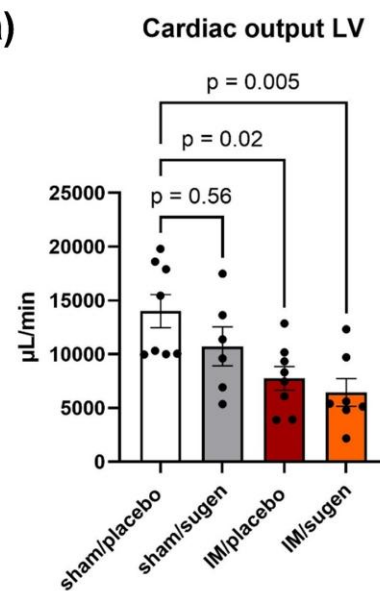
b)



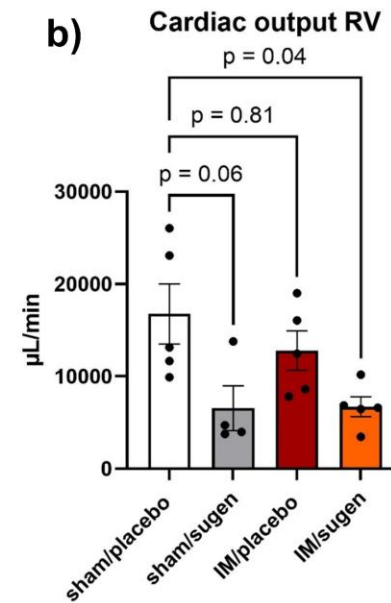
c)



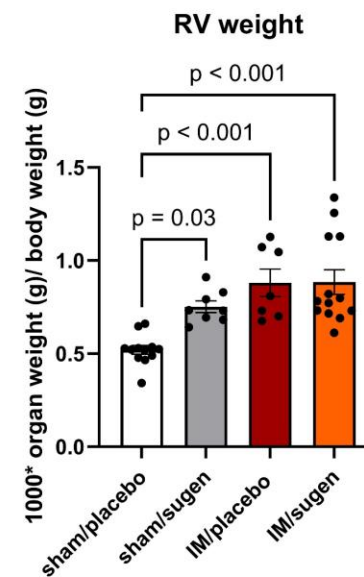
a)



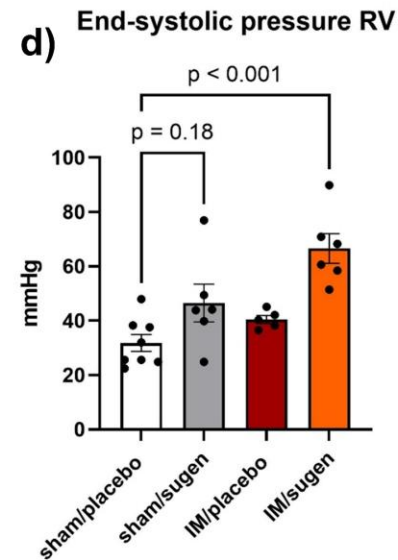
b)



c)



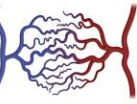
d)



RV failure due to LV dysfunction

LV dysfunction → pulmonary hypertension → RV pressure overload → RV remodeling → RV dysfunction

Role of RV fibrosis in RV dysfunction?



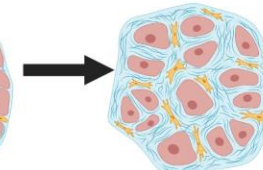
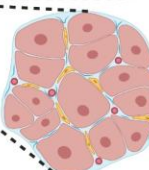
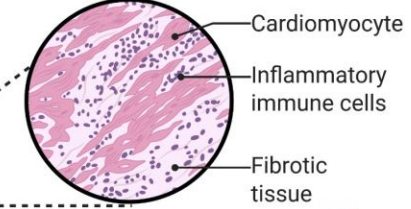
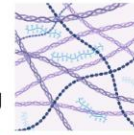
↑ RV afterload

Metabolic and immune mechanisms of fibrosis initiation

Metabolic and inflammatory stimuli trigger transcriptional programs and fibroblast activation

sorbitol, BOHB, TGF- β , IL-1, IL-6, Meox1

↑ ECM forming



Animal model

Biventricular HF
IM + PH (Sugen)

sham/placebo

IM/Sugen

IM/Sugen + sorbitol

IM/Sugen + BOHB

IM/Sugen + kynurenine supplement

Laboratory rat



Fibrotic changes in RV vs LV in biventricular HF



RV LV



IM/sugen



IM/sugen



IM/sugen



IM/sugen

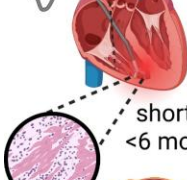
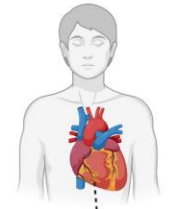


IM/sugen

Human studies

Patients with:

G1) Recent-onset non-ischemic HF



short HF <6 months



non-dilated RV

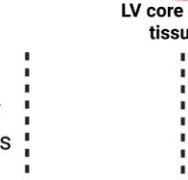
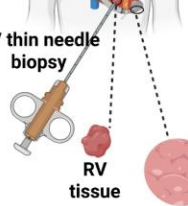
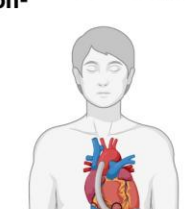


early fibrosis



EARLY STAGE

G2) Advanced HF undergoing LVAD implantation



RV thin needle biopsy



RV tissue

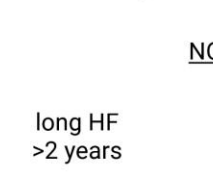
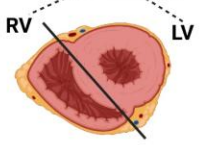
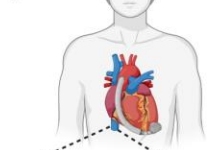


LV core apex tissue



INTERMEDIATE STAGE

G3) end-stage non-ischemic HF HTx patients



RV LV



dilated RV

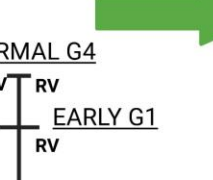
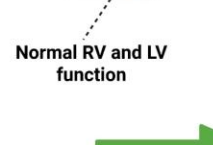
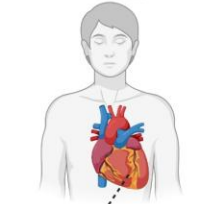


advanced fibrosis



LATE STAGE

G4) Unused donor hearts



Normal RV and LV function



NORMAL G4

LV RV

EARLY G1

RV

INTERMEDIATE G2

LV RV

LATE G3

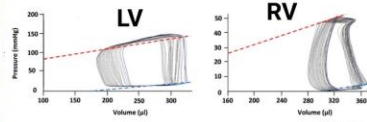
LV RV

Echocardiography



RV diameters
FAC
EF%

Biventricular PV analysis



Illumina
RNA-Seq



Histology



qPCR



Western blot



ELISA



Proteomics



Metabolomics



FAP, POSTN



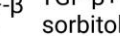
Fibroblast cultures



TGF- β



TGF- β + sorbitol



TGF- β + kynurenine



TGF- β + BOHB





- Genetický model potkanov s exprimovaním osi ANG 1-7 u modelu IM + PAH
- Meranie ex-vivo kontraktility trabekúl



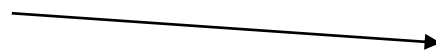
**Matej
Molnár**



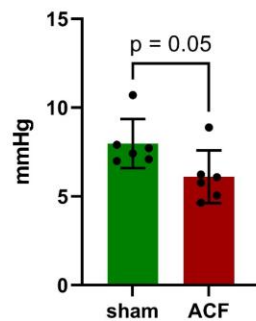
**Thu Thao
Nguyen**



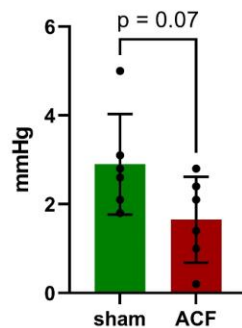
**Jan
Kropáček**



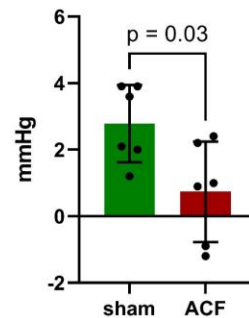
Basal values of arterial pressure



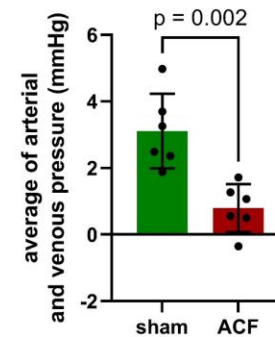
Precapillary resistance (arterial occlusion)



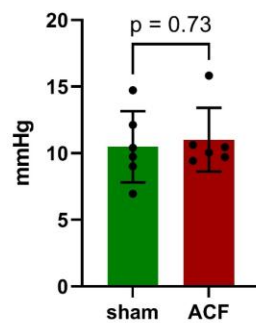
Postcapillary resistance (venous occlusion)



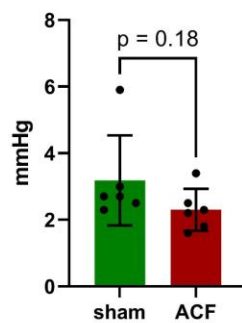
Capillary pressure
(average of arterial and venous pressure after combination of occlusions)



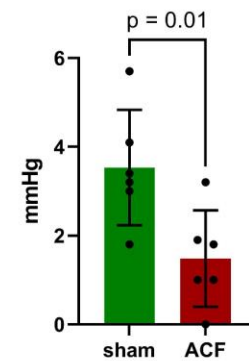
Arterial pressure in hypoxia



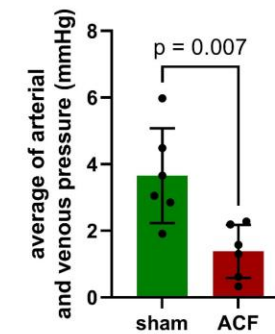
Arterial occlusion in hypoxia



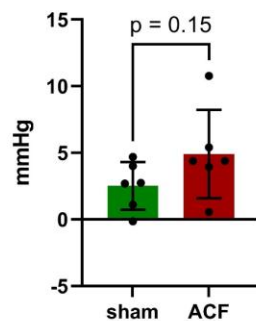
Venous occlusion in hypoxia



Capillary pressure in hypoxia
(average of arterial and venous pressure after combination of occlusions)

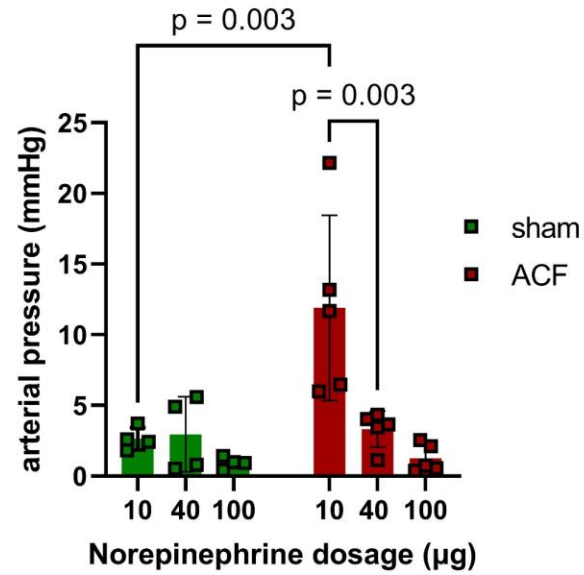


Increase in arterial pressure in hypoxia
(arterial pressure in hypoxia minus basal values)

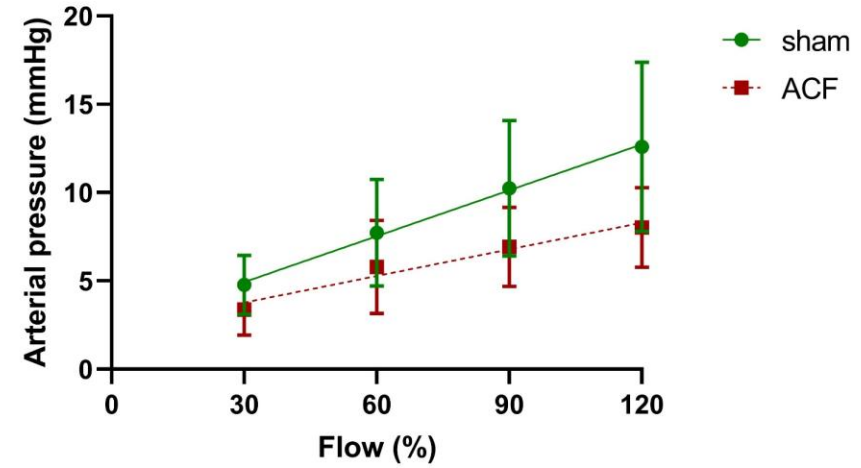


Norepinephrine increase

(pressure values after increase - pressure values before injection)

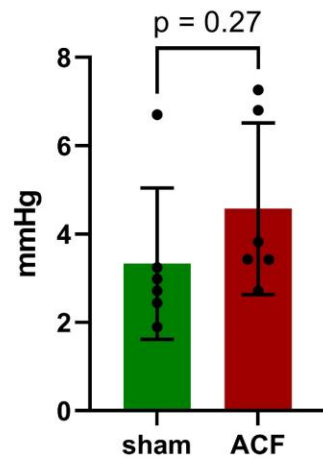


Pressure-flow (P/Q) arterial pressure

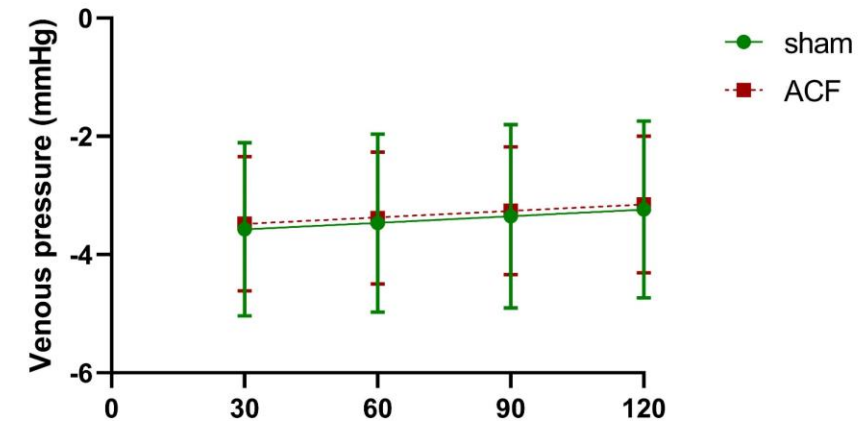


Arterial pressure increase after angiotensin II

(pressure values after increase - pressure values before injection)

