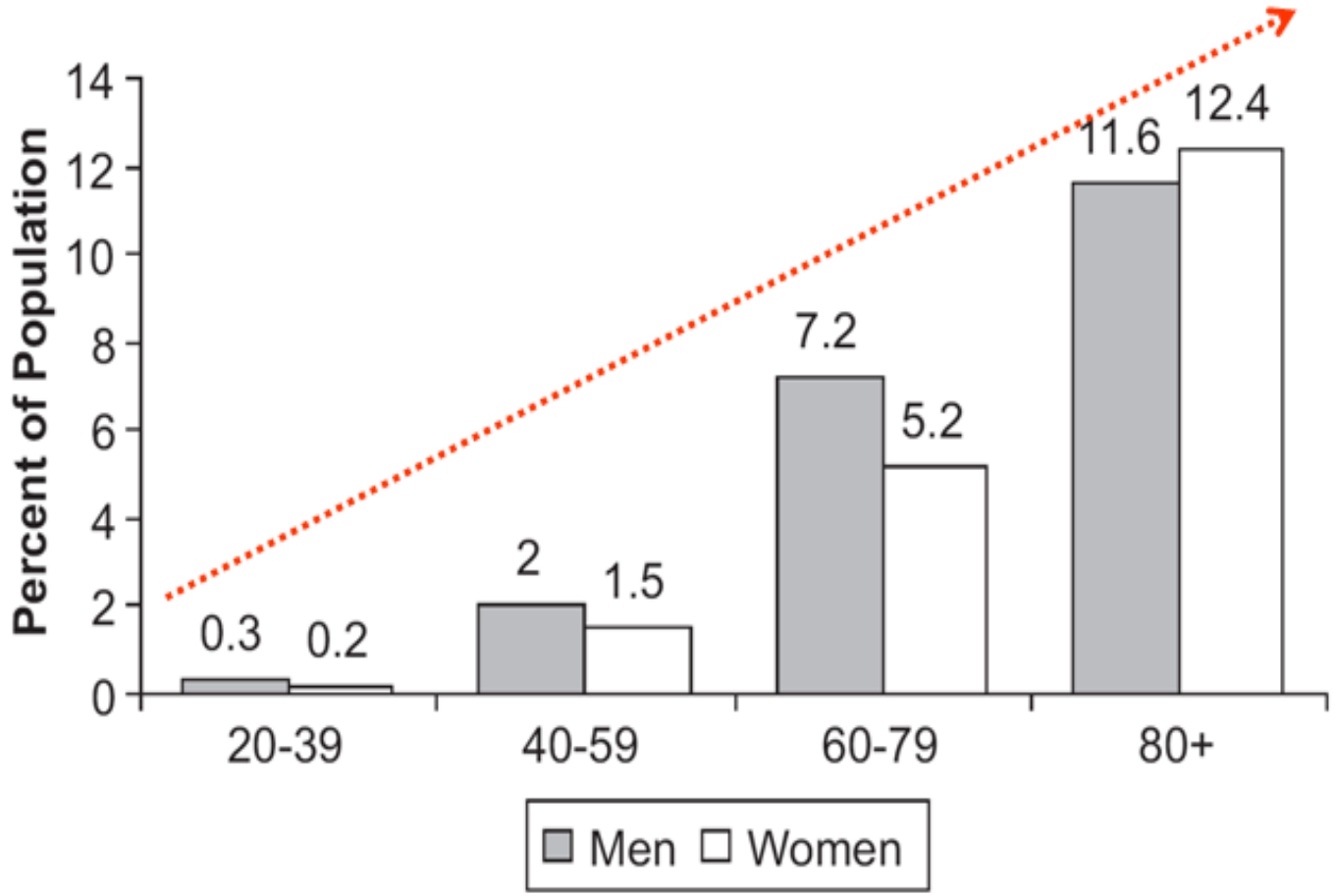
서울대학교병원
SEOUL NATIONAL UNIVERSITY HOSPITAL

Measurement of cardiac function using echocardiography and pressure–volume conductance catheter technique in a new rat model of chronic mitral regurgitation

김경희, 김용진*, 김형관, 손대원, 오병희, 박영배

서울대학교병원 순환기 내과

Background – Prevalence of Heart failure



Heart Disease and Stroke Statistics-2007 Update, Circulation, 2007

Background – Medications improving outcomes

- ACEi

  Risk reduction 35% (mortality and hospitalizations)
- ARB
- β-blockers

  Risk reduction 38% (mortality and hospitalizations)
- Oral nitrates and hydralazine

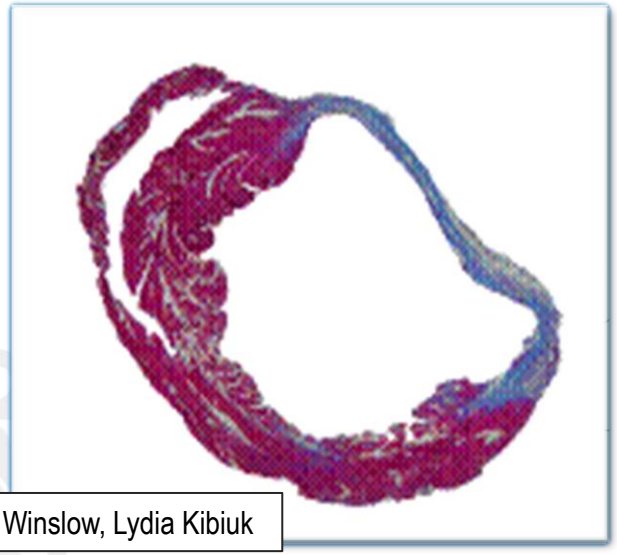
  Benefit vs. placebo; inferior to enalapril (mortality)
- Aldosterone antagonist

4-year mortality remains ~40%

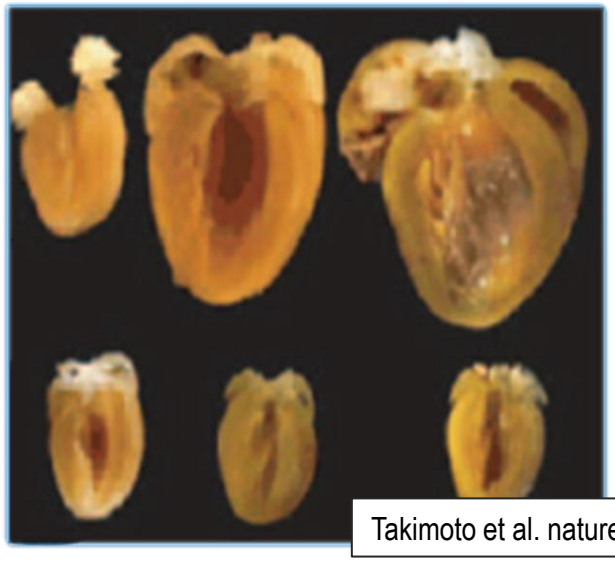
Background – Heart failure models in Animals

- Experimental models are required
  - to understand the progression of the disease
  - to elaborate new therapy

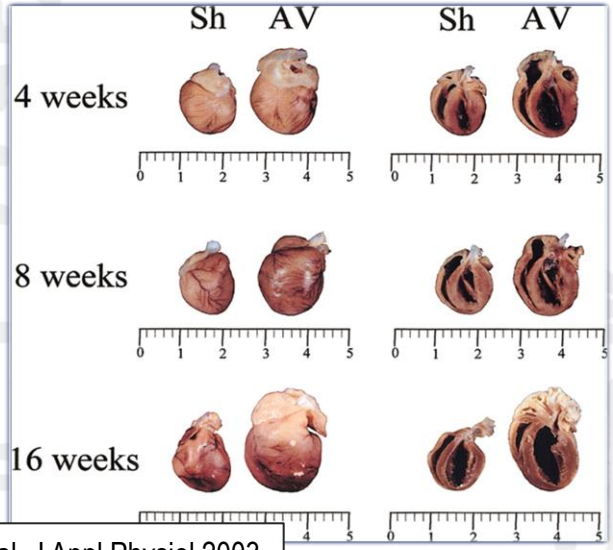
Background – Heart failure models in Rats



2001 Terese Winslow, Lydia Kibiuk



Takimoto et al. nature medicine



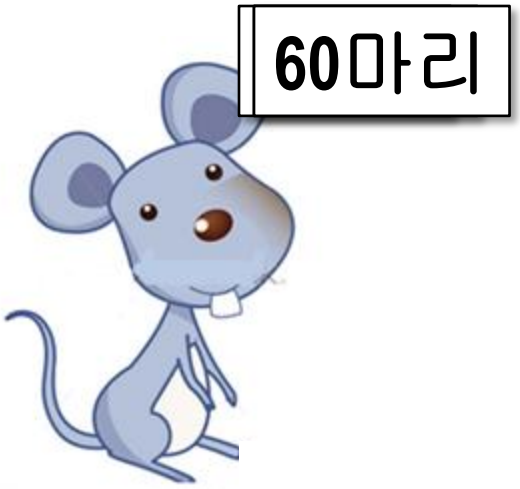
Wang, X. et al. J Appl Physiol 2003

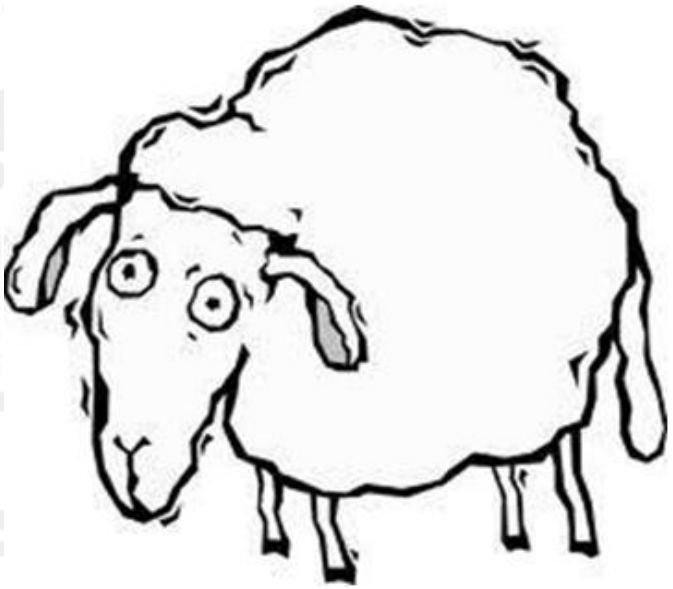
Medication
(streptozocin..)

