Cellular and Molecular Mechanisms for the Development of Heart Failure

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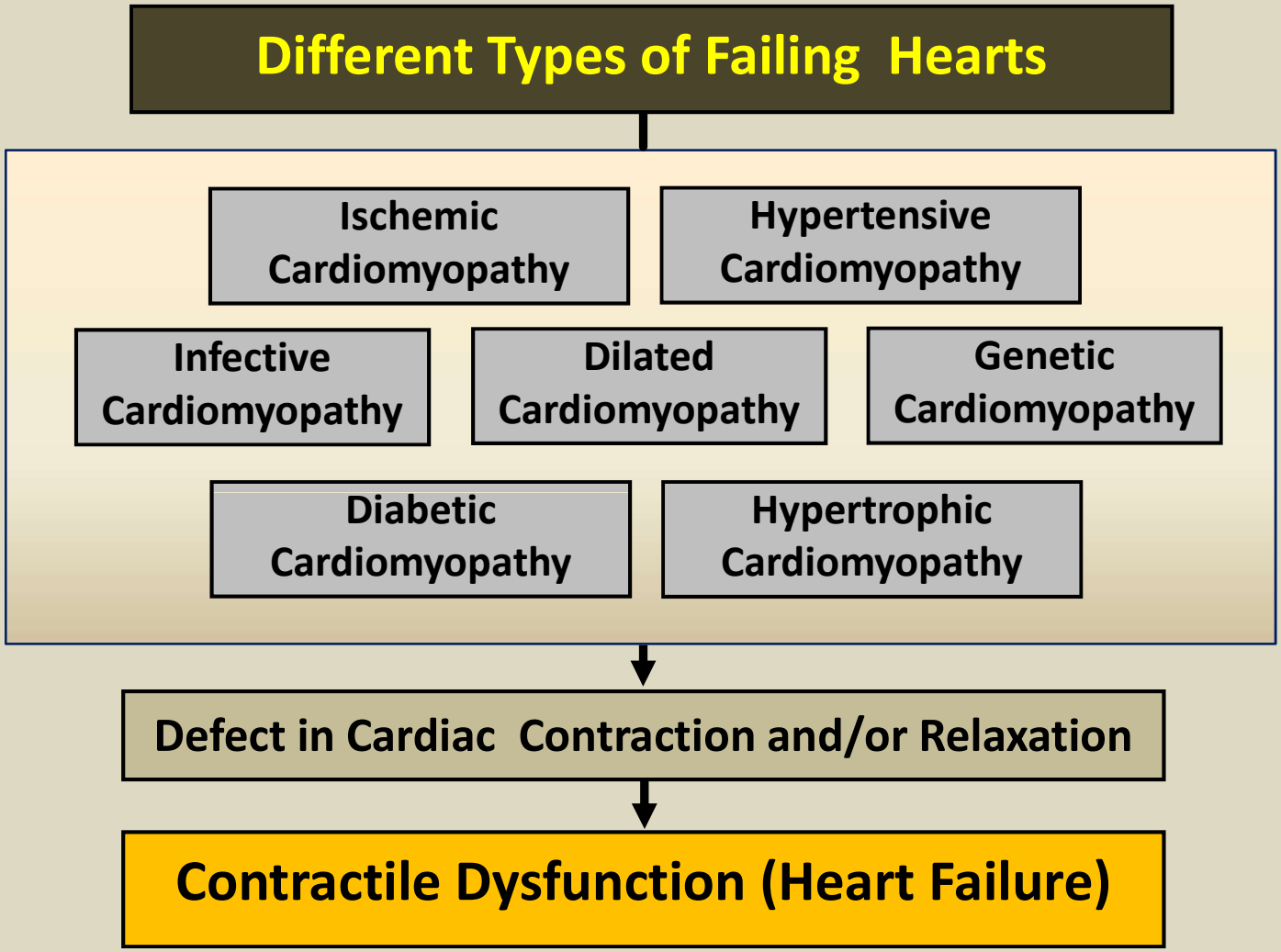