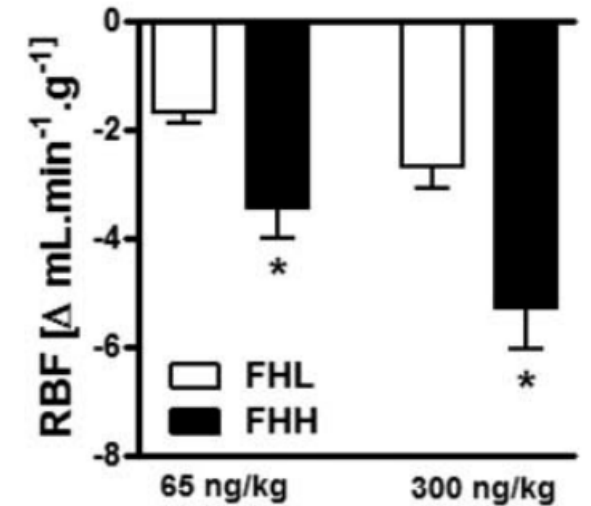
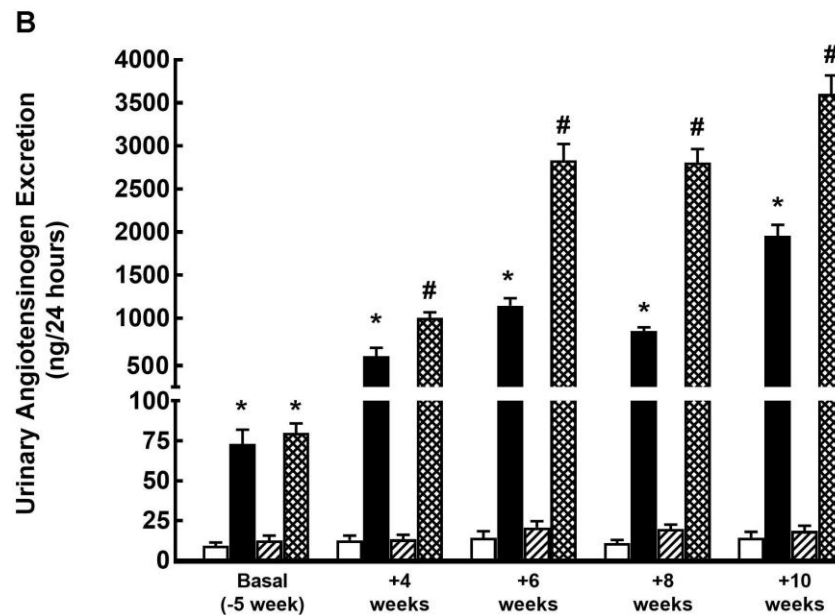
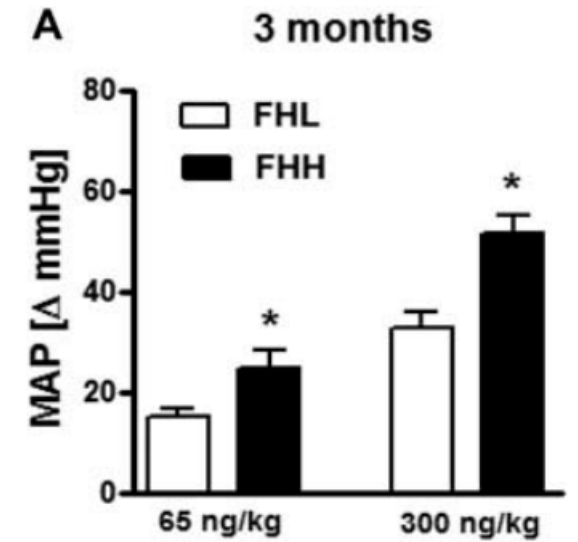
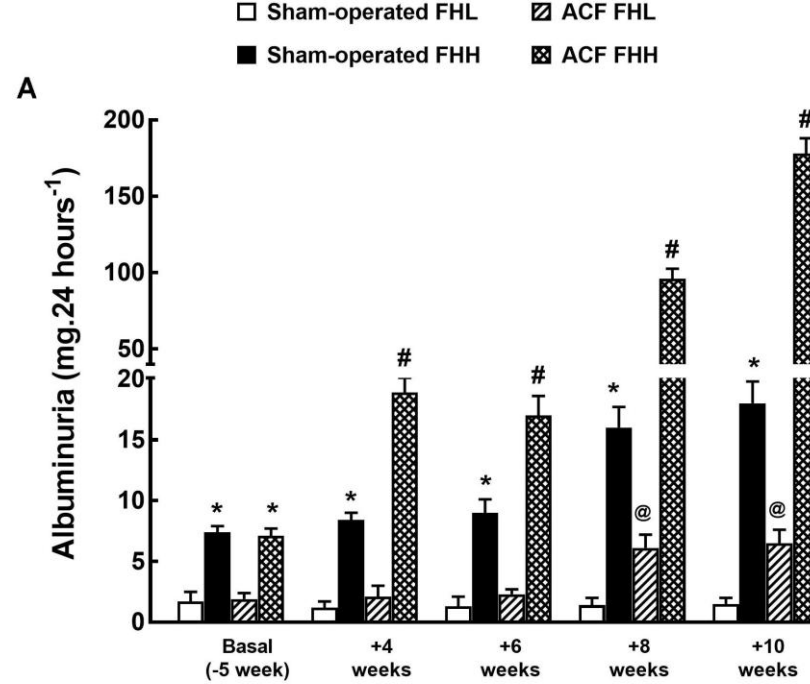


Pressure-flow (PQ) venous pressure



Modely CKD

- Fawn hooded hypertensive rats



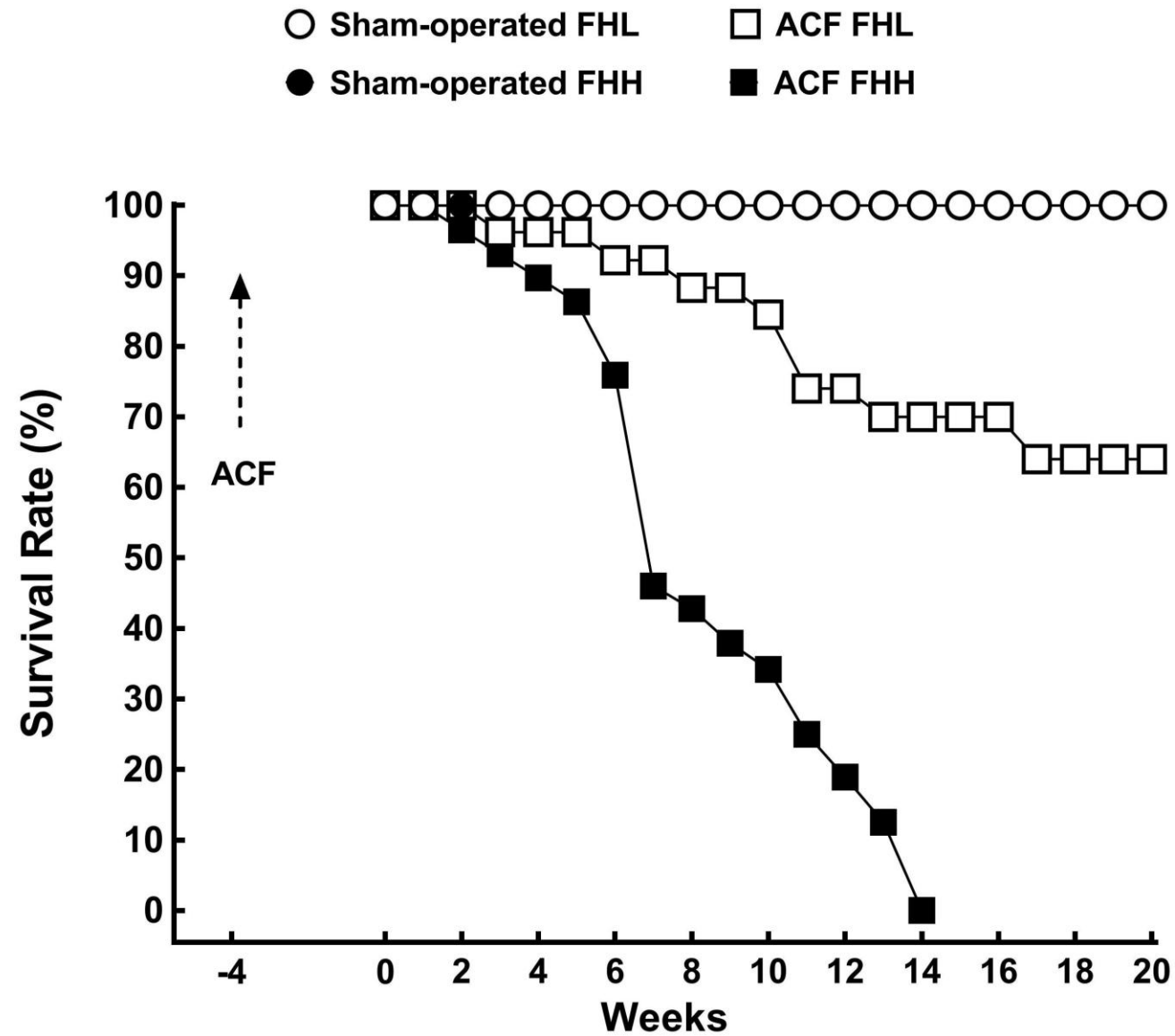
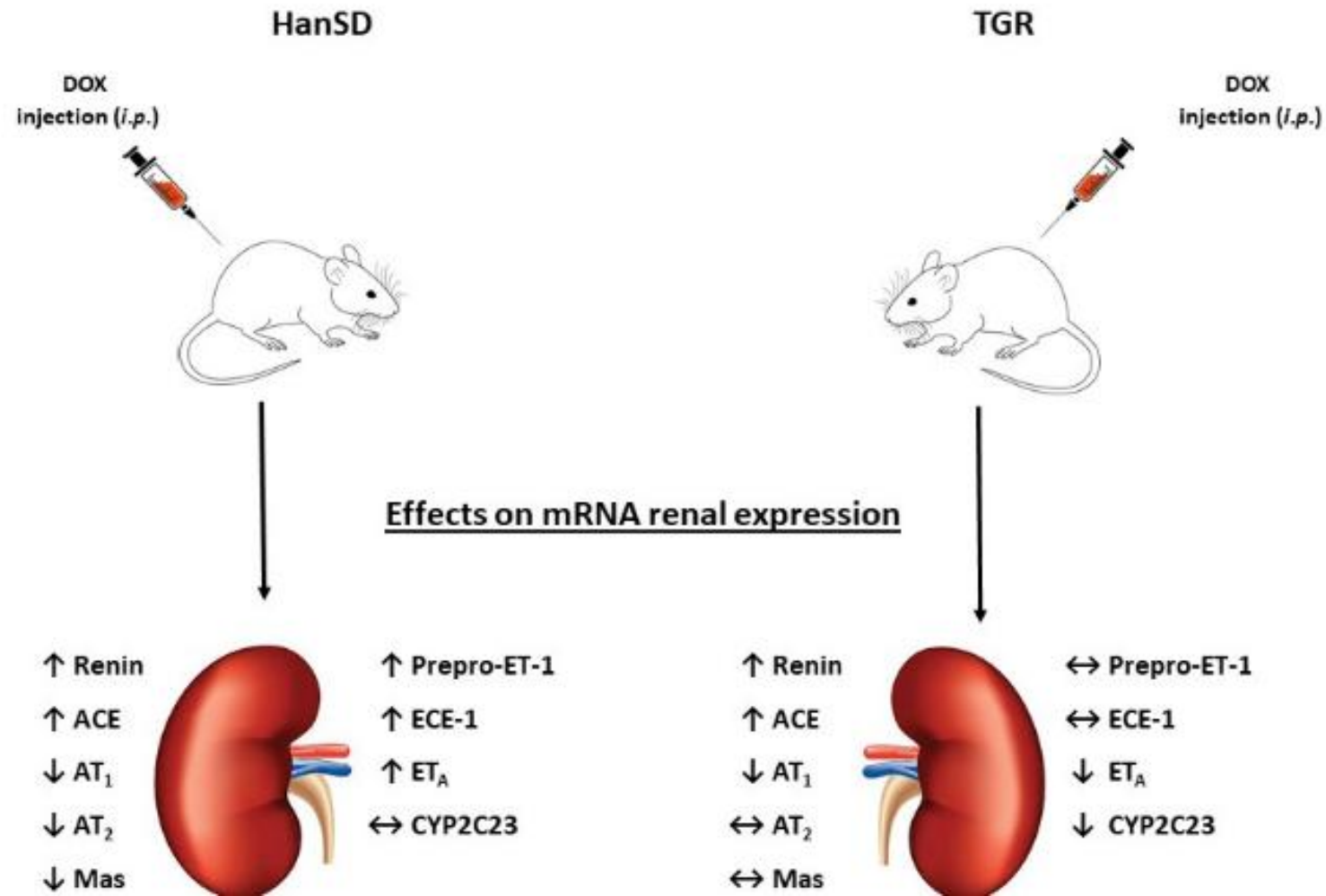


Table 1. Agents which cause cardiotoxicity.

Drug	Cardiotoxic effects	Mechanism of cardiac toxicity	Prevalence of cardiotoxicity	Reference
Trastuzumab	Heart failure	Damage to mitochondria	1–28%	[10]
Sunitinib, Sorafenib	- Heart failure - Acute coronary syndrome - Hypertension	Inhibit tyrosine kinase pathway	3–8%	[11]
5-Fluorouracil	- Dilated cardiomyopathy - Ventricular arrhythmia - Sudden cardiac death	Anthracyclines (Aggregate dose) Doxorubicin (>500mg/m²) Liposomal doxorubicin (>900mg/m²) Epirubicin (>720mg/m²)	Heart failure	Production of free radicals

