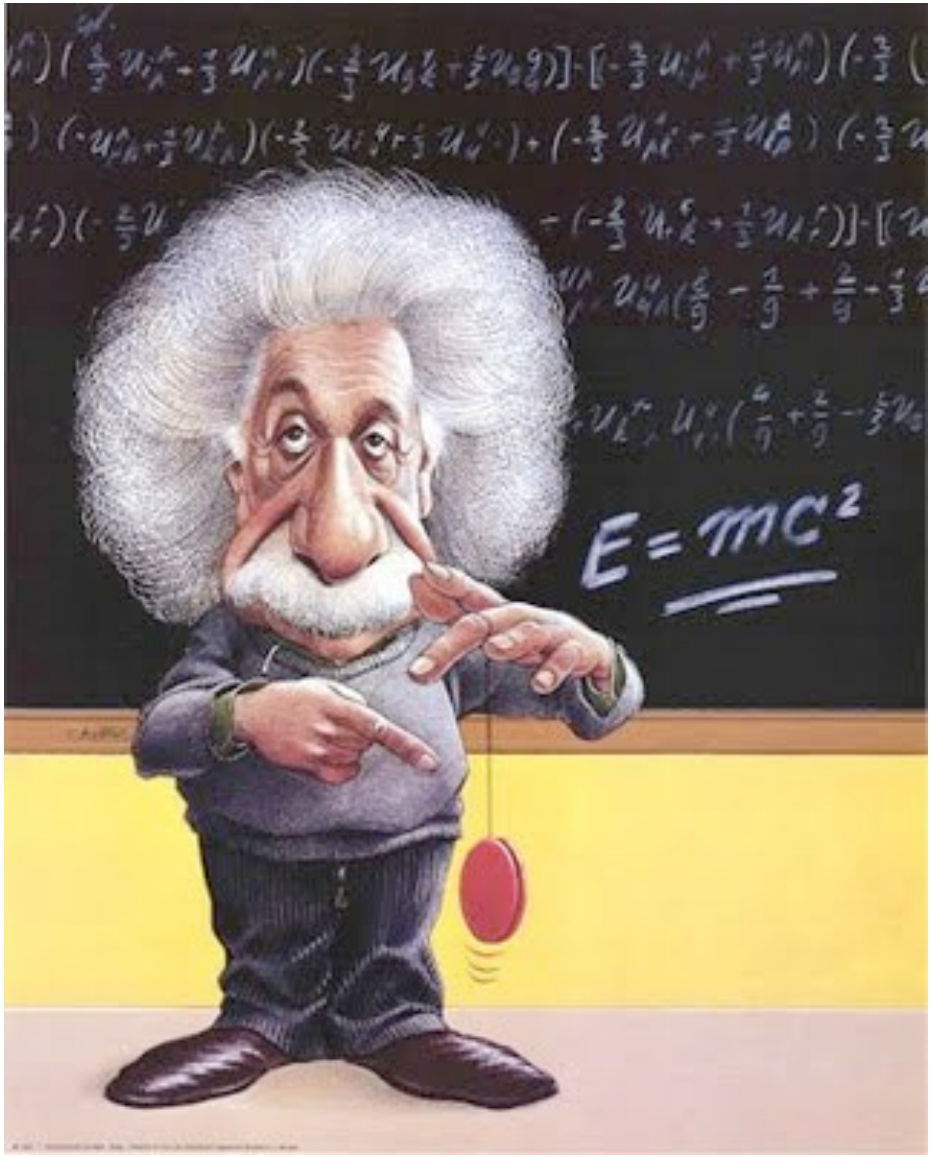
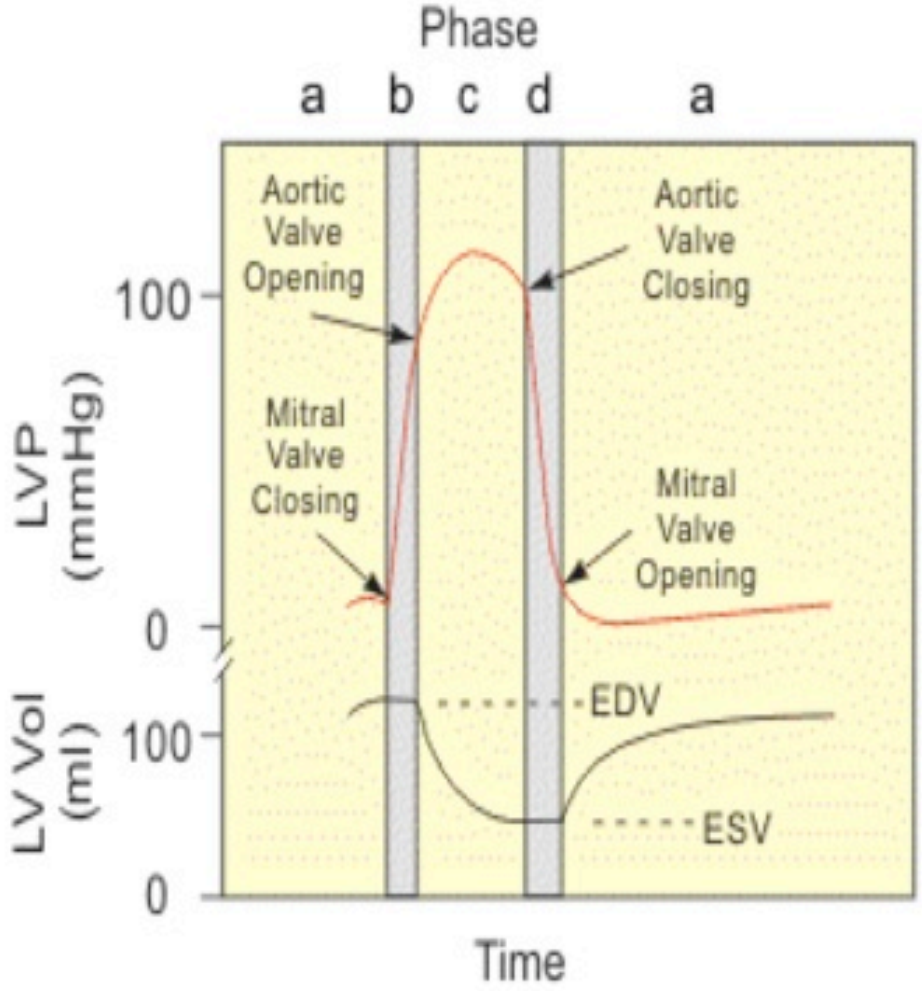
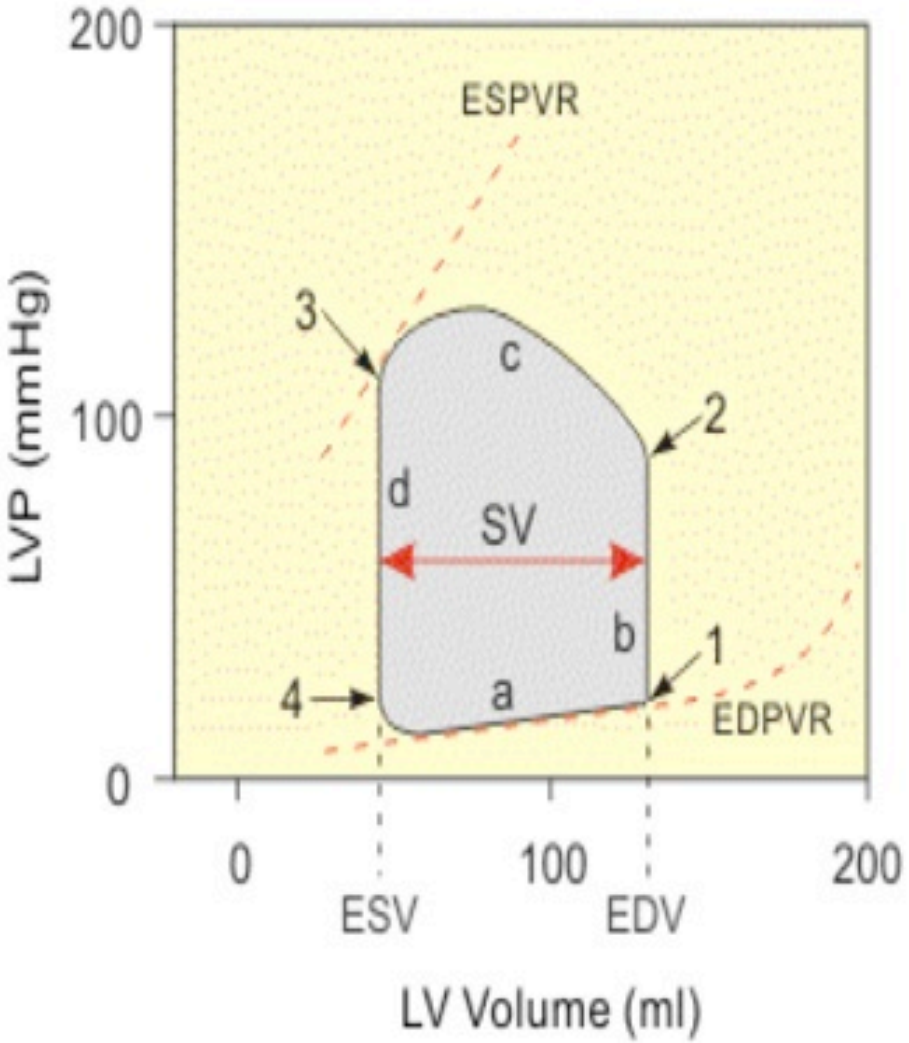
Hemodynamic Refresher