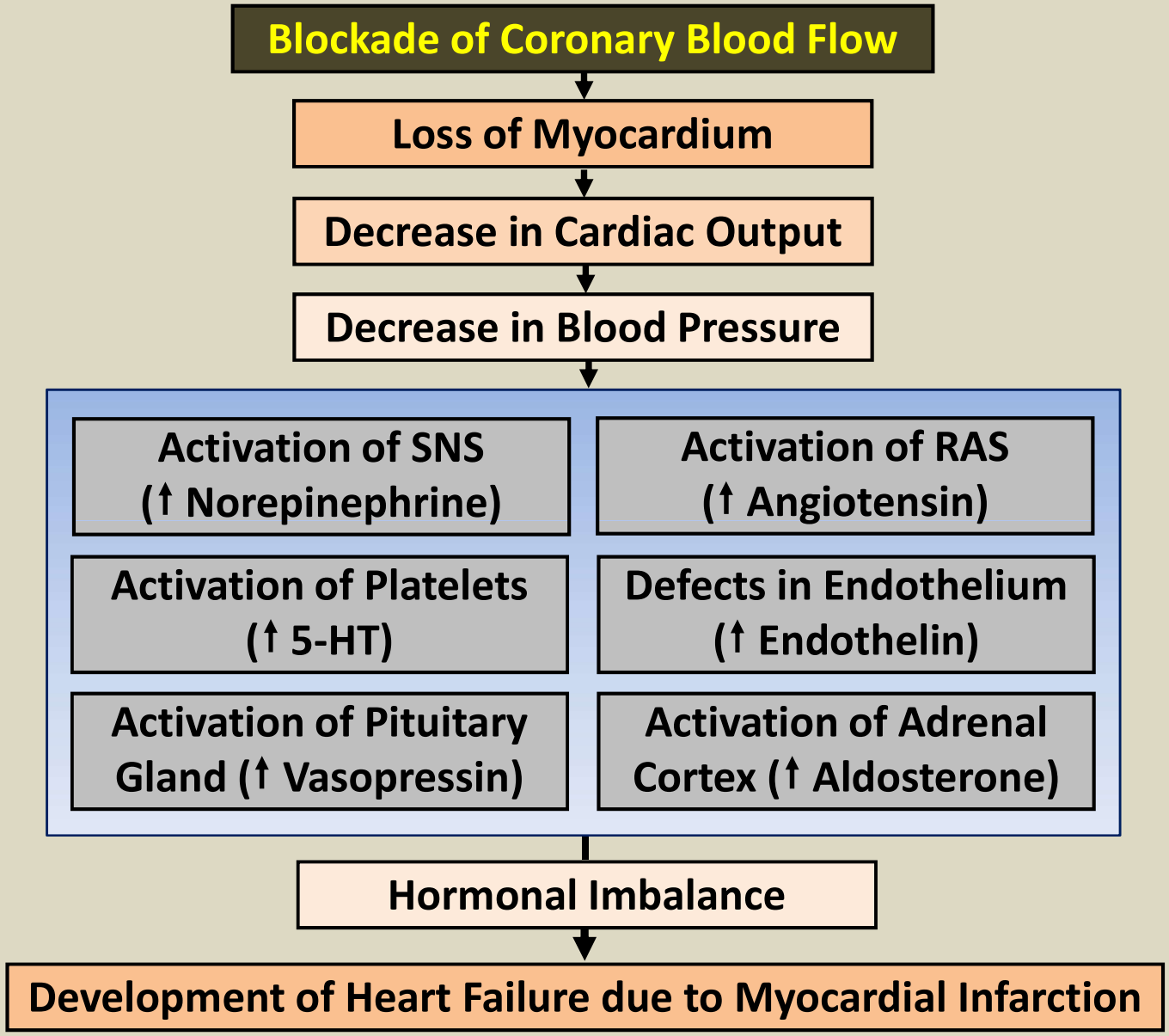
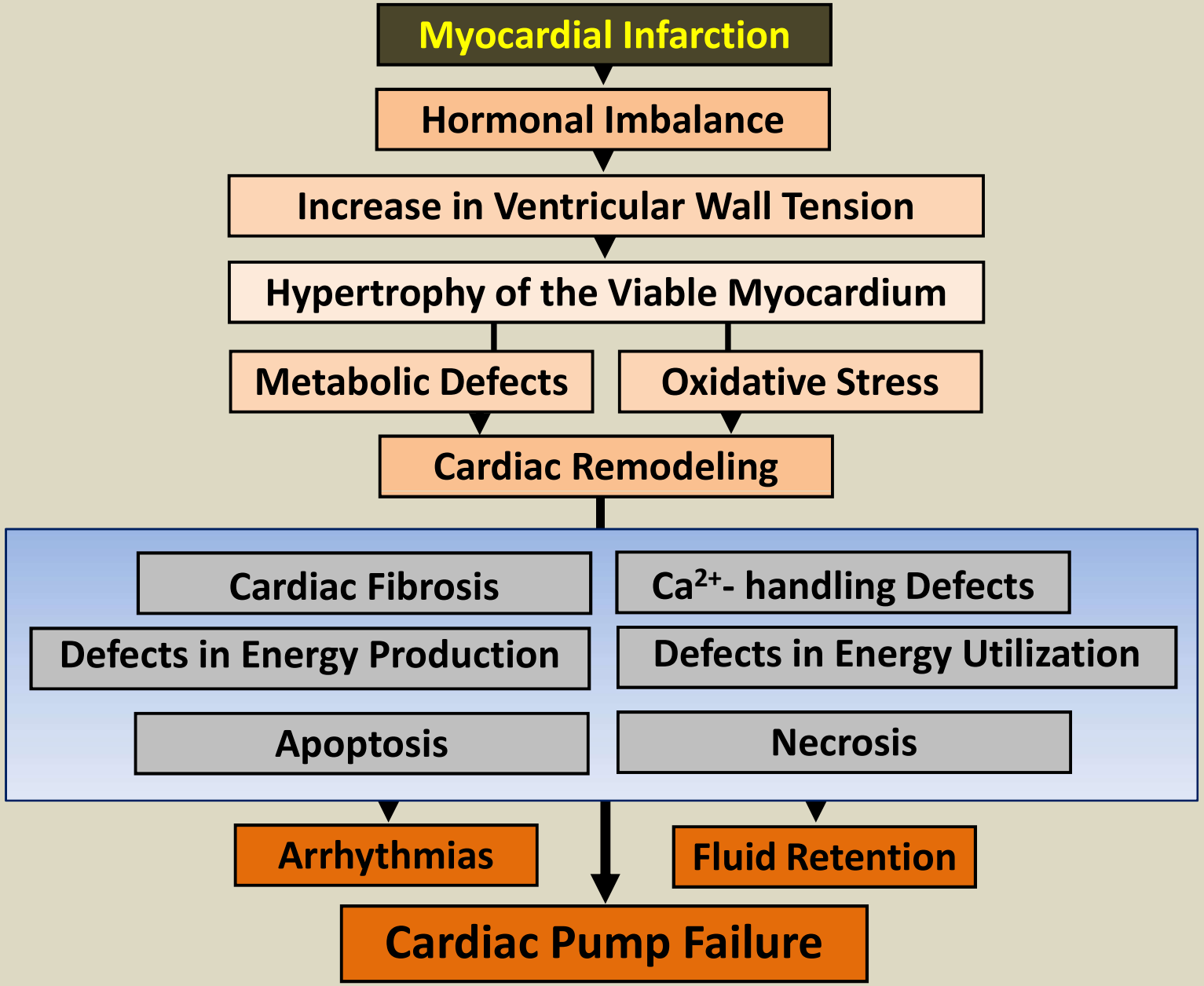
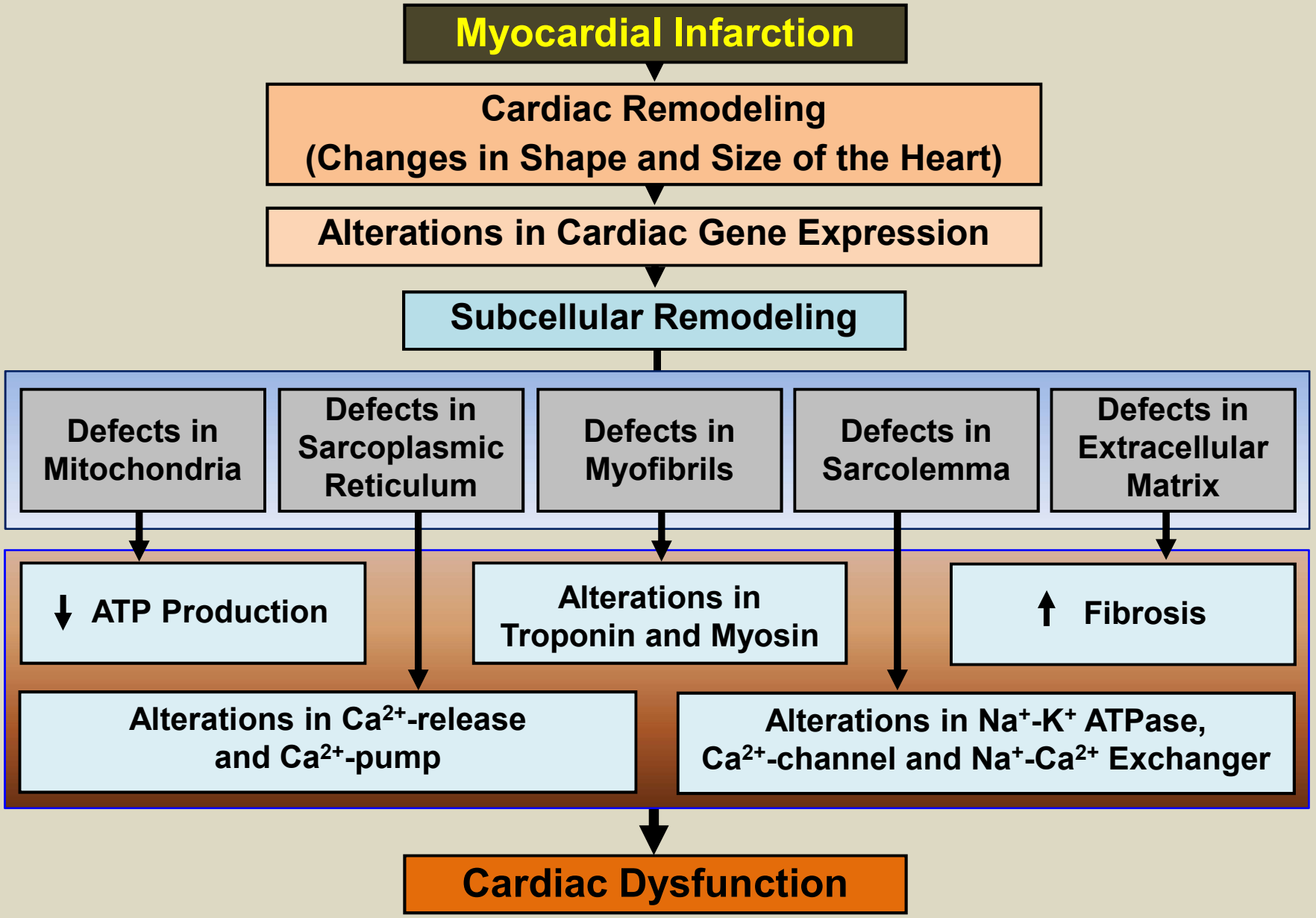
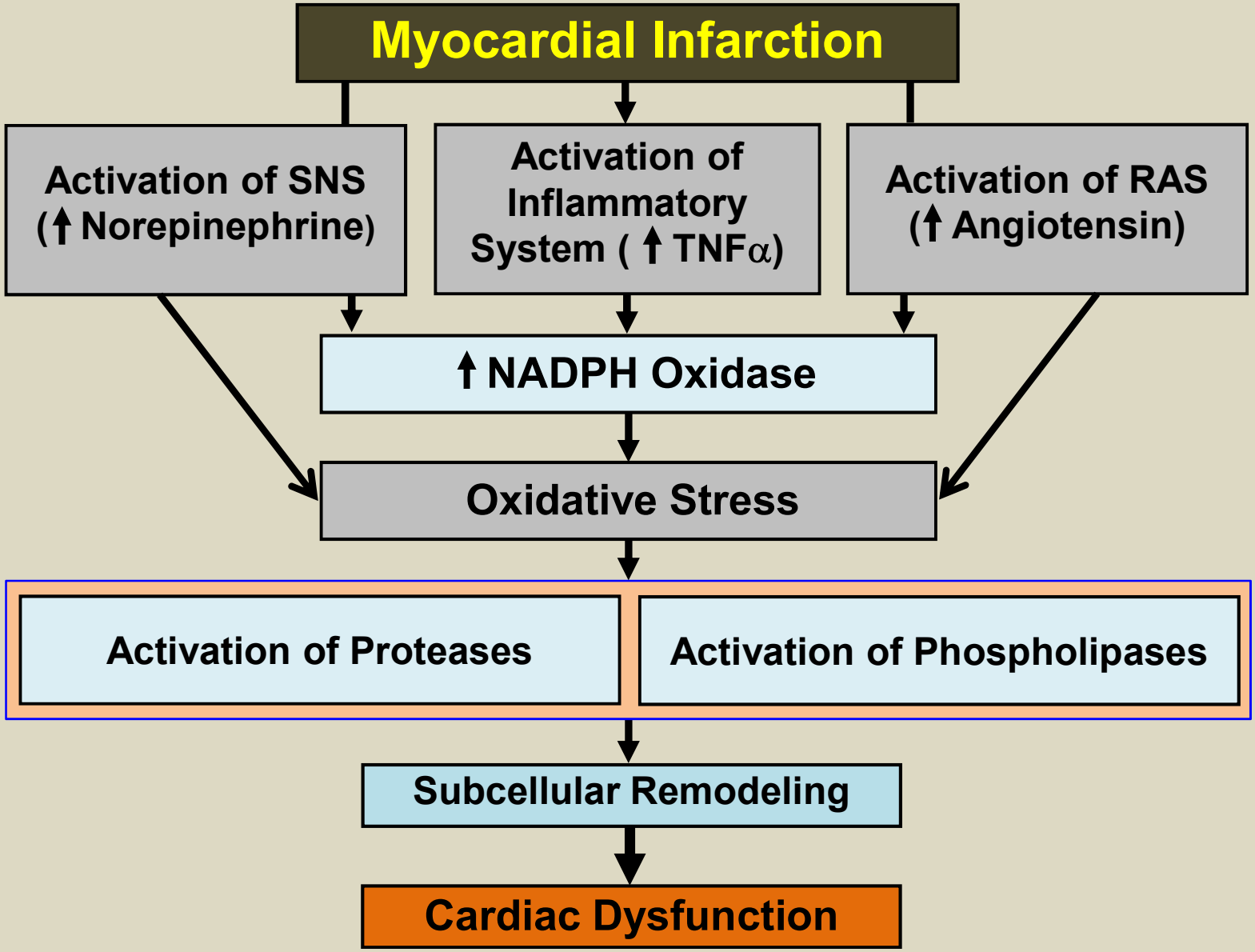
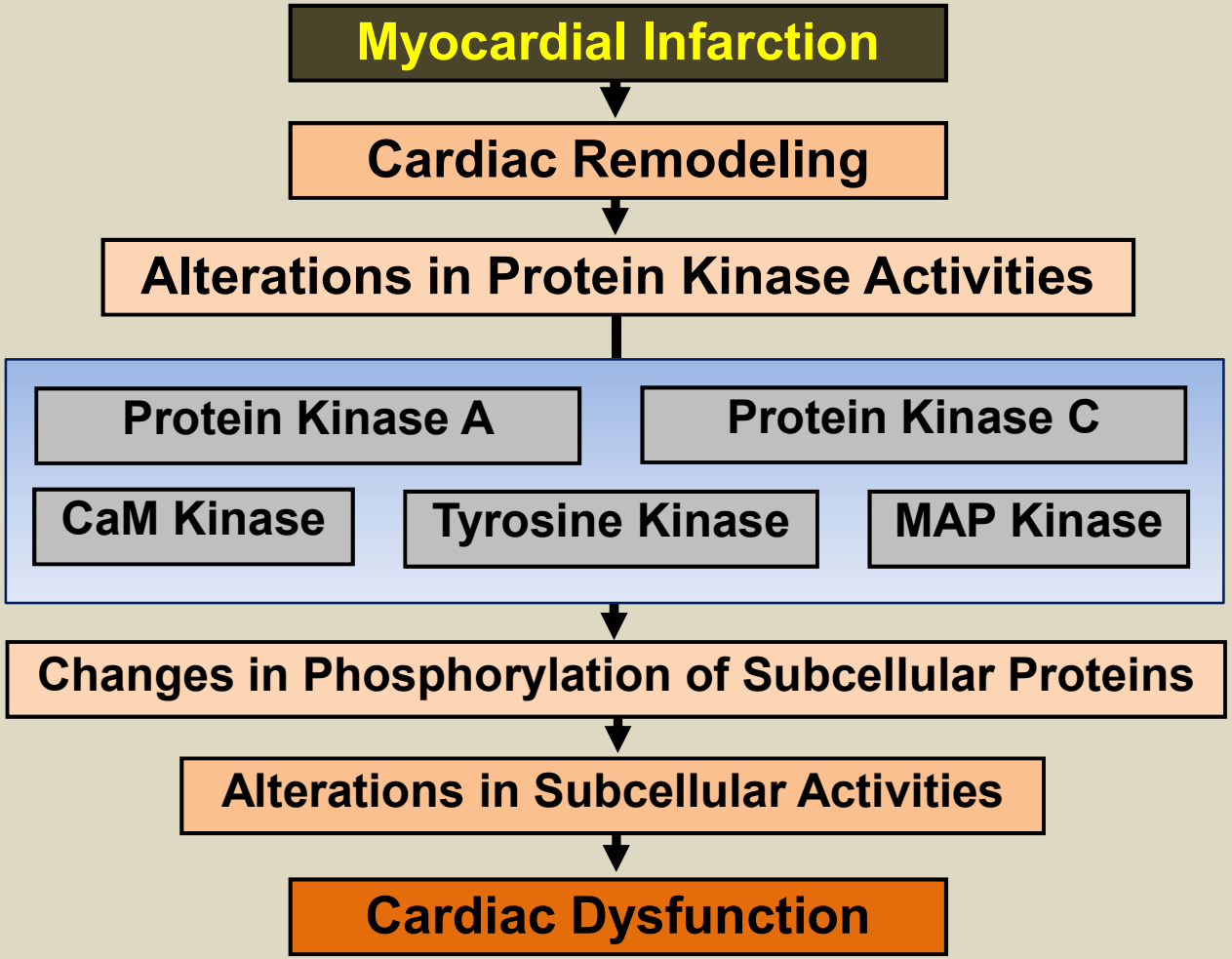