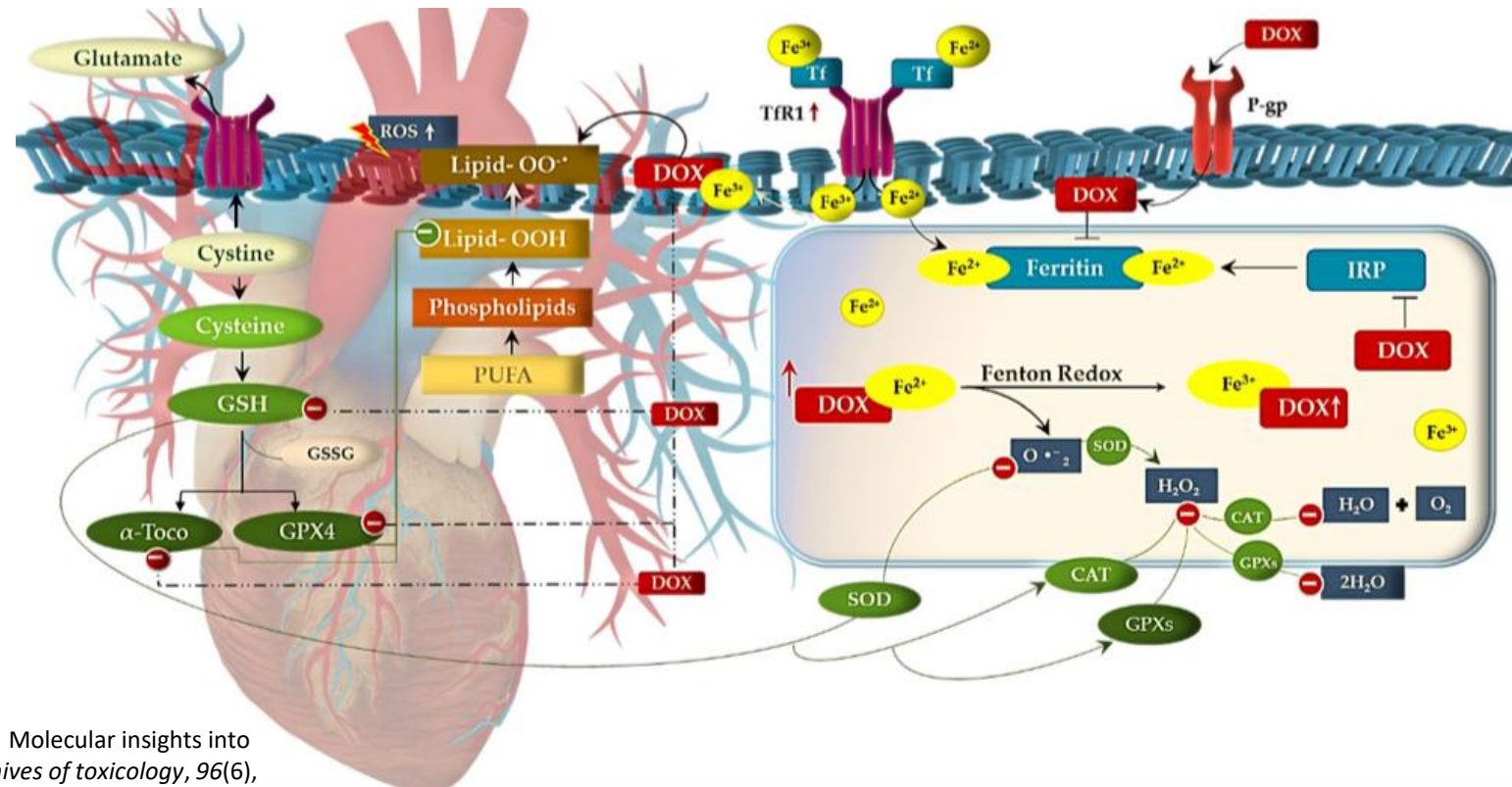
Imatinib, dasatinib, nilotinib	Heart failure	Inhibit <i>ABL</i> tyrosine kinase in cardiac muscle cells	1.7%	[13]
Bevacizumab	- Hypertension - Congestive heart failure	Unknown	50%	[14]
Cisplatin	Hypertension	Generation of oxidative stress	Unknown	[15]
		- Direct cellular toxicity - Lipid peroxidation	2.3–8%	[16]
		Unknown	7–28%	[17]
Anthracyclines (Aggregate dose)	Heart failure	Production of free radicals	2%	[18]

Kardiotoxickou navodené HF

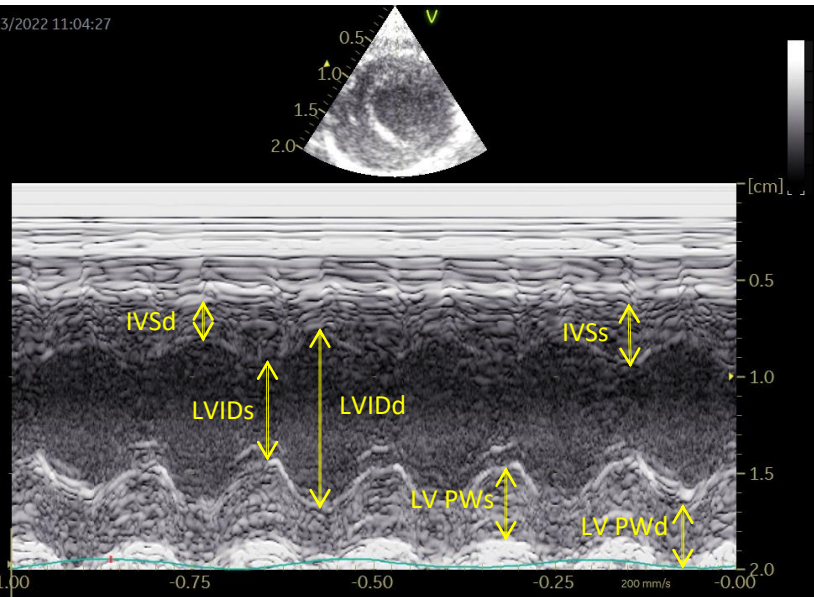


Doxorubicin model HF

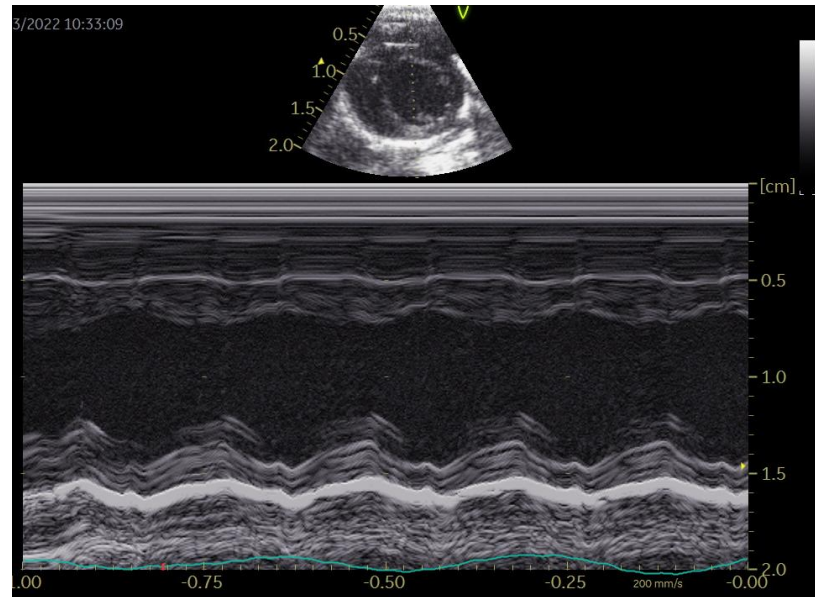
- oxidative stress through cardiac iron overload.
- inflammatory response and resultant.
- mitochondrial dysfunction.
- autophagy.
- apoptosis via the intrinsic pathway.



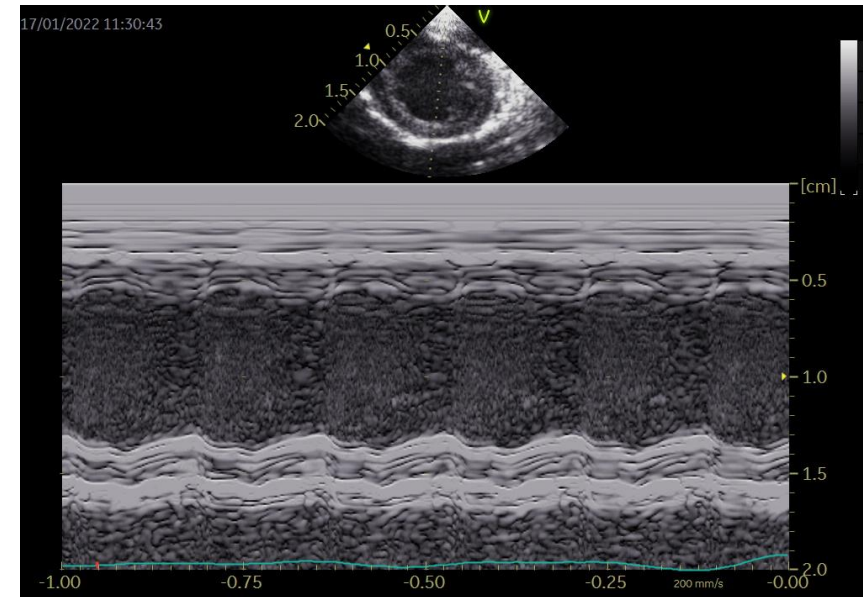
Control TGR



Doxo 2w TGR



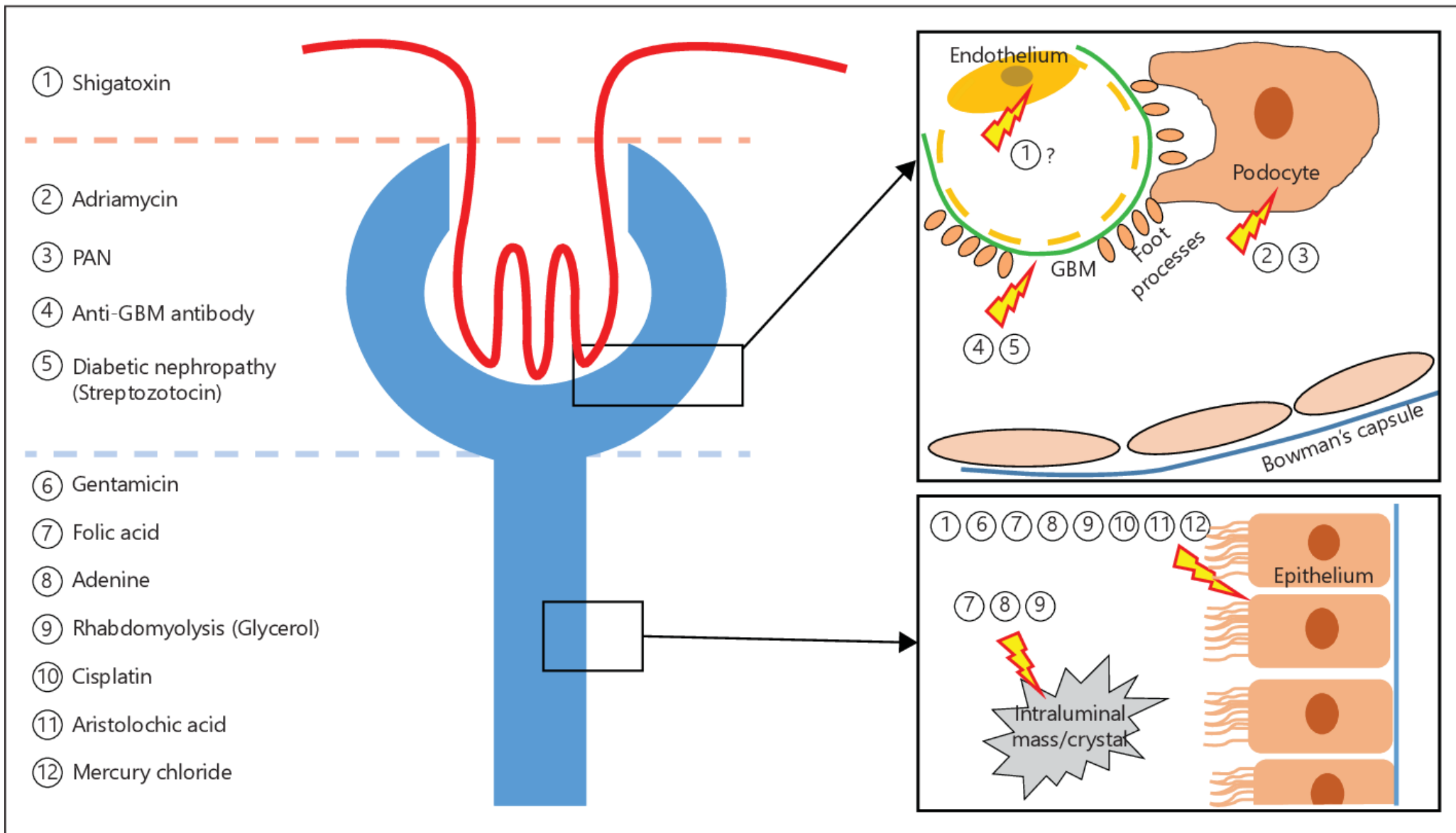
Doxo 5w TGR



IVSd, IVSs – interventricular septum diameter in end-diastole and systole

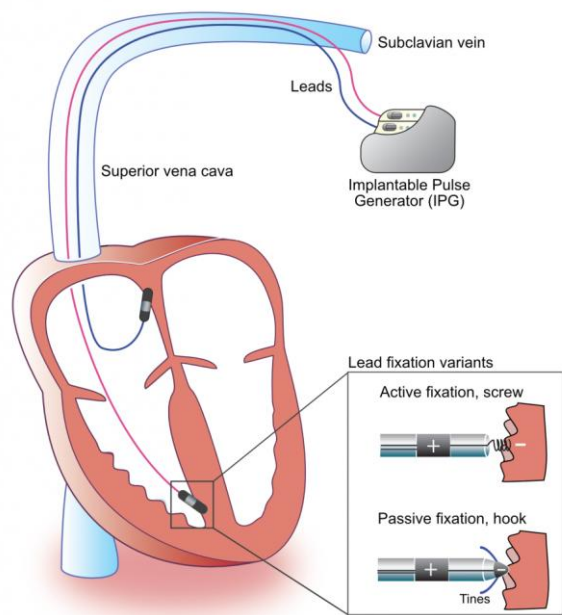
LVIDd, LVIDs – left ventricular internal diameter in end-diastole and systole

LV PWd, LVPWs – left ventricular posterior wall diameter in end-diastole and systole

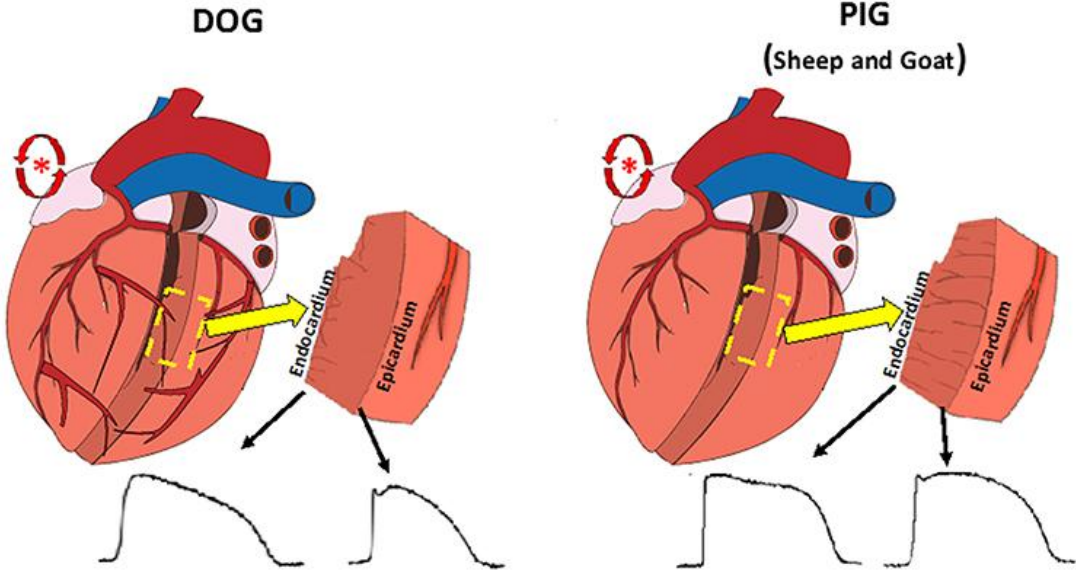


Experimentálne animálne modely atriálnej fibrilácie

- Pacing induced tachycardia
- Electrically induced AF
- Mono-causal AF



Piktel JS, Wilson LD. Translational Models of Arrhythmia Mechanisms and Susceptibility: Success and Challenges of Modeling Human Disease. Front Cardiovasc Med. 2019 Sep 10;6:135. doi: 10.3389/fcvm.2019.00135. PMID: 31552276; PMCID: PMC6748164.