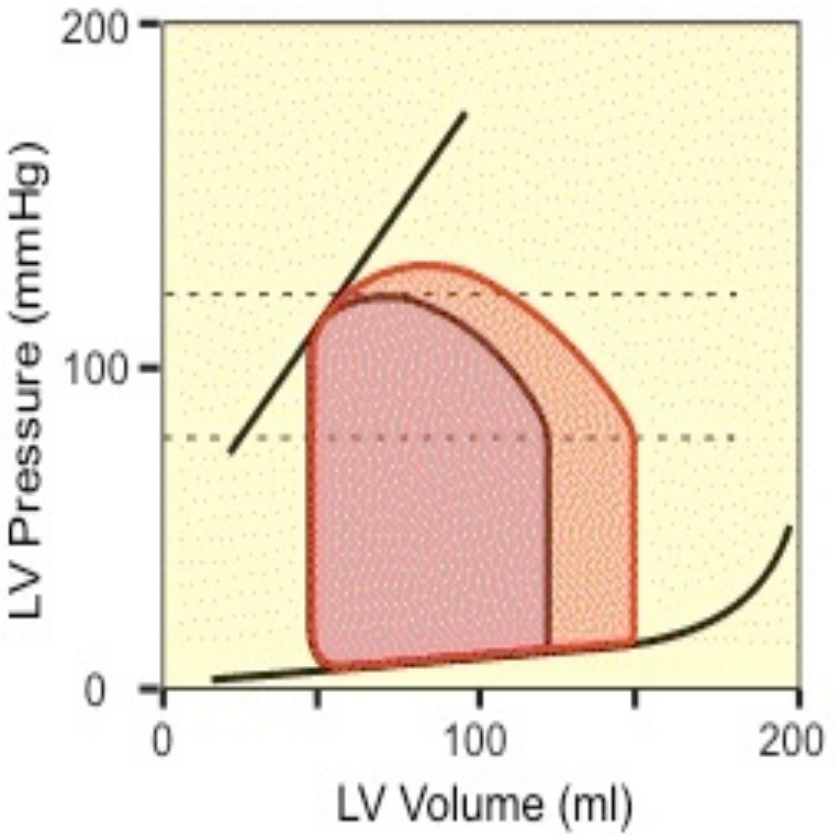
LV Pressure Volume Loops



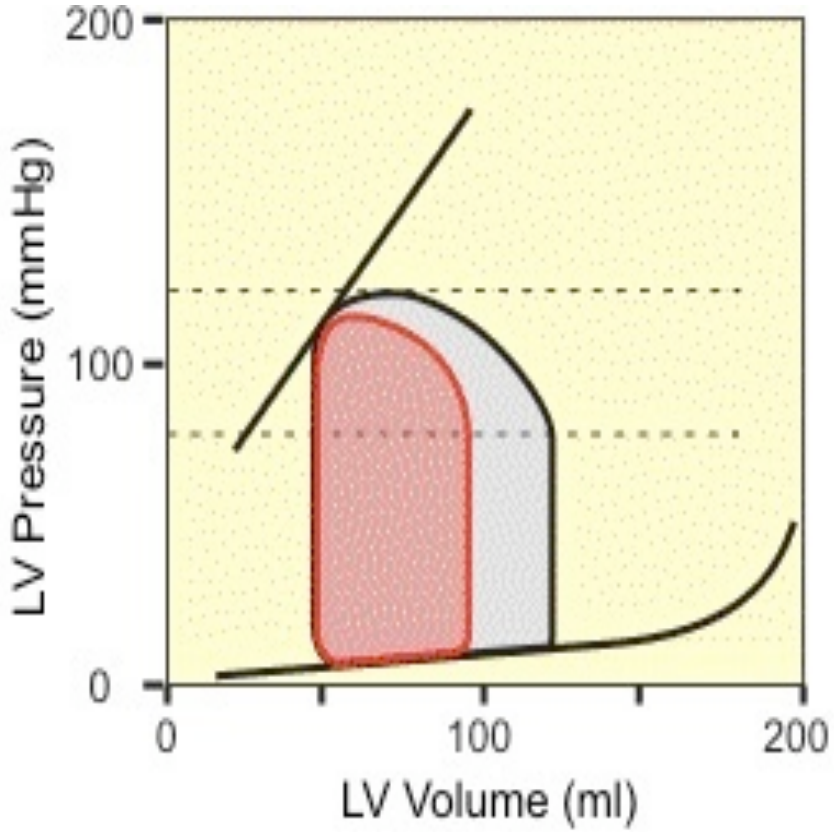


Effect of Acute Changes in Preload

Increasing preload

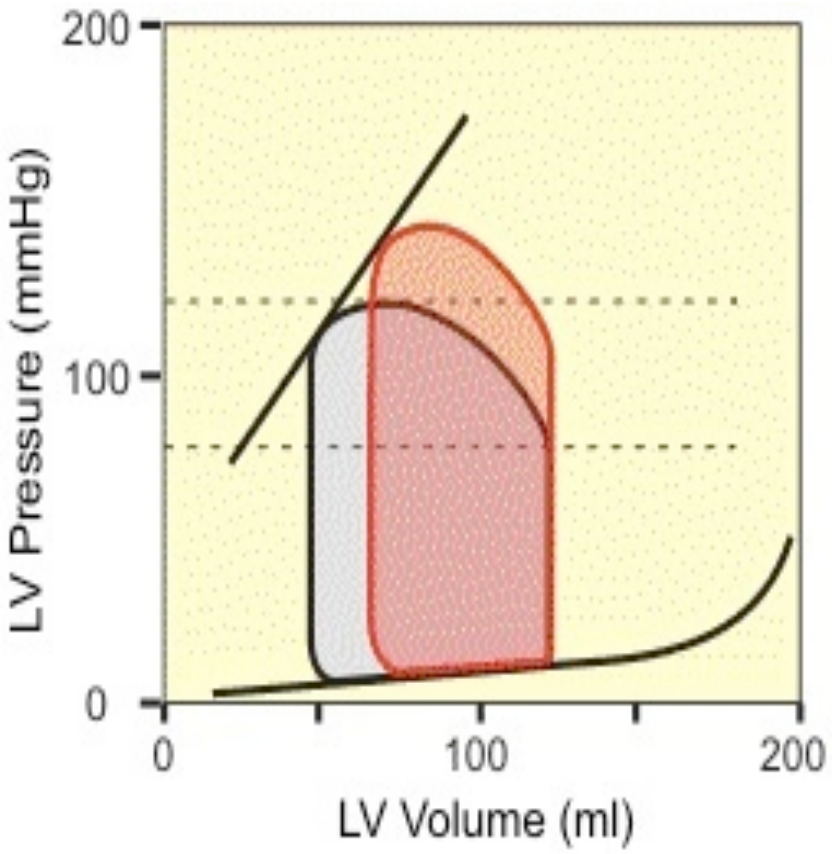


Decreasing preload

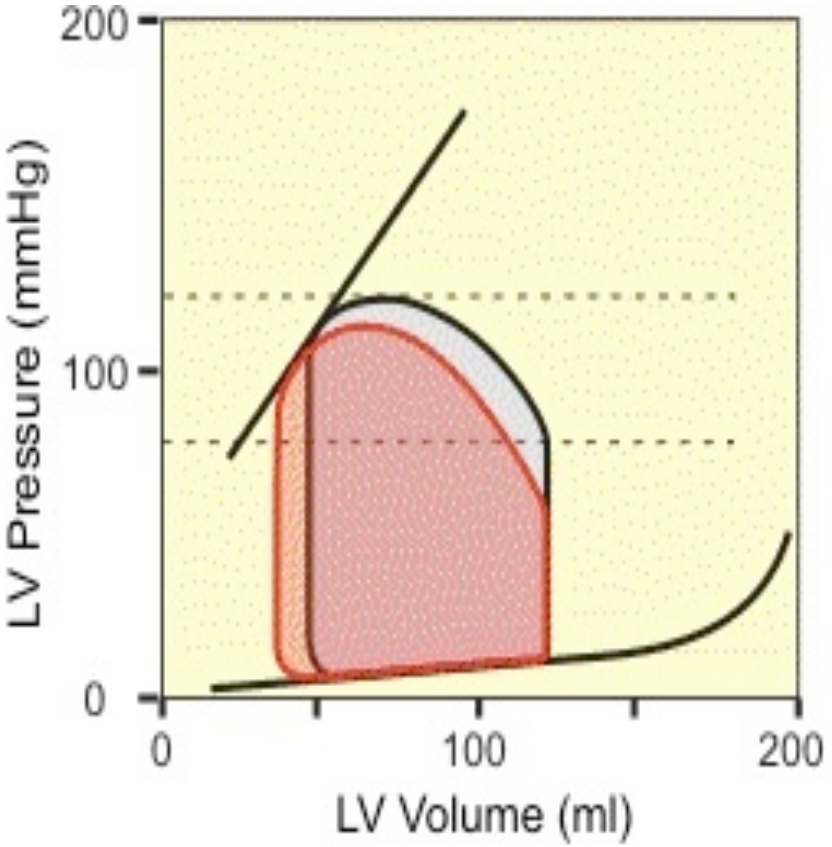


