Antiplatelet Agents as a Novel Therapy of Heart Failure due to Myocardial Infarction

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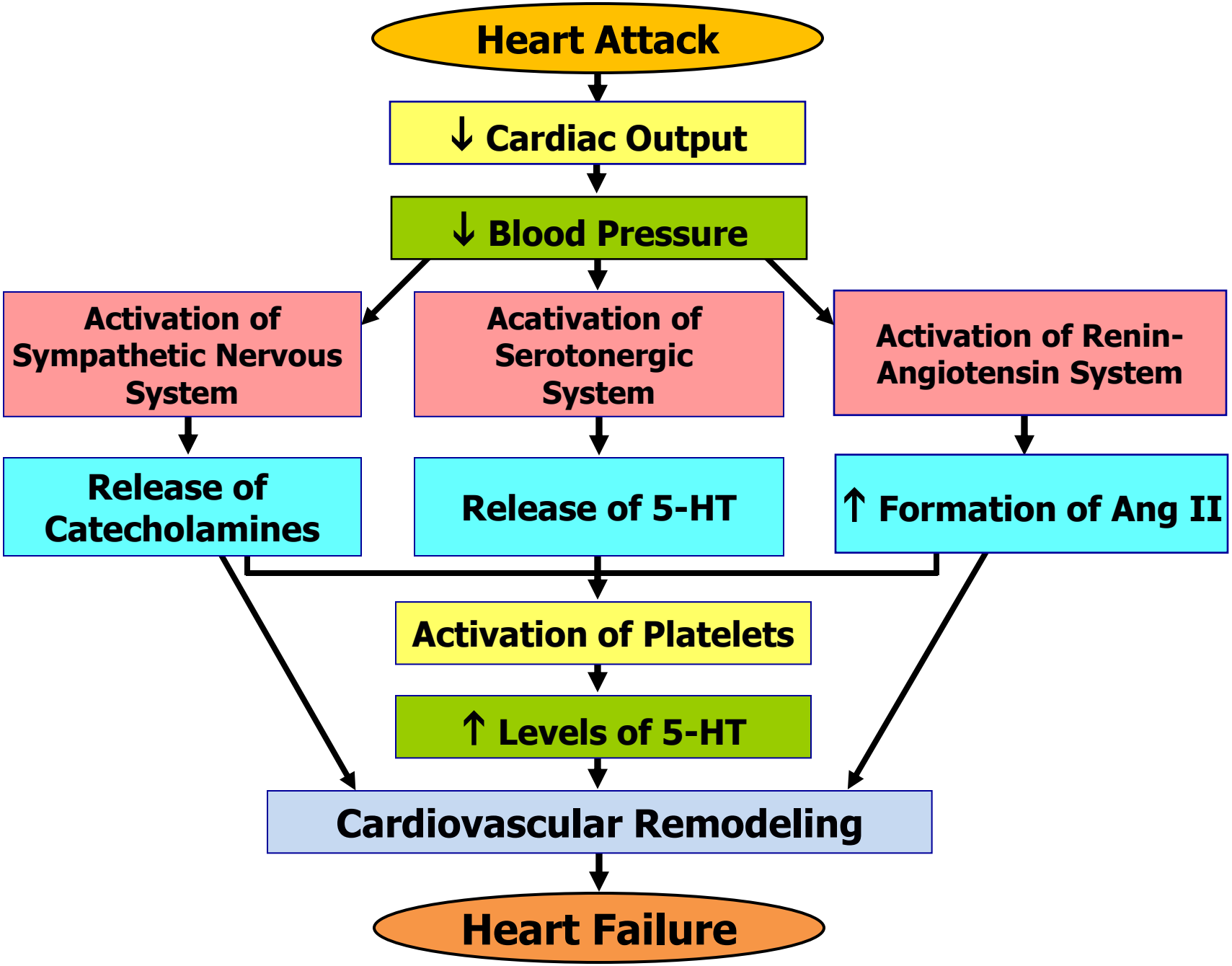
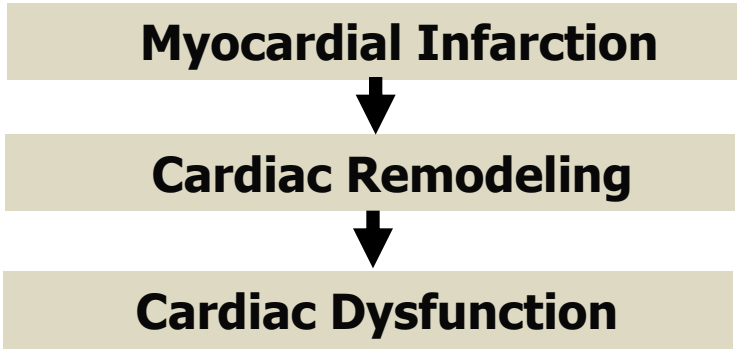

Heart Attack
↓ Cardiac Output
↓ Blood Pressure
Activation of Sympathetic Nervous System
Acativation of Serotonergic System
Activation of Renin-Angiotensin System
Release of Catecholamines
Release of 5-HT
↑ Formation of Ang II
Activation of Platelets
↑ Levels of 5-HT
Cardiovascular Remodeling
Heart Failure

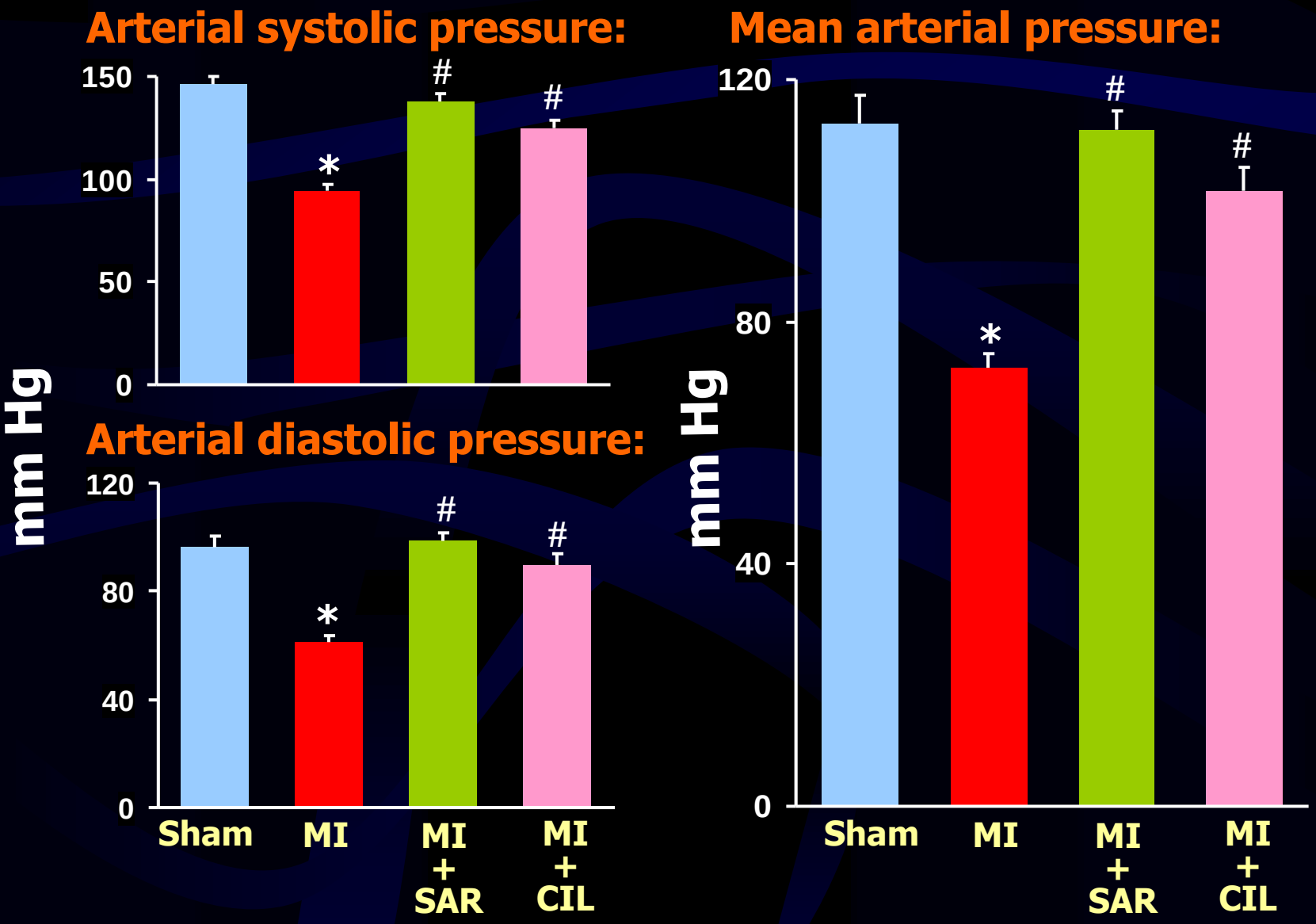
Rat Model of MI and Antiplatelet Drugs Treatment