Cardiac Anatomy and Electrophysiology	Dog	Pig	Sheep	Goat
Heart Size vs. man	Similar	Very similar	Similar	Smaller
Coronary Anatomy	Extensive collaterals	Very similar to man	Similar to man but variability between animals	Similar to man and uniform between animals
Purkinje Network	Not transmural: similar to man	Transmural	Transmural	Transmural
Cellular Electrophysiology	Similar APs and ionic currents, maybe more heterogeneous	Similar APs and ionic currents, but lacks I_{to}	Similar APs and transmural heterogeneities	Similar APs to man
VF susceptibility	Similar to man	High	High	
Disease Models				
MI induced VT/VF	++	++	+	+
Cardiac Resuscitation	+	++		
Ischemic Heart Failure	+	++	+	
Non ischemic HF	++	+		
LQTS/Proarrhythmia	++	+		
AF/AFI	++	++		++

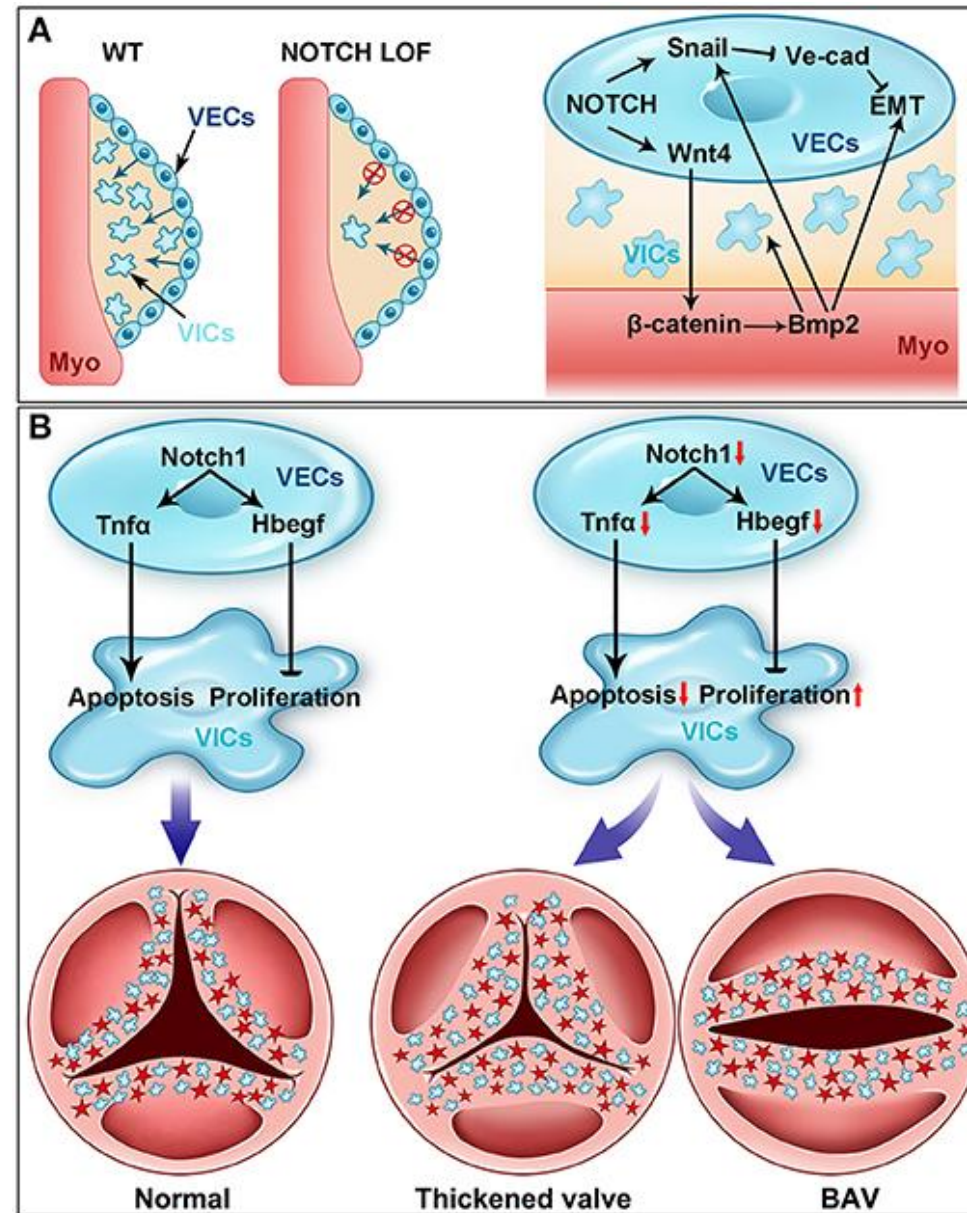
Experimentálne animálne modely chlopňových vád

Kalcifikované ochorenie aortálnej chlopne (Calcific aortic valve disease)

- Mouse: Male Notch1+/- mice fed for 10 months with a Western diet
- New Zealand White rabbits subjected to 1K1C model

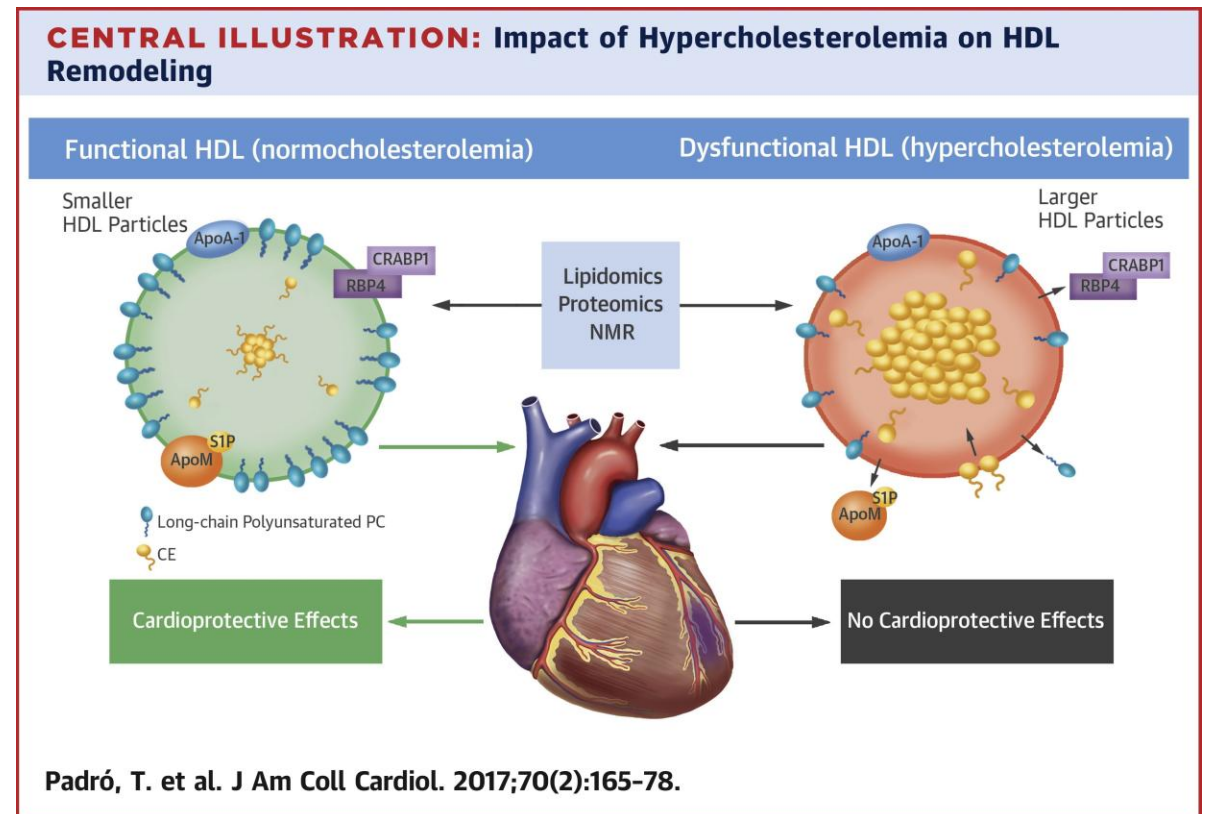
Chlopňová nedomykavosť a stenóza

- Pacing-induced heart failure with tricuspidal insufficiency (sheep)
- Supravalvular aortic stenosis by surgical banding of the aorta (Cat, dog, sheep, pig)



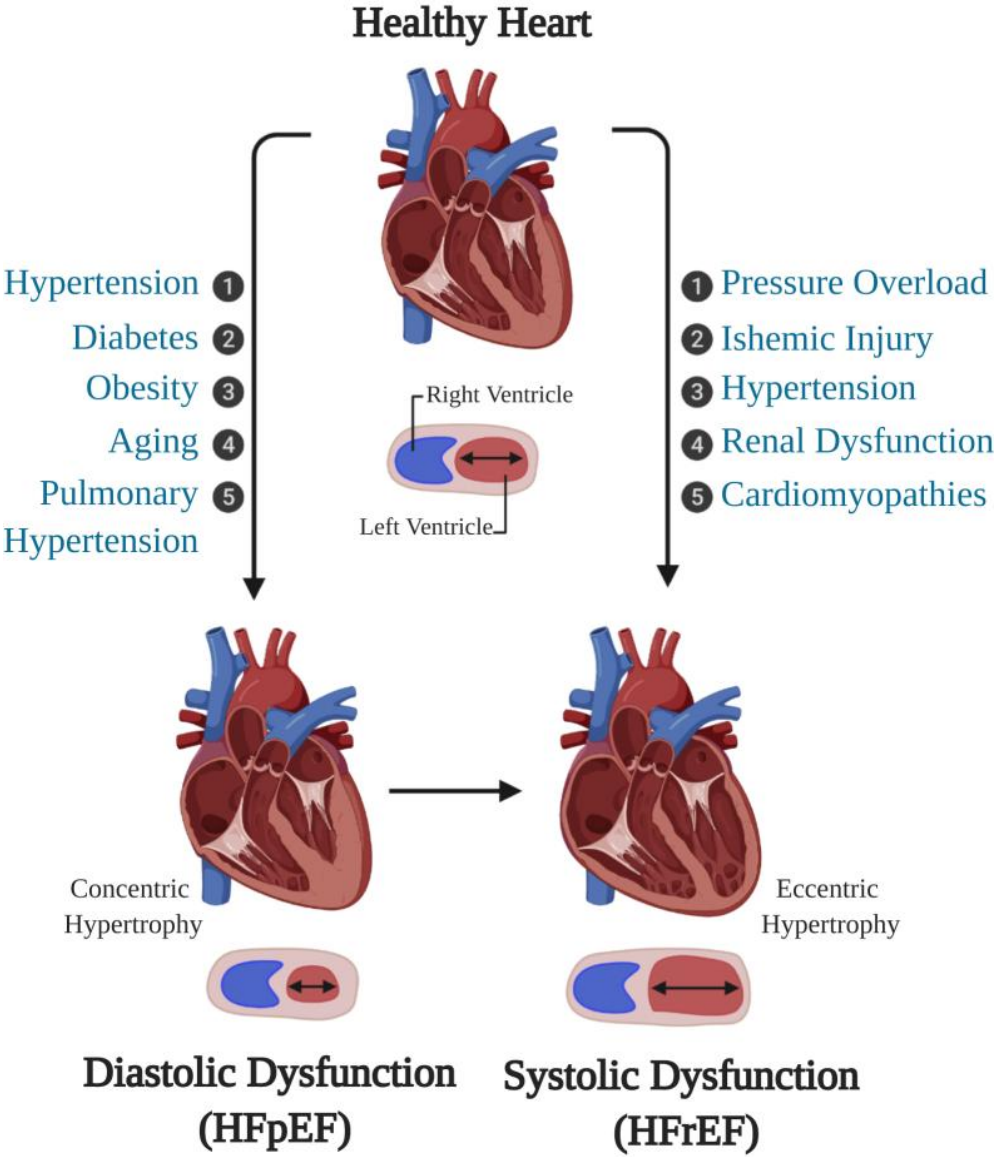
Experimentálne animálne modely aterosklerózy

- Familial hypercholesterolaemia (pig)
- Transgenic mice with lack of genes involved in lipid metabolism (LDL-receptor, apolipoprotein E)



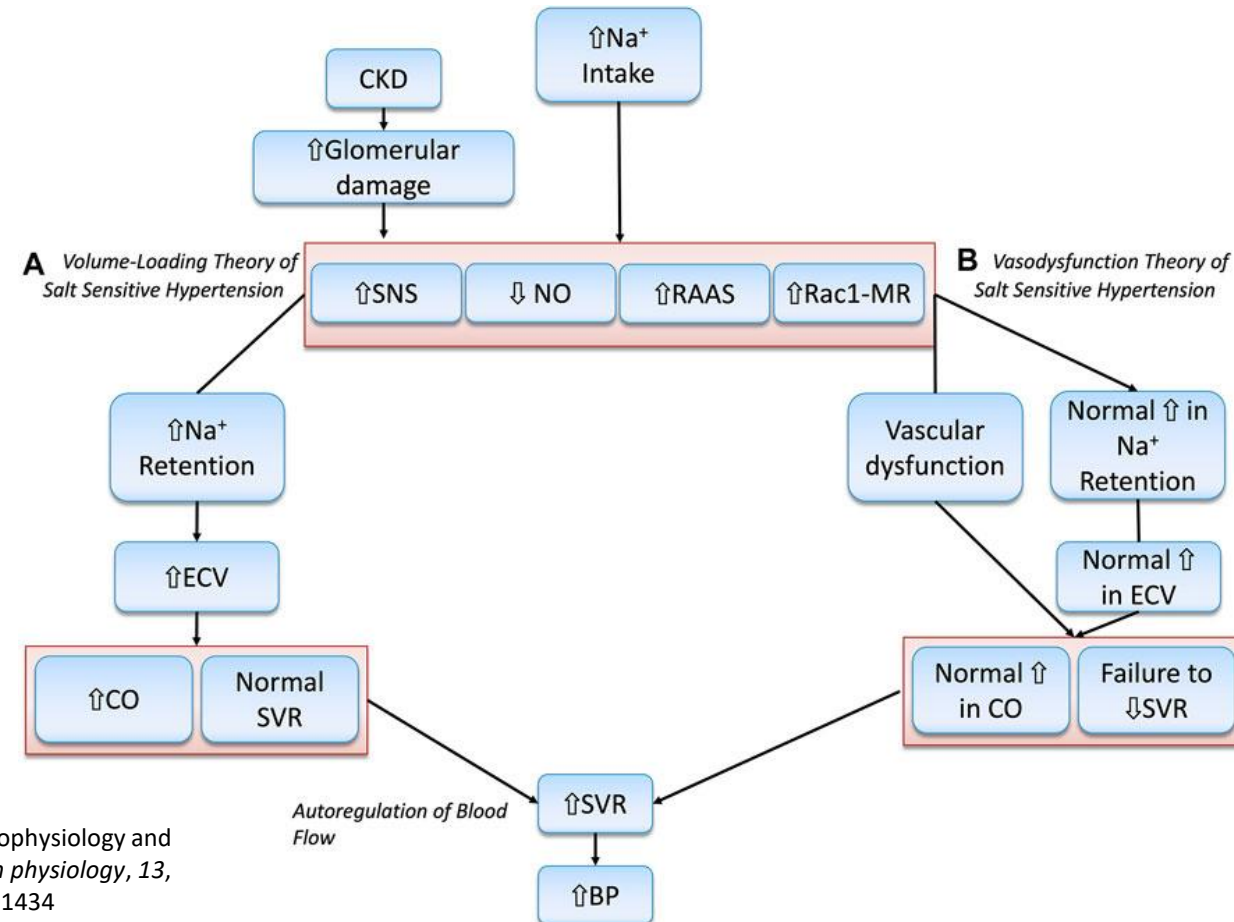
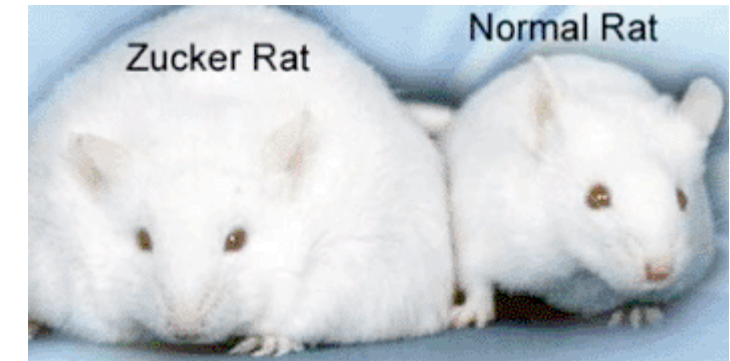
HFpEF a HFrEF