Effect of Acute Changes in Afterload

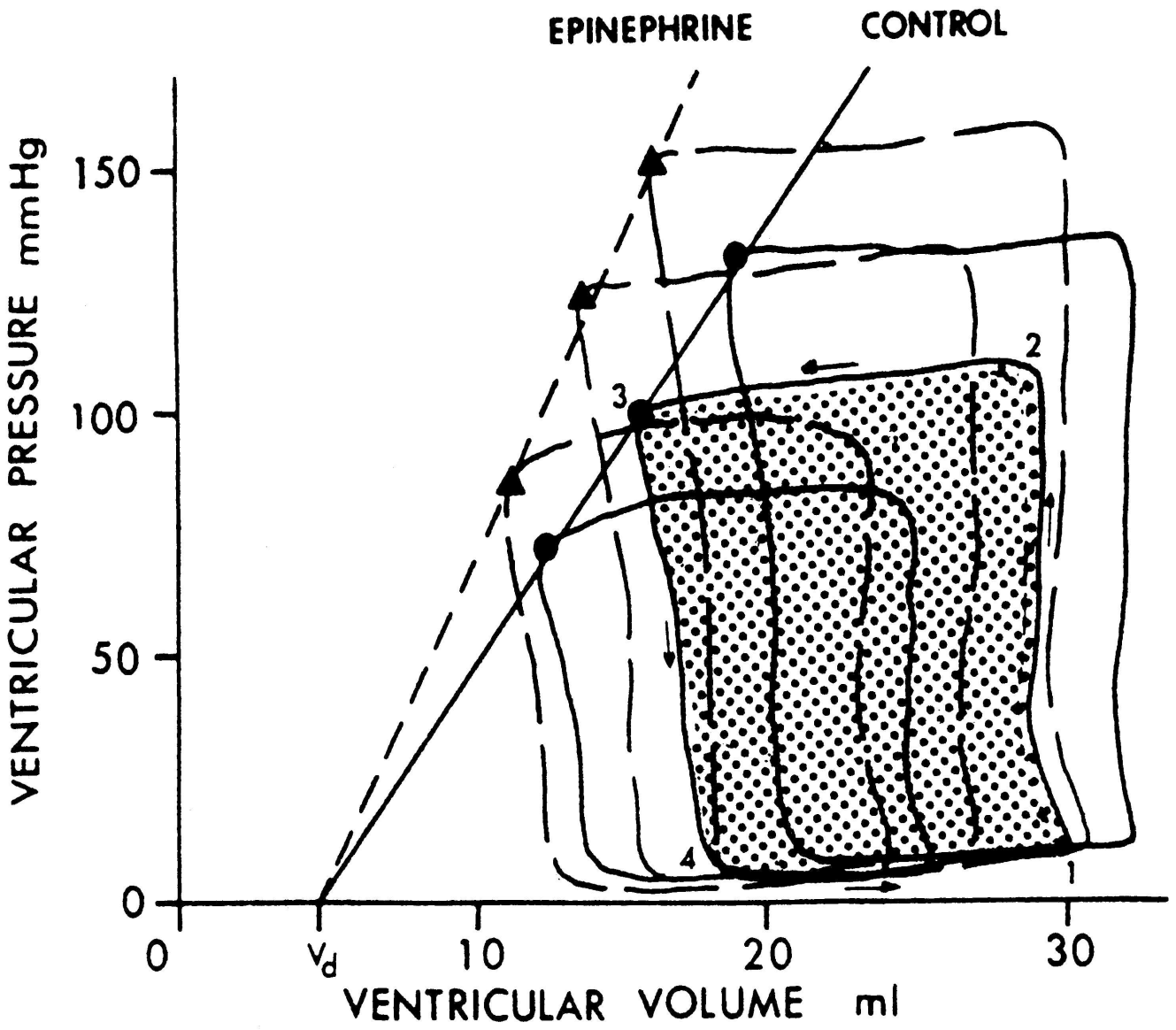
Increasing afterload



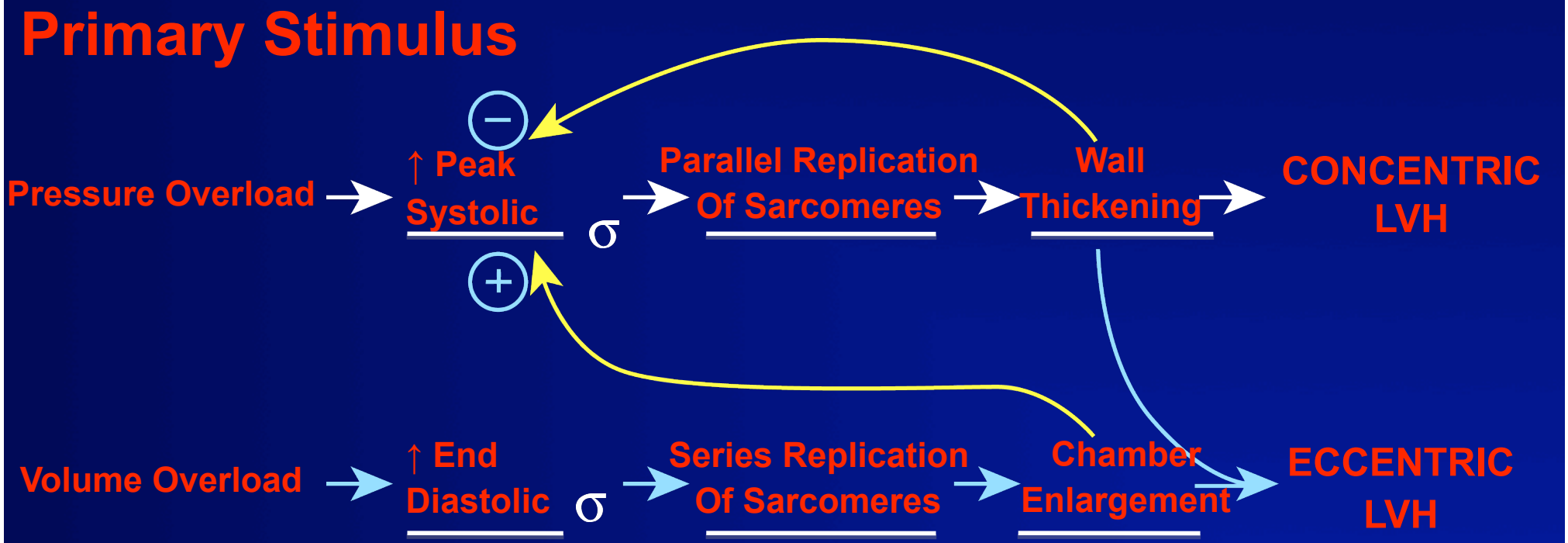
Decreasing afterload



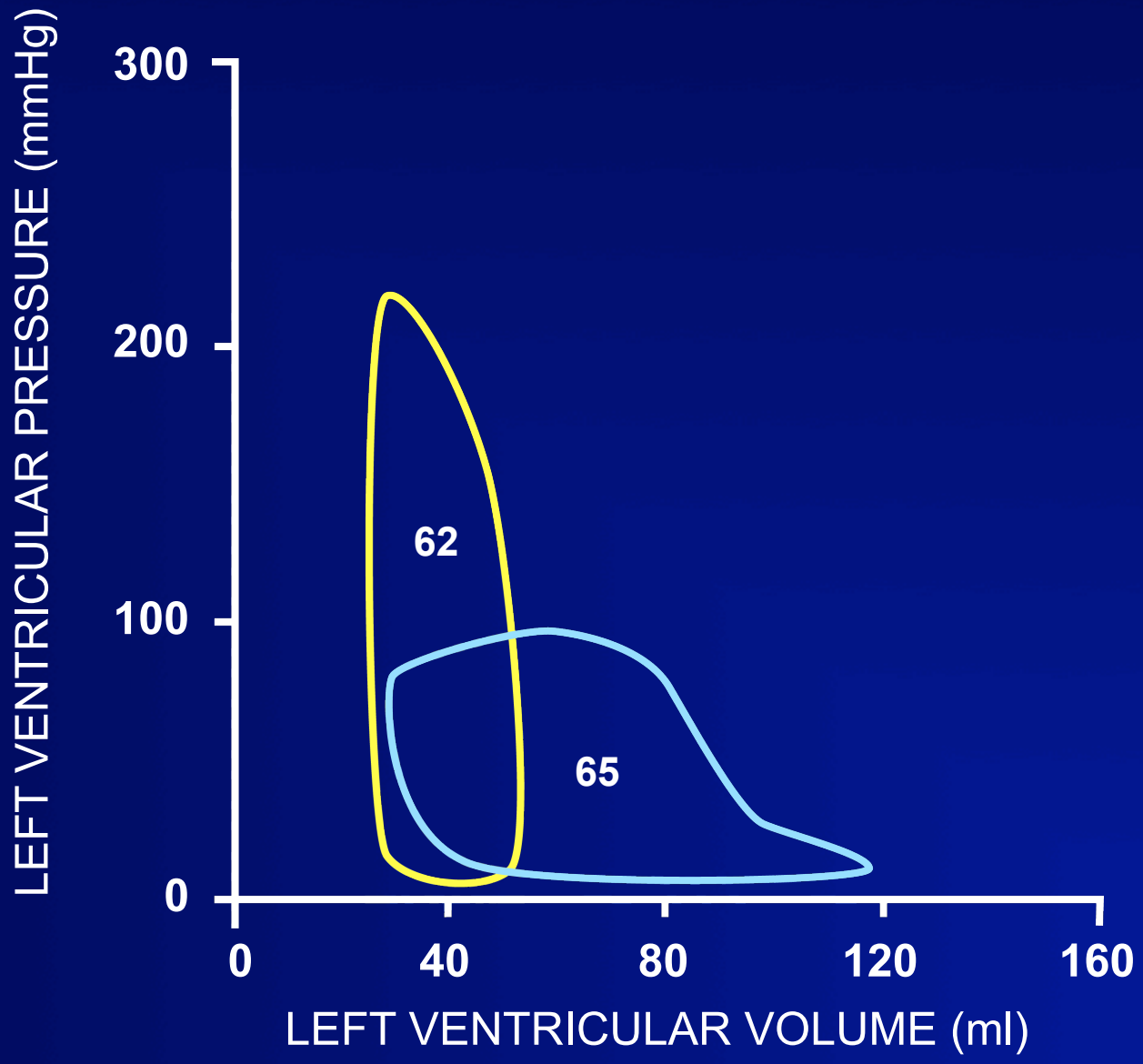
Assessment of LV Contractility: LV E_{max}