Different Types of Failing Hearts
Ischemic Cardiomyopathy
Hypertensive Cardiomyopathy
Infective Cardiomyopathy
Dilated Cardiomyopathy
Genetic Cardiomyopathy
Diabetic Cardiomyopathy
Hypertrophic Cardiomyopathy
Defect in Cardiac Contraction and/or Relaxation
Contractile Dysfunction (Heart Failure)

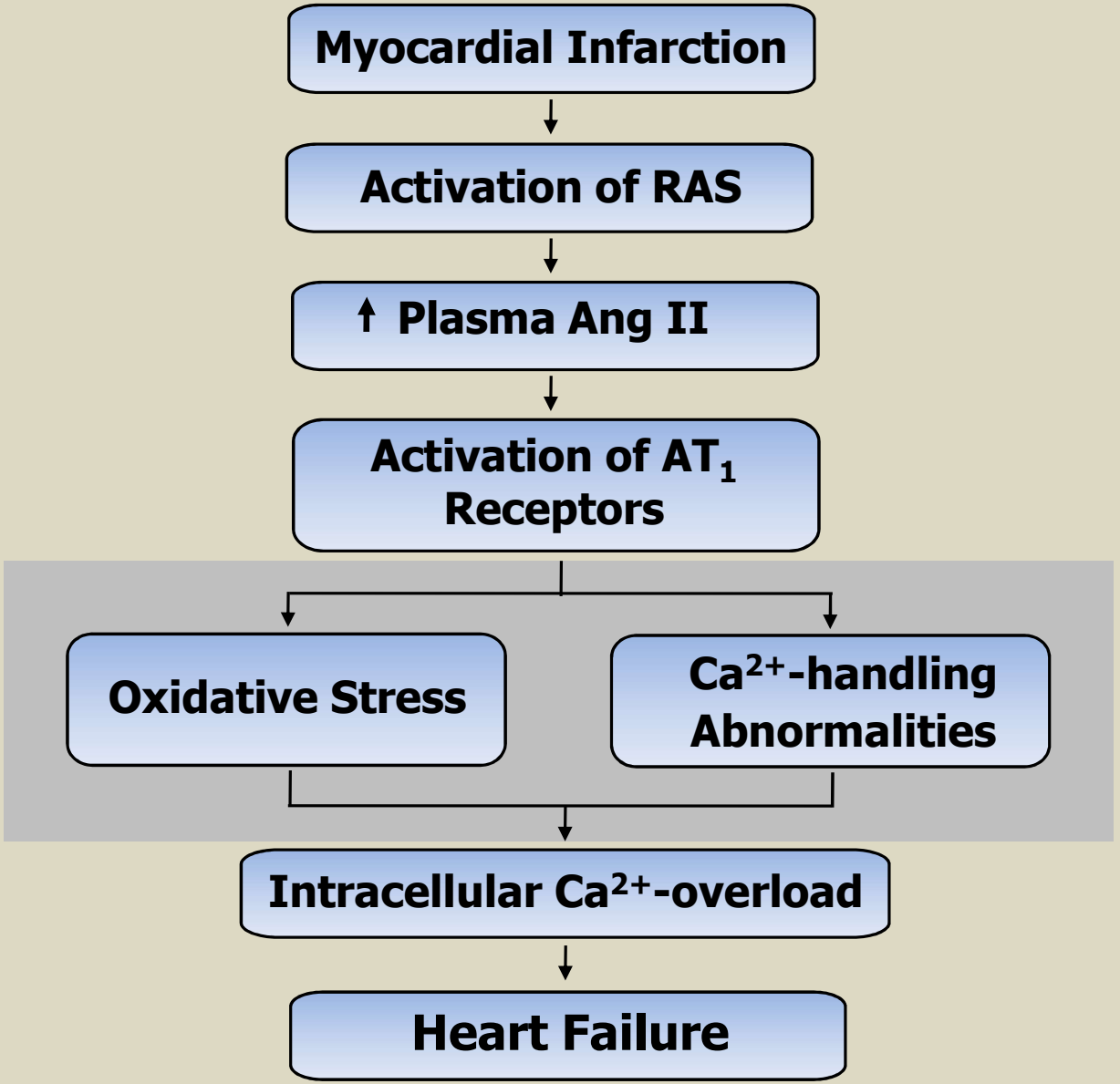

Blockade of Coronary Blood Flow
Loss of Myocardium
Decrease in Cardiac Output
Decrease in Blood Pressure
Activation of SNS (↑ Norepinephrine)
Activation of RAS (↑ Angiotensin)
Activation of Platelets (↑ 5-HT)
Defects in Endothelium (↑ Endothelin)
Activation of Pituitary Gland (↑ Vasopressin)
Activation of Adrenal Cortex (↑ Aldosterone)
Hormonal Imbalance
Development of Heart Failure due to Myocardial Infarction

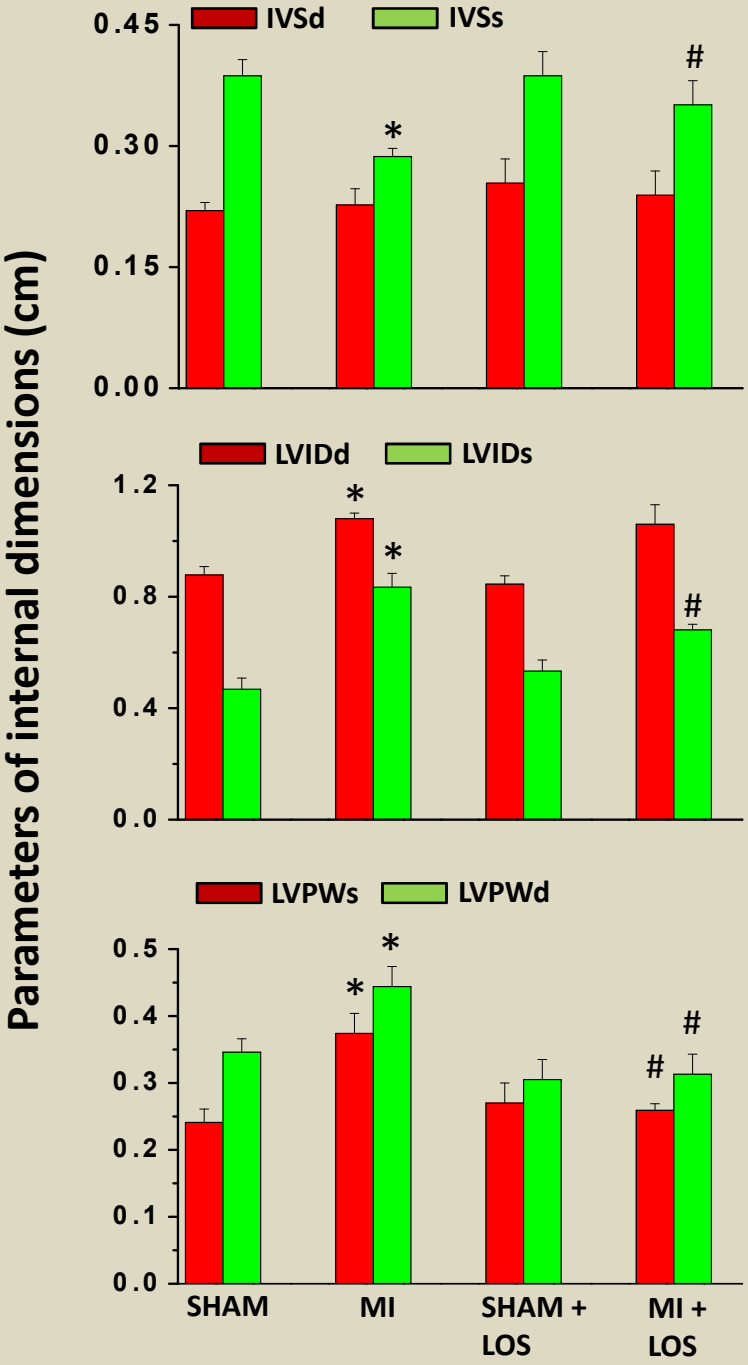

Myocardial Infarction
Hormonal Imbalance
Increase in Ventricular Wall Tension
Hypertrophy of the Viable Myocardium
Metabolic Defects
Oxidative Stress
Cardiac Remodeling
Cardiac Fibrosis
Ca2+- handling Defects
Defects in Energy Production
Defects in Energy Utilization
Apoptosis
Necrosis
Arrhythmias
Fluid Retention
Cardiac Pump Failure