Background – Mitral regurgitaion

- Representative heart failure due to volume overload
- Rapidly growing
- Unique pathophysiology
- Investigation of pharmacologic treatment of chronic MR

Background – MR models in Animals





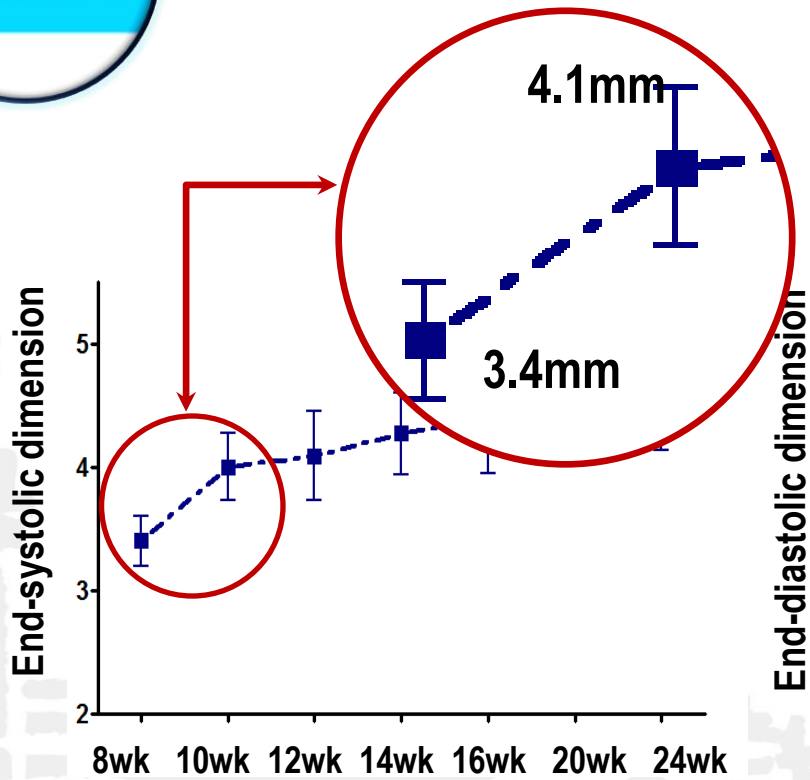
Goal of this Study

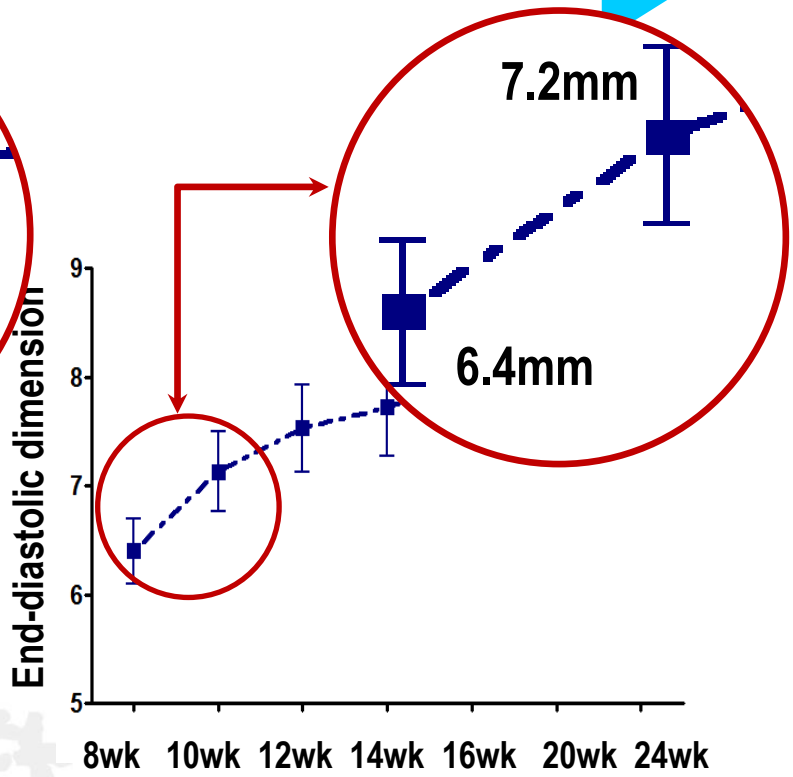
Making heart failure model in rats with mitral regurgitation

1. Set appropriate small animal model
2. Impact of mitral regurgitation on left ventricular anatomic remodeling and exercise performance

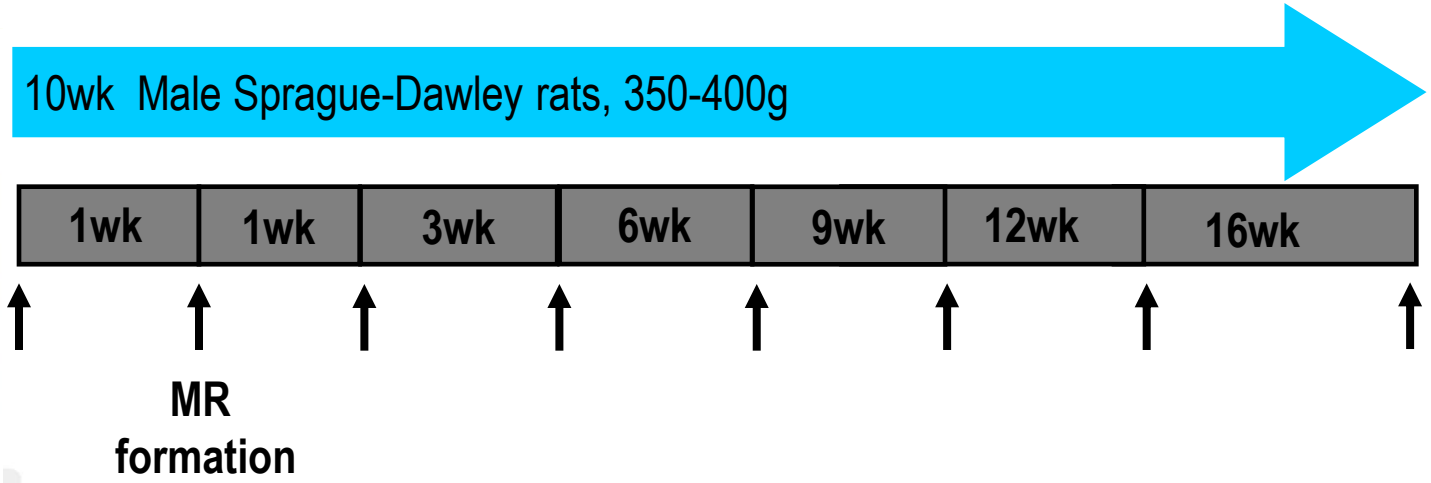
Method; experimental protocol

10wk Male Sprague-Dawley rats, 300-350g





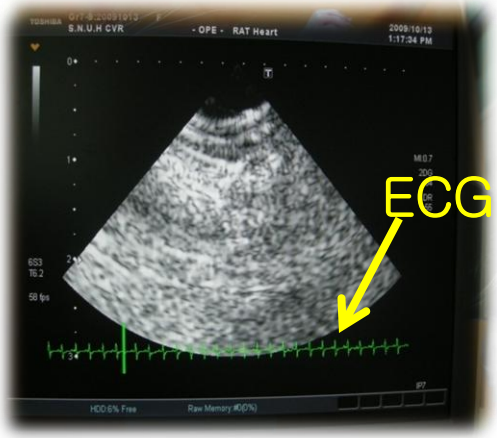
Method; experimental protocol

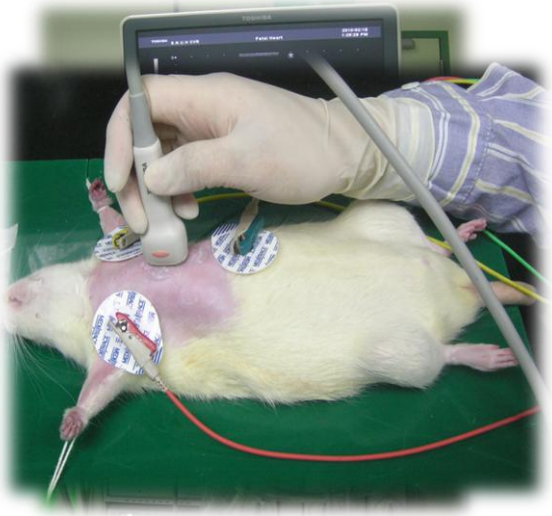


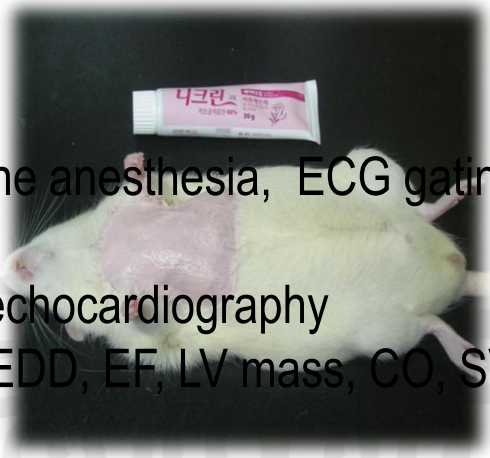
Baseline	MR 1wk	MR3wk	MR6wk	MR9wk	MR12wk	MR16wk
EchoCG	EchoCG	EchoCG	EchoCG	EchoCG	EchoCG	EchoCG
Exercise	Bwt	Exercise	Exercise	Exercise	Exercise	Exercise
BP		BP	Bwt	BP	Bwt	PV loop
Bwt		Bwt		Bwt		Tissue harvest