Effects of Chronic Increases in Preload or Afterload on LV Hypertrophy Pattern

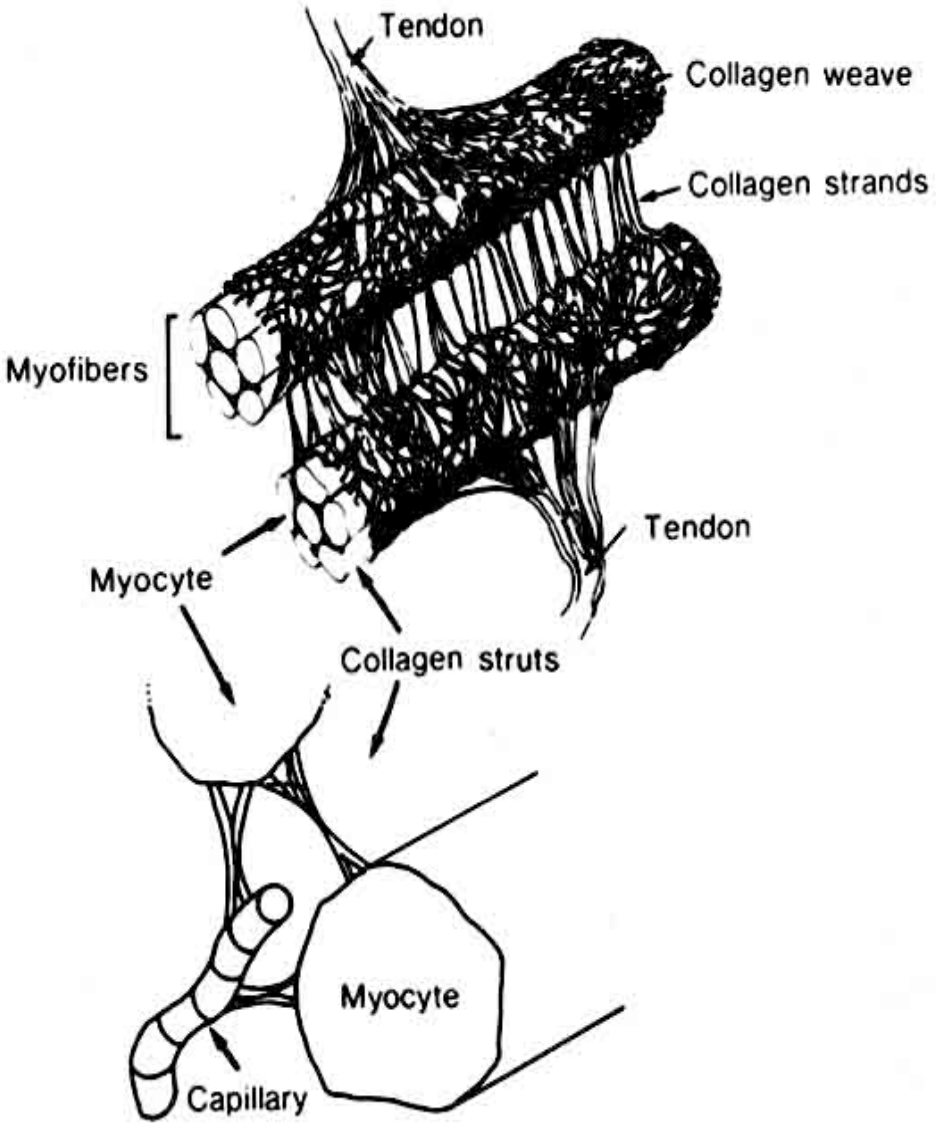


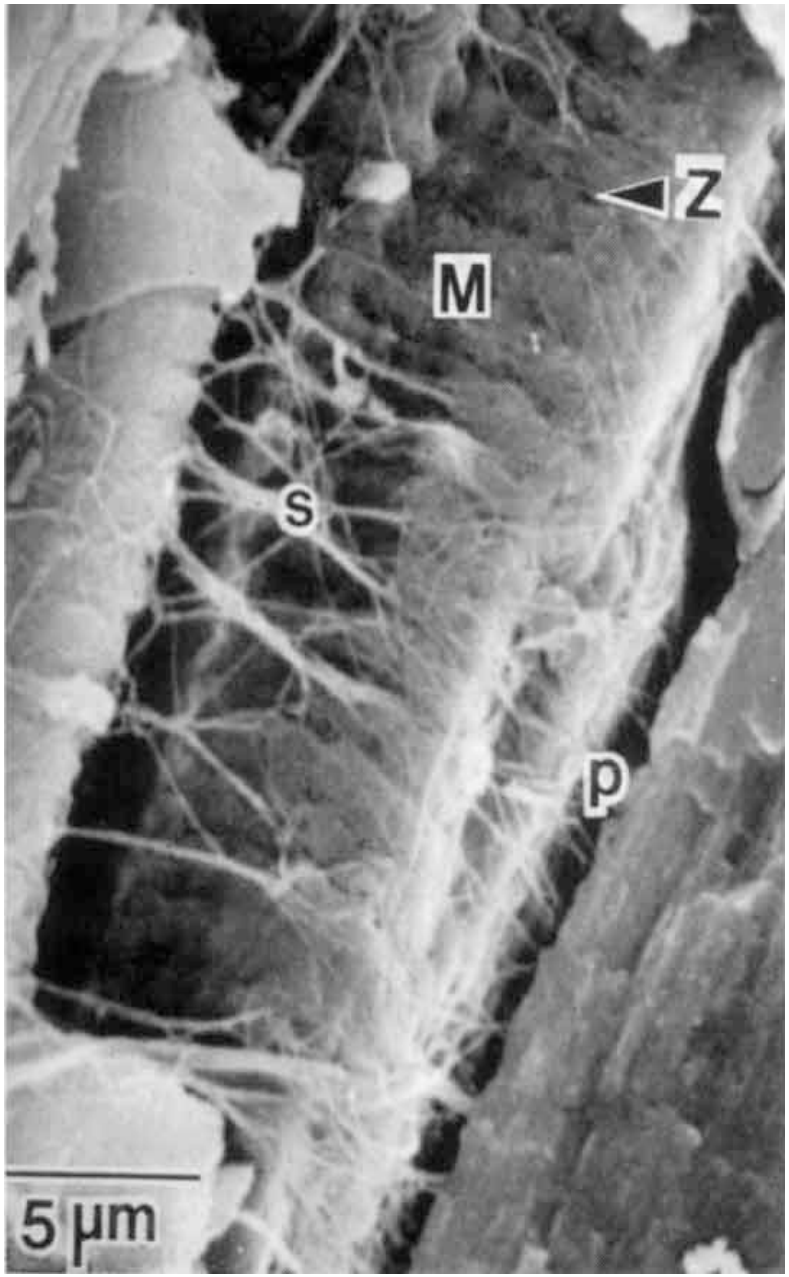
Grossman 1980, Am J Med



Carabello et al 1992, Am J Physiol

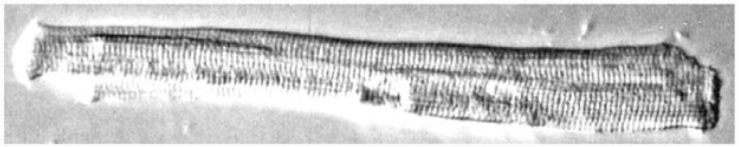
Collagen Skeleton of the Heart

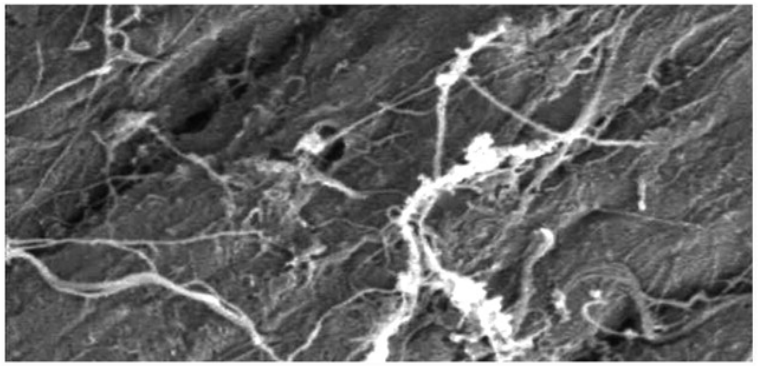




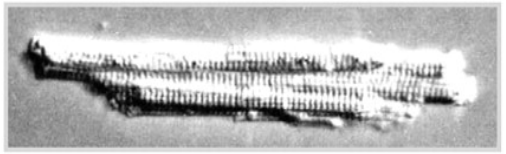
Diastolic Dysfunction

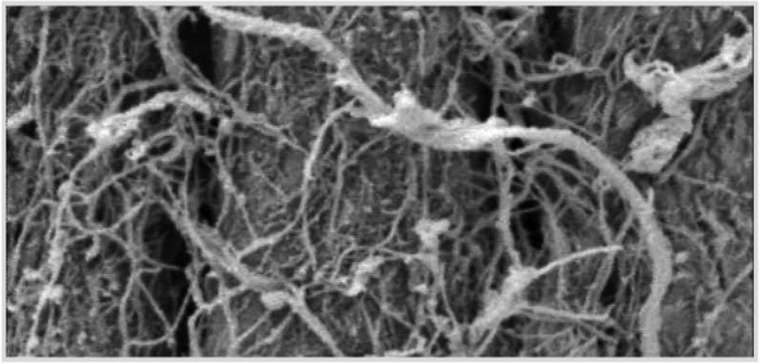
DCM-Systolic Heart Failure



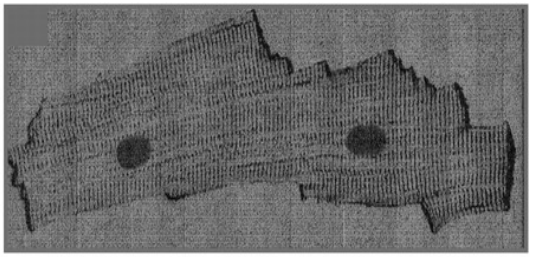


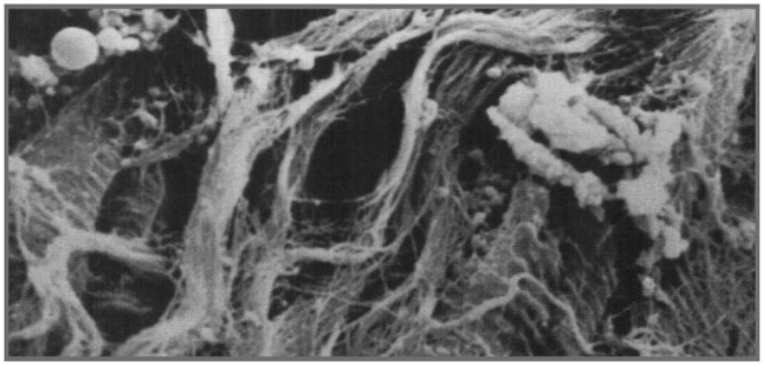
Normal

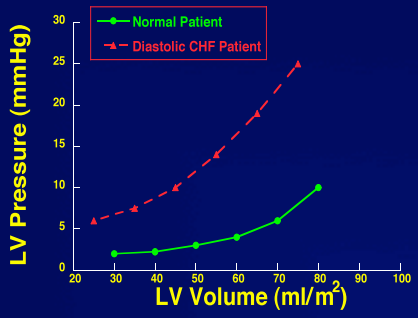




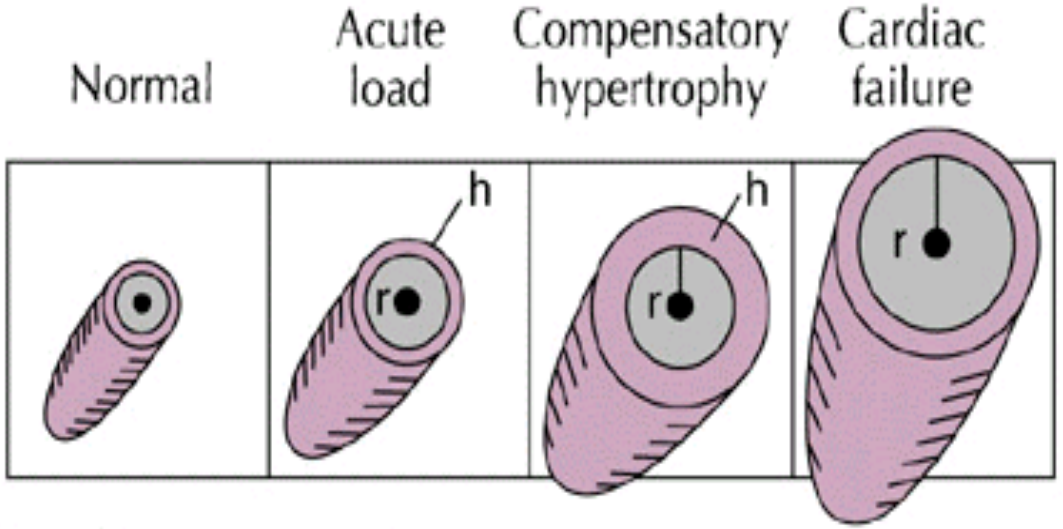
POH-Diastolic Heart Failure






Normal Patient
Diastolic CHF Patient
LV Pressure (mmHg)
LV Volume (ml/m2)
0
5
10
15
20
25
30
20
30
40
50
60
70
80
90
100