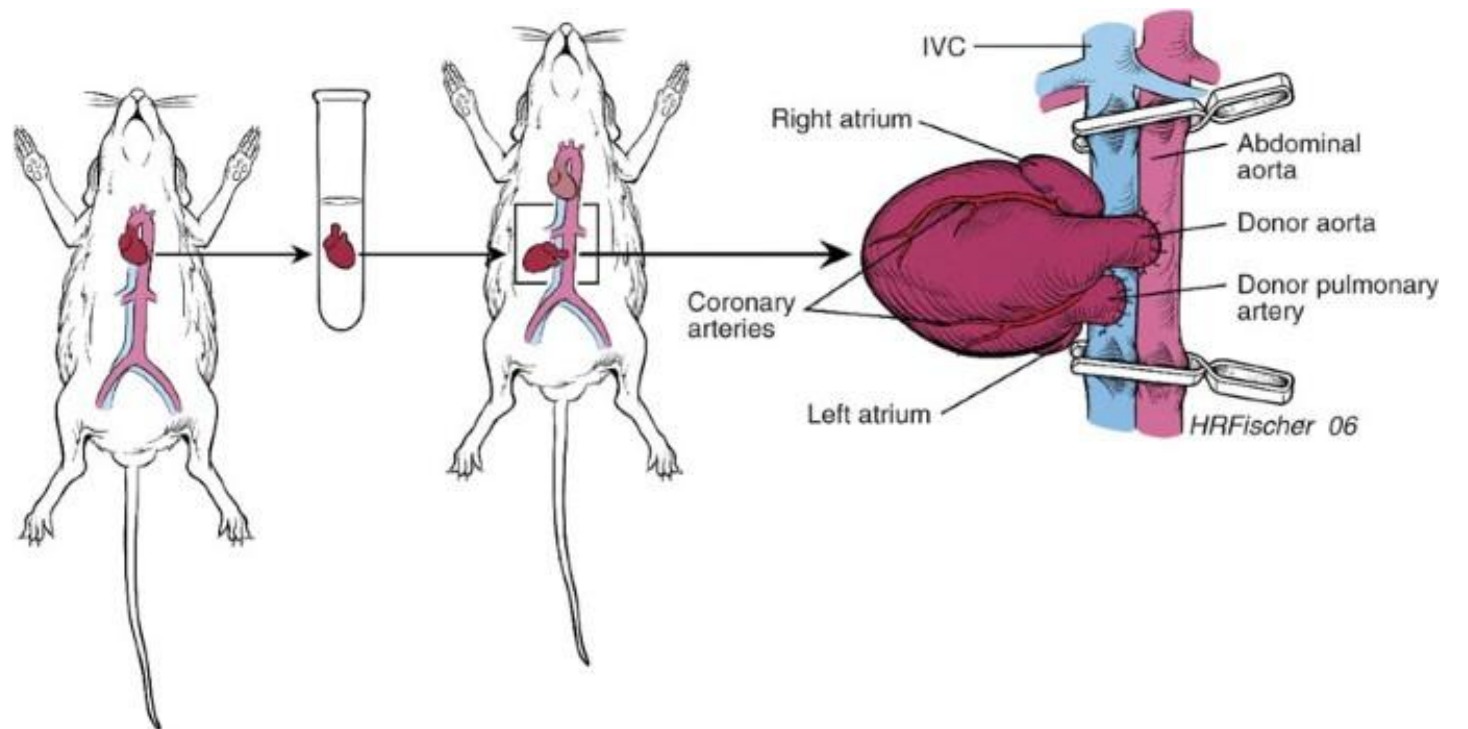
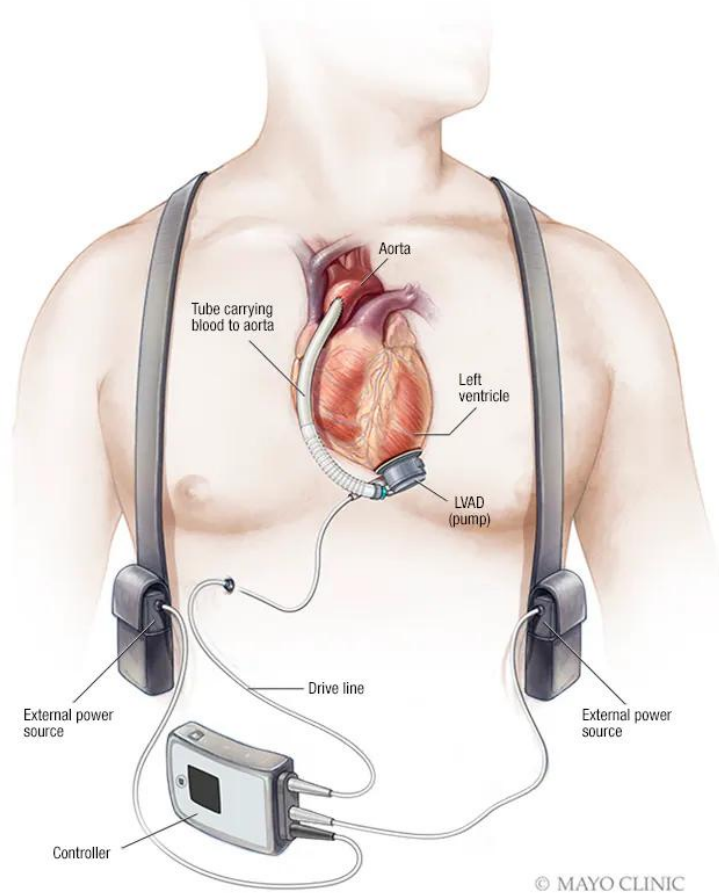
HFpEF vs HFrEF More Information Online WWW.DIFFERENCEBETWEEN.COM		
	HFpEF	HFrEF
DEFINITION	HFpEF is a complex cardiovascular syndrome caused by left ventricular diastolic dysfunction	HFrEF is a complex cardiovascular syndrome caused by left ventricular systolic dysfunction
PHASE	Diastolic phase	Systolic phase
EJECTION FRACTION	Greater than 50%	Lower than 40%
CAUSE	Left ventricle's muscles are too stiff or thickened	Muscles of left side of the heart do not squeeze properly
RESULT	Left ventricle fails to fill with blood properly	Left ventricle fails to pump the amount of blood that body needs
DYSFUNCTION	Left ventricular diastolic dysfunction	Left ventricular systolic dysfunction



HFpEF experimentálne modely

- ZDF (Zucker Diabetic Fatty) rats
- Otsuka Long-Evans Tokushima Fatty rats
- Dahl Salt-sensitive-Obese rats
- Rats with aortic banding
- LV pressure overload by an implantable stent or inflatable aortic cuff in pigs or cats
- L-NAME plus high-fat diet in mice





Množstvo animálnych modelov genetických modifikácií

Gene	Human phenotype	Animal model	Animal phenotype	Pathogenesis
a-MHC	HCM	murine TG R403Q [51]	HCM	myocyte disarray, fibrosis, atrial dilation
Caveolin3	HCM	murine KO [52]	HCM, DCM, cardiac dysfunction	ERK1/2 activation, Src signaling
Caveolin3	HCM	murine TG P104L [53]	HCM, enhanced contractility, apoptosis	nNOS production, altered endoplasmic reticulum (ER) stress response
Caveolin3	HCM	zebrafish KO [54]	cardiac edema	myoblast fusion defects
Titin	DCM, HCM	zebrafish [55]	cardiac edema, poor contraction	blockage of sarcomere assembly
Tropomyosin	HCM	murine TG E180G [56]	HCM, fibrosis and atrial enlargement	increased myofilament sensitivity to Ca ²⁺ .
Tropomyosin	HCM	murine TG D175N [57]	HCM, contractility and relaxation reduction	thin filament enhanced Ca ²⁺ sensitivity
Troponin T	CM	murine TG MyHC [58]	HCM, reduced number of myocytes	multiple cellular mechanisms
Troponin T	CM	murine TG R92Q [60]	mitochondrial pathology, diastolic dysfunction	induction of ANP and bMHC
Troponin T		zebrafish KO [64]	sarcomere loss and myocyte disarray	dysregulation of thin filament protein expression
Troponin I	HCM	murine TG R145G [65]	HCM, diastolic dysfunction, death.	increased Ca ²⁺ sensitivity and hypercontractility
Troponin I	HCM	rabbit TG R145G [66]	HCM and Cx43 disorganization	altered fractal pattern of the repolarization phase
Troponin I	HCM	murine KO [67]	acute HF, shortened sarcomeres	reduced Ca ²⁺ sensitivity, elevated resting tension
MyBPC	HCM	murine TG [68]	sarcomere disorganization	stable truncated protein
MyBPC		murine KO [69]	HCM, reduced myofilament stiffness	abnormal sarcomere shortening velocity
MyBPC	HCM	cat TG [70]	sarcomeric disorganization	
Myopalladin	DCM HCM	murine TG Y20C [63]	HCM and heart failure	desmin, DPS, Cx43 and vinculin disruption
CARP	HCM DCM	murine TG αMHC [62]	HCM in response to pressure overload stress	reduced TGF-β, ERK1/2, MEK and Smad3
CARP	HCM DCM	murine KO [71]	No cardiac phenotype	
Talin	HCM	murine CS-KO [61]	HCM, hypercontraction to pressure overload	blunted ERK1/2, p38, Akt, and Gsk3 after stress
SGLT1		Tg CS-siRNA KD [72]	HCM, HF	
Meox1		Tg CS [73]	HCM	
ROCK		murine KO [74]	HCM	re-activation of fetal gene expression
cMyBPC	CM	murine KO [75]	HCM	dysregulation of Xirp2 and Zbtb16
β-MHC		rabbit TG R403Q [76]	HCM	reduced rates of force development and relaxation
CSRP3	HCM	murine KI C58G [77]	HCM	protein depletion via Bag3 and proteasomal overload
MYH7	HCM	pig KI R723G [78]	HCM, HF	myocyte disarray and malformed nuclei
TNNT2		murine R92Q; E163R [79]	HCM	altered myofilament Ca ²⁺ sensitivity
αMHC	HCM	murine Arg403Gln [80]	HCM	altered repolarizing voltage-gated K ⁺ (Kv) current
ERBB2		murine Tg [81]	HCM, diastolic dysfunction	ErbB2 signaling

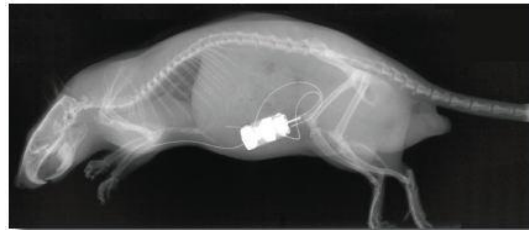
Gene	Human phenotype	Animal model	Animal phenotype	Pathogenesis
Sarcoglycan (delta)	DCM	murine KO [82]	focal necrosis, fibrosis after stress	destabilization of dystrophin glycoprotein complex (DGC), membrane permeability defect, Ca ²⁺ imbalance
Sarcoglycan (delta)	DCM	murine KI S151A [83]	mild DCM	
Sarcospan	DMD	murine KO [84]	progressive DMD, extensive degeneration and regeneration.	
Laminin-a2		murine KO [85]	DCM	disruption of extracellular matrix (ECM) - cytoskeleton connection
Dystrophin	XL-DCM	murine [86]	dilated ventricles	destabilization of DGC, sarcolemma-actin connection, Ca ²⁺ alteration
Dystrophin	XL-DCM	zebrafish [87]	mutants are less active	
Dystrophin	XL-DCM	canine [88]	DMD and DCM phenotype	decrease in Ca ²⁺ sensitivity and tension generation
Tropomyosin	DCM	murine KO [89]	homozygous null mice are embryonic lethal (E8-E11.5)	
Tropomyosin	DCM	murine TG E54K [90]	DCM, impaired cardiac function	blunted response to beta-agonist stimulation
Desmin	DCM	murine TG R173del179 [91]	DCM, intra-sarcoplasmic granular aggregates	
Desmin	DCM	zebrafish [92]	disorganized muscles, small larvae	vulnerability during eccentric work
Desmin	DCM	murine KO [93]	DCM, mitochondrial abnormalities, necrosis	multisystem disruption of muscle architecture
MLP	DCM	murine KO [94]	DCM with hypertrophy and heart failure	altered mechano-sensation
Nebulette	DCM	murine TG [95]	DCM, mitochondrial abnormalities	stretch induced alteration of Z-disk assembly
Nexilin	DCM	zebrafish [96]	Z-disk damage, heart failure	stretch induced Z-disk destabilization
Telethonin	DCM	murine KO [97]	heart failure following biomechanical stress	modulation of nuclear p53 turnover after stress
Telethonin	DCM	zebrafish [98]	deformed muscle structure and impaired swimming ability	disruption of sarcomere-T-tubules ILK
Cypher/ ZASP	DCM	murine KO [99]	DCM, Z disk disruption, muscle weakness	a-actinin or other Z-line components disruption
Filamin C	DCM	medaka zacrofish KI680X [100]	DCM, myocardial wall rupture	Disrupted structure of cardiac and skeletal muscles
Lamin A	DCM	murine KO N195K [101]	nucleo-cytoplasmic shuttling of Mlk1	modulation of actin polymerization via Mlk1
Lamin A	DCM	murine KO [102]	Cardiomyocyte degeneration and mineralization	emerin dislocation
αMHC-cre		CS-Cre [103]	DCM	activated p38, JNK, p53, Bax
Dhcr24 x cTnT R141W		Double Tg Dhcr24 x cTnT [104]	DCM	activation of PI3K/Akt/HKII pathway
MST1 x Gal3		murine TG x KO [105]	DCM, HF	dysregulated transcriptional signaling
MGAT1		CS KO [106]	DCM	altered Ca ²⁺ handling
RBM20	DCM	murine KI S637A [107]	DCM	disturbed nuclear localization of RBM20
MLP x MYBPC3	Varied CMs	Double KO [108]	DCM	increased Ca ²⁺ sensitivity
FXR1		CS-KO [109]	DCM	altered levels of FCRI
GSK-3β x cTnT		KO, DKO [110]	DCM, HF	myocardial fibrosis, and cardiomyocyte apoptosis
NEXN	DCM	KO [111]	DCM, EFE	collagen and elastin deposits
BIN1		CS-KO [112]	DCM	mislocalization of the Cav1.2