Daily monitoring: pain, appetite/drinking, behavior and responsiveness

Method; Echocardiography







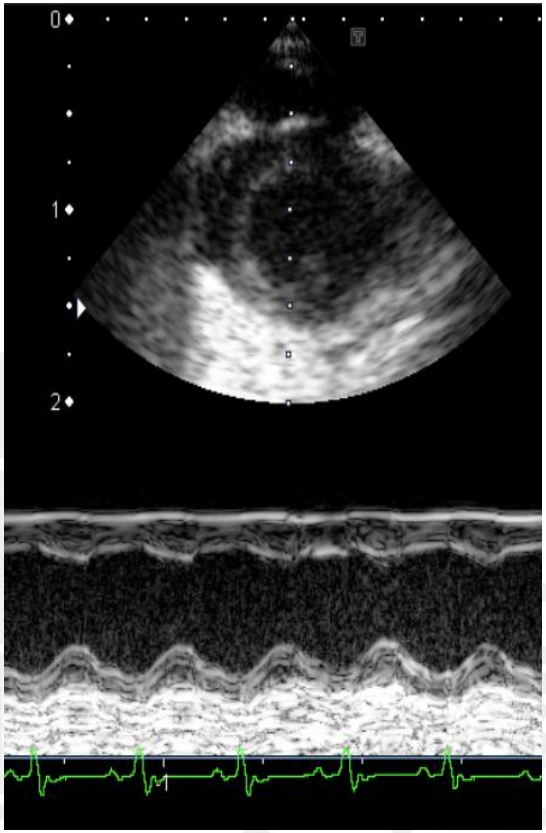
Isoflurane anesthesia, ECG gating

Check echocardiography
(ESD, EDD, EF, LV mass, CO, SV, ESV, EDV, E/E')