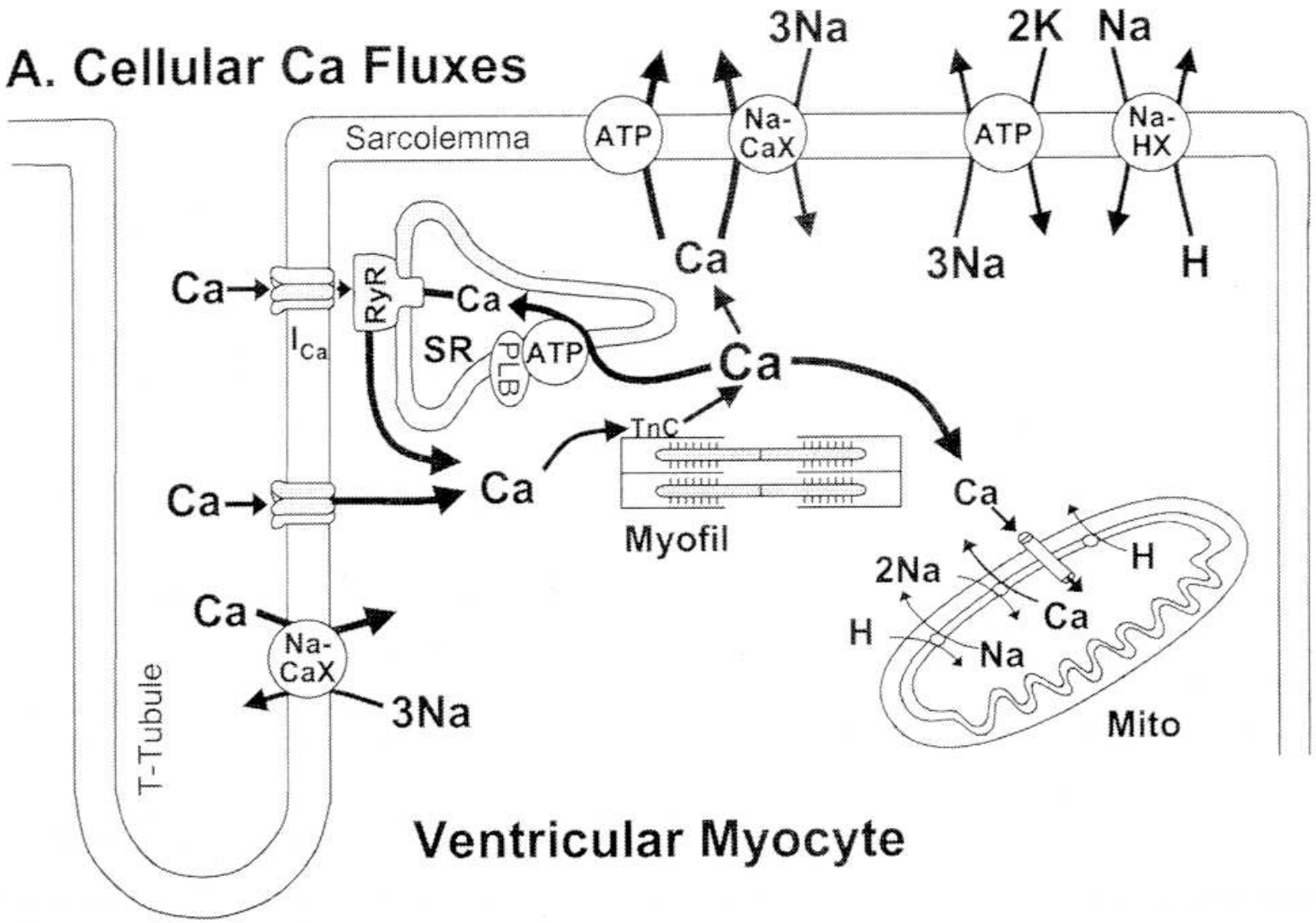
Transition to Heart Failure



LV systolic pressure	N	+	+	+
LV radius	N	+	+	+
LV wall thickness	N	N	+	+
LV diastolic volume	N	+	+/–	++
Systolic wall stress	N	+	N	+
Diastolic wall stress	N	+	N	+

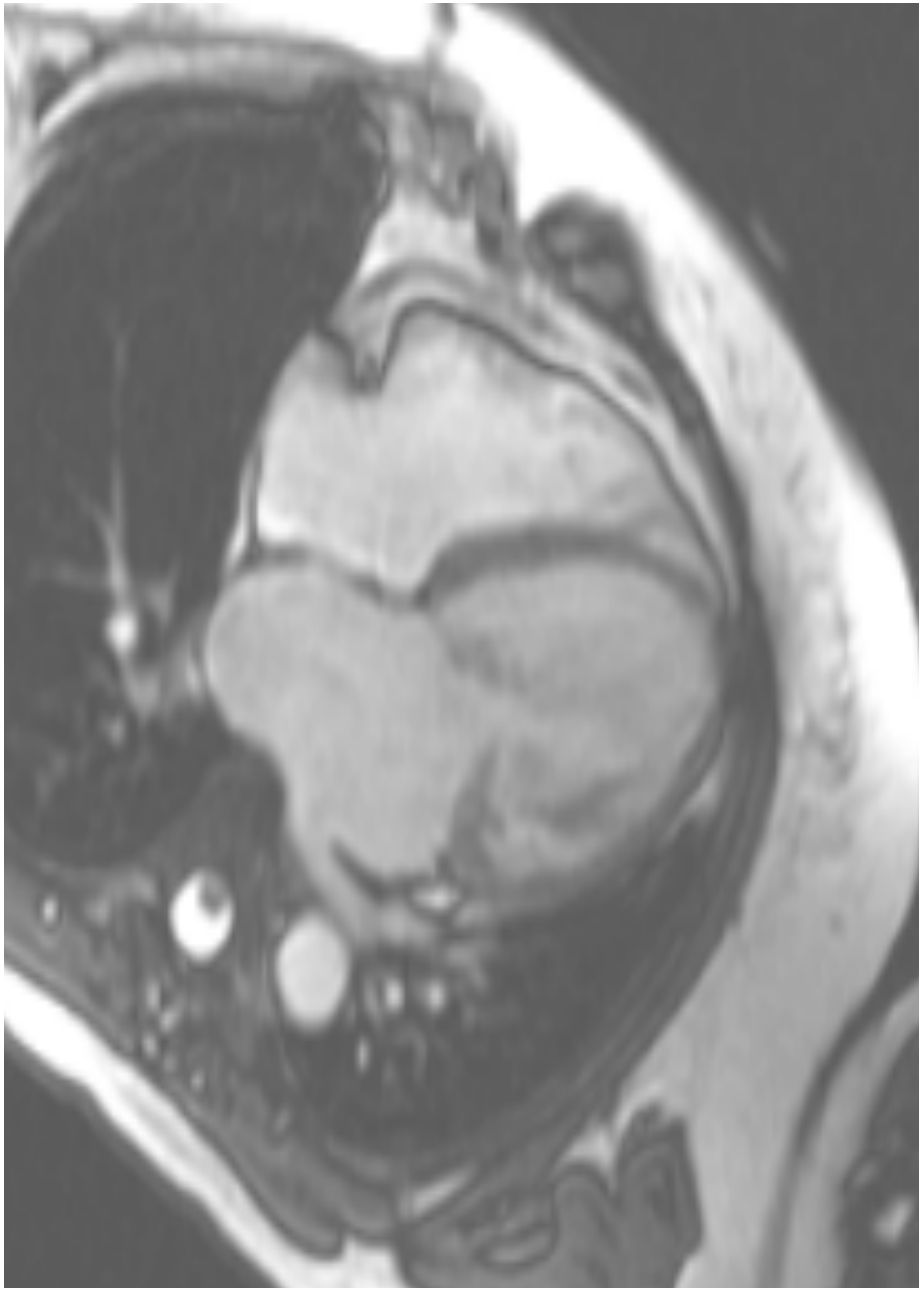
Colucci WS: Heart Failure: Cardiac Function and Dysfunction, 1995