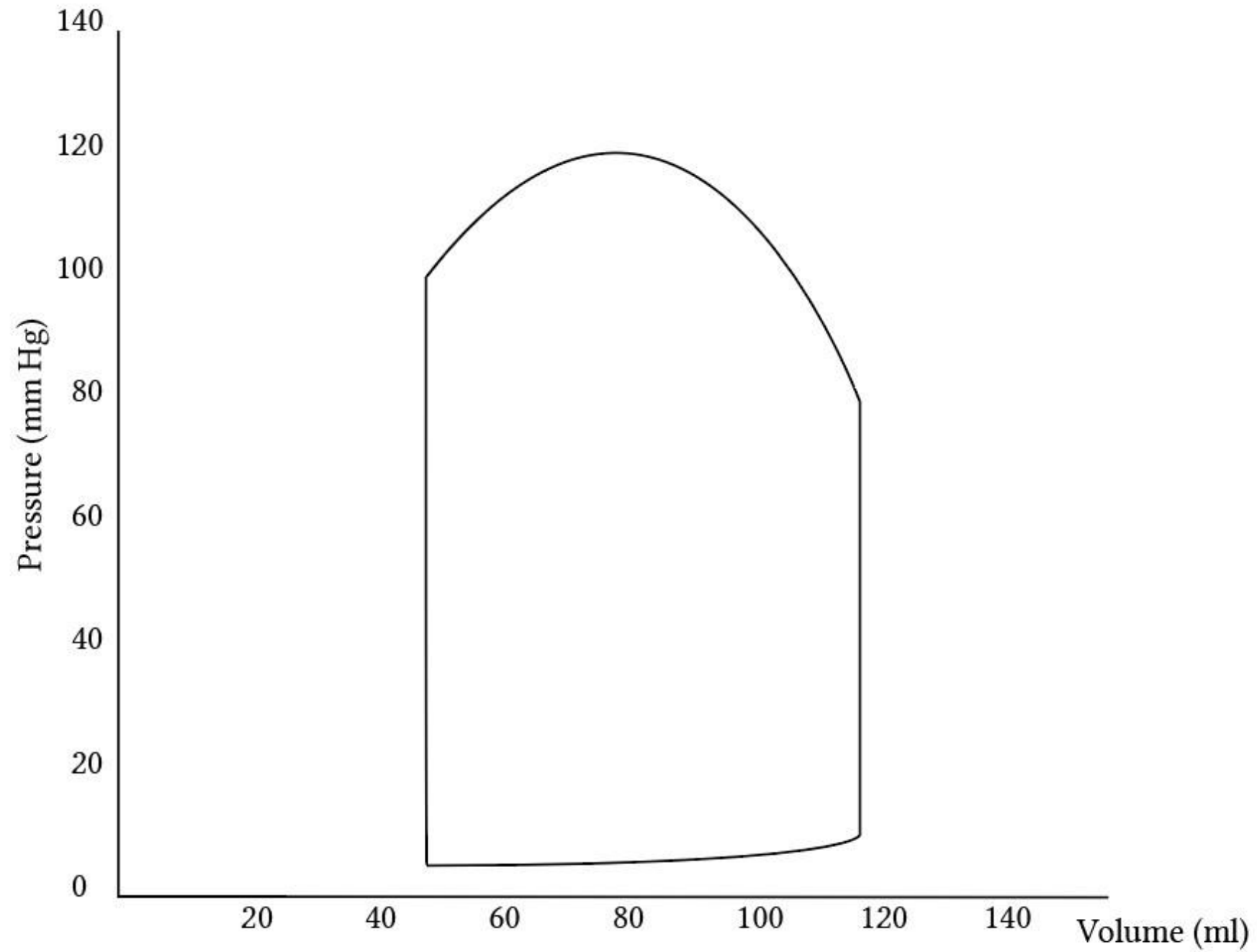
Gene	Human phenotype	Animal model	Animal phenotype	Pathogenesis
cTnI	CMs	murine KO [67]	shortened sarcomeres and elevated resting tension	reduced myofilament Ca ²⁺ sensitivity
cTnI	RCM	murine Tg R193H [114]	RCM	increased Ca ²⁺ sensitivity
cTnI	RCM	murine Tg R145W [115]	diastolic dysfunction	prolonged force and intracellular Ca ²⁺ transients
MYPN	RCM	murine KI Q529X [116]	disrupted intercalated discs, heart failure	desmin, DSP, connexin43 and vinculin disruption
myosin		E143K [117]	RCM	

Gene	Human phenotype	Animal model	Animal phenotype	Pathogenesis
alpha-dystrobrevin	DMD, LVNC	murine KO	Muscle dystrophy, cardiomyopathy	Alteration in cyclic GMP levels
NKX2-5	CHD	murine KI R52G [141]	LVNC, atrial septal anomalies	cardiomyocyte differentiation and heart development
NKX2-5	CHD	inducible Cx40-cre ERT2 [142]	hypertrabeculation, heart failure	cardiomyocyte differentiation and heart development
Fkbp1a		murine KO [143]	DCM, VSD and LVNC	immunoregulation and protein folding and trafficking
Jarid2		murine KO [144]	VSD, LVNC, Double outlet RV	dysregulated embryogenesis
Mest		murine KO [145]	thickness and less dense compact myocardium	dysregulated embryogenesis
Mib1		murine KO [146]	LVNC	dysregulated Notch signaling
BRAF		murine KI Q241R [147]	embryonic/neonatal lethality, LVNC	
CASZ1		murine KO [148]	hypoplasia of myocardium, VSD	abnormal genes expression
ANT2		murine KO [149]	embryonic lethality, LVNC	failure in cardiac developmental
Daam1		murine KO [150]	VSD, LVNC, Double outlet RV	Wnt/PCP signaling
S1PR1		murine KO [151]	LVNC, VSD	SIP signaling
NUMB / NUMBL		murine KO [152]	LVNC	ERBB2, YAP1 STAT5 signaling
RLF		murine KO [153]	LVNC	NOTCH pathway
LRP2		murine KO [154]	LVNC, aortic arch and coronary artery anomalies, VSD	
SLC39A8		murine KO [155]	LVNC, ECM accumulation	decrease MTF1 activity
DTNA		murine Tg N49S [156]	DCM, LVNC, cardiac dysfunction	
SRC-1/3		murine KO [157]	LVNC	up-regulate cyclin E2, cyclin B1 and myocardin
INO80		murine KO [158]	LVNC, defect in coronary vessels	upregulation of E2F-activated genes a
Tafazzin (TAZ)	LVNC	murine KD [159]	Neonatal death, LVNC, VSD	Fatty acid metabolism

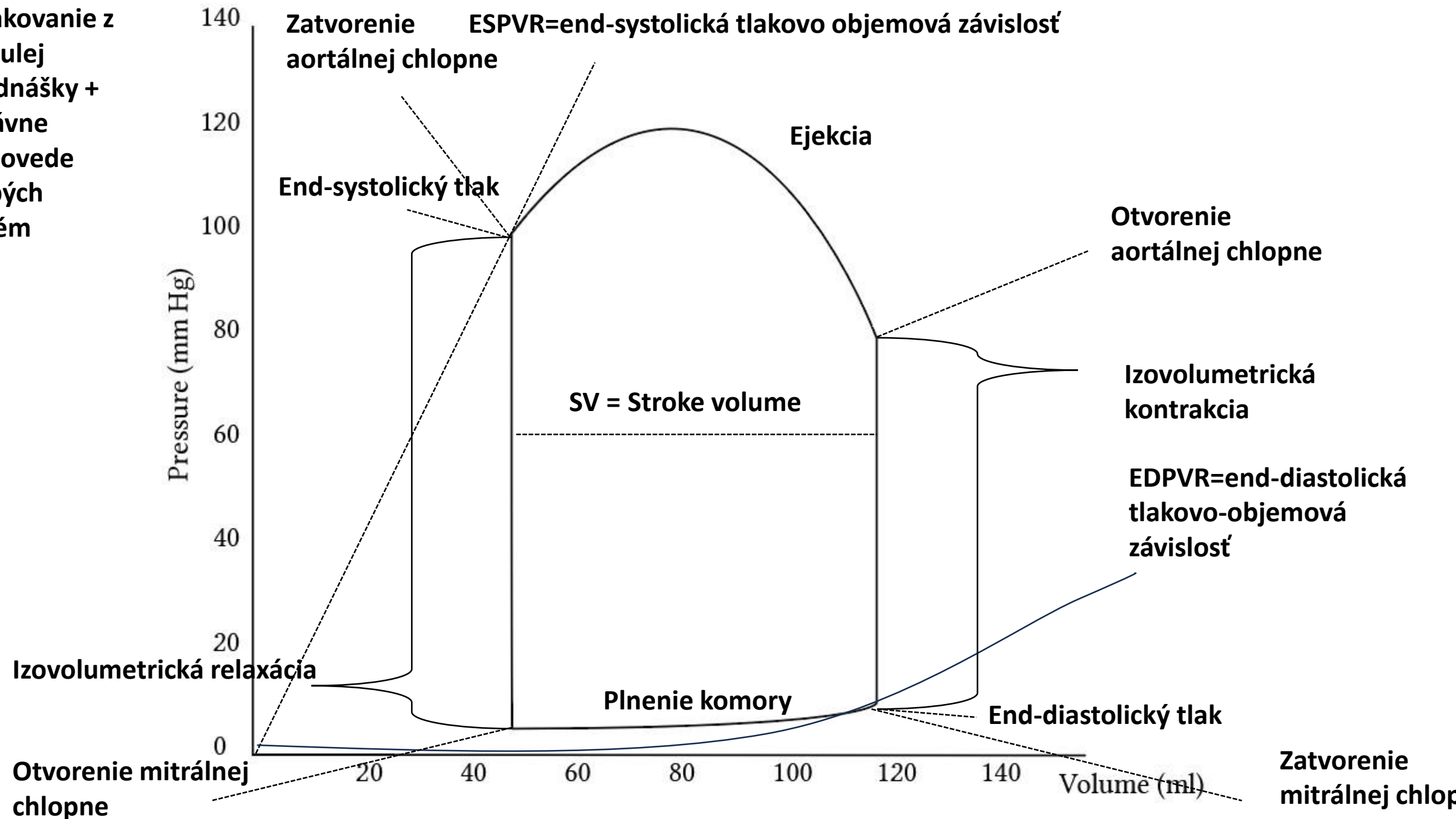
Kvantifikácia HF a obličkových funkcií

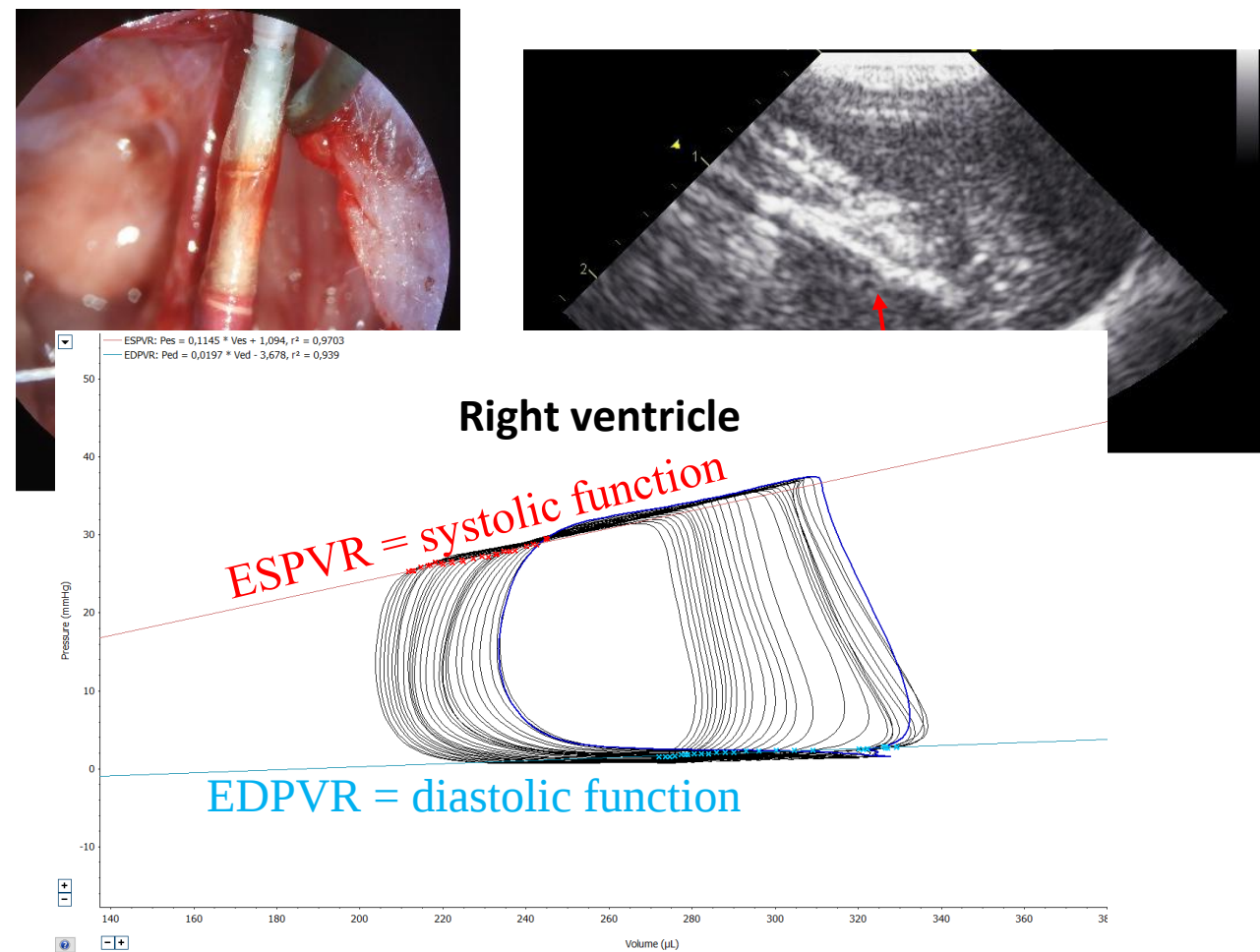
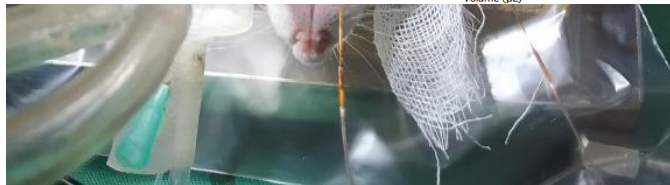
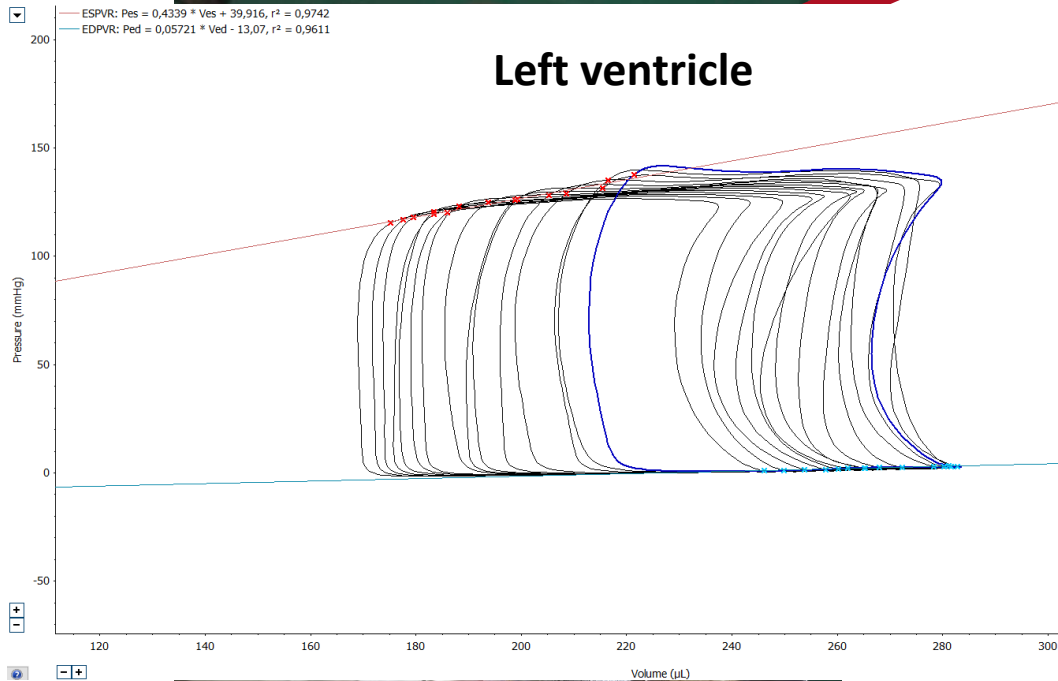
- Testy renálnych funkcií (GFR, proteinúria, albuminúria)
- Rádiotelemetria
- Echo
- PV analýza (univentricular/biventricular)
- ECG
- Histológia a IHC (IM stress area, fibróza)
- Biochemické markery: Troponín, Nppa, katecholamíny (NA), ANG, sérum kreatinín, kyselina močová
- Génové a proteínové expresie