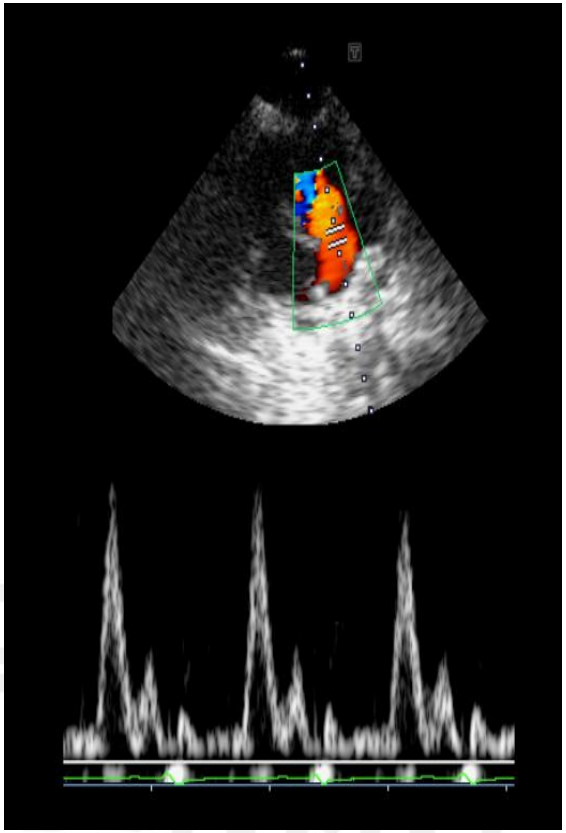
Baseline HR 280- 330 회/min,

Method; Echocardiography

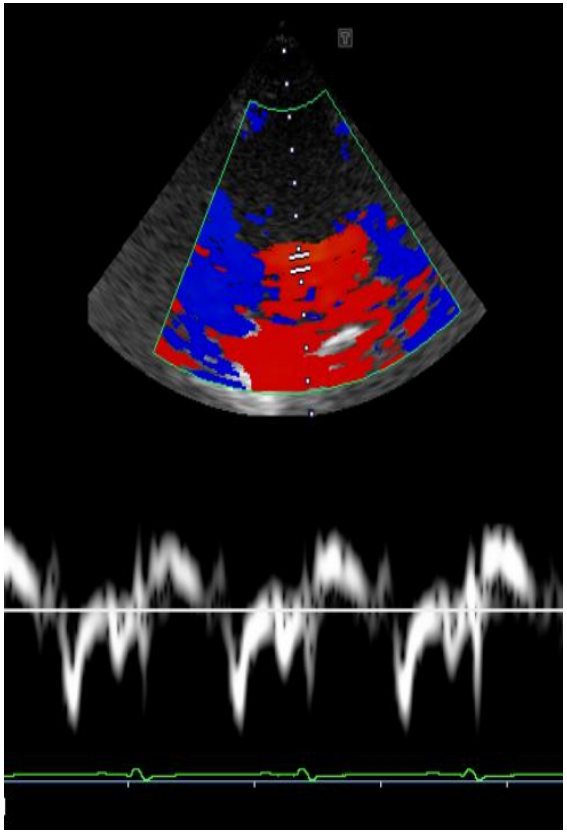
(A) 2D & M-mode
Color doppler



(B) Spectral doppler
Mitral inflow

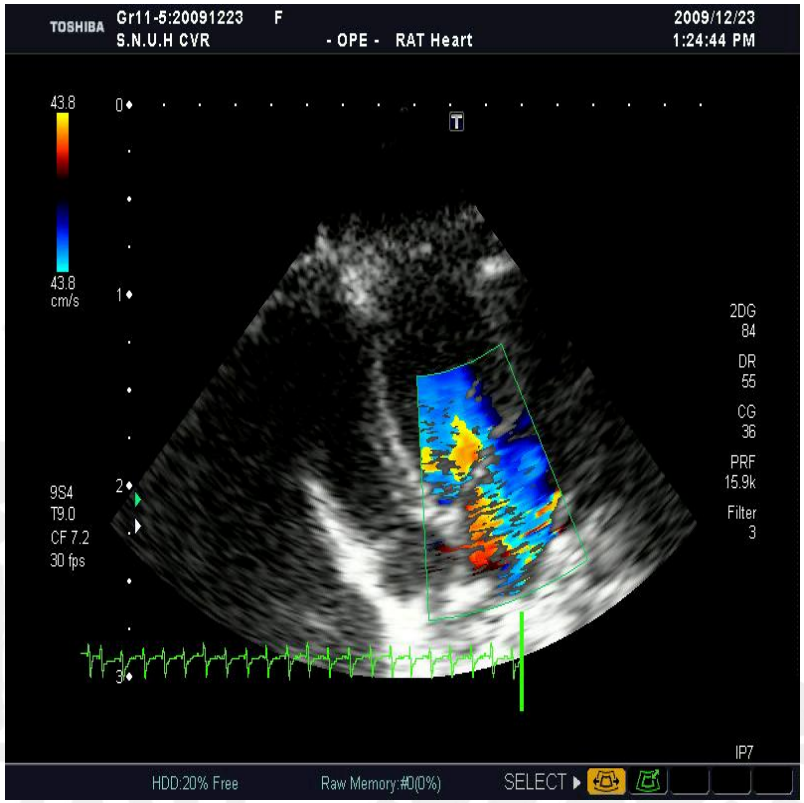


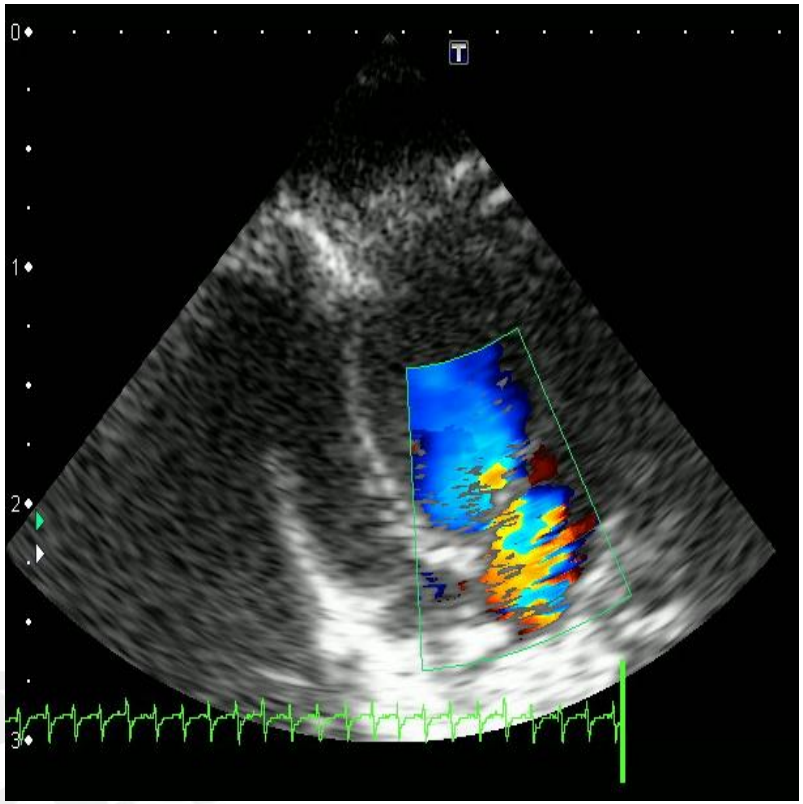
(C) Tissue doppler
Mitral annulus



Method; MR formation

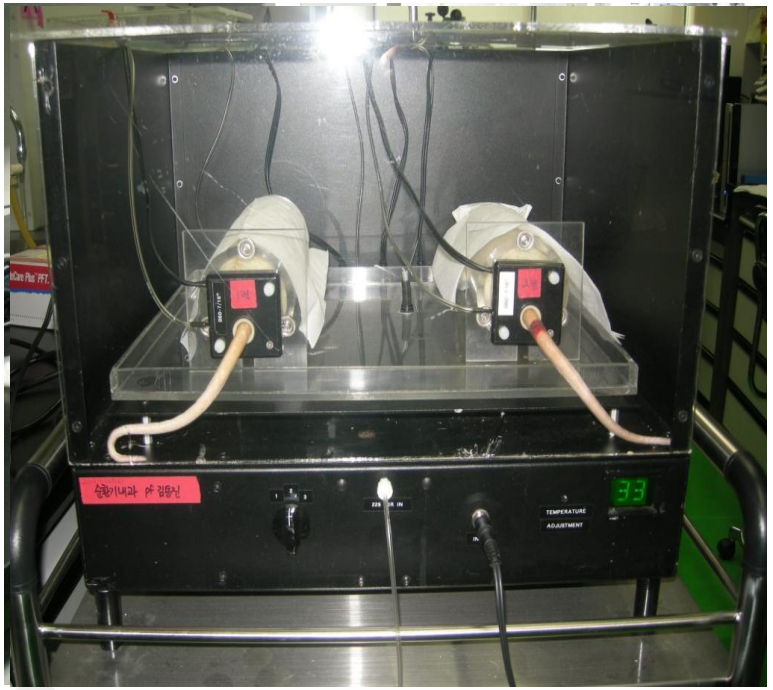
Method; 1 week after MR formation





Method; Exercise test and BP monitoring

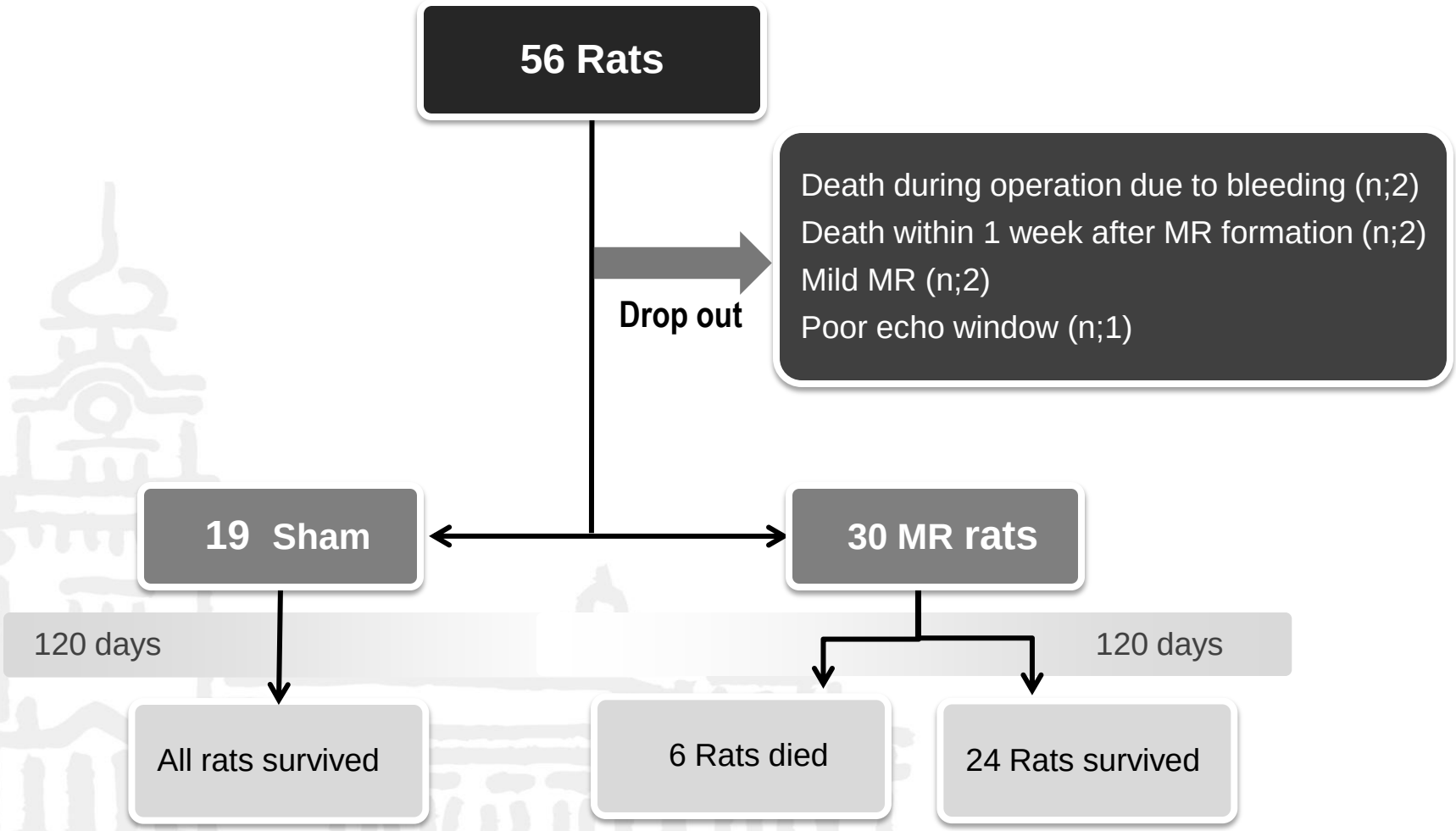
Rota – treadmil test



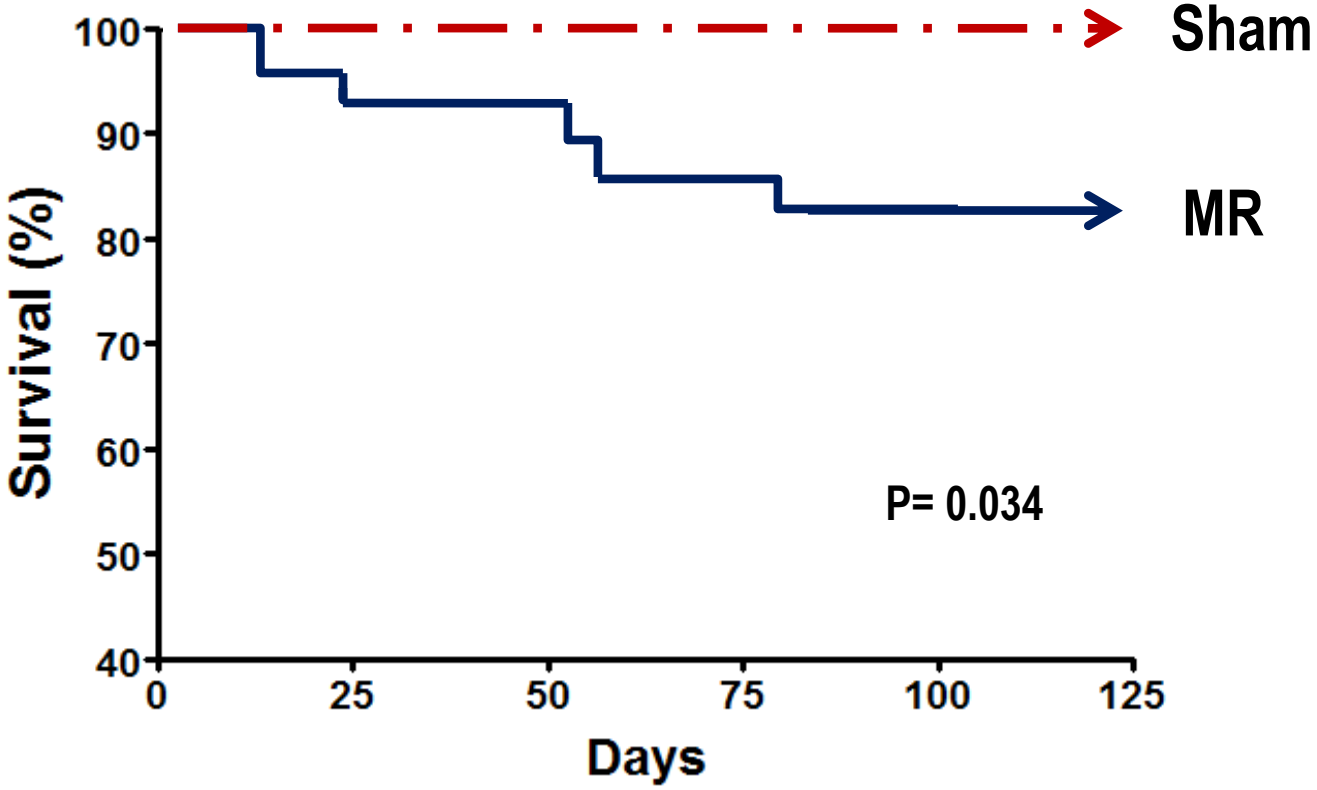
Noninvasive BP monitoring
by tail cuff method