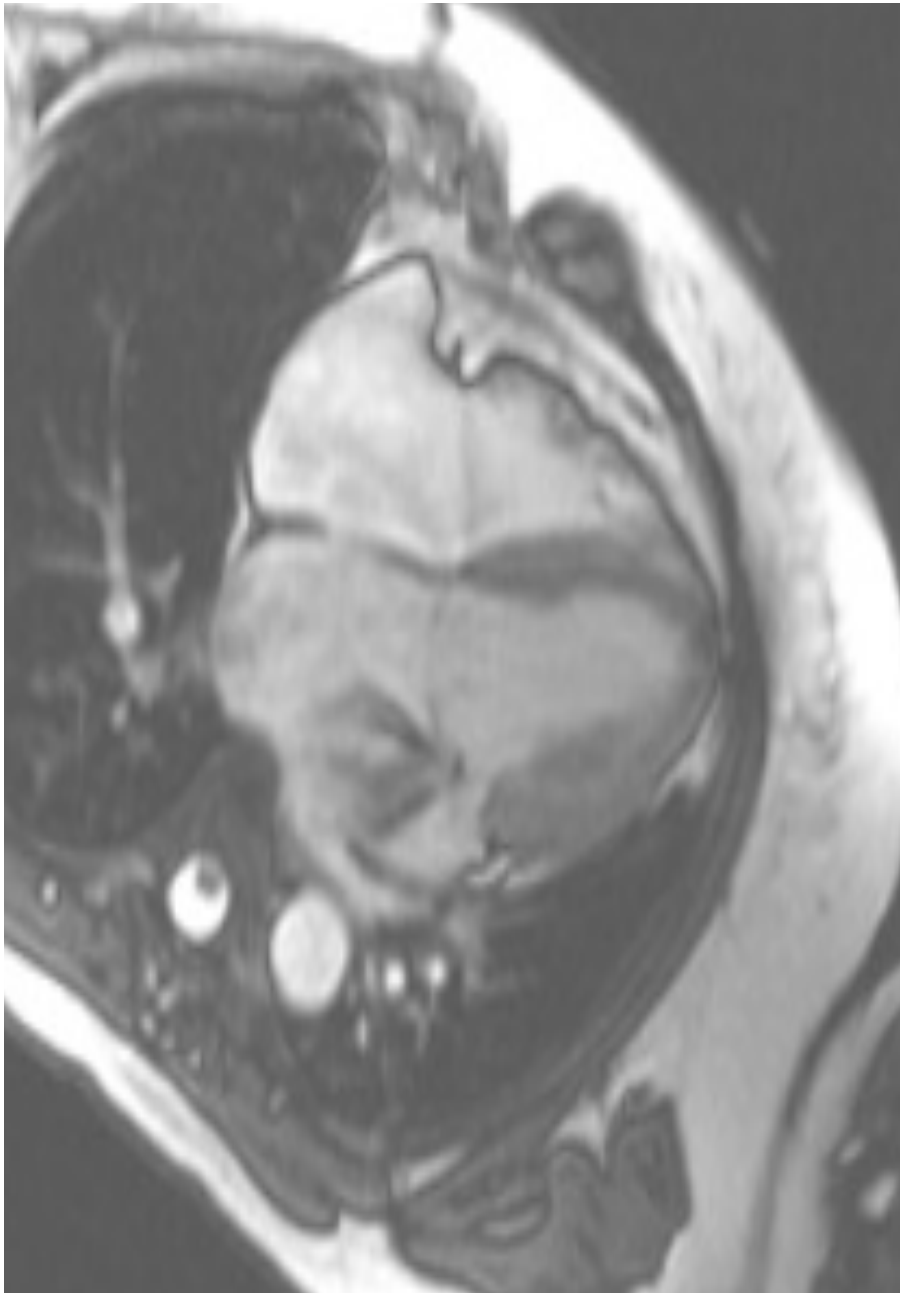
Calcium Homeostasis in Cardiomyocyte



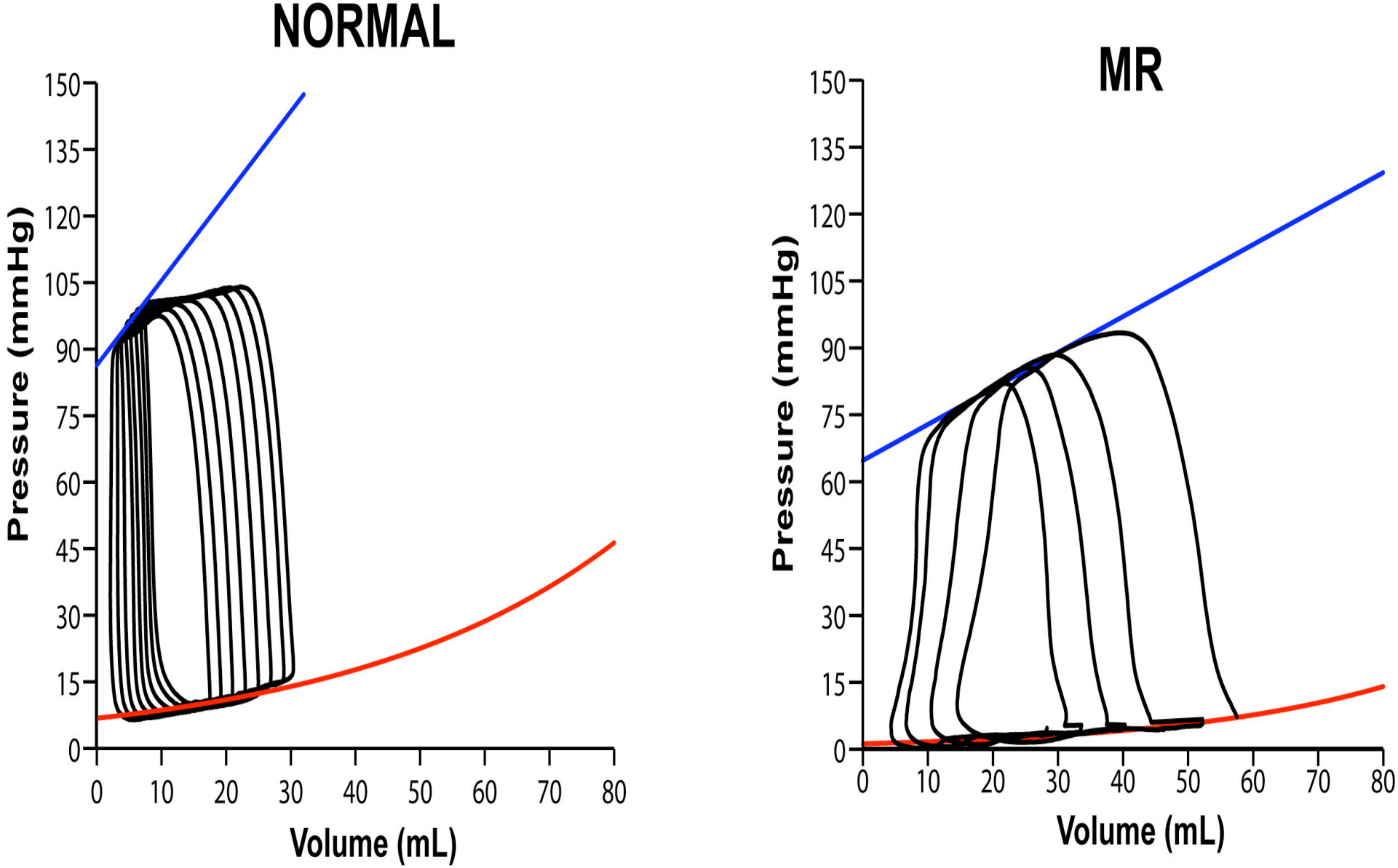
Bers *Circ Res* 87:275, 2000

Patient with Isolated MR



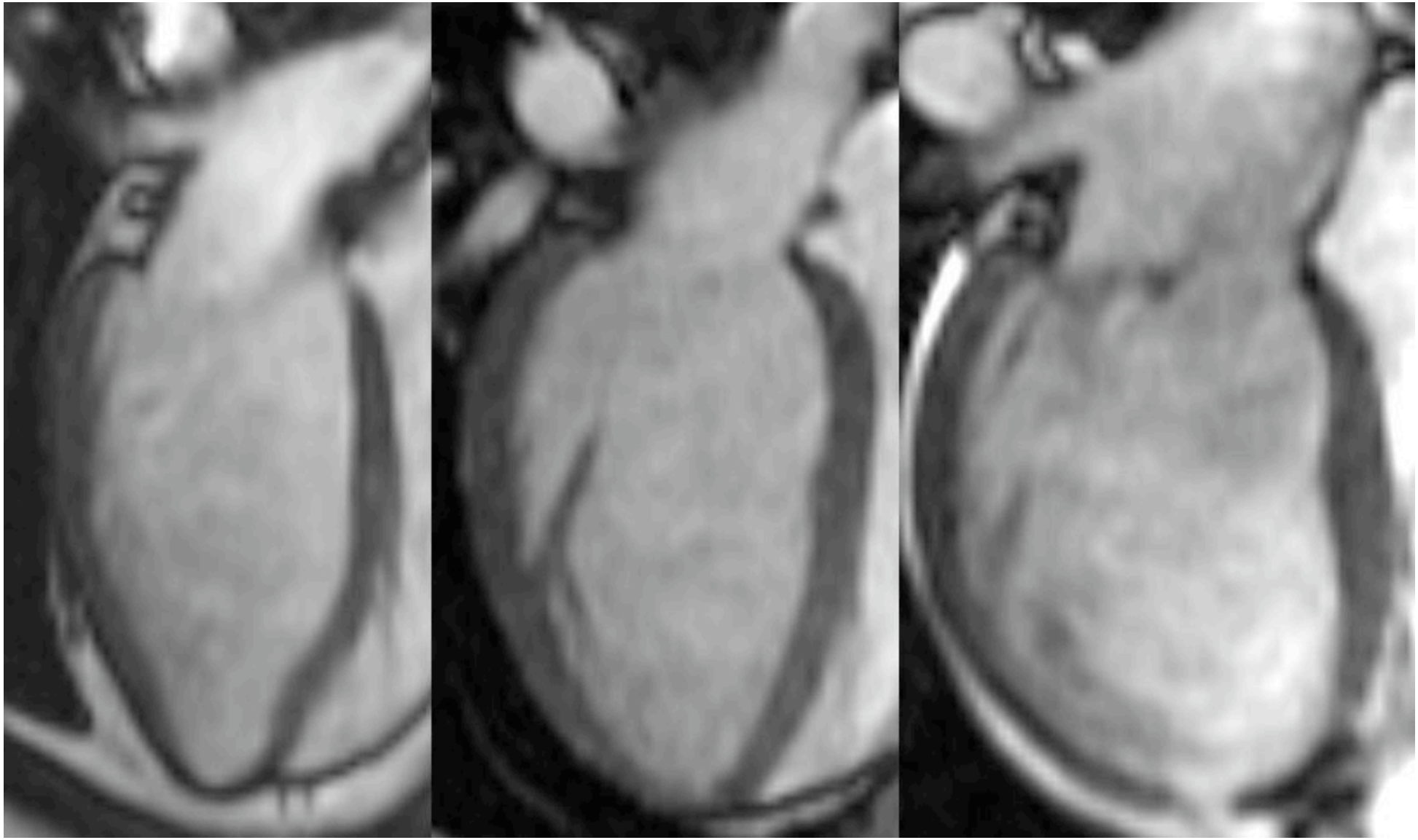


Ejection Dynamics in Chronic MR: Decreased LV E_{max} Despite Normal LVEF



Pathologic vs Physiologic LVH

Normal | Marathon Runner | Chronic Mitral Regurgitation

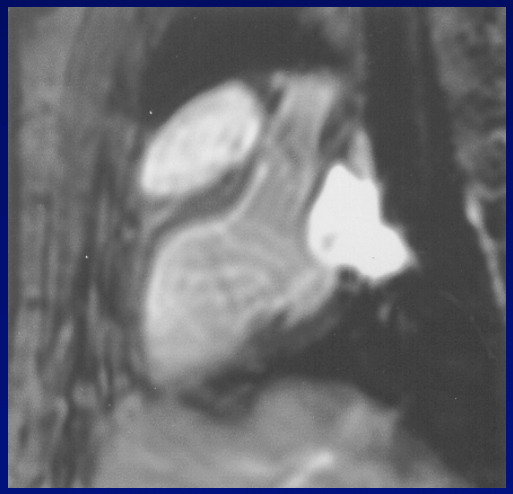


Magnetic Resonance Imaging After 4 Months of MR

Dell'Italia, *AJP* 269:H2065, 1995

BASELINE

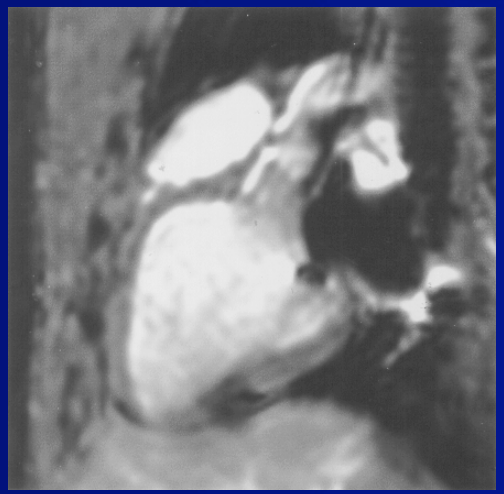
END-DIASTOLE



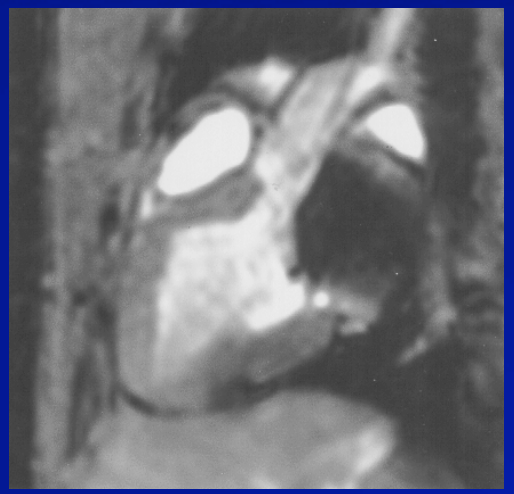
END-SYSTOLE

MITRAL REGURGITATION

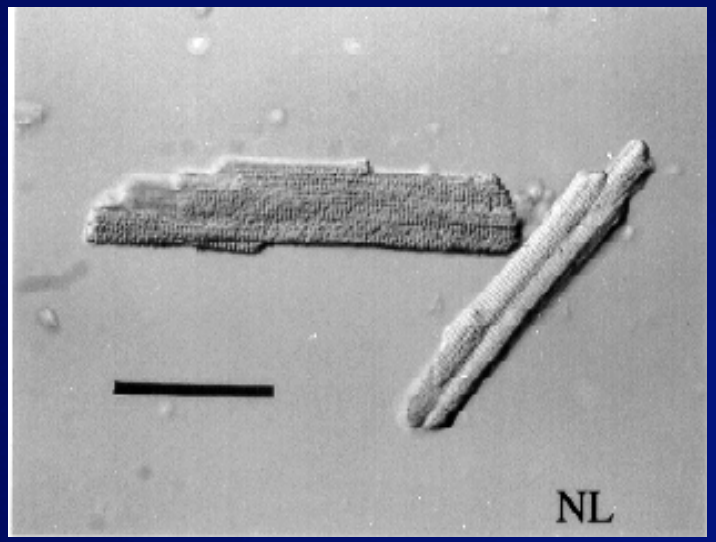
END-DIASTOLE