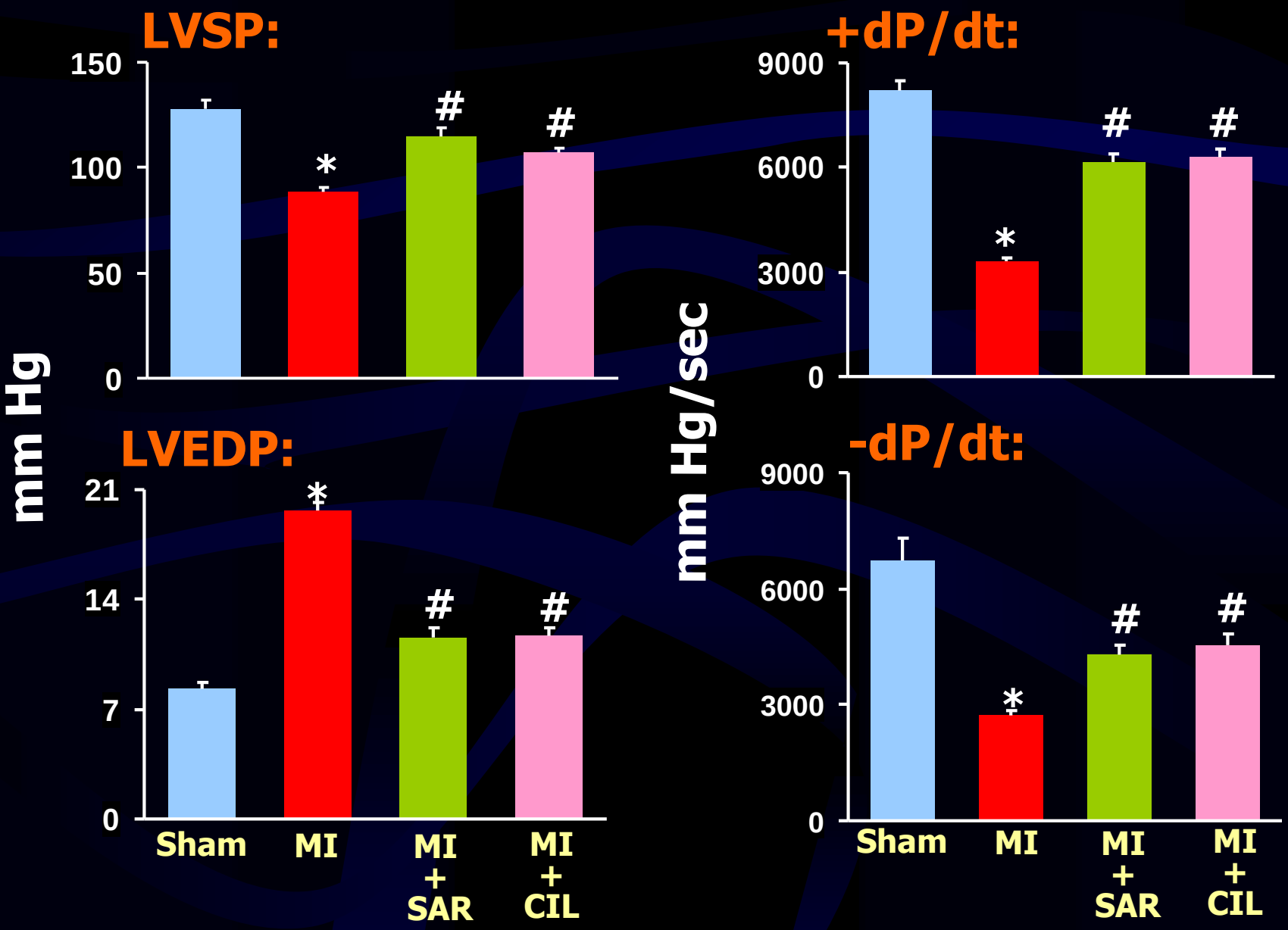
- **Sham Control – 8 Weeks**
- **Coronary Occlusion – 8 Weeks**
- **Sarpogrelate – 5 HT Antagonist (5 mg/kg/day) for 5 weeks after 3 weeks of MI**
- **Cilostazol – Phosphodiestarase III Inhibitor (5 mg/kg/day) for 5 weeks after 3 weeks of MI**



General characteristics of control and myocardial infarcted animals with or without sarpogrelate/cilostazol treatment

Parameters	Sham	MI	MI + SAR	MI + CIL
Body wt (g)	573 ± 14	510 ± 9*	529 ± 11	524 ± 10
Ventricular wt (g)	1.37 ± 0.04	1.50 ± 0.04*	1.41 ± 0.04#	1.43 ± 0.04#
Ventricular wt/Body wt (mg/g)	2.38 ± 0.03	3.03 ± 0.08*	2.71 ± 0.05#	2.77 ± 0.07#
Right ventricle wt (g)	0.28 ± 0.02	0.43 ± 0.04*	0.32 ± 0.04#	0.31 ± 0.04#
Scar wt (g)	----------	0.17 ± 0.01	0.16 ± 0.01	0.16 ± 0.02
Lungs wet/dry wt ratio	4.53 ± 0.06	5.21 ± 0.09*	4.82 ± 0.04#	4.79 ± 0.07#
Liver wet/dry wt ratio	3.18 ± 0.02	3.31 ± 0.06	3.31 ± 0.05	3.27 ± 0.03