Method; Pressure-volume conductance catheter technique

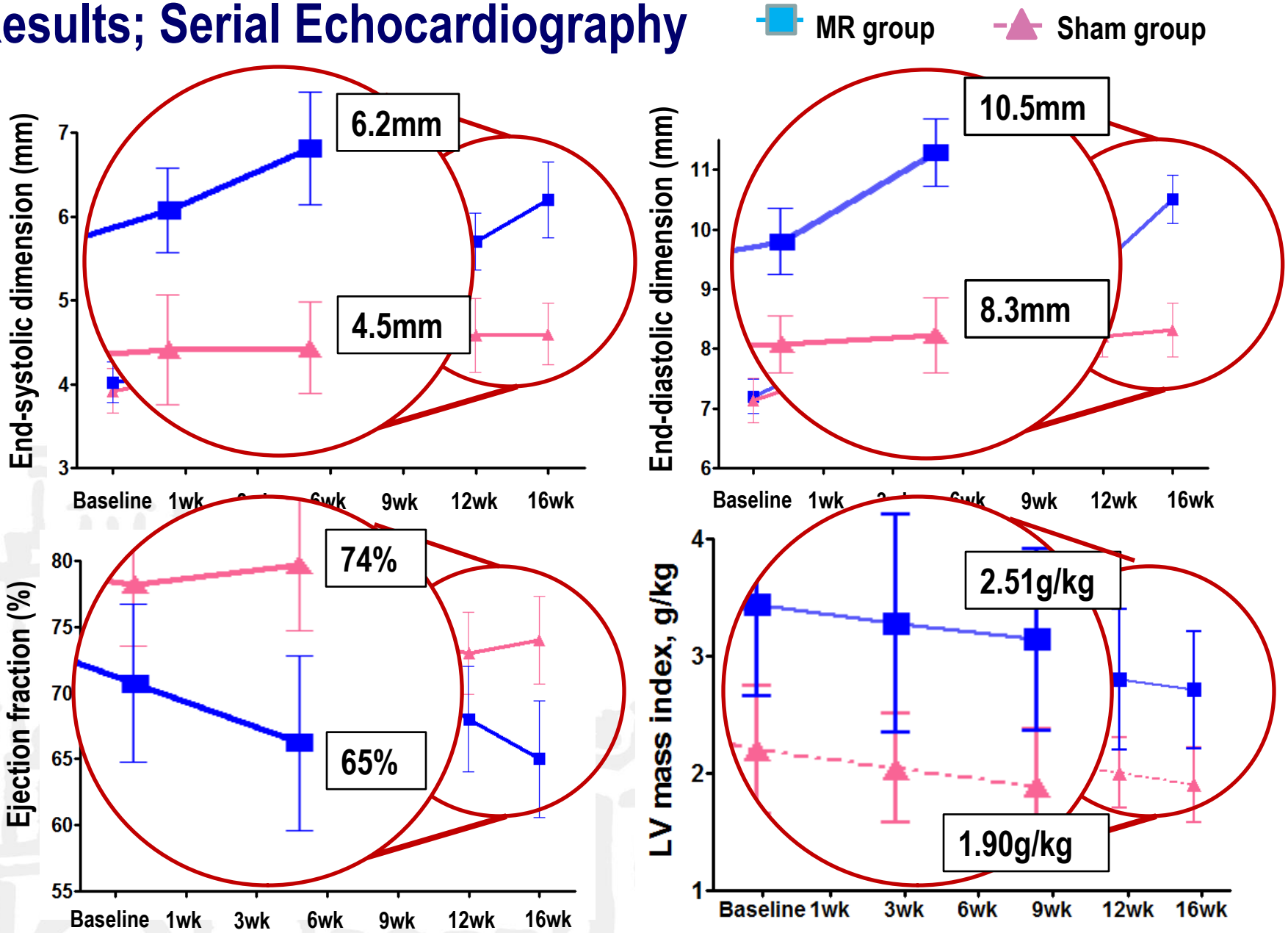
Results


56 Rats
Drop out
Death during operation due to bleeding (n;2)
Death within 1 week after MR formation (n;2)
Mild MR (n;2)
Poor echo window (n;1)
19 Sham
30 MR rats
120 days
120 days
All rats survived
6 Rats died
24 Rats survived

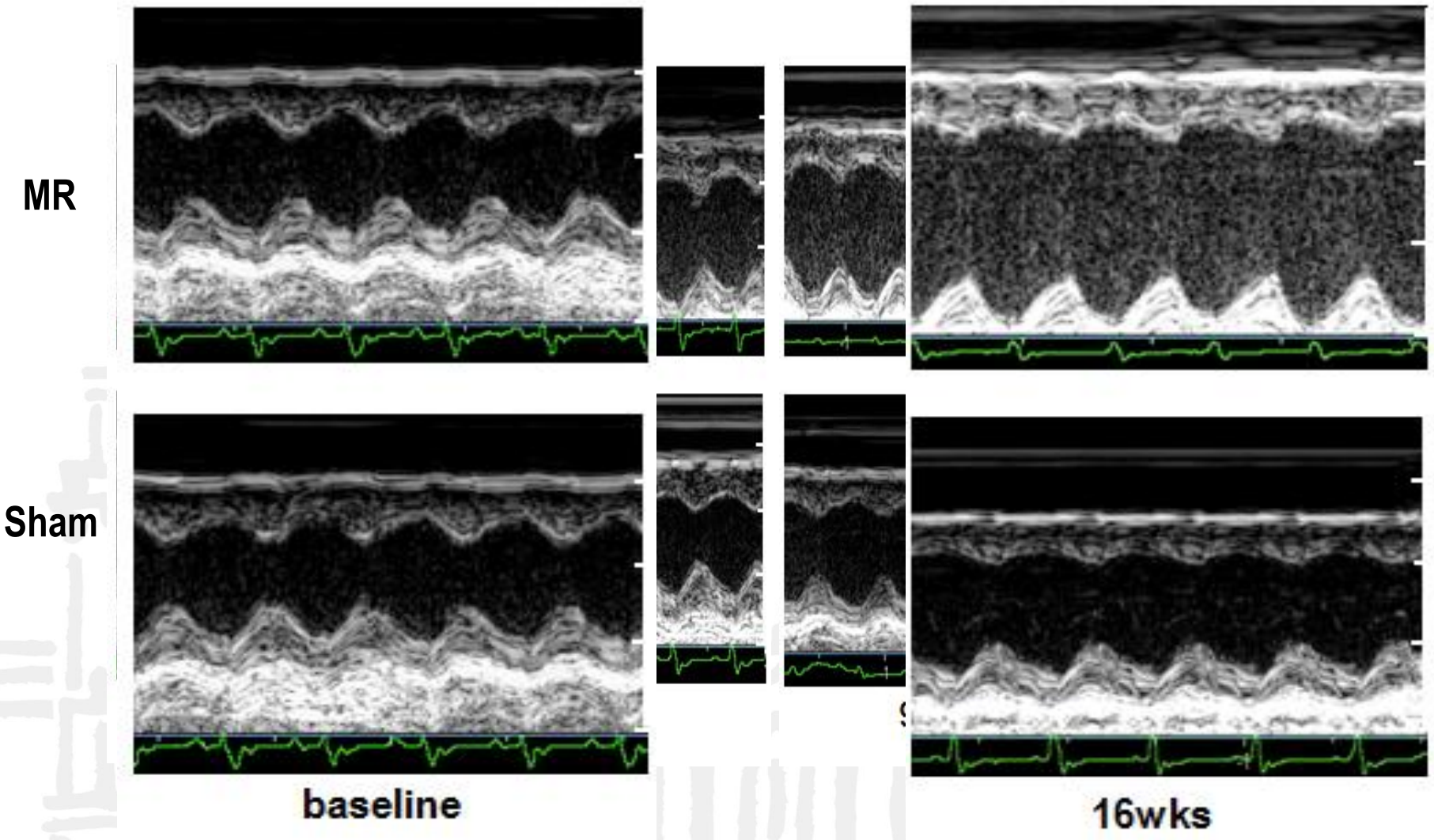
Results; Survival analysis



Results; Serial Echocardiography

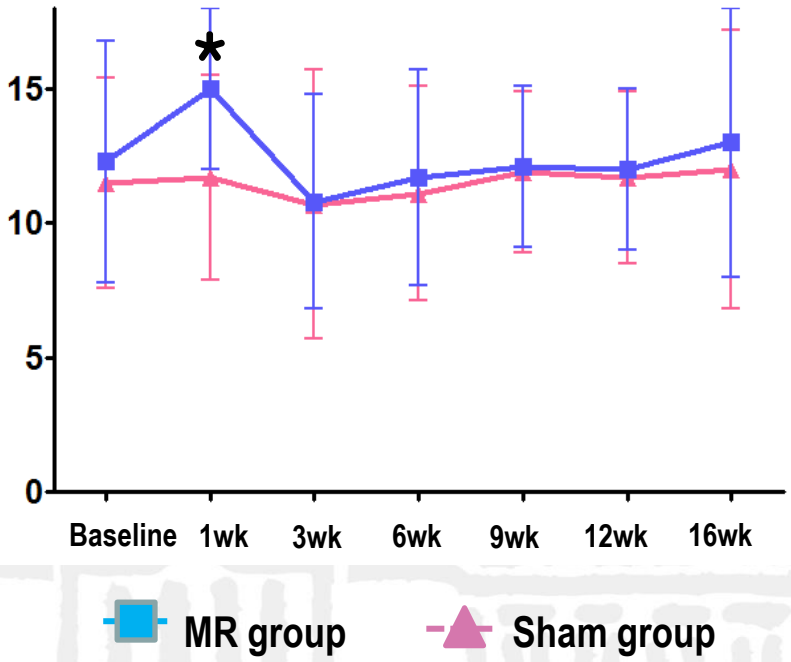


Results; Serial Echocardiography



Results; Serial Echocardiography

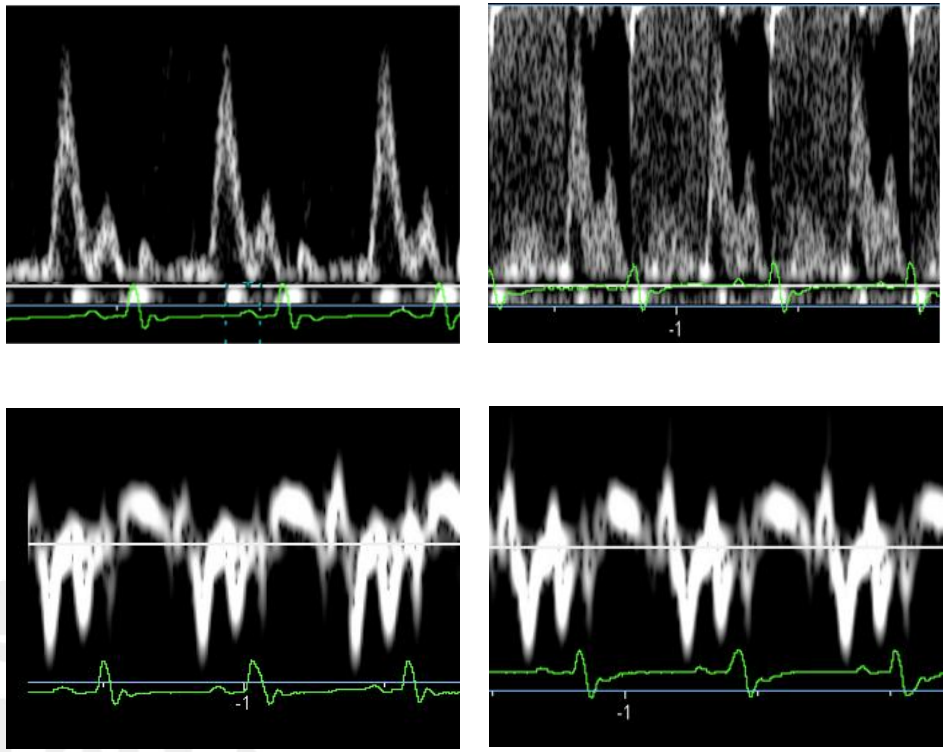
Mtral inflow E-septal tissue Doppler velocity
E' ratio (E/E')