Opakovanie z
minulej
prednášky +
správne
odpovede
slepých
schém





Miklovic, M., Kala, P., & Melenovsky, V. (2023). Simultaneous biventricular pressure-volume analysis in rats. *Journal of physiology and pharmacology : an official journal of the Polish Physiological Society*, 74(2), 10.26402/jpp.2023.2.02. <https://doi.org/10.26402/jpp.2023.2.02>

Original articles

M. MIKLOVIC^{1,2}, P. KALA^{1,3}, V. MELENOVSKY^{1,4}

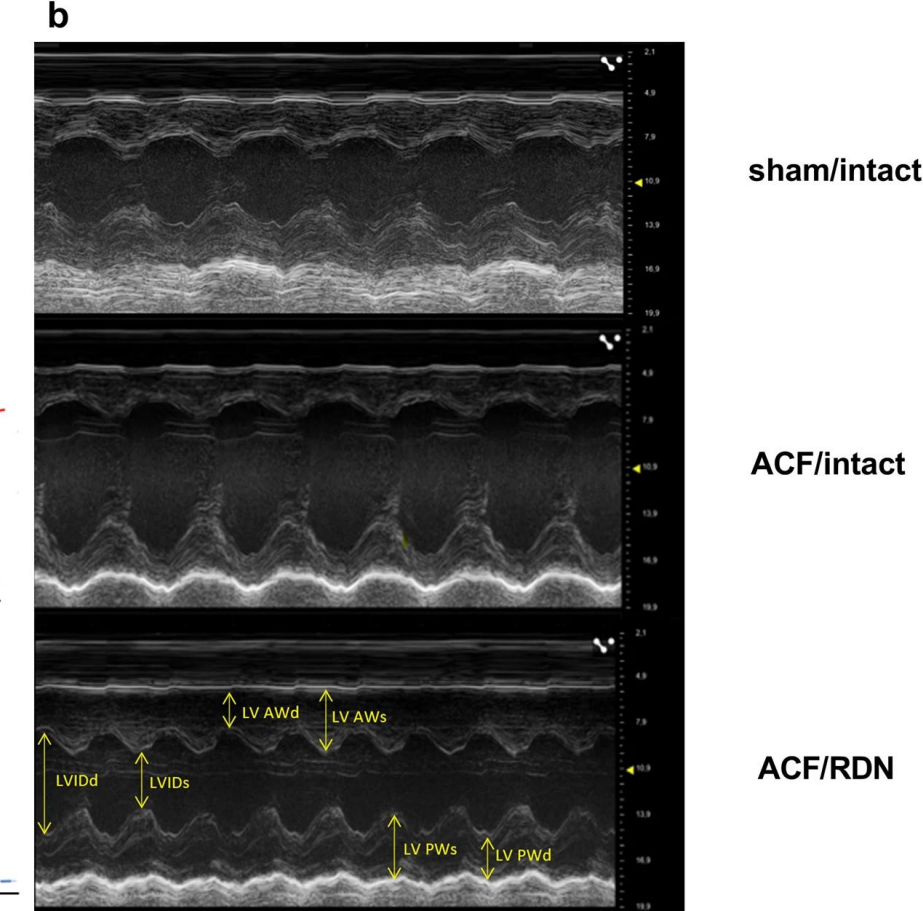
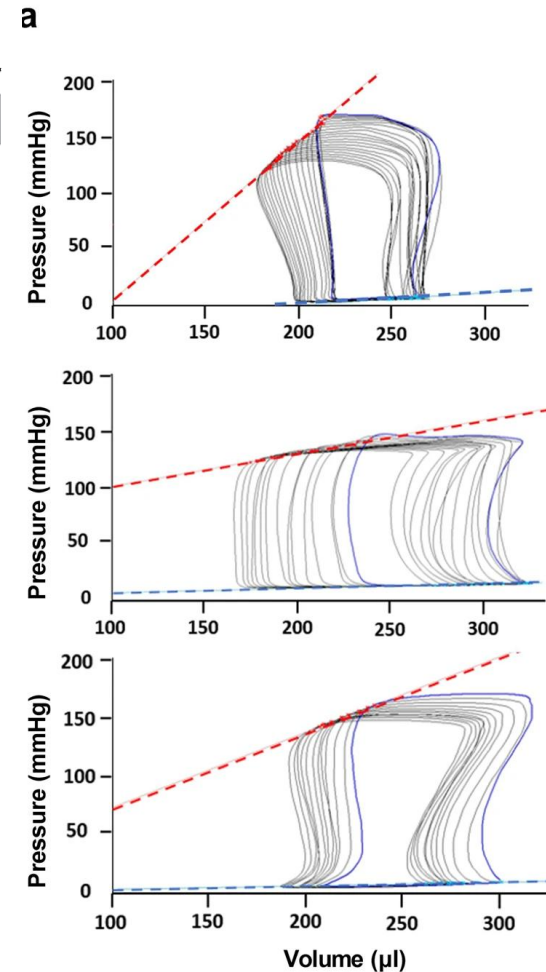
SIMULTANEOUS BIVENTRICULAR PRESSURE-VOLUME ANALYSIS IN RATS

¹Center for Experimental Medicine, Institute for Clinical and Experimental Medicine - IKEM, Prague, Czech Republic; ²Department of Pathophysiology, ^{2nd} Faculty of Medicine, Charles University, Prague, Czech Republic; ³Department of Cardiology, University Hospital Motol and ^{2nd} Faculty of Medicine, Charles University, Prague, Czech Republic; ⁴Department of Cardiology, Institute for Clinical and Experimental Medicine - IKEM, Prague, Czech Republic

Renal denervation improves cardiac function independently of afterload and restores myocardial norepinephrine levels in a rodent heart failure model

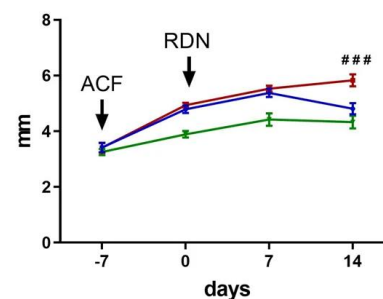
Matúš Miklovič^{1,2} · Olga Gawryś¹ · Zuzana Honetschlägerová¹ · Petr Kala^{1,3} · Zuzana Husková¹ · Soňa Kikerlová¹ · Zdeňka Vaňourková¹ · Šárka Jíchová¹ · Alena Kvasilová⁴ · Misuzu Kitamoto⁴ · Hana Maxová^{1,2} · Guillermo Puertas-Frias⁵ · Tomáš Mráček⁵ · David Sedmera⁴ · Vojtěch Melenovský^{1,6}

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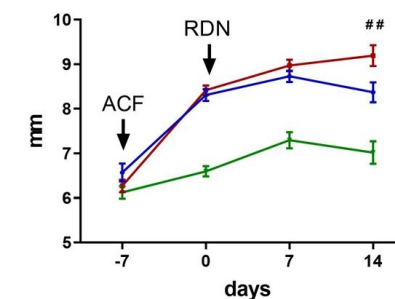


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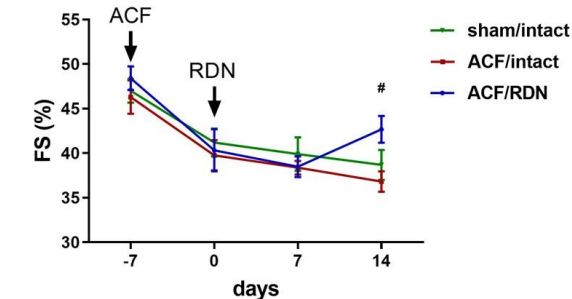
Diameter of the left ventricle in systole

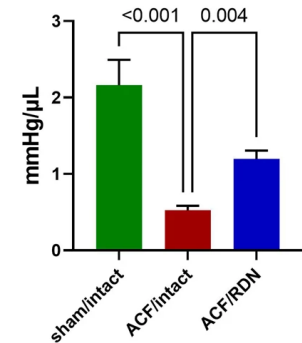
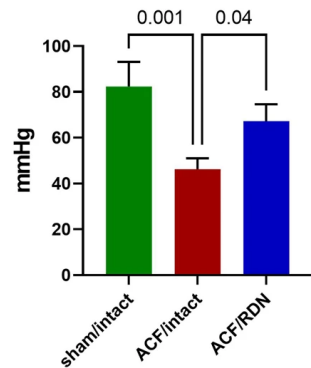
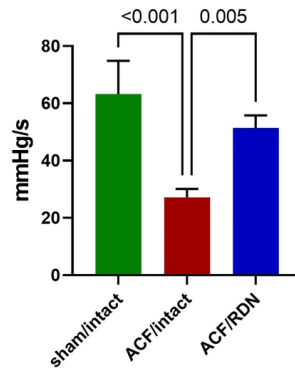
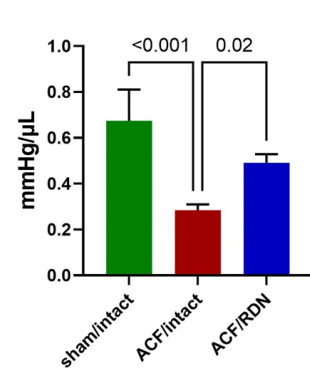
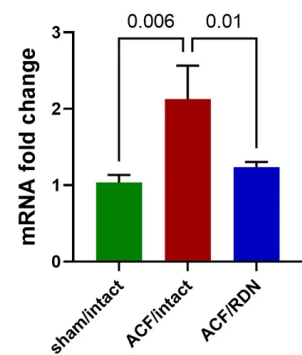
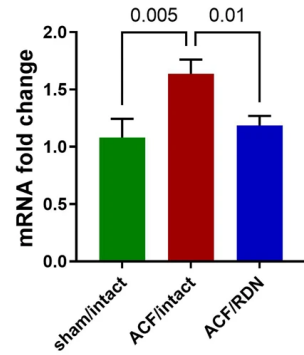
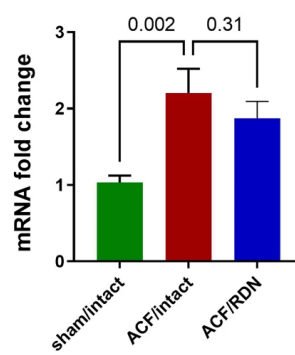
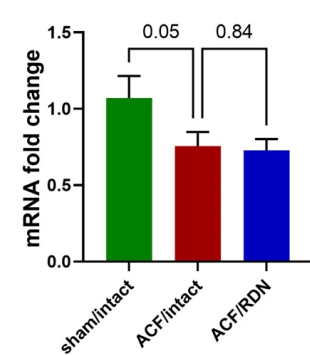
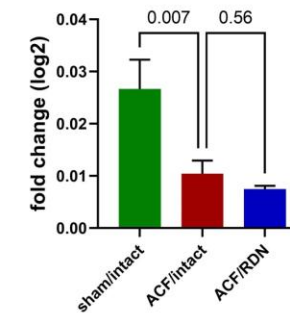
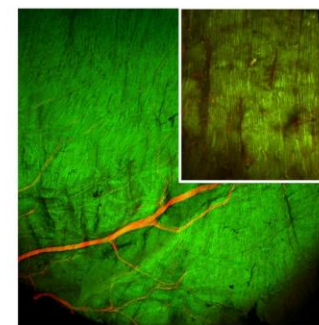
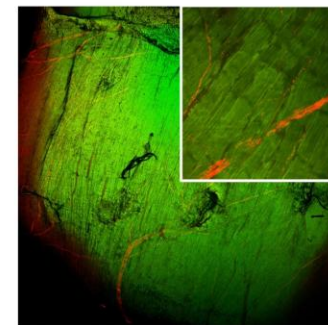