Arterial systolic pressure:
150
100
50
0
mm Hg
*
#
#
Arterial diastolic pressure:
120
80
40
0
mm Hg
*
#
#
Sham
MI
MI + SAR
MI + CIL
Mean arterial pressure:
120
80
40
0
mm Hg
*
#
#
Sham
MI
MI + SAR
MI + CIL


LVSP:
150
100
50
0
*
#
#
+dP/dt:
9000
6000
3000
0
*
#
#
mm Hg
mm Hg/sec
LVEDP:
21
14
7
0
*
#
#
-dP/dt:
9000
6000
3000
0
*
#
#
Sham
MI
MI + SAR
MI + CIL
Sham
MI
MI + SAR
MI + CIL

Echocardiographic parameters of control and myocardial infarcted animals with or without sarpogrelate/cilostazol treatment

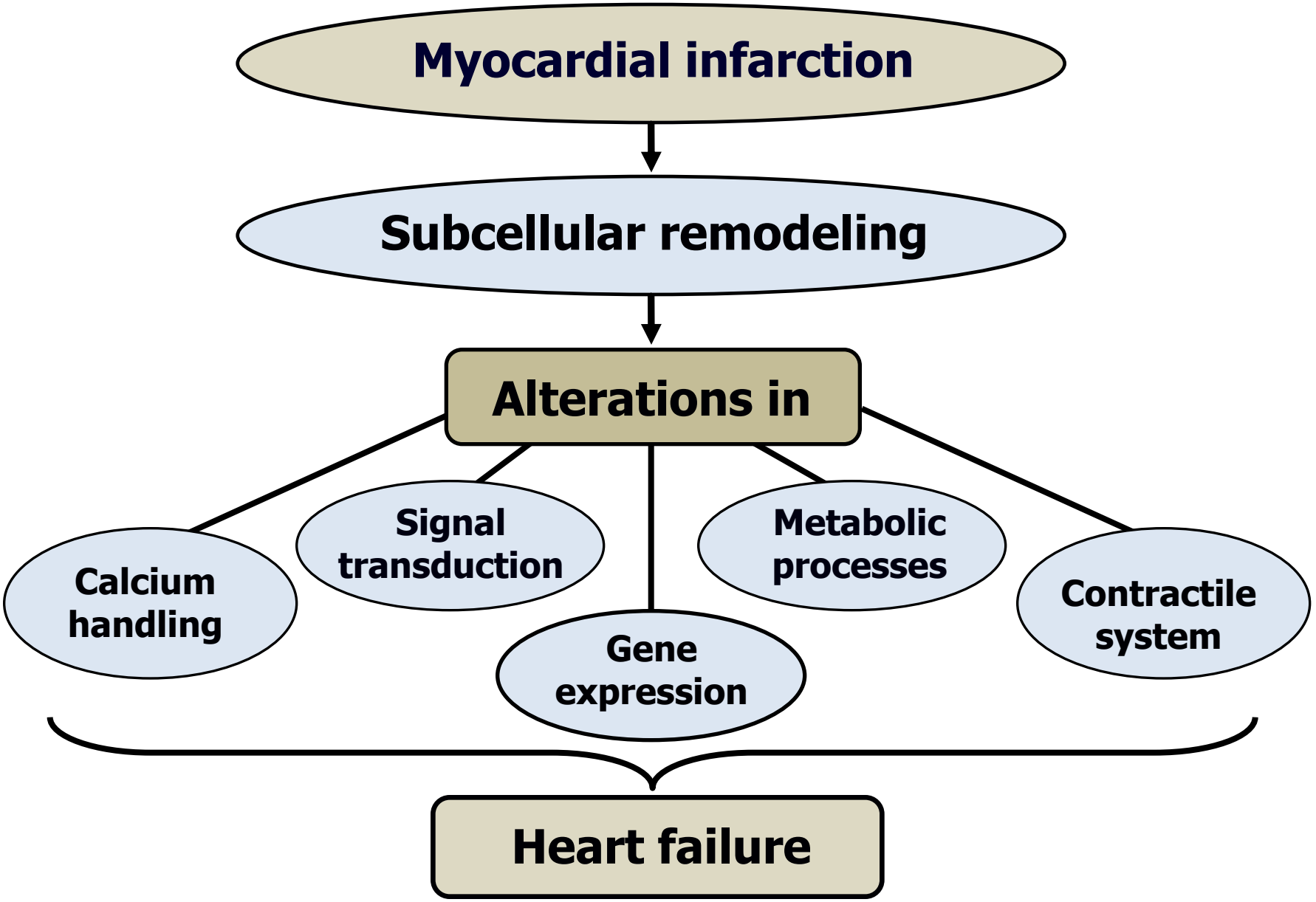
Parameters	Sham	MI	MI + SAR	MI + CIL
CO (ml/min)	325 ± 26.5	240 ± 27.1*	342 ± 30.4#	348 ± 5.4#
HR (beats/min)	317 ± 3.7	355 ± 7.5*	340 ± 4.6	348 ± 5.4
SV (ml/min)	1.03 ± 0.09	0.72 ± 0.08*	1.03 ± 0.09#	1.04 ± 0.06#
EF (%)	80.4 ± 1.2	40.2 ± 1.6*	63.9 ± 2.7#	68.6 ± 1.8#
FS (%)	44.2 ± 1.2	15.9 ± 0.75*	32.7 ± 1.1#	32.7 ± 1.3#

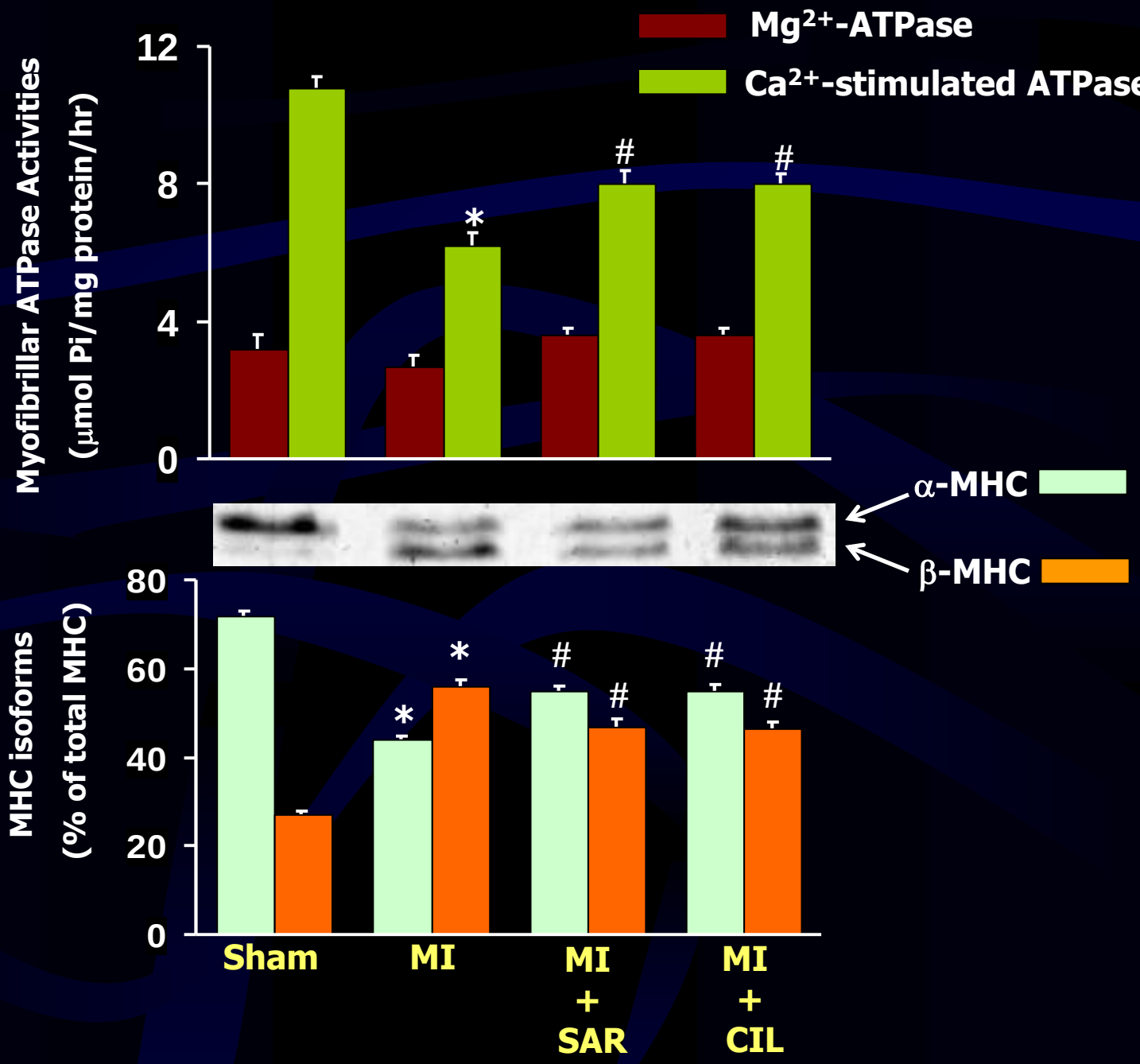
CO: Cardiac output; HR: Heart rate; SV: Stroke volume; EF: Ejection fraction; FS: Fractional shortening