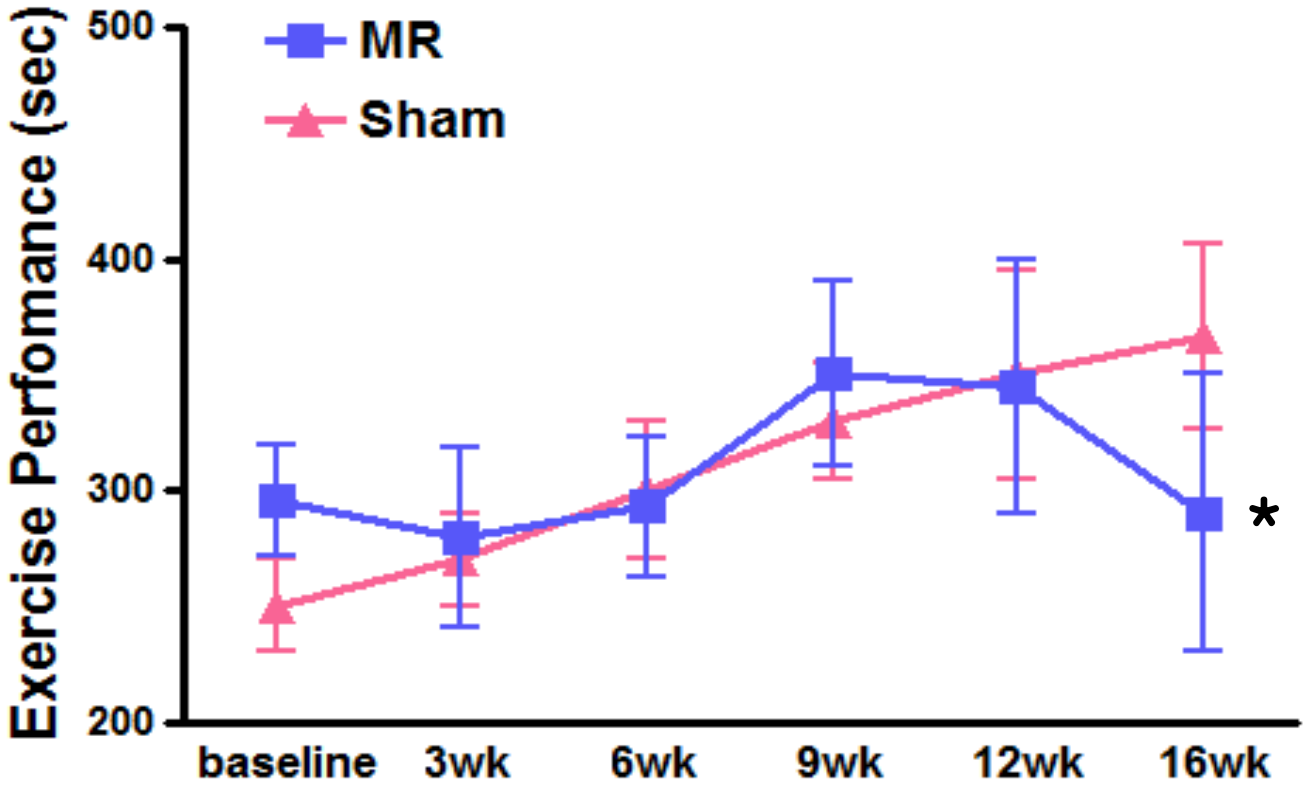
9 weeks after operation

Sham

MR

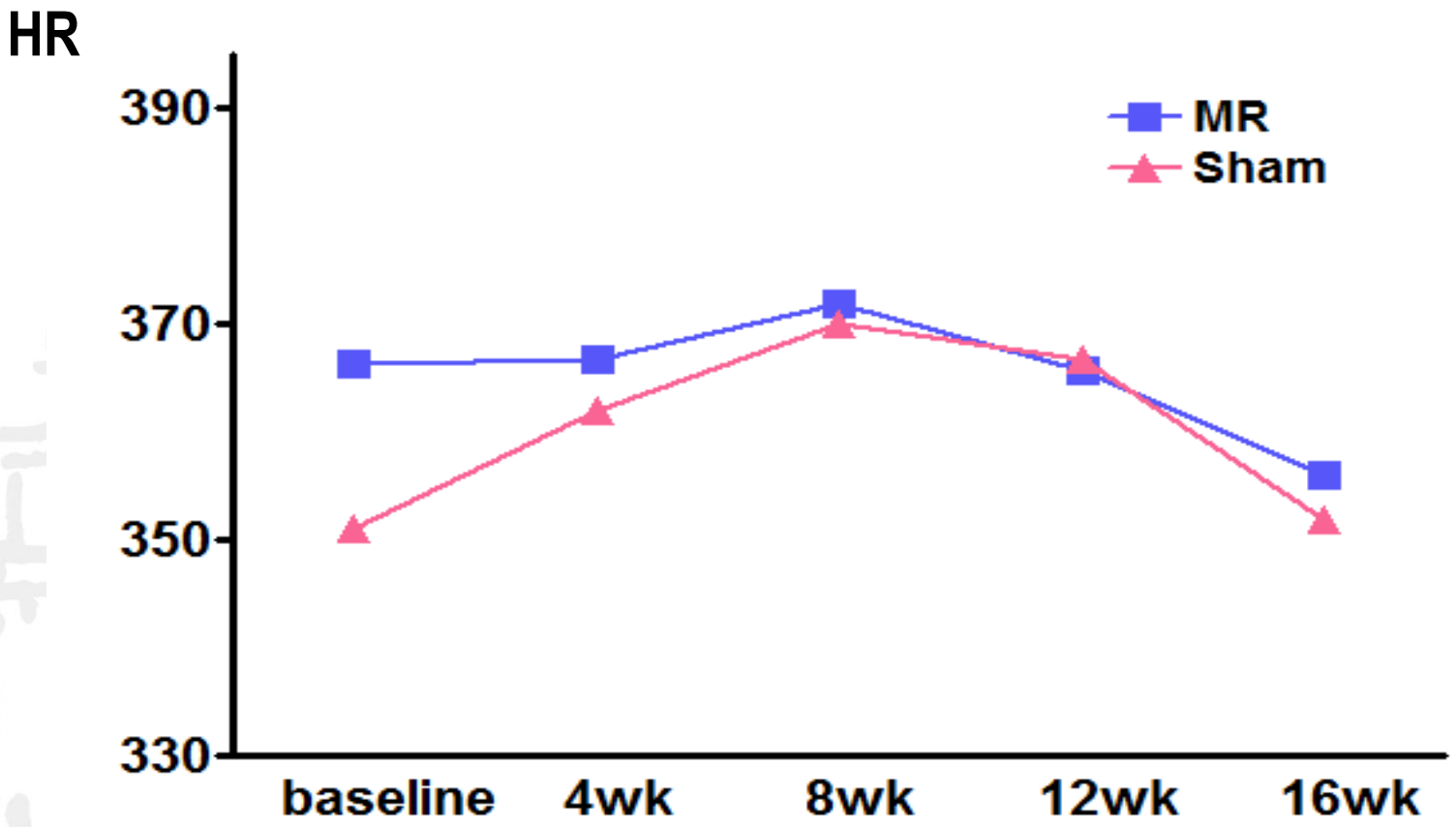


Results; Exercise test



* p < 0.05, compared with sham

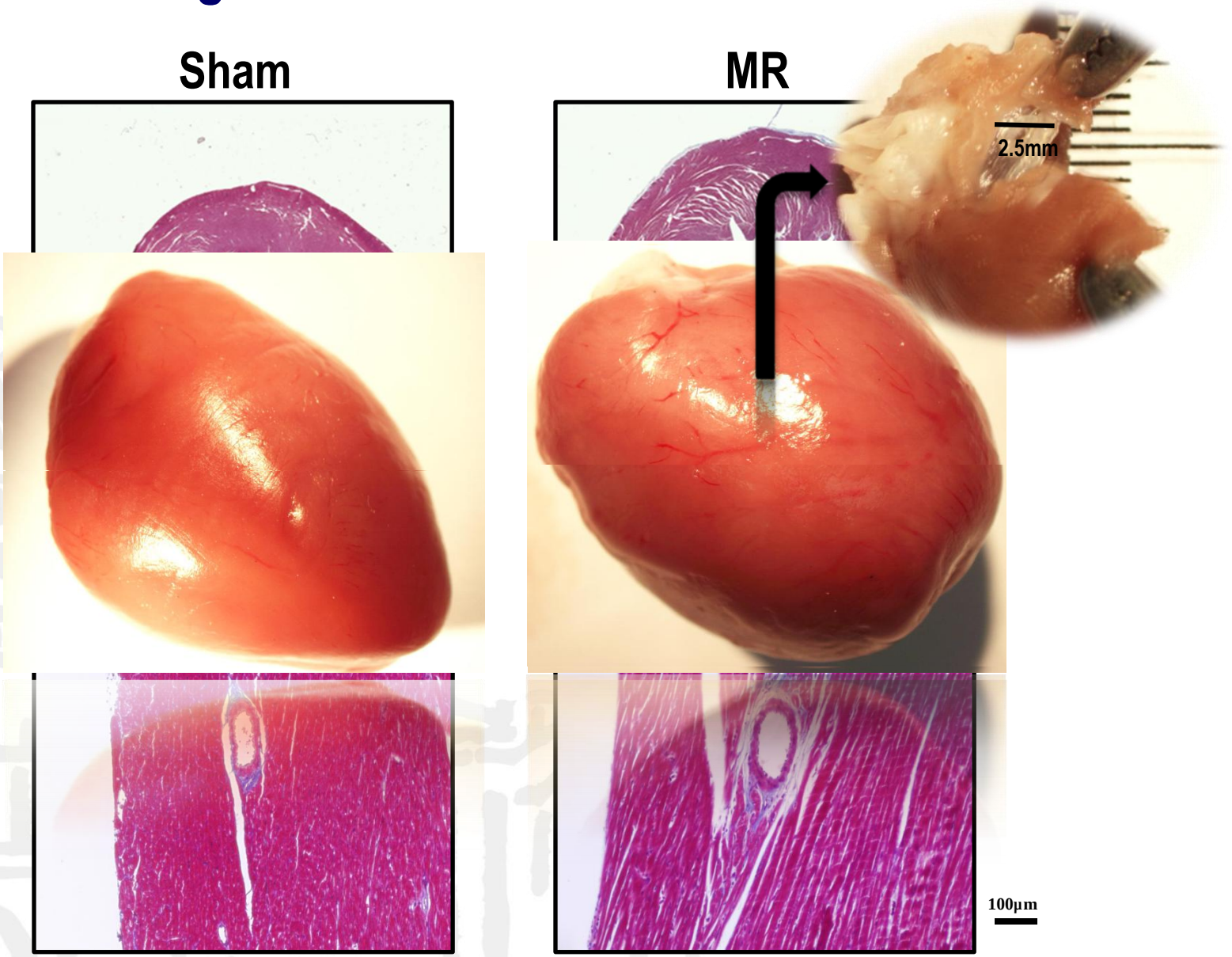
Results; Non invasive BP monitoring



Results; Hemodynamic parameters measured by the Pressure-Volume conductance catheter system