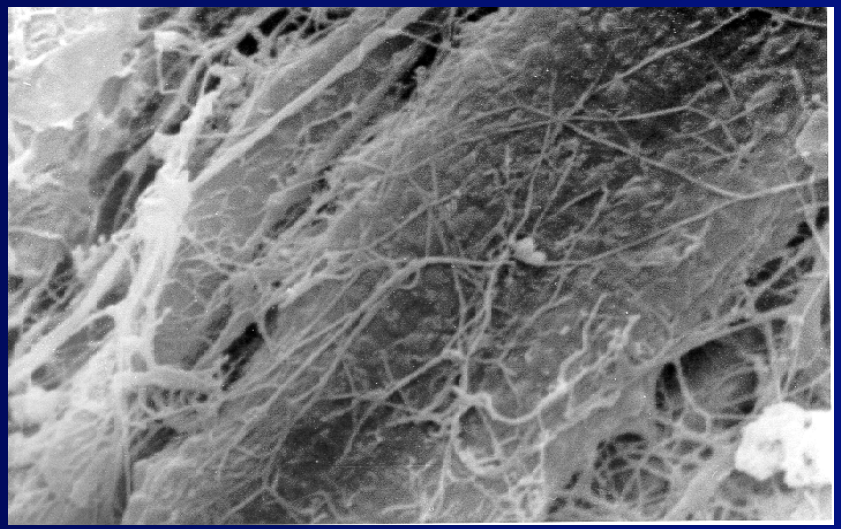


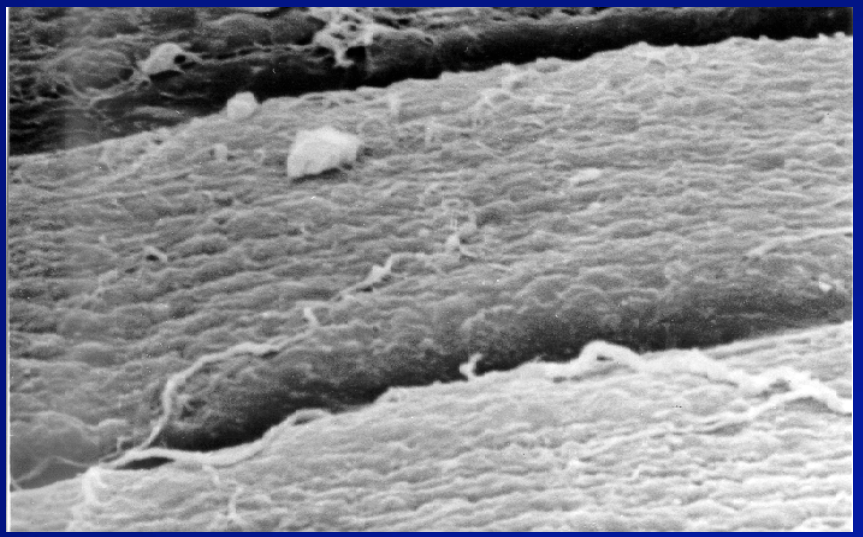
END-SYSTOLE



LV Remodeling of Cardiomyocyte and Extracellular Matrix in Canine MR

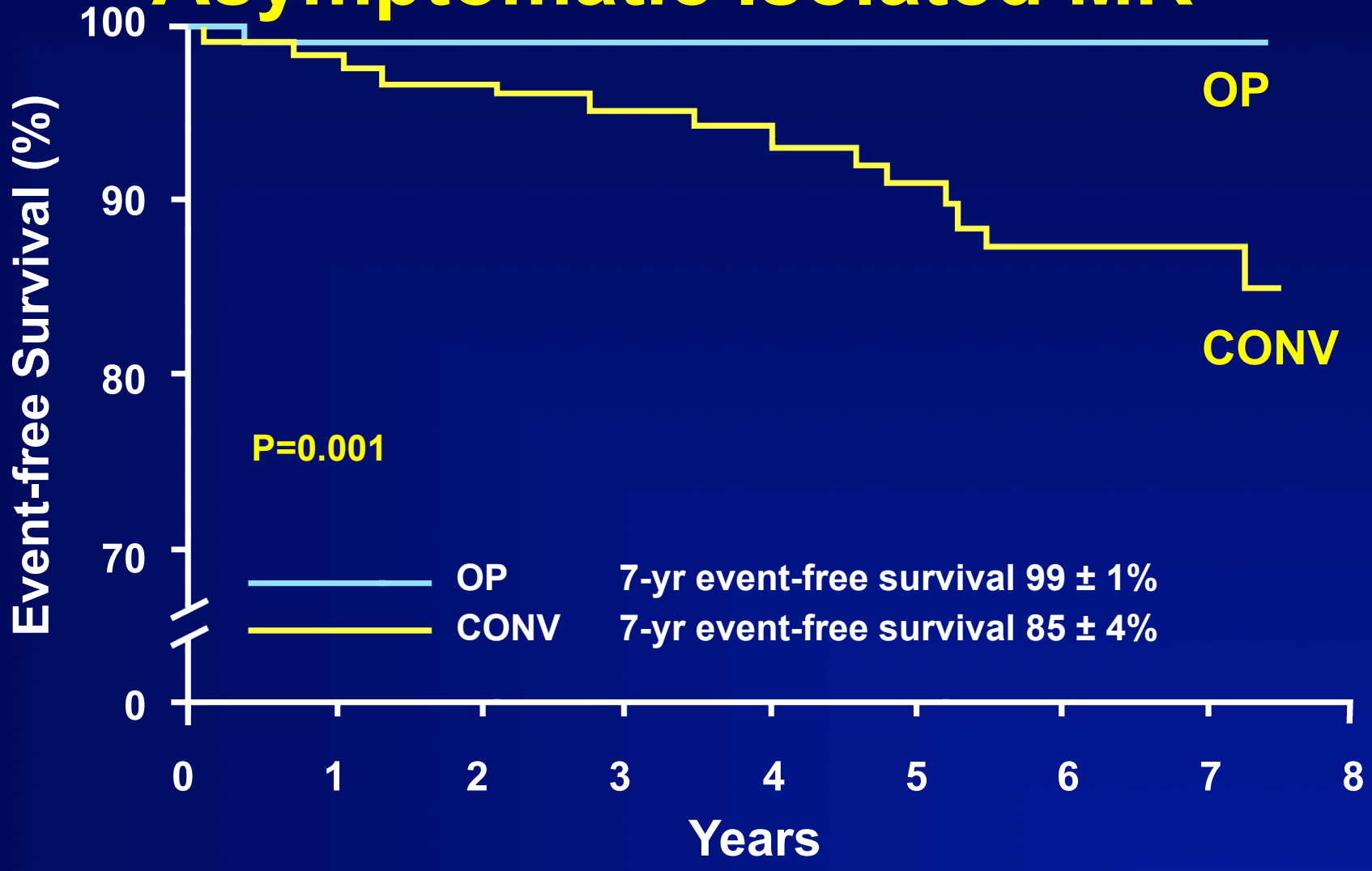






Dell'Italia, *AJP* 273:H961, 1997

Asymptomatic Isolated MR



Pts. at risk:					
OP	127	125	106	72	43
CONV	127	125	105	78	44

Increased Oxidative Stress and Cardiomyocyte Myofibrillar Degeneration in Patients With Chronic Isolated Mitral Regurgitation and Ejection Fraction >60%

Mustafa I. Ahmed, MD,* James D. Gladden, BS,* Silvio H. Litovsky, MD,*
Steven G. Lloyd, MD, PHD,* Himanshu Gupta, MD,* Seidu Inusah, MS,* Thomas Denney JR, PHD,‡
Pamela Powell, MS,* David C. McGiffin, MD,* Louis J. Dell'Italia, MD*†