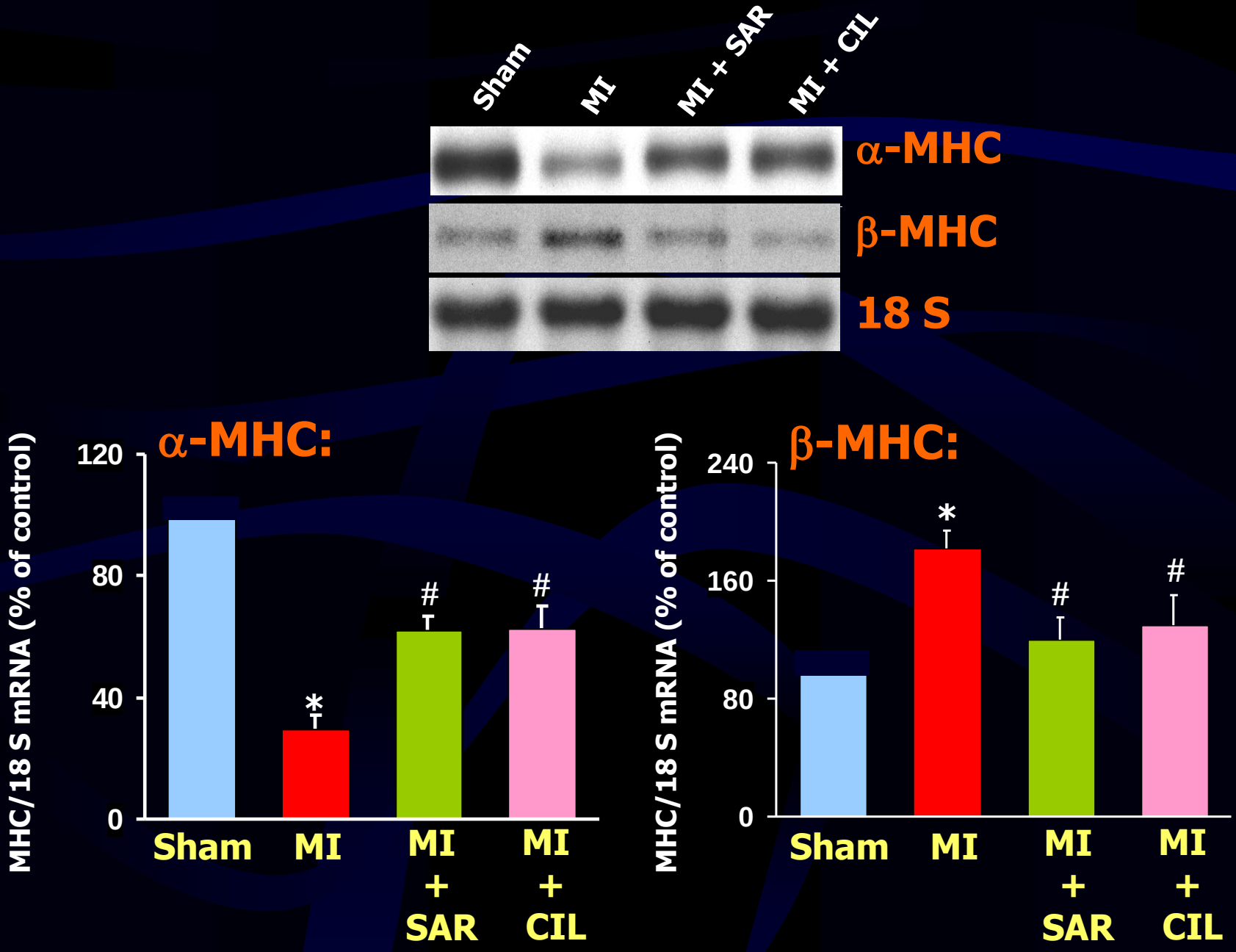
Echocardiographic parameters of control and myocardial infarcted animals with or without sarpogrelate/cilostazol treatment