	Sham	MR	P value
HR, beats/min	333±42	342±51	0.93
EDV, μl	730.2±38.2	1210±64.3	< 0.01
ESV, μl	227.5±22.6	472.0±77.0	< 0.01
EF, %	69.5±4.0	61.7±3.5	< 0.01
SV, μl	503.4±38.1	738.0±107.4	< 0.01
LV ESP, mmHg	103.3±6.5	105.4±6.3	0.78
LV EDP, mmHg	8.2±2.0	13.5±3.3	0.03
+dP/dt, mmHg/s	5124.0±557	3967.2±335	0.02
-dP/dt, mmHg/s	-3781.3±722.0	-3542.9±631.9	0.07
ESPVR, mmHg/dl	36.1±13.3	29.1±10.9	0.03
EDPVR, mmHg/dl	0.4±0.4	0.6±0.5	0.06

Results; Pathologic results



Conclusion

- Successful development a rat model of chronic MR
- Evaluating cardiac function using serial echocardiography and pressure–volume analysis
- Furthermore, evaluation of exercise perfomance and tissue finding

Conclusion

- It could be used
  - for investigating potential biological treatment target of chronic MR
  - for understanding this distinctive pathophyiology of MR
  - for heart failure model due to volume overload

Conclusion

- a New Animal Model of Chronic Mitral Regurgitation in Rats.

THANK YOU

•MR 성공률과 단기 생존률 95%

•Echocardiography; 1000회 이상

•Pressure-volume loop; 200마리 이상

→ consistency

Animal model

MR model

** model

** model

1

Hemodynamic evaluation

BP monitoring

Exercise

Echo

P-V loop

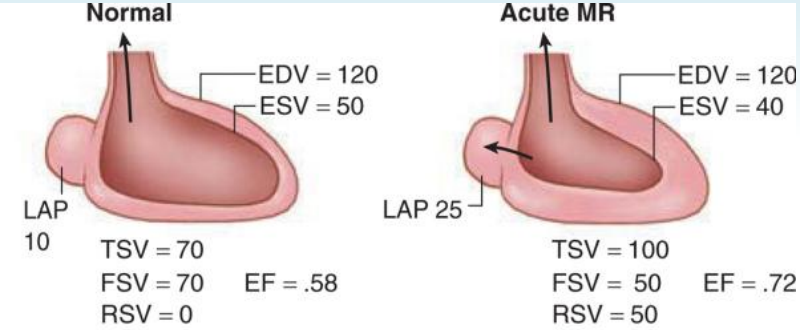
2

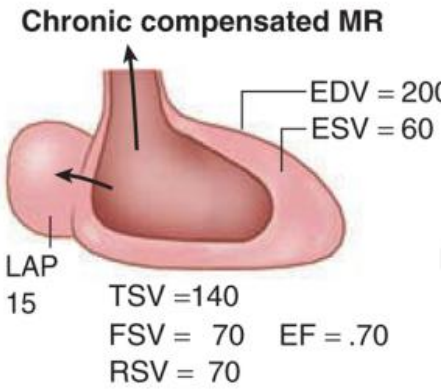
Next..

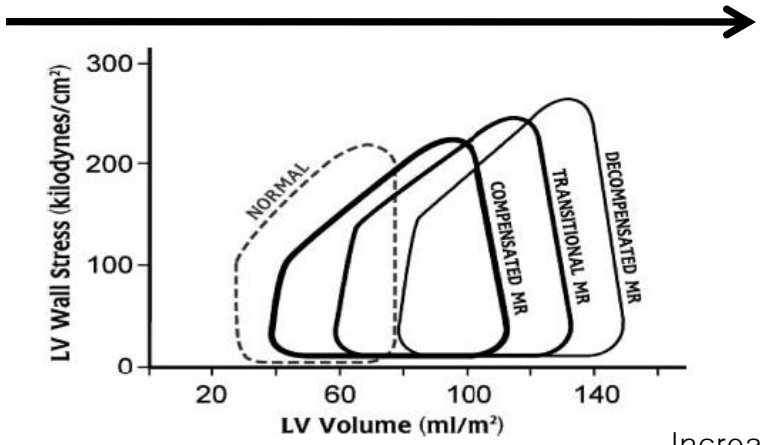
3

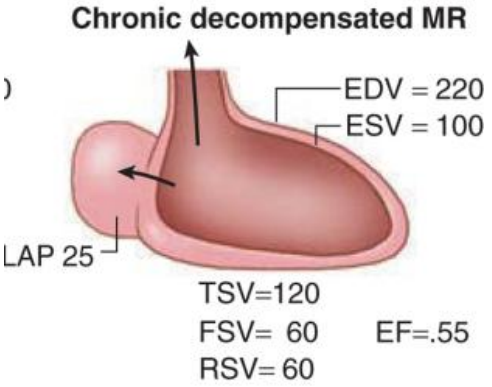
- Cardiac output, ml/min
- control 167.4±6.3 MR 252.3±24

Pathophysiology of chronic MR







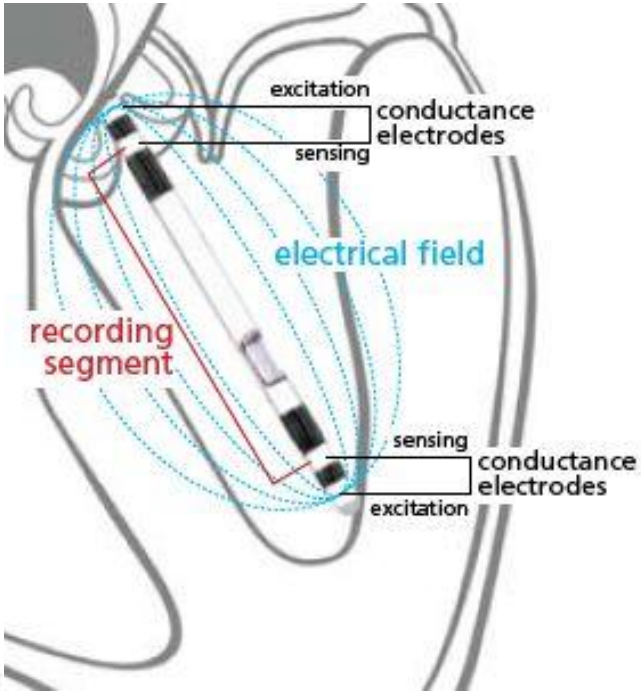


New sarcomere are added in series
Eccentric LVH develops
Cardiomyocytes: increase in length
Preload at the sarcomere level: not increased ➔enhanced stroke volume is mediated through a normal performance of each unit of an enlarged circumstance

Increased end diastolic and end-systolic volume

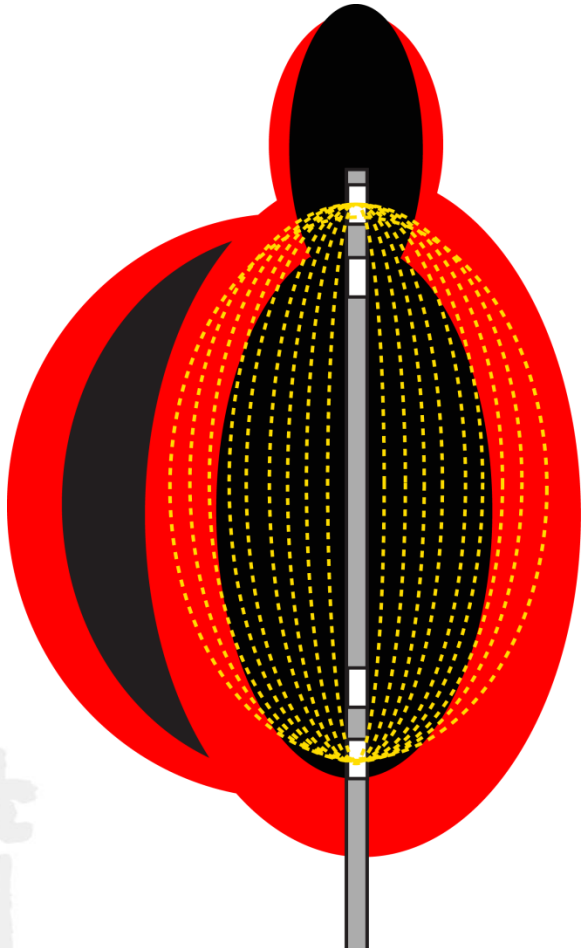
PV loop Measurement Technique

- Miniature catheter advanced through the carotid artery into the Ventricle.
- Four metal rings on the catheter used for volume measurement
  - Constant current applied across outside 2 electrodes
  - Voltage change across inside electrodes corresponds to conductance change
- Baan's equation (1980's) used to calculate volume