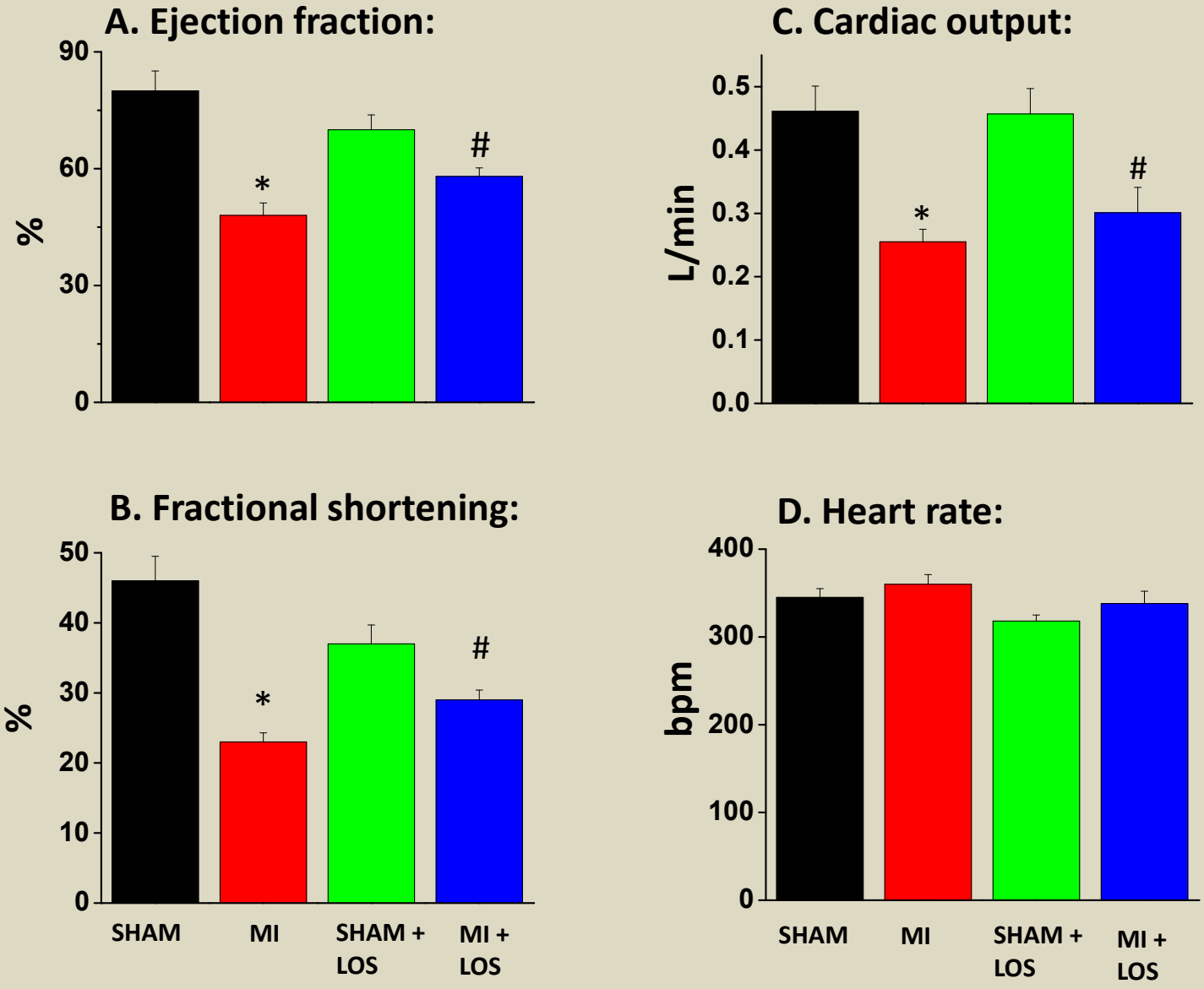

Myocardial Infarction
Cardiac Remodeling
(Changes in Shape and Size of the Heart)
Alterations in Cardiac Gene Expression
Subcellular Remodeling
Defects in Mitochondria
Defects in Sarcoplasmic Reticulum
Defects in Myofibrils
Defects in Sarcolemma
Defects in Extracellular Matrix
ATP Production
Alterations in Troponin and Myosin
Fibrosis
Alterations in Ca2+-release and Ca2+-pump
Alterations in Na+-K+ ATPase, Ca2+-channel and Na+-Ca2+ Exchanger
Cardiac Dysfunction


Myocardial Infarction
Activation of SNS (↑ Norepinephrine)
Activation of Inflammatory System (↑ TNFα)
Activation of RAS (↑ Angiotensin)
↑ NADPH Oxidase
Oxidative Stress
Activation of Proteases
Activation of Phospholipases
Subcellular Remodeling
Cardiac Dysfunction

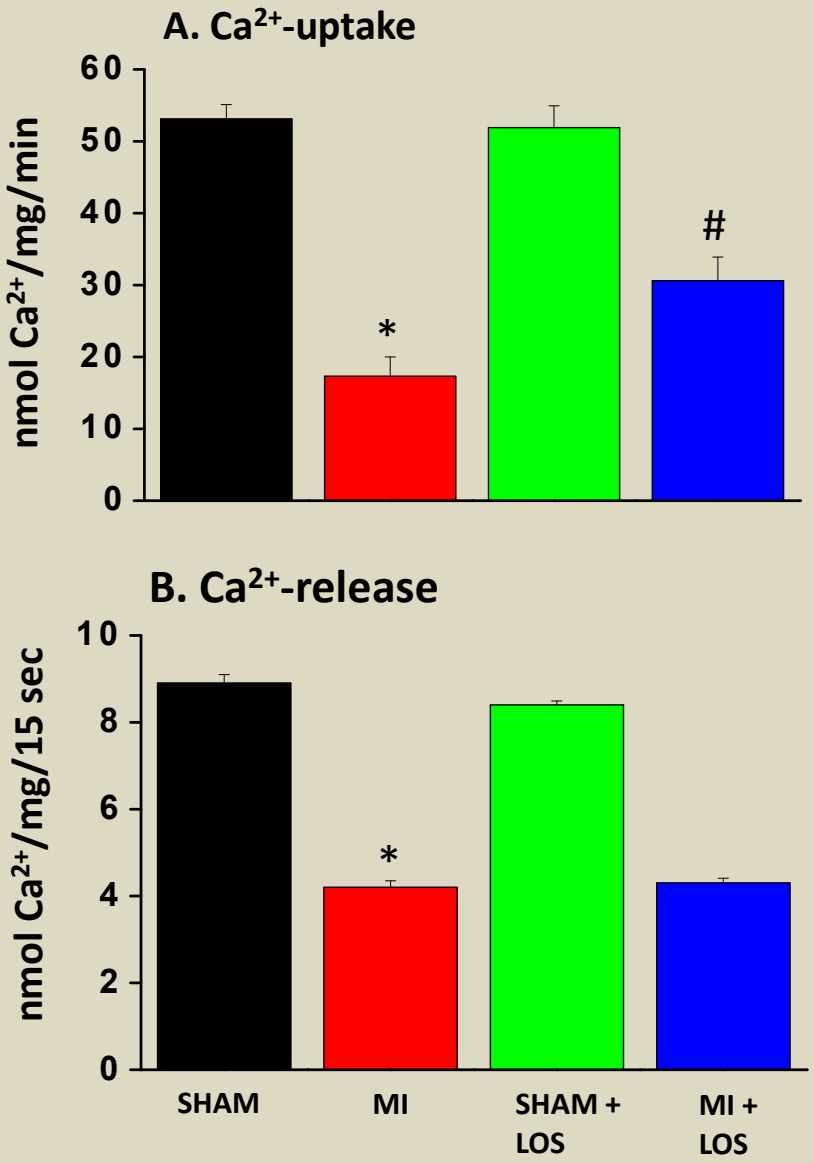

Myocardial Infarction
Cardiac Remodeling
Alterations in Protein Kinase Activities
Protein Kinase A
Protein Kinase C
CaM Kinase
Tyrosine Kinase
MAP Kinase
Changes in Phosphorylation of Subcellular Proteins
Alterations in Subcellular Activities
Cardiac Dysfunction


Myocardial Infarction
Activation of RAS
↑ Plasma Ang II
Activation of AT1 Receptors
Oxidative Stress
Ca2+-handling Abnormalities
Intracellular Ca2+-overload
Heart Failure