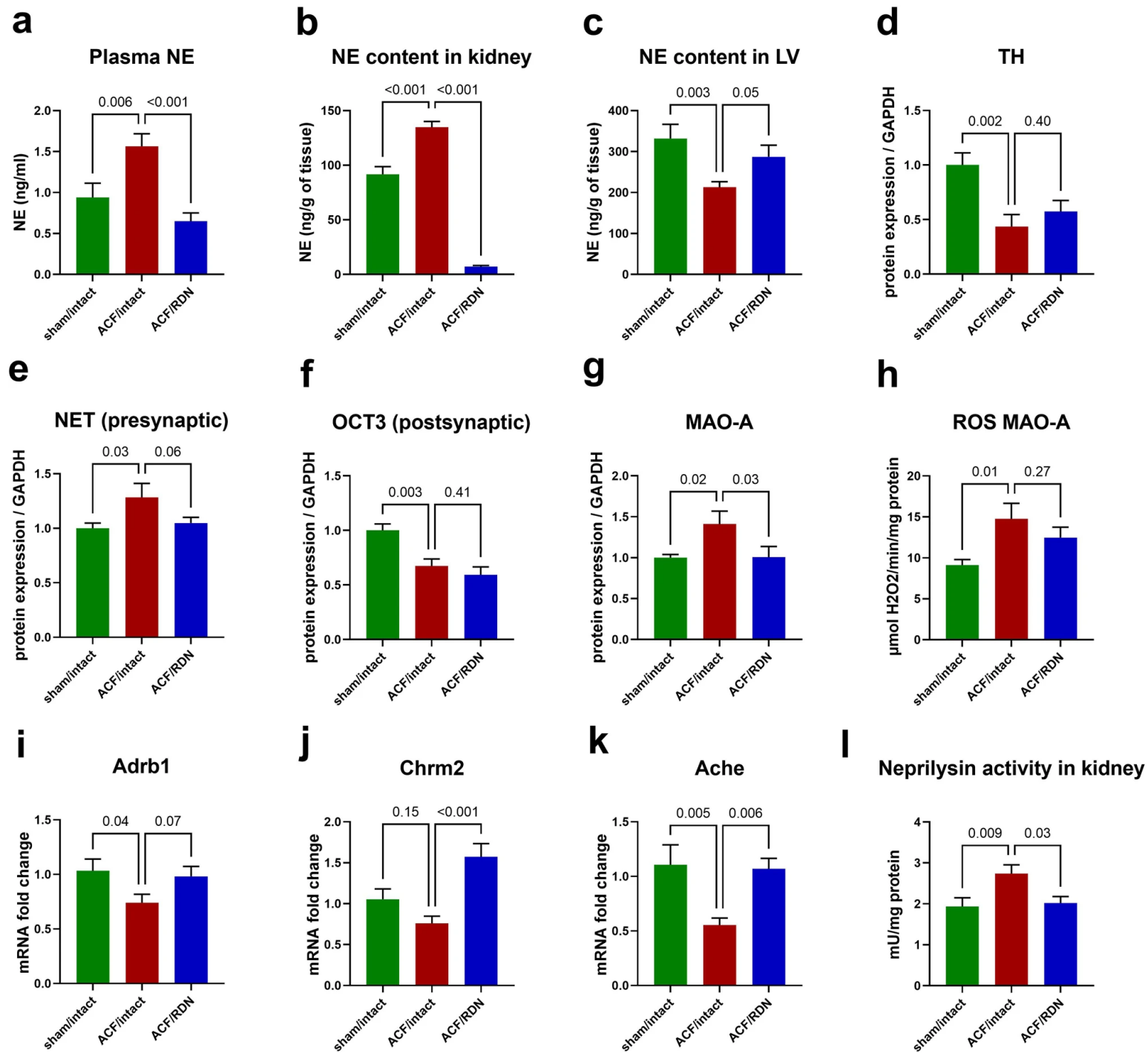
Diameter of the left ventricle in diastole



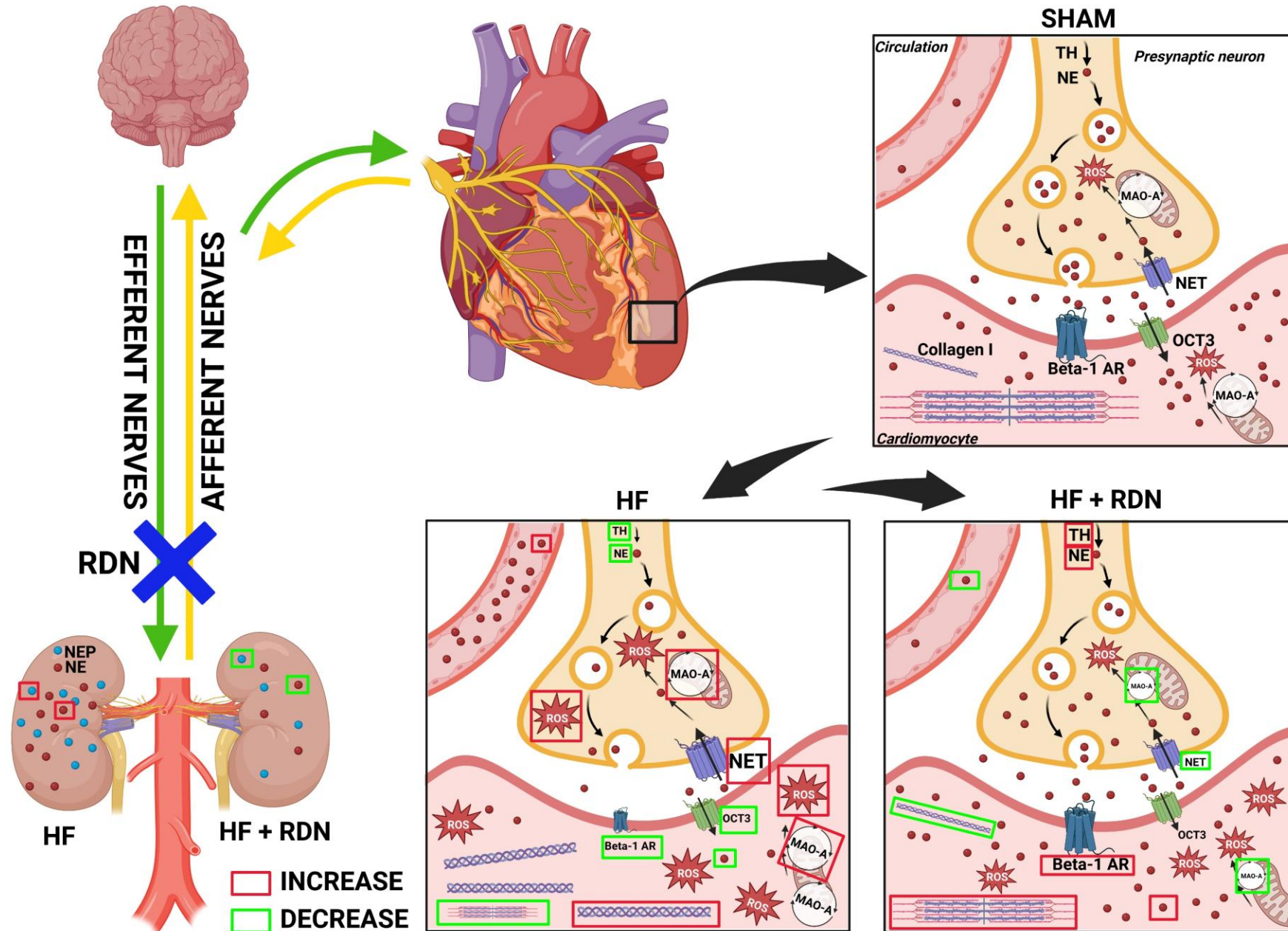
Fractional shortening



a**End-systolic elastance****Preload recruitable stroke work****dP/dt max****Ees/Ea****b****Col1a1/Col3a1 ratio****Myh 7/6 ratio****Nppa****Acadm****a****Sympathetic innervation (TH)****c****d**



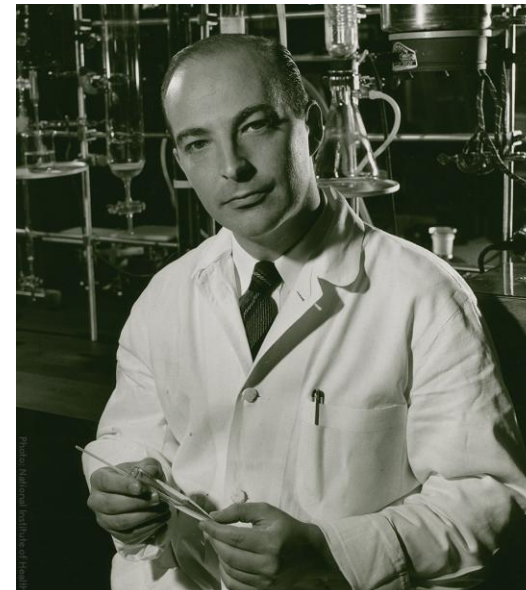
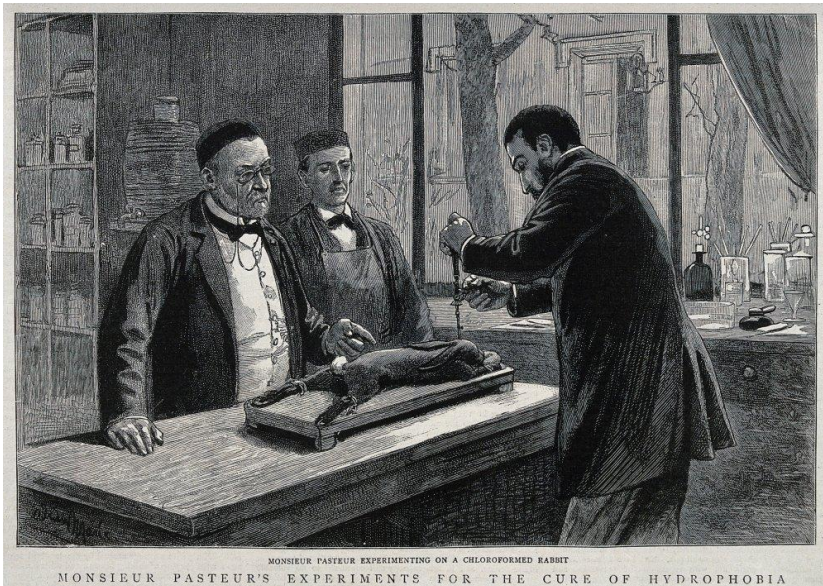
Effects of renal denervation in heart failure due to volume overload



Miklovič, M., Gawryś, O., Honetschlägerová, Z. *et al.* Renal denervation improves cardiac function independently of afterload and restores myocardial norepinephrine levels in a rodent heart failure model. *Hypertens Res* (2024). <https://doi.org/10.1038/s41440-024-01580-3>

Čo môžu experimentálne štúdie priniesť študentom medicíny/doktorom?

- Pochopenie mechanizmov kardiovaskulárnych ochorení
- Testovanie potenciálnych liečiv – účasť na projektoch základného a preklinického výskumu a translačného výskumu
- Vlastný projekt - množstvo skúseností, spoluúčasť/písanie grantu
- Experimentálna kardiochirurgia-zručnosť
- Prezentovanie výsledkov, práca v tíme, rozšírenie obzorov a metodík
- Publikovanie v impaktovaných časopisoch, účasť na konferenciách
- Šanca objaviť doposiaľ nepoznané patofyziologické mechanizmy a prispieť k poznaniu závažných KVS chorôb



“Basic research
has proven over
and over to be
the lifeline of
practical
advances in
medicine.”

ARTHUR KORNBERG
Nobel Prize in Physiology
or Medicine 1959

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Vojtěch
Melenovský,
CSc.**



**prof. MUDr.
Luděk
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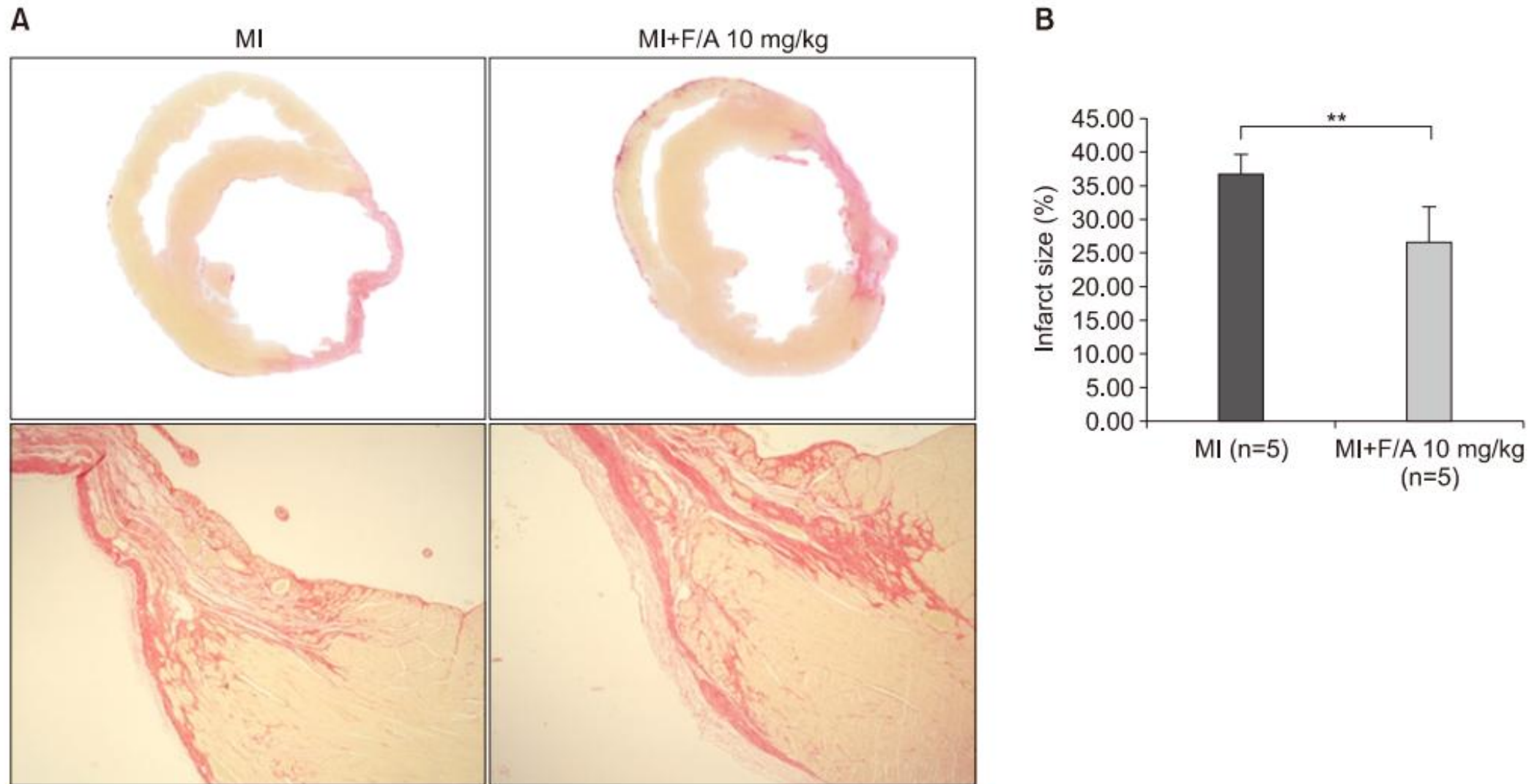


FIG. 3. (A) Picrosirius red stain and (B) measurement of infarct size (%). MI: myocardial infarction, F/A: fimasartan/amlodipine. ** $p < 0.01$.