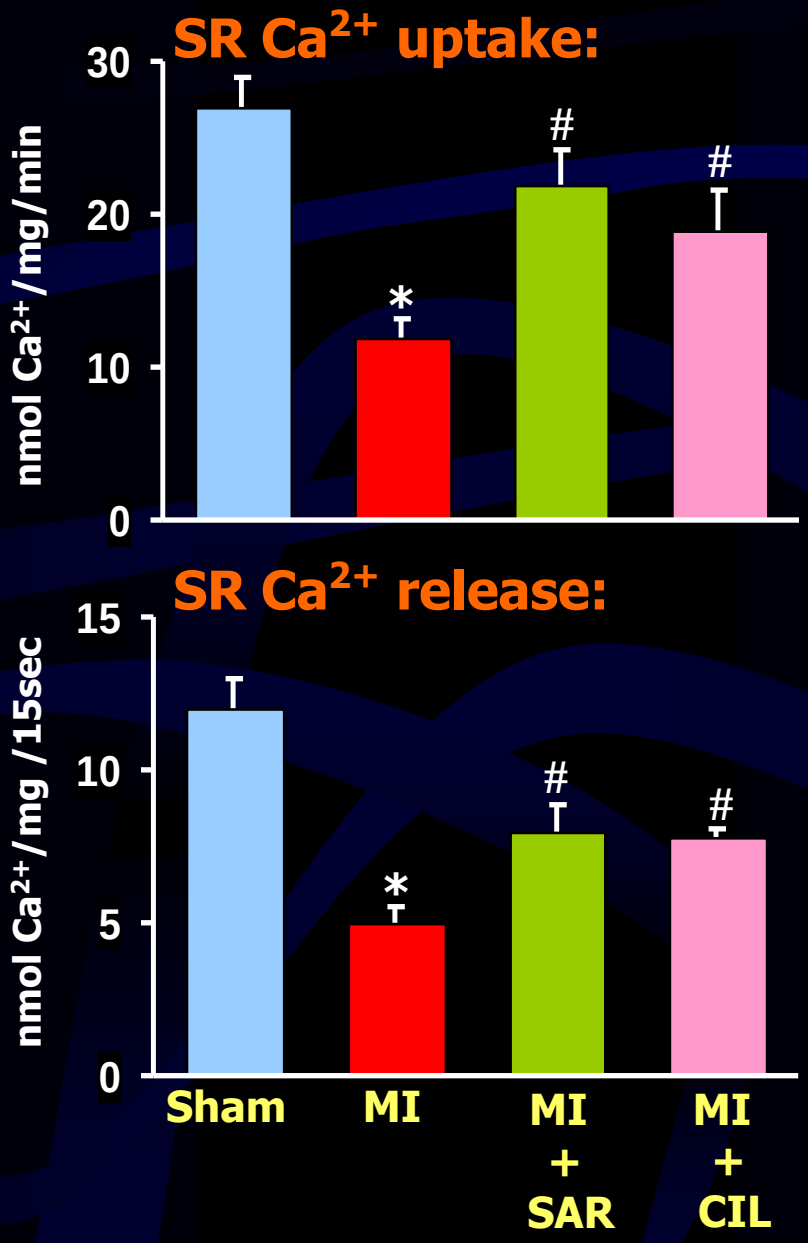
Parameters	Sham	MI	MI + SAR	MI + CIL
$LVID_s$ (cm)	0.43 ± 0.02	0.99 ± 0.01*	0.68 ± 0.04#	0.69 ± 0.03#
$LVID_d$ (cm)	0.77 ± 0.02	1.16 ± 0.01*	0.93 ± 0.03#	0.97 ± 0.03#
LVESV (ml)	0.21 ± 0.02	1.99 ± 0.07*	0.82 ± 0.13#	0.81 ± 0.09#
LVEDV (ml)	1.02 ± 0.07	3.06 ± 0.09*	1.87 ± 0.16#	1.98 ± 0.16#

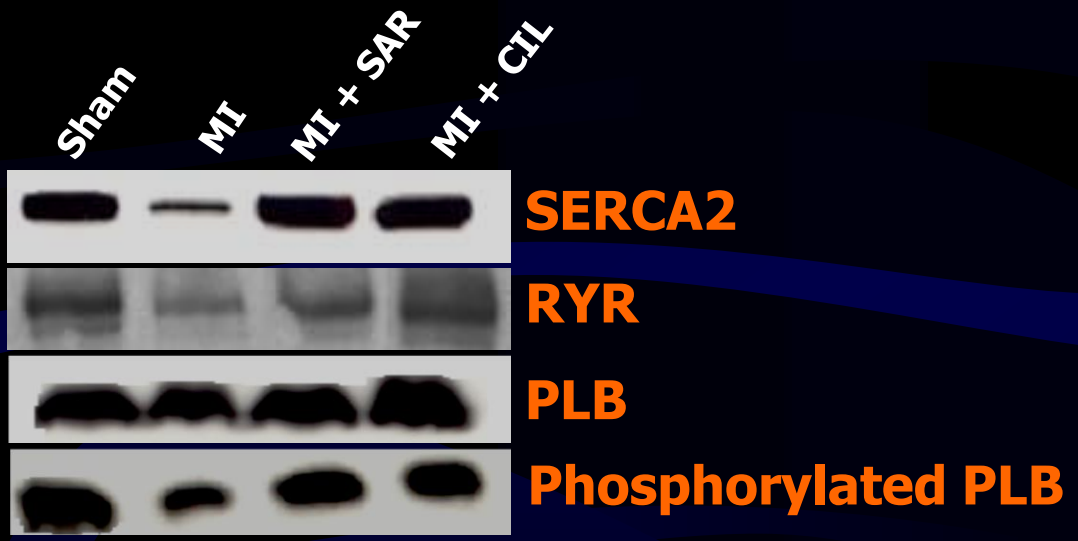
$LVID_s$: Left ventricular intrinsic systolic diameter; $LVID_d$: Left ventricular intrinsic diastolic diameter; LVESV: Left ventricular end systolic volume; LVEDV: Left ventricular end diastolic volume