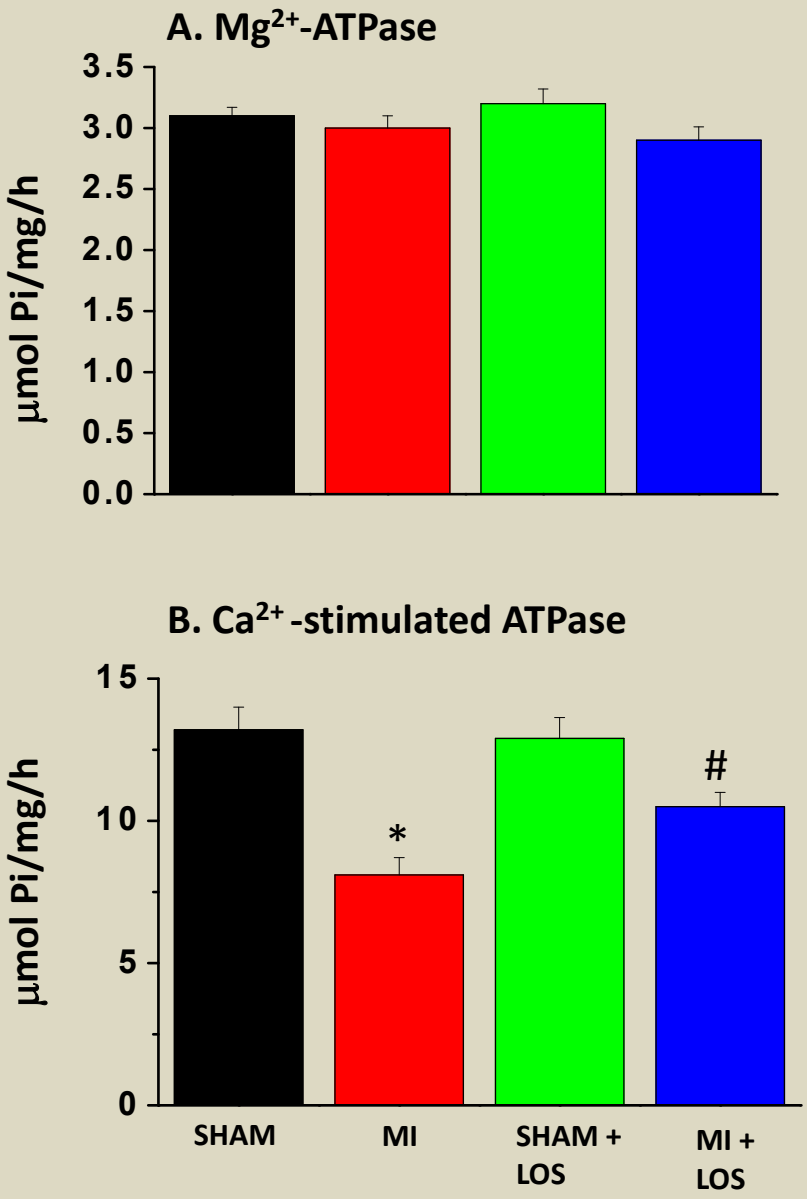

Parameters of internal dimensions (cm)
IVSd
IVSs
0.45
0.30
0.15
0.00
LVIDd
LVIDs
1.2
0.8
0.4
0.0
LVPWs
LVPWd
0.5
0.4
0.3
0.2
0.1
0.0
SHAM
MI
SHAM + LOS
MI + LOS


A. Ejection fraction:
%
90
60
30
0
*
#
C. Cardiac output:
L/min
0.5
0.4
0.3
0.2
0.1
0.0
*
#
B. Fractional shortening:
%
50
40
30
20
10
0
*
#
SHAM
MI
SHAM + LOS
MI + LOS
D. Heart rate:
bpm
400
300
200
100
0
SHAM
MI
SHAM + LOS
MI + LOS