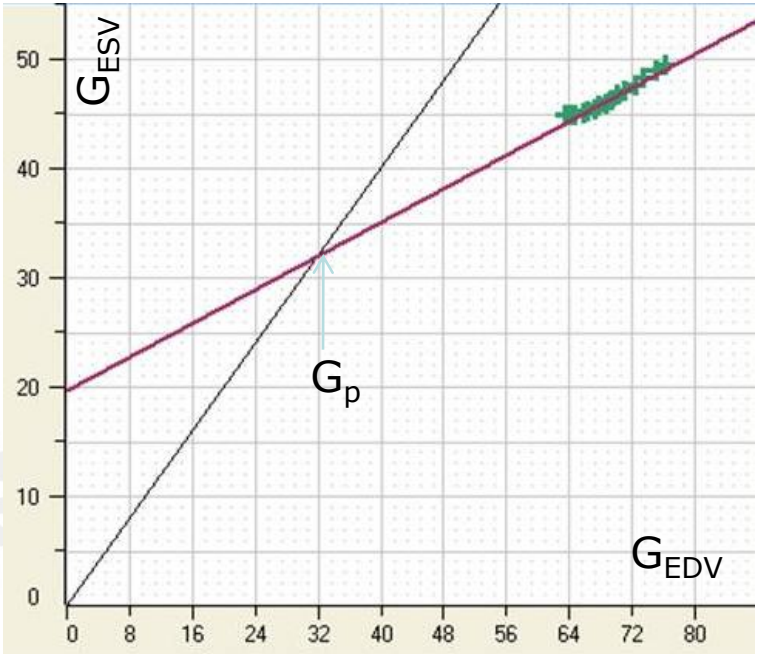
Volume Measurement – Theory

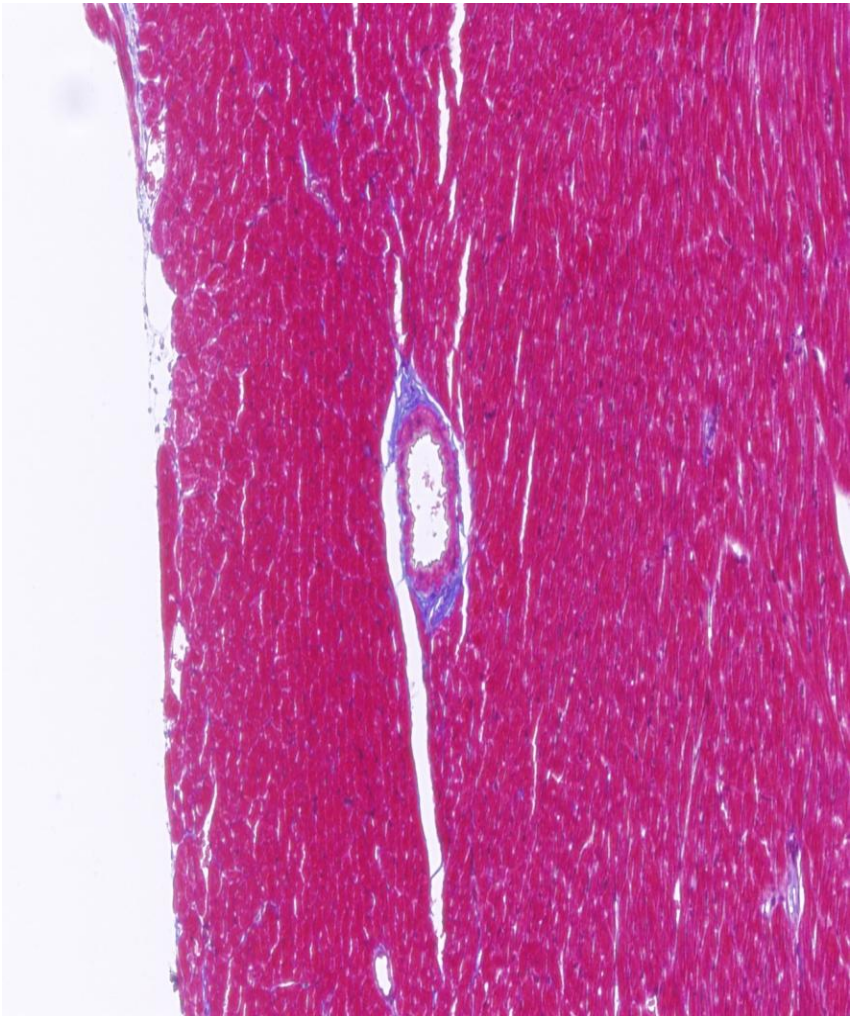
- $G_{meas} = G_{blood} + G_p$
- G_p is parallel conductance of muscle and must be removed to estimate volume
- Hypertonic saline bolus injection
  - Conductance signal increases
  - $G_{b\text{-}ED}$ & $G_{b\text{-}ES}$ both increase
- Conductivity of blood changes but not the conductivity of the muscle

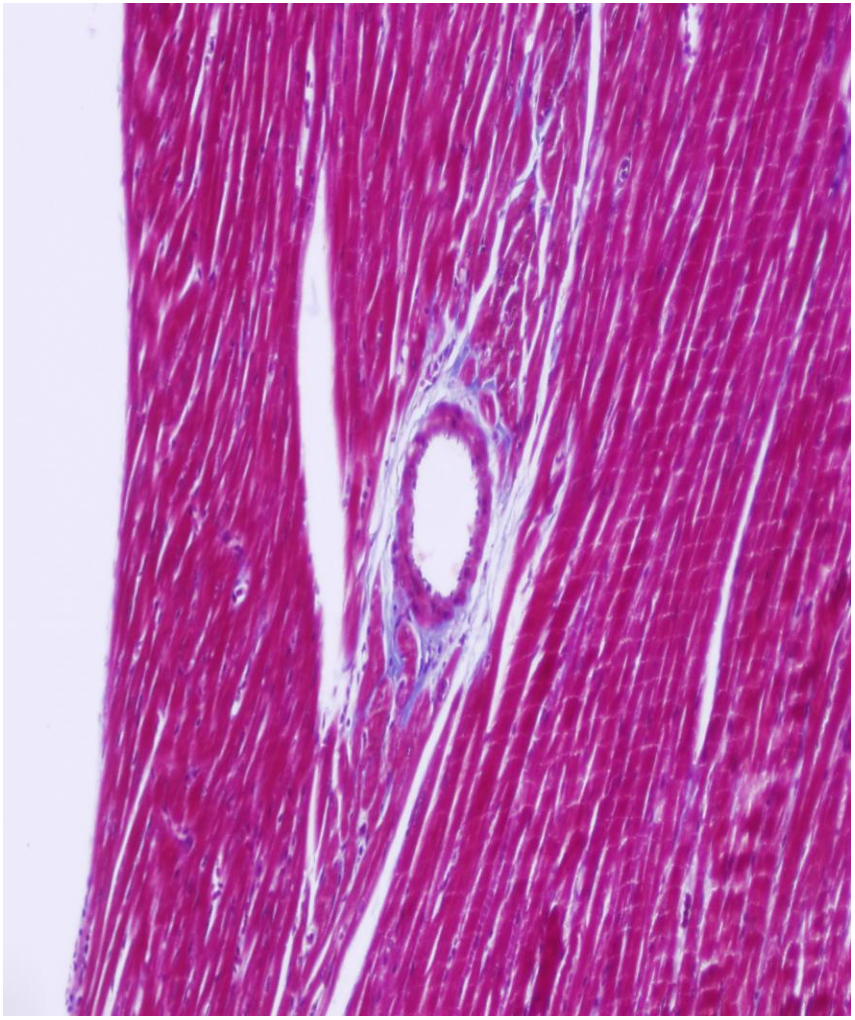


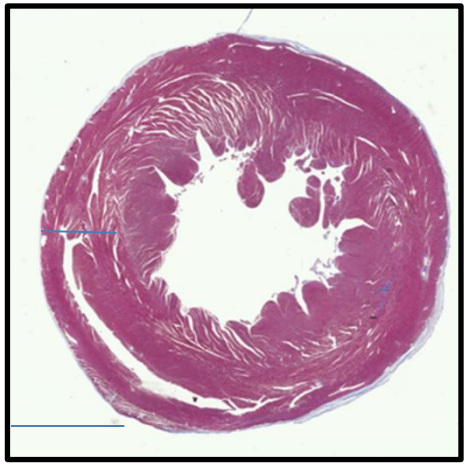
Hypertonic Saline Injection

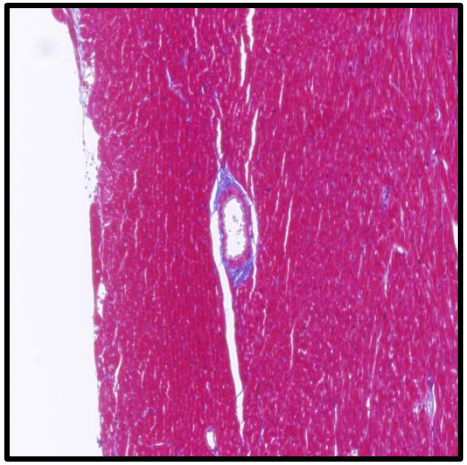
- G_{EDV} & G_{ESV} graphed on X-Y scatter plot
- Slope line superimposed on line of identity
- Point of intersection of both lines indicates parallel conductance (G_p)
- This technique can be difficult in small animals like mice and rats

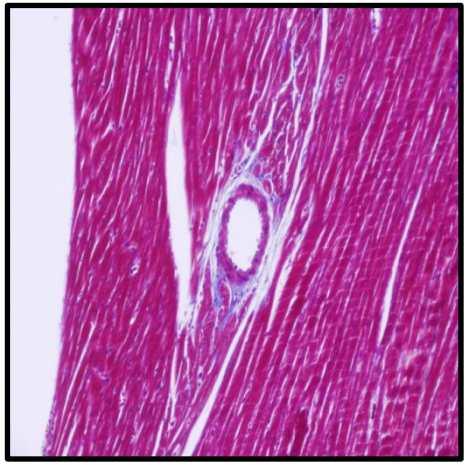












Acknowledgement

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김용진 선생님

이혜원, **BS**

김하나, **BS**