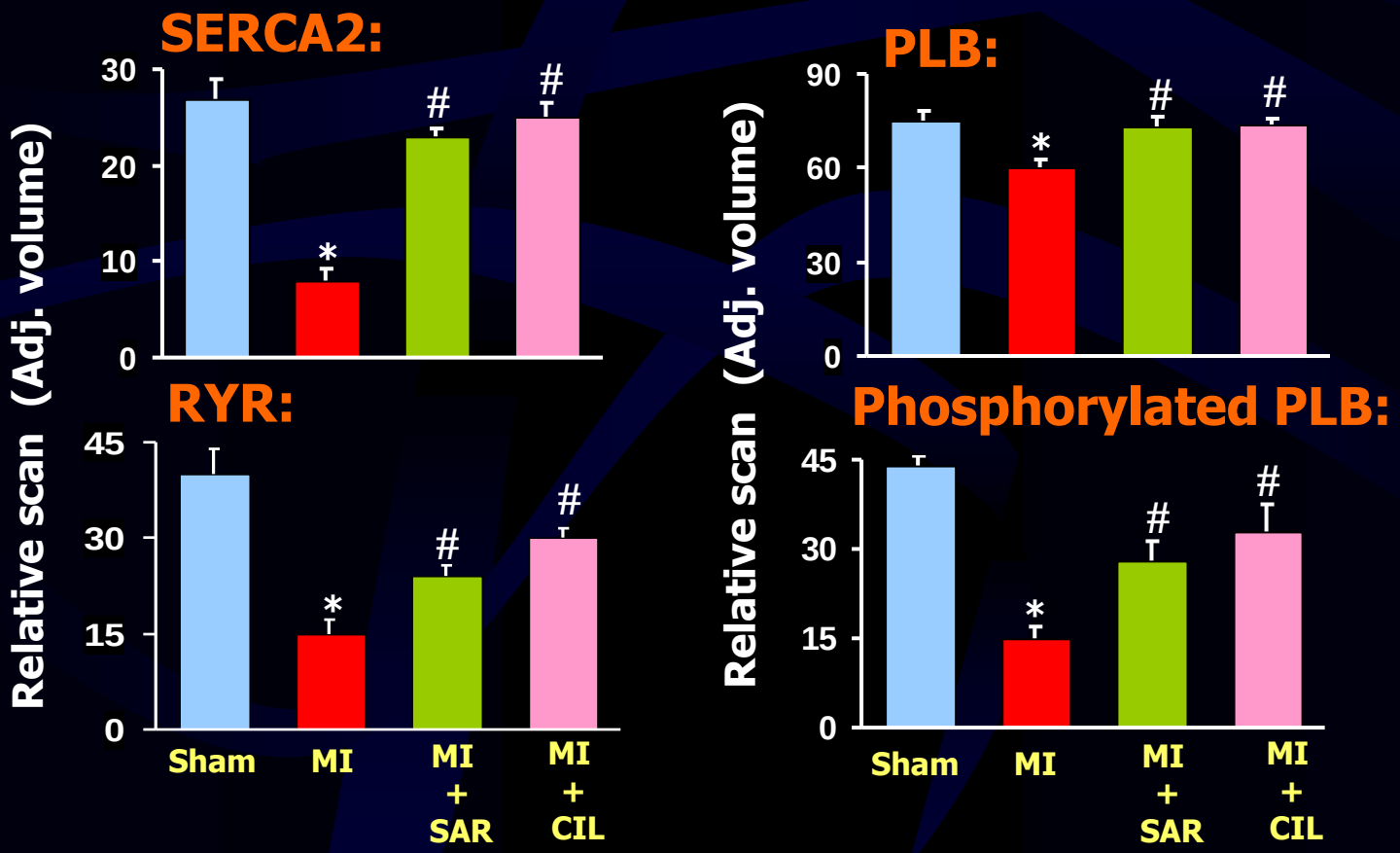

Myocardial infarction
Subcellular remodeling
Alterations in
Calcium handling
Signal transduction
Gene expression
Metabolic processes
Contractile system
Heart failure

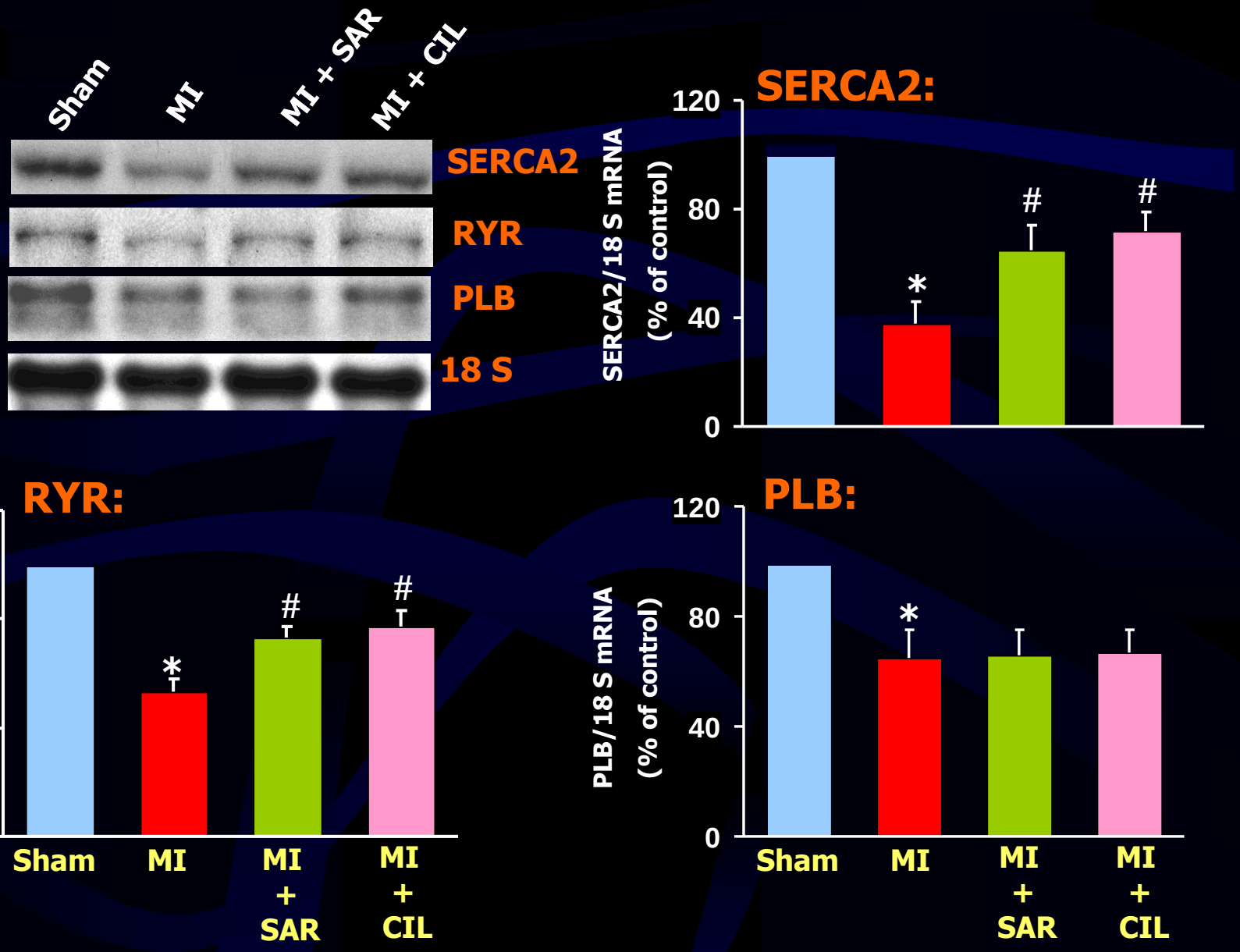

Mg2+-ATPase
Ca2+-stimulated ATPase
Myofibrillar ATPase Activities
(μmol Pi/mg protein/hr)
12
8
4
0
*
#
#
α-MHC
β-MHC
MHC isoforms
(% of total MHC)
80
60
40
20
0
*
*
#
#
#
#
Sham
MI
MI
+
SAR
MI
+
CIL


Sham
MI
MI + SAR
MI + CIL
α-MHC
β-MHC
18 S
α-MHC:
MHC/18 S mRNA (% of control)
120
80
40
0
*
#
#
Sham
MI
MI + SAR
MI + CIL
β-MHC:
MHC/18 S mRNA (% of control)
240
160
80
0
*
#
#
Sham
MI
MI + SAR
MI + CIL


SR Ca2+ uptake:
nmol Ca2+/mg/min
30
20
10
0
*
#
#
SR Ca2+ release:
nmol Ca2+/mg /15sec
15
10
5
0
*
#
#
Sham
MI
MI + SAR
MI + CIL