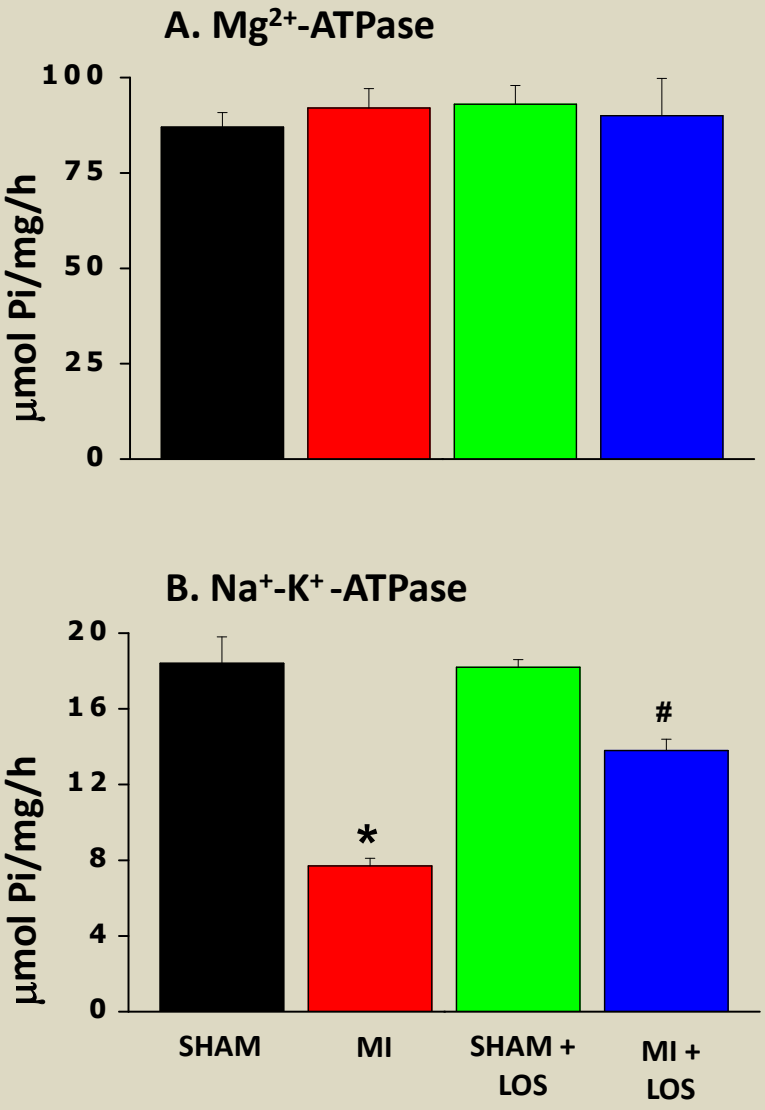
Sarcoplasmic reticulm

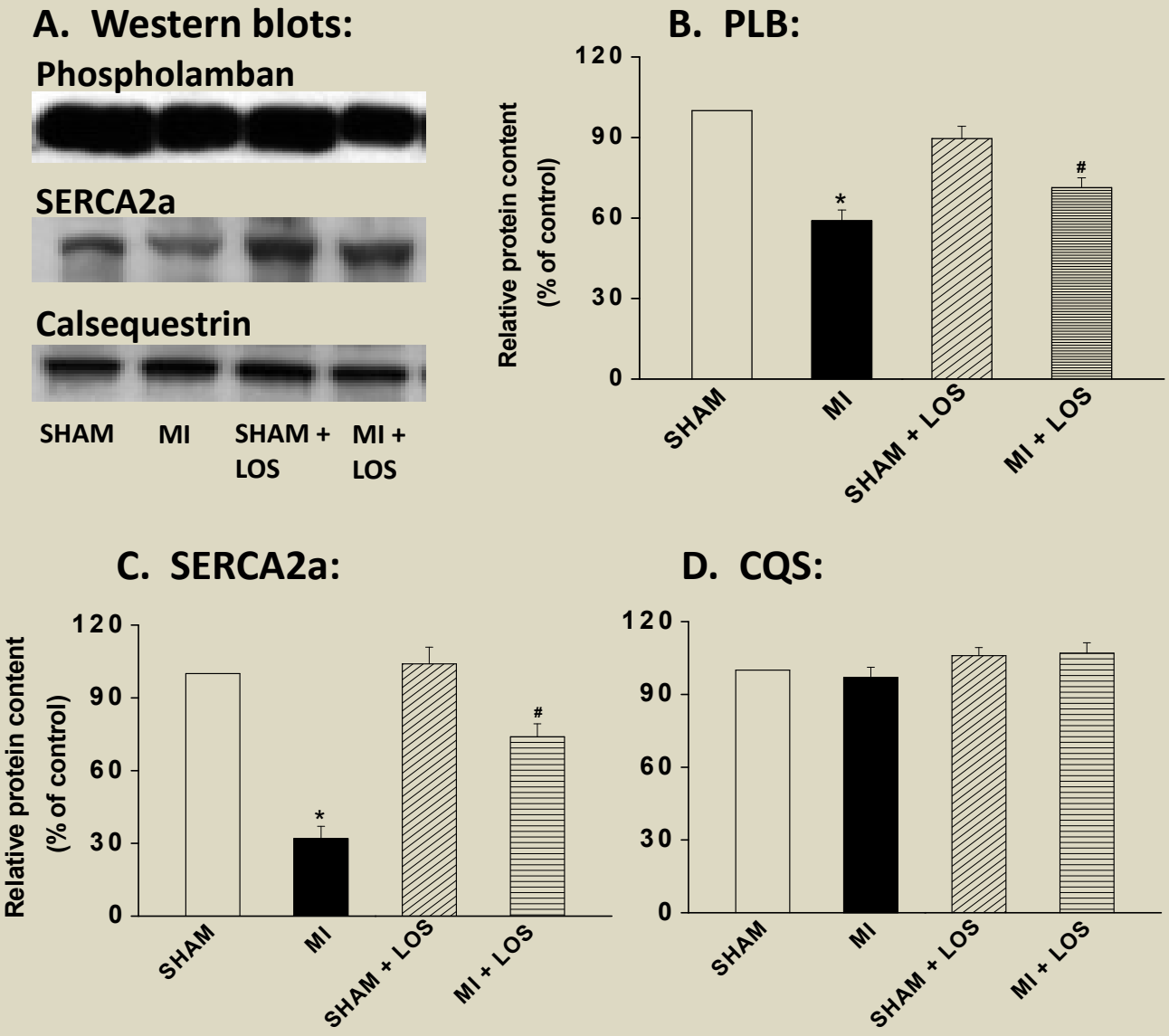


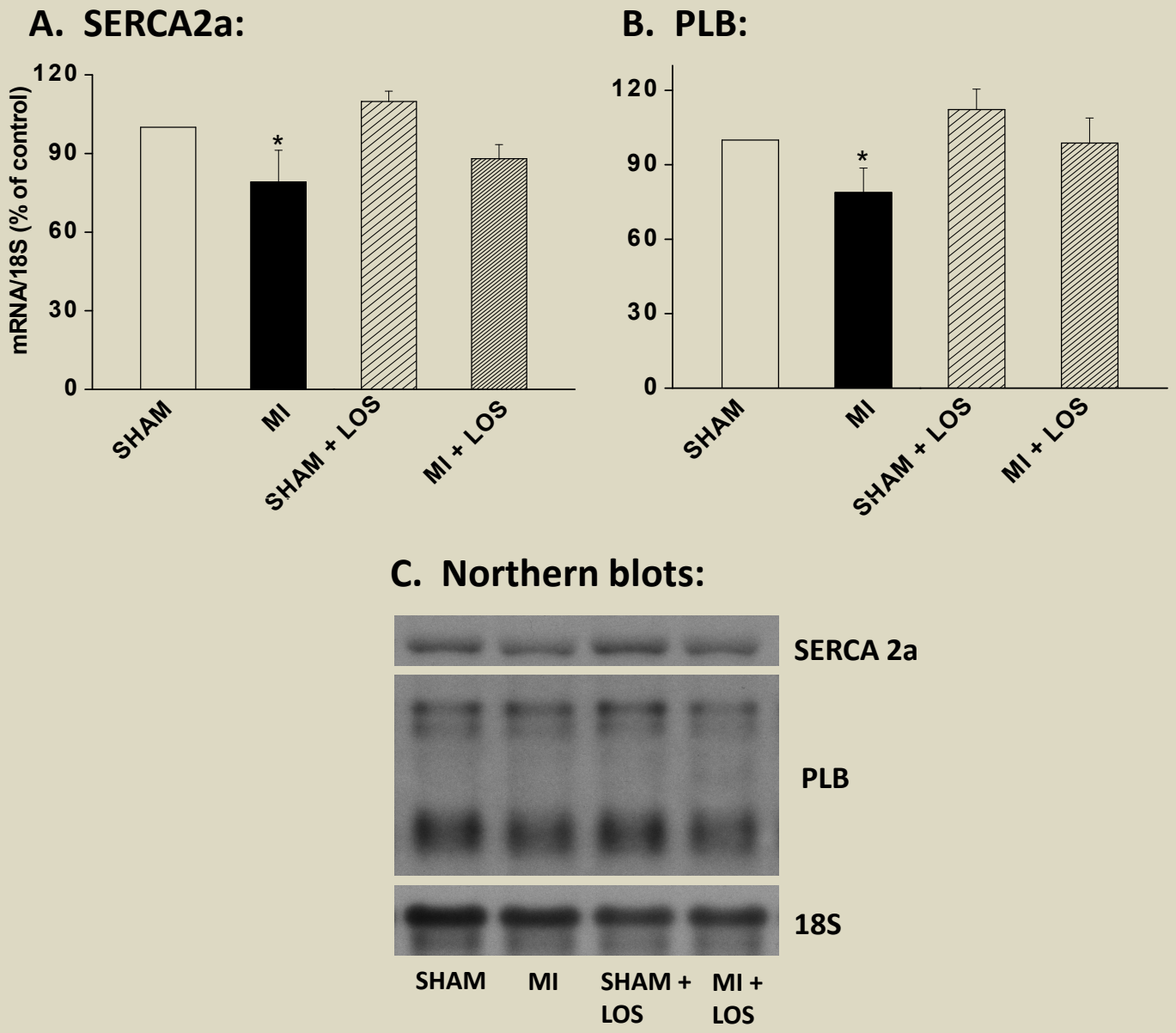
Myofibrils

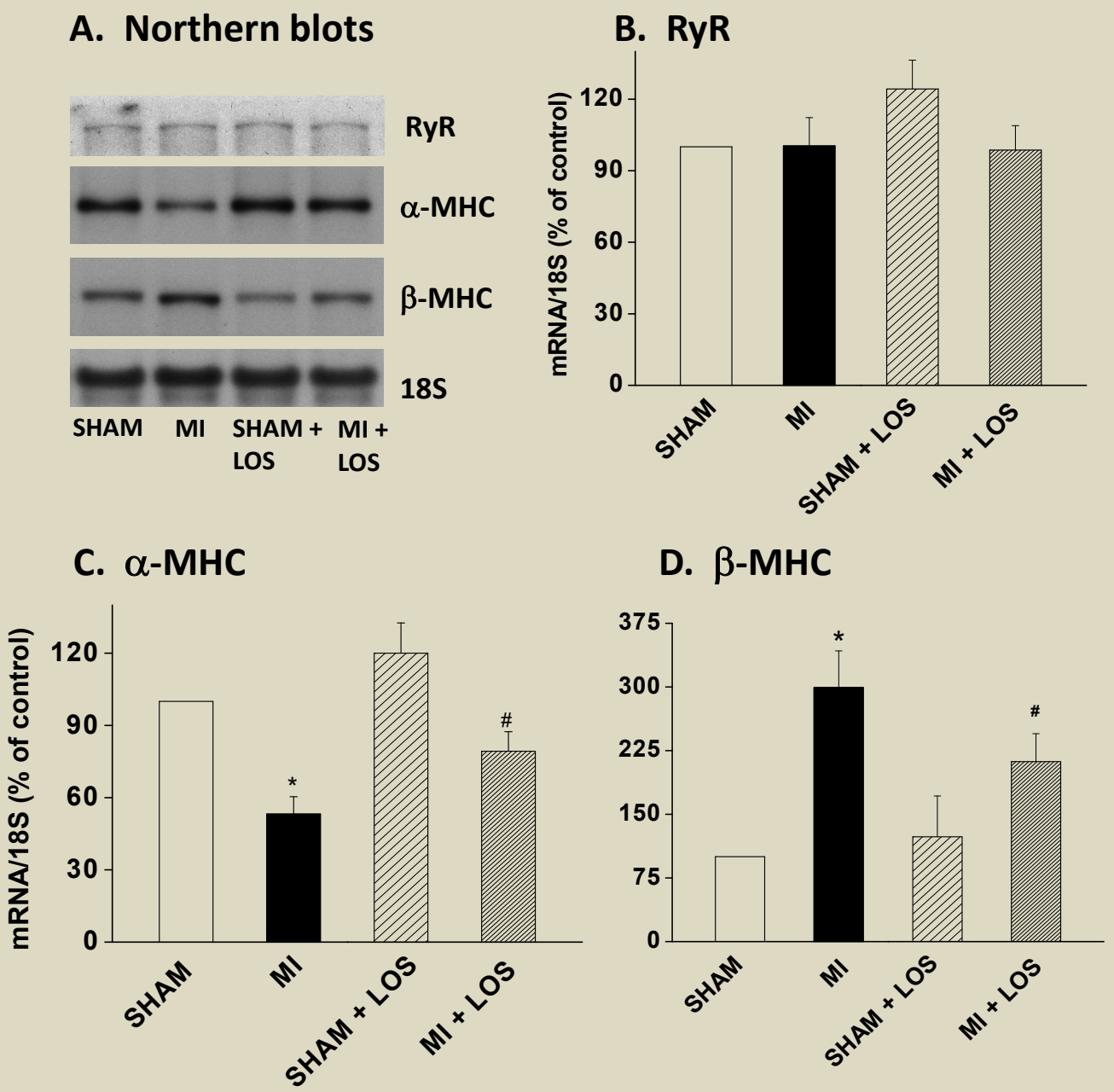

A. Mg2+-ATPase
µmol Pi/mg/h
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
B. Ca2+-stimulated ATPase
µmol Pi/mg/h
15
10
5
0
*
#
SHAM
MI
SHAM + LOS
MI + LOS

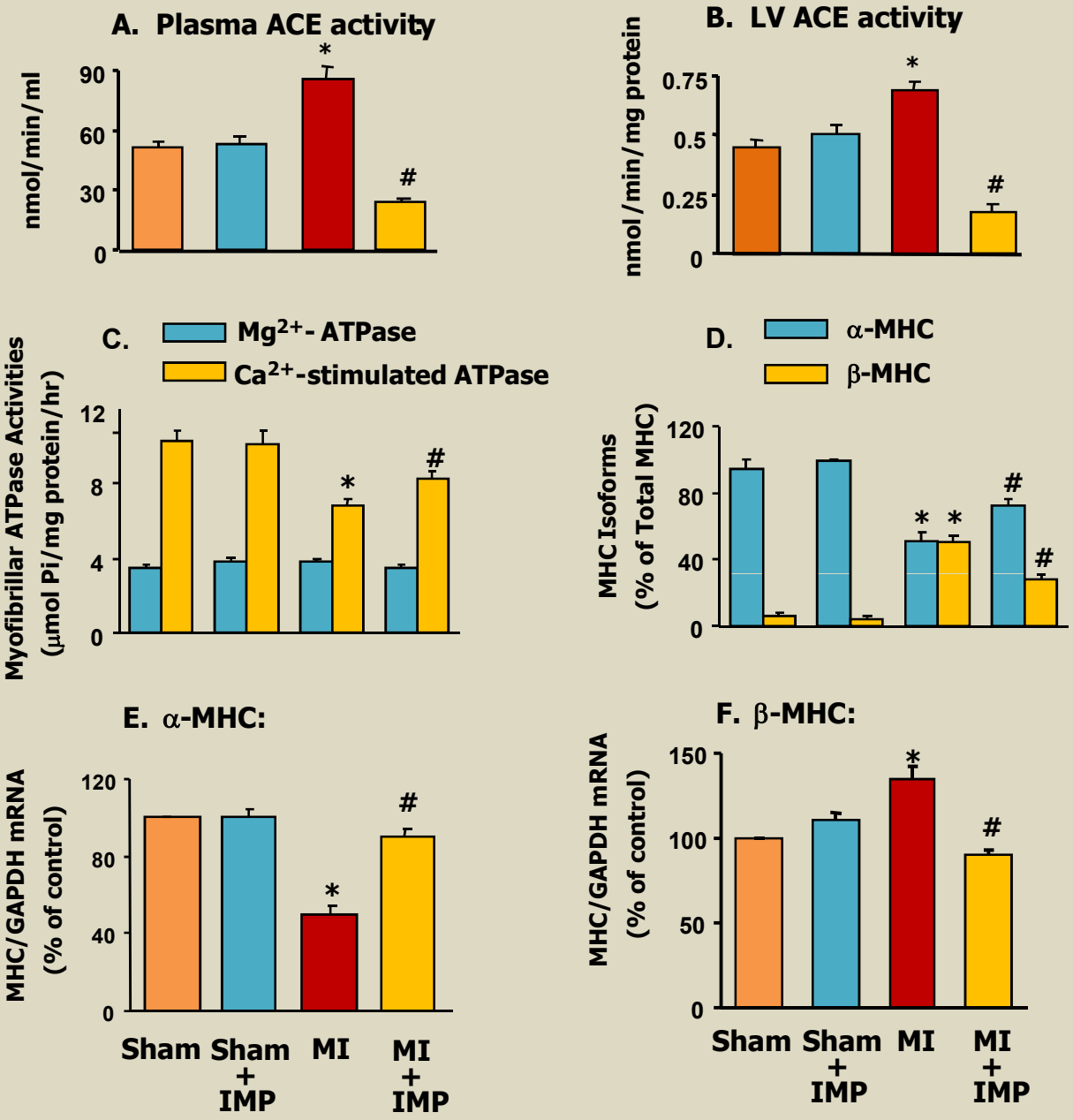
Sarcolemma

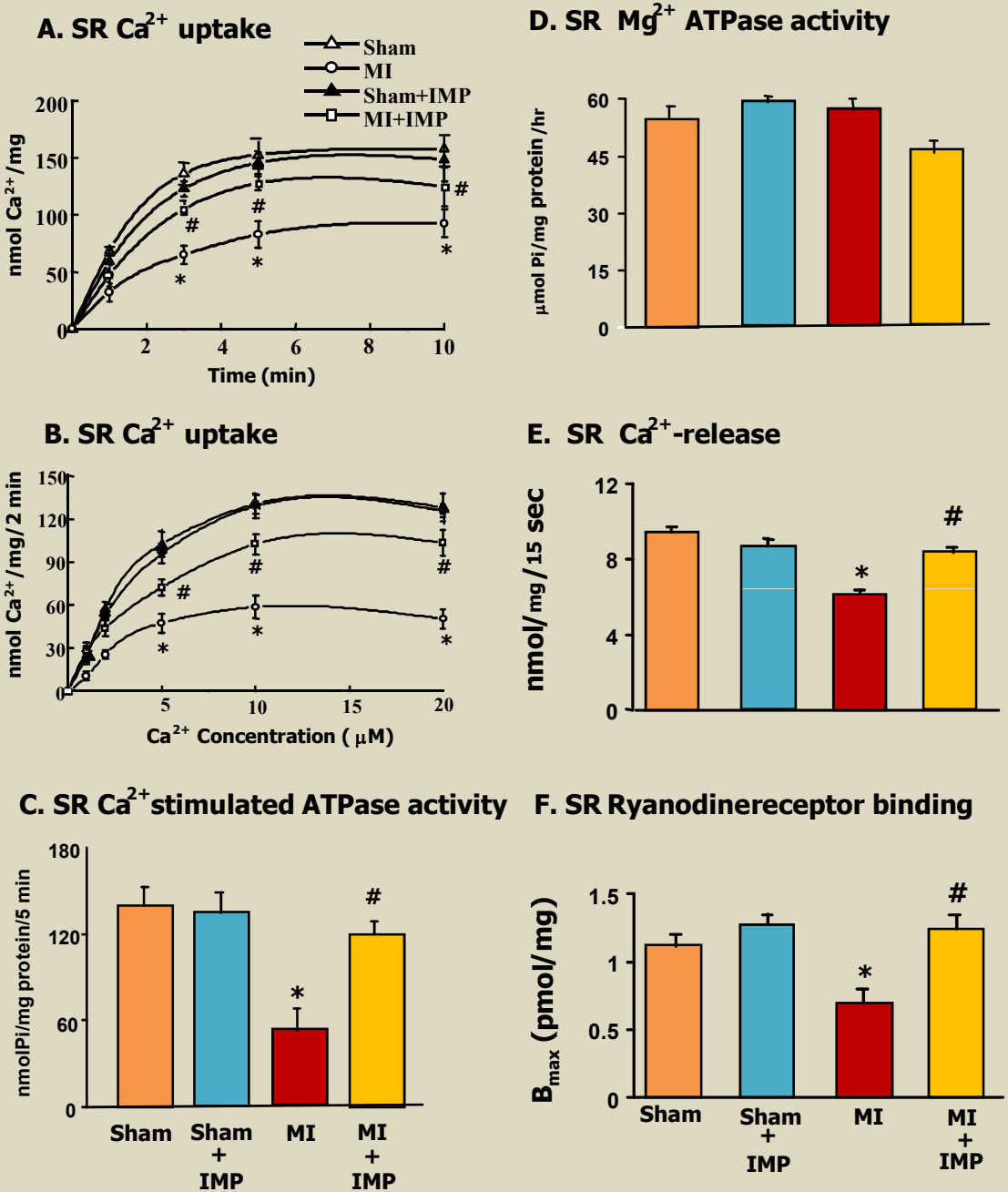

A. Mg2+-ATPase
µmol Pi/mg/h
100
75
50
25
0
B. Na+-K+ -ATPase
µmol Pi/mg/h
20
16
12
8
4
0
*
#
SHAM
MI
SHAM + LOS
MI + LOS

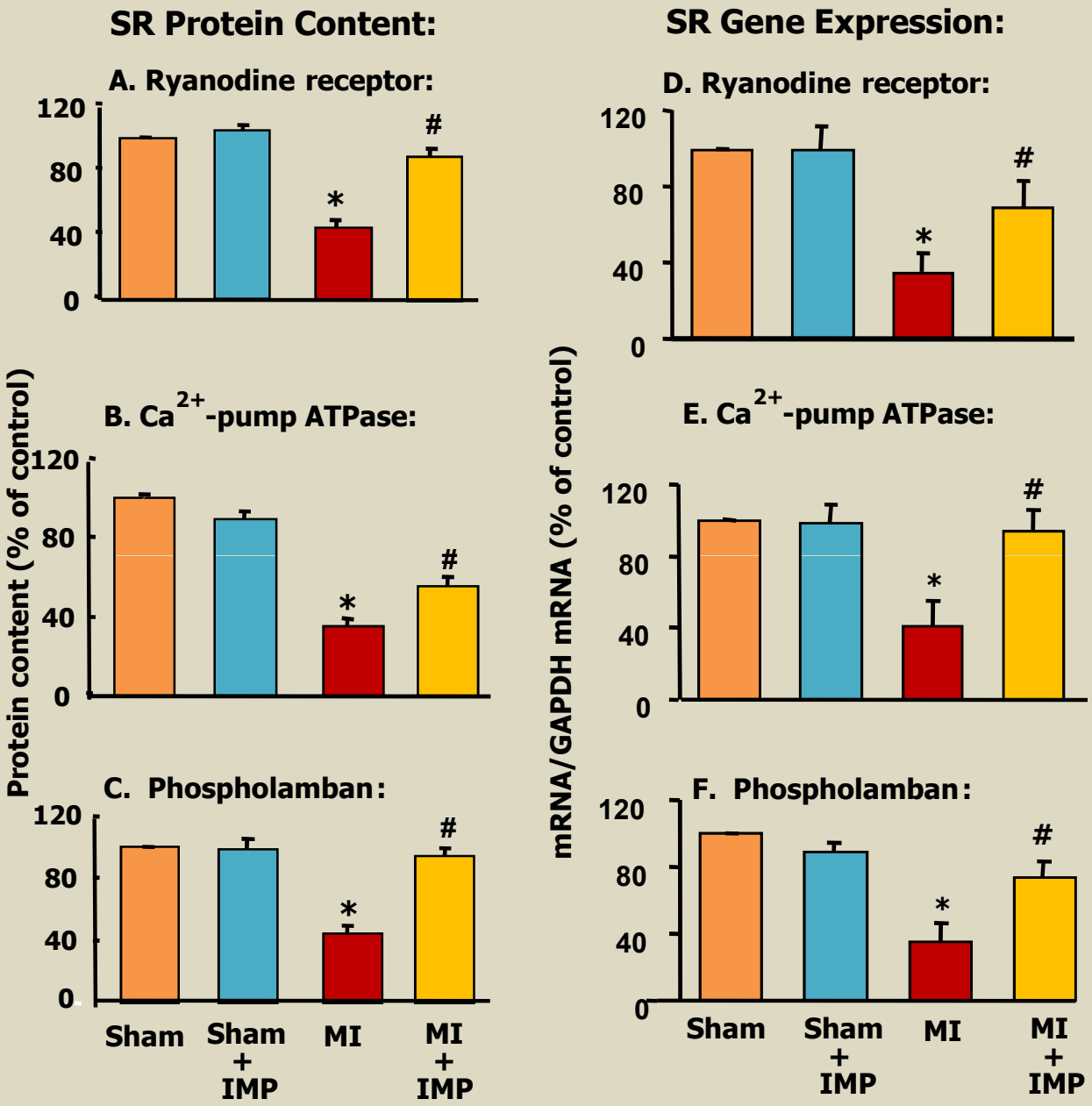

A. Western blots:
Phospholamban
SERCA2a
Calsequestrin
SHAM
MI
SHAM + LOS
MI + LOS
B. PLB:
Relative protein content (% of control)
120
90
60
30
0
*
#
SHAM
MI
SHAM + LOS
MI + LOS
C. SERCA2a:
Relative protein content (% of control)
120
90
60
30
0
*
#
SHAM
MI
SHAM + LOS
MI + LOS
D. CQS:
120
90
60
30
0
SHAM
MI
SHAM + LOS
MI + LOS