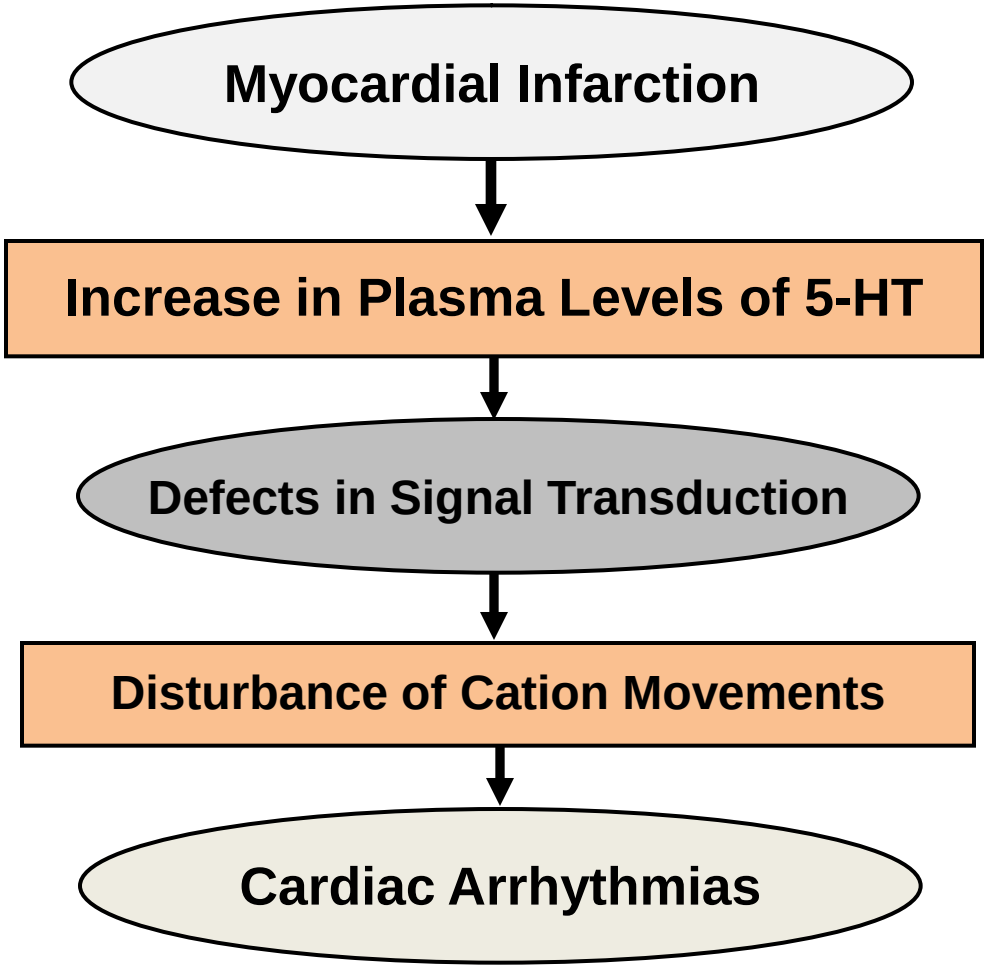

Sham
MI
MI + SAR
MI + CIL
SERCA2
RYR
PLB
Phosphorylated PLB


SERCA2:
RYR:
PLB:
Phosphorylated PLB:
Relative scan (Adj. volume)
Sham
MI
MI + SAR
MI + CIL


Sham
MI
MI + SAR
MI + CIL
SERCA2
RYR
PLB
18 S
SERCA2:
SERCA2/18 S mRNA
(% of control)
120
80
40
0
*
#
#
RYR:
RYR/18 S mRNA
(% of control)
120
80
40
0
*
#
#
Sham
MI
MI + SAR
MI + CIL
PLB:
PLB/18 S mRNA
(% of control)
120
80
40
0
*
Sham
MI
MI + SAR
MI + CIL

Effect of sarpogrelate and cilostazol on sarcolemmal Na^+-K^+ ATPase and Na^+-Ca^{2+} exchange activities in rats subjected to myocardial infarction

Group	Mg^{2+}-ATPase (µmol Pi/mg/hr)	Na^+-K^+ ATPase (µmol Pi/mg/hr)	Na^+-Ca^{2+} exchange (µmol Ca^{2+}/mg/2s)
Control	88± 7.4	22.4 ± 3.5	5.2 ± 0.4
MI	91 ± 8.2	8.6 ± 0.9*	2.2 ± 0.3*
MI + sarpogrelate	91 ± 8.9	13.4 ± 1.7#	3.9 ± 0.2#
MI + cilostazol	567 ± 8.6	13.9 ± 1.6#	4.1 ±0.4#


Myocardial Infarction
Increase in Plasma Levels of 5-HT
Defects in Signal Transduction
Disturbance of Cation Movements
Cardiac Arrhythmias

Effect of sarpogrelate and cilostazol on plasma norepinephrine and epinephrine levels in rats subjected to myocardial infarction

Group	Plasma norepinephrine (pg/ml)	Plasma epinephrine (pg/ml)
Control	125± 11	264 ± 16
MI	406 ± 26*	577 ± 33*
MI + sarpogrelate	388 ± 28	545 ± 29
MI + cilostazol	567 ± 30#	692 ± 35#

Effect of sarpogrelate and cilostazol on cardiac β_1-adrenoceptors and adenylyl cyclase activities in rats subjected to myocardial infarction

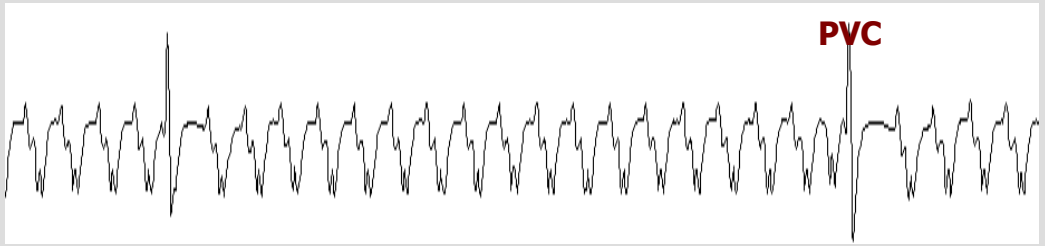
Parameters	β_1-adrenoceptors		Adenylyl cyclase (pmol cAMP/mg/min)	
	Kd (pM)	Bmax (fmol/mg)	Basel	Isoproteronol-stimulated
Control	35.4 ± 2.9	42.9 ± 3.3	148 ± 9	187 ± 21
MI	39.6 ± 3.1	20.7 ± 1.4*	107 ± 9*	88 ± 16*
MI + sarpogrelate	39.4 ± 2.8	33.6 ± 2.2#	134 ± 8#	162 ±15#
MI + cilostazol	38.7 ± 2.9	30.8 ± 1.7#	131 ± 7#	154 ± 17#

Effect of sarpogrelate and cilostazol on cardiac apoptosis and TNF-α levels in rats subjected to myocardial infarction

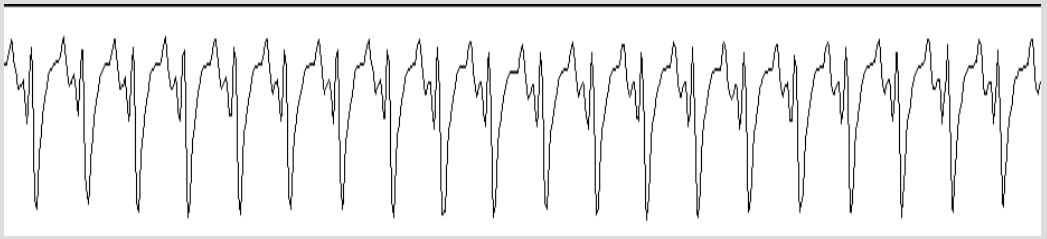
Group	TNF-α (pg/mg)	Apoptosis (Absorbance)
Control	6.9 ± 1.7	0.01± 0.002
MI	18.6 ± 2.4*	0.04 ± 0.001*
MI + sarpogrelate	13.3 ± 1.7#	0.03 ± 0.002#
MI + cilostazol	12.6 ± 1.2#	0.03 ± 0.004#

Sham
Lead I

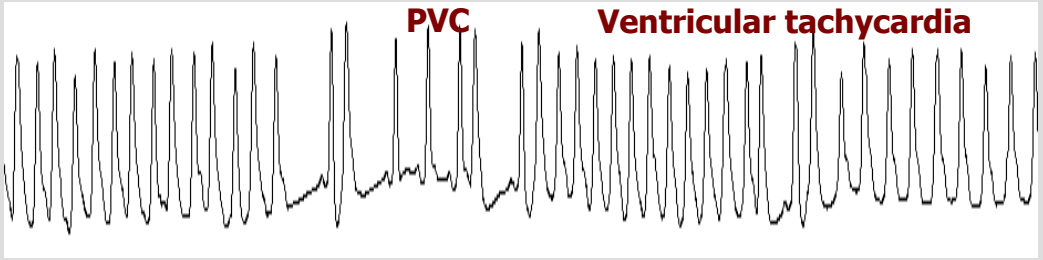
MI
Lead I



MI + SAR
Lead I

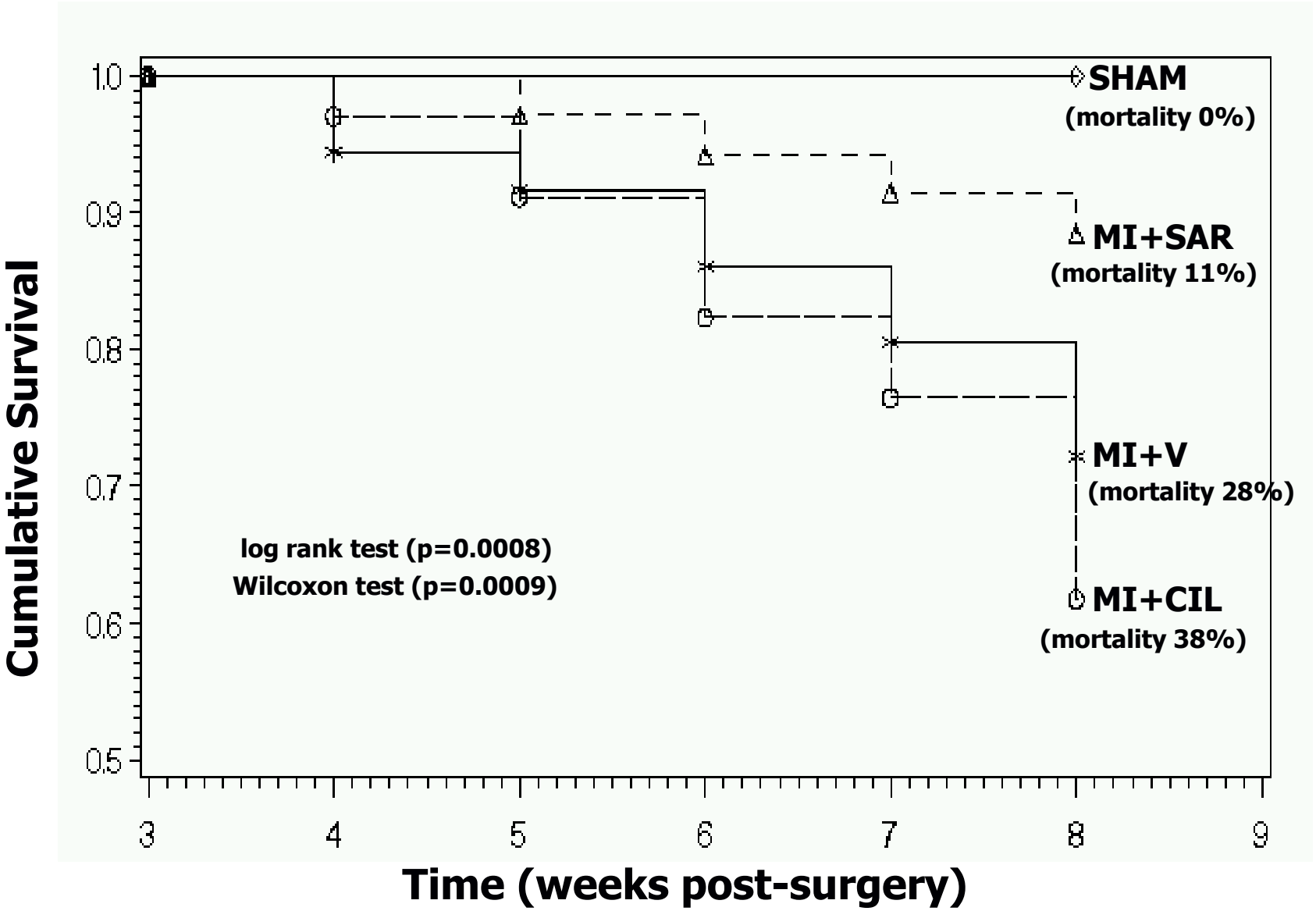


MI + CIL
Lead I



Electrocardiographic parameters of control and myocardial infarcted animals with or without sarpogrelate/cilostazol treatment

Parameters	Sham	MI	MI + SAR	MI + CIL
PR interval (sec)	0.051 ± 0.002	0.057 ± 0.001*	0.057 ± 0.002	0.056 ± 0.002
QT interval (sec)	0.077 ± 0.001	0.090 ± 0.001*	0.090 ± 0.002	0.085 ± 0.002
RR interval (sec)	0.185 ± 0.003	0.174 ± 0.003*	0.178 ± 0.004	0.173 ± 0.006
Incidence of Ventricular tachycardia (%)	----------	38*	16#	67#
Episodes of VT	----------	1.8 ± 0.3*	0.6 ± 0.2#	2.4 ± 0.4


Cumulative Survival
1.0
0.9
0.8
0.7
0.6
0.5
3
4
5
6
7
8
9
Time (weeks post-surgery)
SHAM
(mortality 0%)
MI+SAR
(mortality 11%)
MI+V
(mortality 28%)
MI+CIL
(mortality 38%)
log rank test (p=0.0008)
Wilcoxon test (p=0.0009)

Acute effects of sarpogrelate or cilostazol on ventricular arrhythmias due to coronary ligation

Parameters	Control	SAR	CIL
Incidence of arrhythmias	6/6 (100 %)	9/9 (100 %)	9/9 (100 %)
Time of onset of arrhythmias (sec)	42 ± 15.1	148 ± 28.7*	67 ± 20
Incidence of single PVCs	6/6 (100 %)	9/9 (100 %)	9/9 (100 %)
Number of single PVCs	114 ± 18.2	81 ± 17.7	181 ± 24.1*
Incidence of salvos	4/6 (67 %)	5/9 (56 %)	8/9 (89 %) *
Number of salvos	3.7 ± 0.63	4.2 ± 0.97	4.9 ± 0.81

Acute effects of sarpogrelate or cilostazol on ventricular tachycardia and fibrillation due to coronary ligation

Parameters	Control	SAR	CIL
Incidence of VTs	4/6 (67 %)	1/9 (11 %)*	7/9 (78 %)
Number of episodes of VTs	2.2 ± 0.51	3.0 ± 0.14	4.9 ± 0.46*
Duration of VTs (sec)	2.8 ± 0.18	1.1 ± 0.21*	3.0 ± 0.38
Incidence of VFs	4/6 (67 %)	0/9 (0 %)*	6/9 (67 %)
Number of episodes of VFs	1.0 ± 0.00	0*	2.0 ± 0.26*
Duration of VFs (sec)	0.25 ± 0.03	0*	0.63 ± 0.04*
Survival	100 %	100 %	100 %