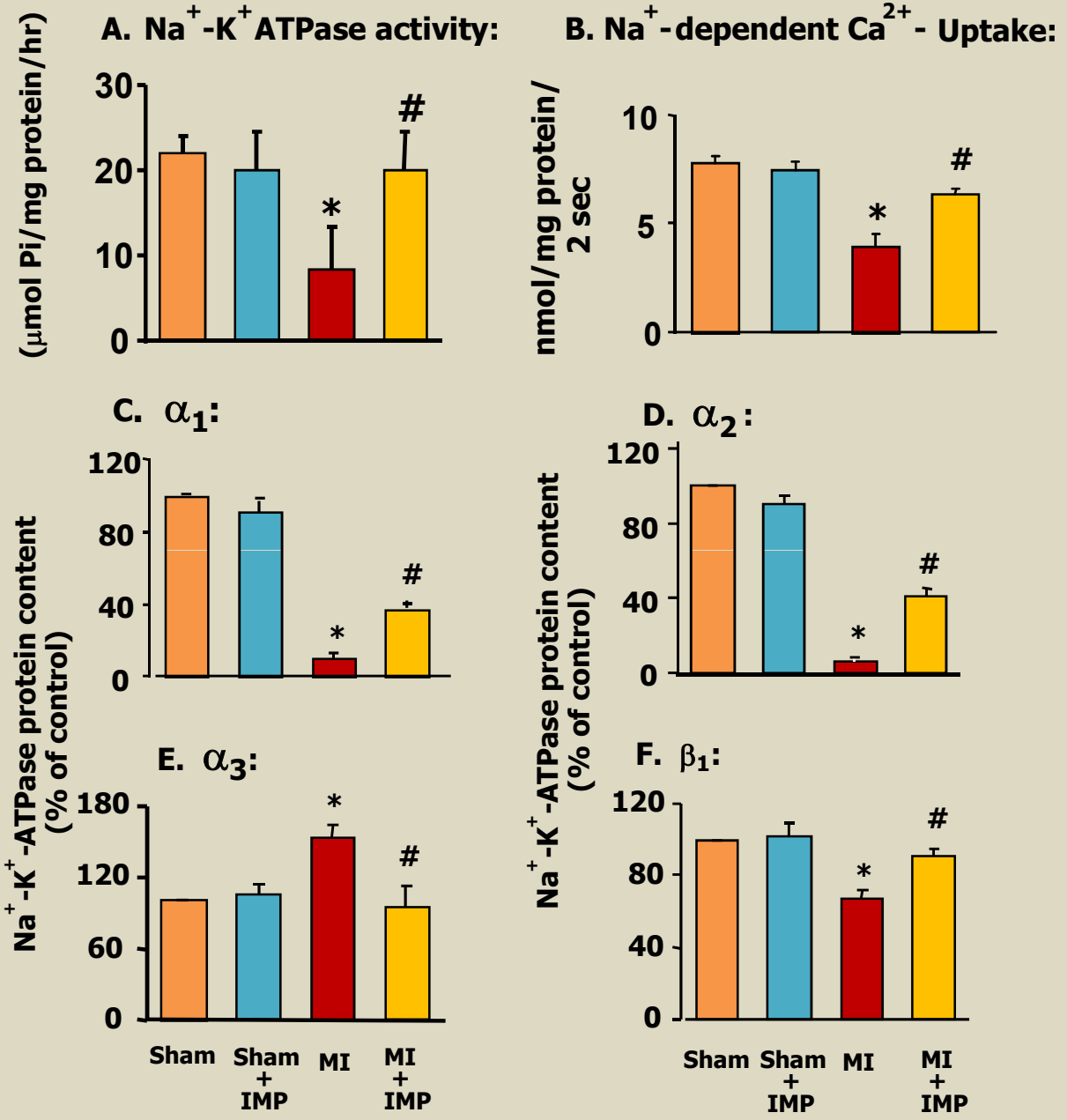

A. SERCA2a:
mRNA/18S (% of control)
120
90
60
30
0
*
SHAM
MI
SHAM + LOS
MI + LOS
B. PLB:
120
90
60
30
0
*
SHAM
MI
SHAM + LOS
MI + LOS
C. Northern blots:
SERCA 2a
PLB
18S
SHAM
MI
SHAM + LOS
MI + LOS

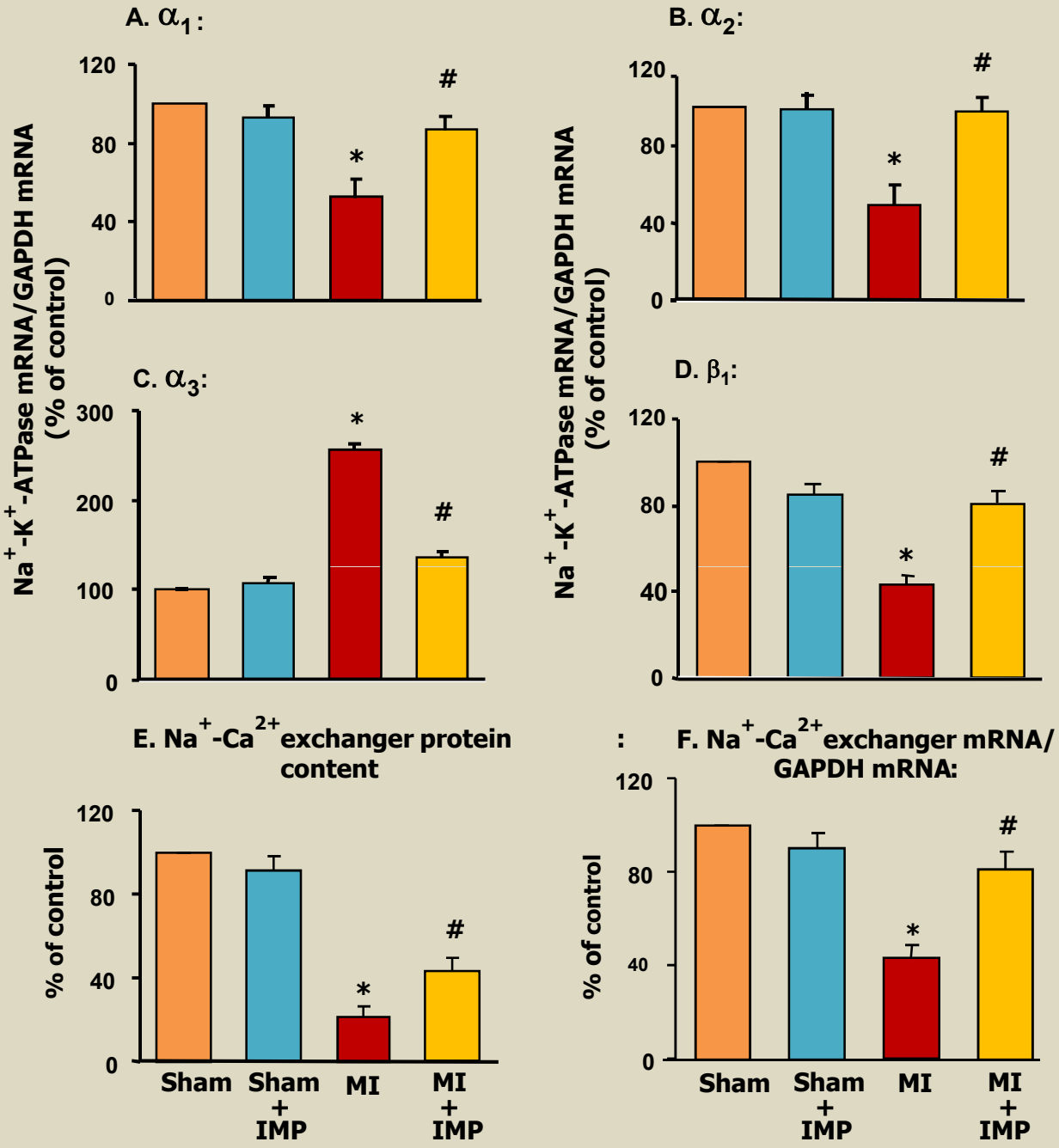

A. Northern blots
RyR
α-MHC
β-MHC
18S
SHAM
MI
SHAM + LOS
MI + LOS
B. RyR
mRNA/18S (% of control)
120
90
60
30
0
SHAM
MI
SHAM + LOS
MI + LOS
C. α-MHC
mRNA/18S (% of control)
120
90
60
30
0
*
#
SHAM
MI
SHAM + LOS
MI + LOS
D. β-MHC
375
300
225
150
75
0
*
#
SHAM
MI
SHAM + LOS
MI + LOS


A. Plasma ACE activity
nmol/min/ml
90
60
30
0
*
#
B. LV ACE activity
nmol/min/mg protein
0.75
0.5
0.25
0
*
#
C.
Mg2+- ATPase
Ca2+-stimulated ATPase
Myofibrillar ATPase Activities
(μmol Pi/mg protein/hr)
12
8
4
0
*
#
D.
α-MHC
β-MHC
MHC Isoforms
(% of Total MHC)
120
80
40
0
*
*
#
#
E. α-MHC:
MHC/GAPDH mRNA
(% of control)
120
80
40
0
*
#
Sham
Sham + IMP
MI
MI + IMP
F. β-MHC:
MHC/GAPDH mRNA
(% of control)
150
100
50
0
*
#
Sham
Sham + IMP
MI
MI + IMP


A. SR Ca2+ uptake
Sham
MI
Sham+IMP
MI+IMP
nmol Ca2+ /mg
Time (min)
B. SR Ca2+ uptake
nmol Ca2+ /mg/2 min
Ca2+ Concentration (μM)
C. SR Ca2+stimulated ATPase activity
nmolPi/mg protein/5 min
Sham
Sham + IMP
MI
MI + IMP
D. SR Mg2+ ATPase activity
μmol Pi/mg protein /hr
E. SR Ca2+-release
nmol/mg/15 sec
F. SR Ryanodinereceptor binding
Bmax (pmol/mg)


SR Protein Content:
A. Ryanodine receptor:
B. Ca2+-pump ATPase:
C. Phospholamban:
Protein content (% of control)
SR Gene Expression:
D. Ryanodine receptor:
E. Ca2+-pump ATPase:
F. Phospholamban:
mRNA/GAPDH mRNA (% of control)
120
80
40
0
*
#
Sham
Sham + IMP
MI
MI + IMP


A. Na+-K+ATPase activity:
(μmol Pi/mg protein/hr)
30
20
10
0
*
#
B. Na+-dependent Ca2+- Uptake:
nmol/mg protein/
2 sec
10
5
0
*
#
C. α1:
120
80
40
0
*
#
D. α2:
120
80
40
0
*
#
E. α3:
180
120
60
0
*
#
F. β1:
120
80
40
0
*
#
Na+-K+-ATPase protein content
(% of control)
Sham
Sham + IMP
MI
MI + IMP


A. α1:
B. α2:
C. α3:
D. β1:
Na+-K+-ATPase mRNA/GAPDH mRNA (% of control)
E. Na+-Ca2+exchanger protein content
F. Na+-Ca2+exchanger mRNA/ GAPDH mRNA:
% of control
120
80
40
0
300
200
100
*
#
Sham
Sham + IMP
MI
MI + IMP