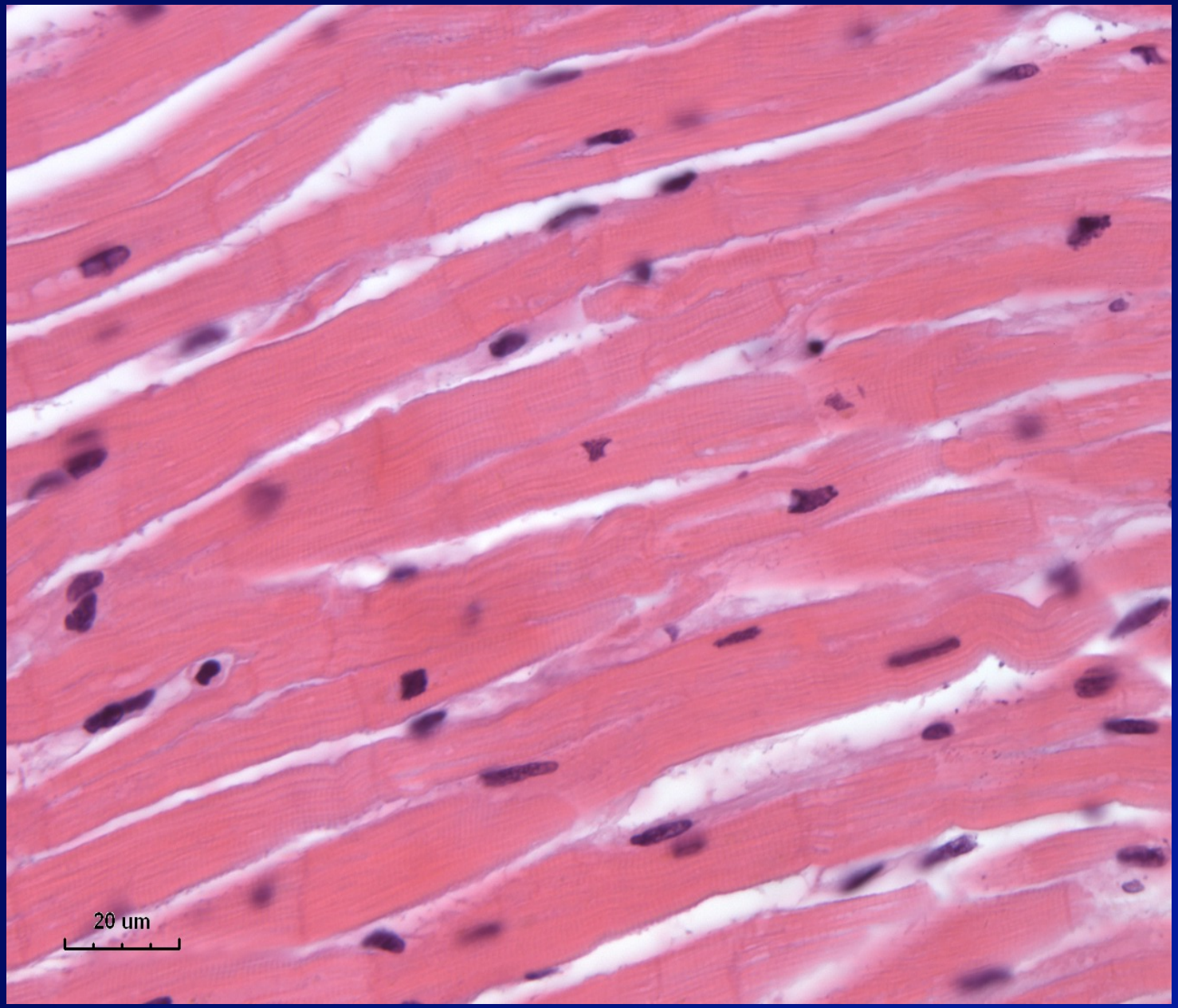
Birmingham and Auburn, Alabama

Ahmed *J Am Coll Cardiol* Feb 16, 2010

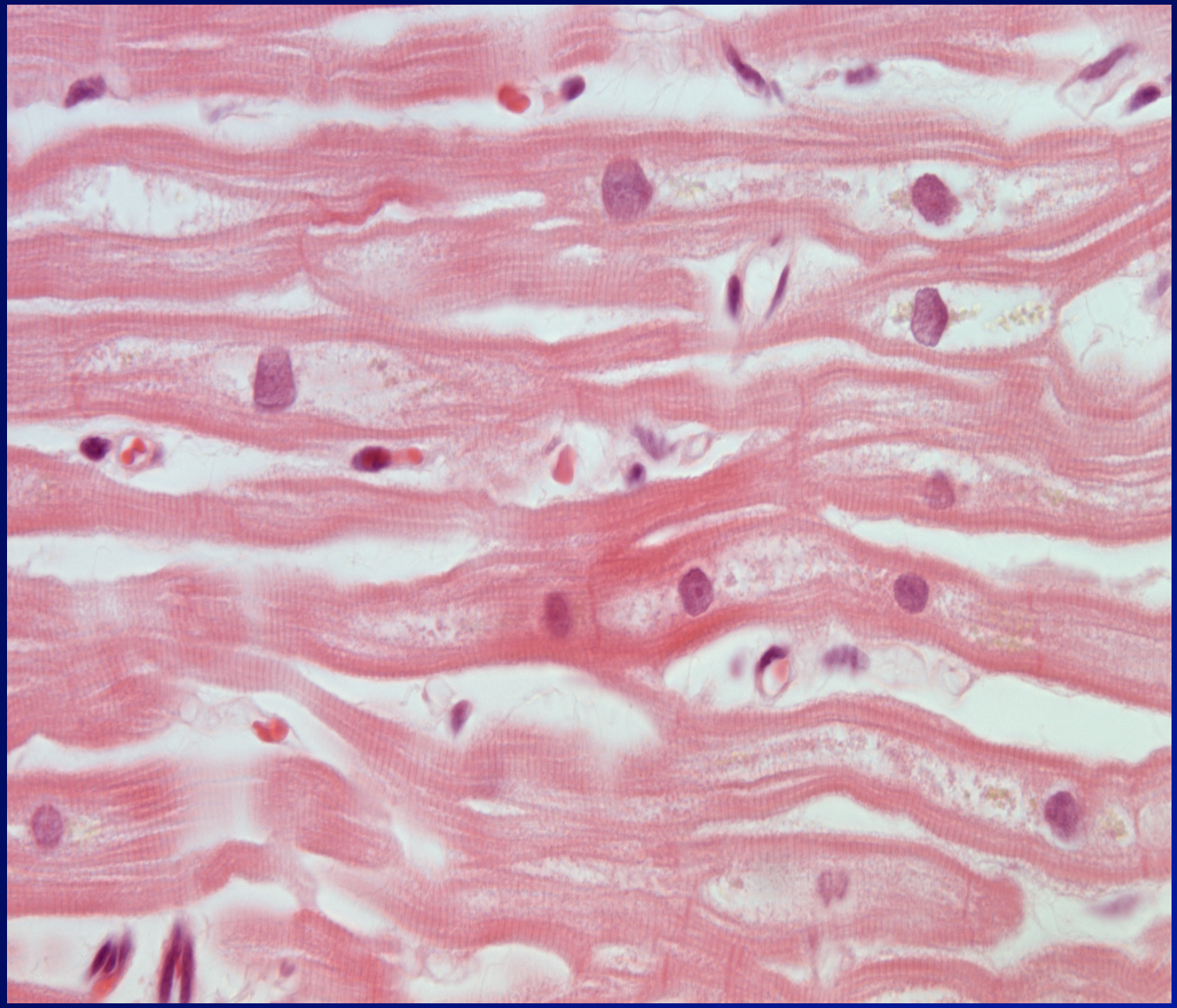
LV MRI Parameters in MR Patients

	Normal (n = 39)	Pre-MV Repair (n = 23)	6 Months post op (n = 23)
LVEDD (mm)	51 ± 1	62 ± 1*	55 ± 2#
LVESD	33 ± 1	38 ± 2*	37 ± 2
LV Mass (g)	96 ± 4	145 ± 9*	113 ± 6#
LVEDVI (ml/ m^2)	68 ± 2	116 ± 5*	79 ± 5#
LVESVI (ml/ m^2)	24 ± 2	43 ± 3*	38 ± 4*
LV SV (ml)	82 ± 3	136 ± 10	81 ± 4*#
LV EF (%)	65 ± 1	65 ± 2	54 ± 2*#
LVEDV / Mass	1.39 ± 0.06	1.58 ± 0.11*	1.35 ± 0.09*#

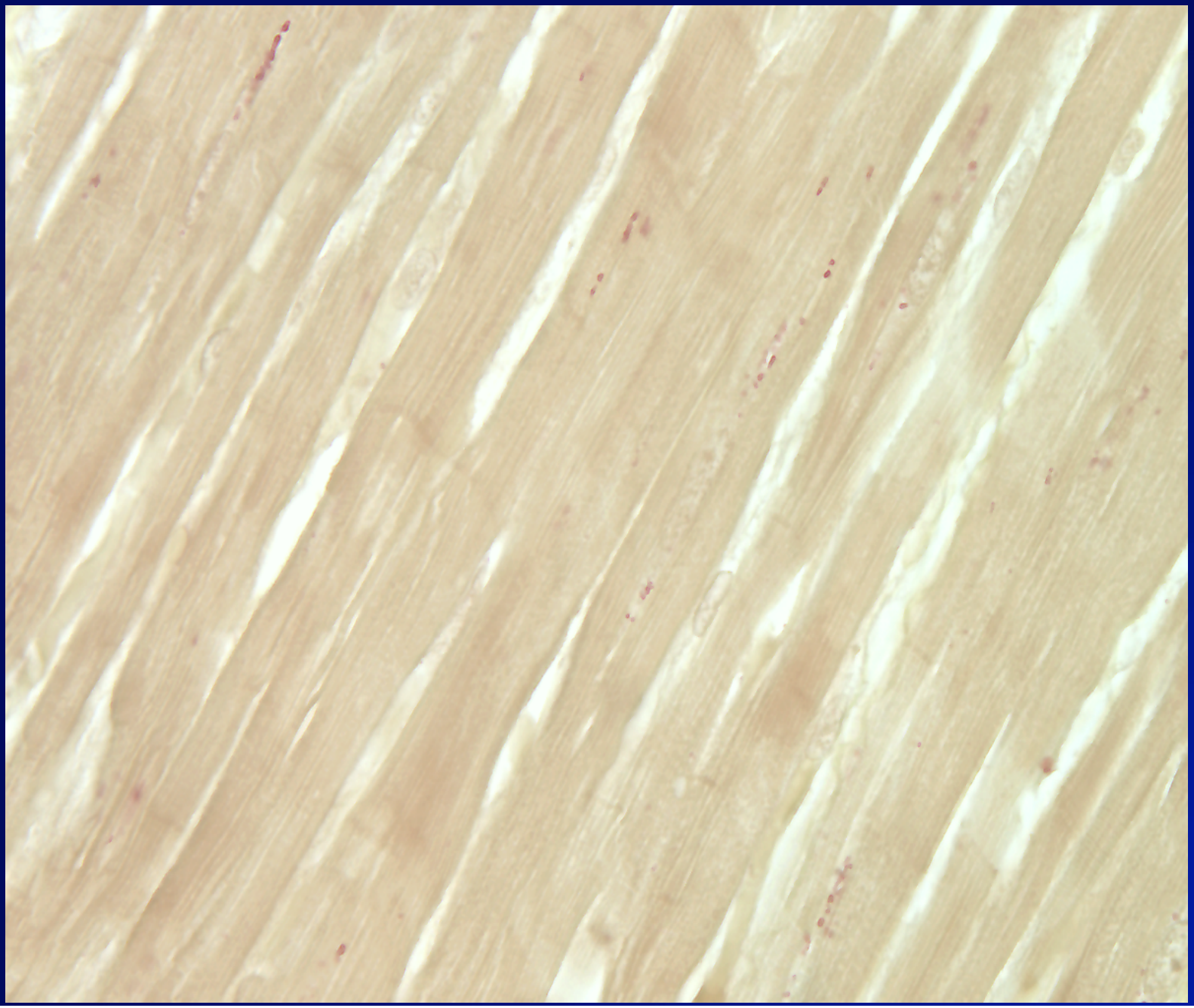
Normal Human Cardiomyocyte



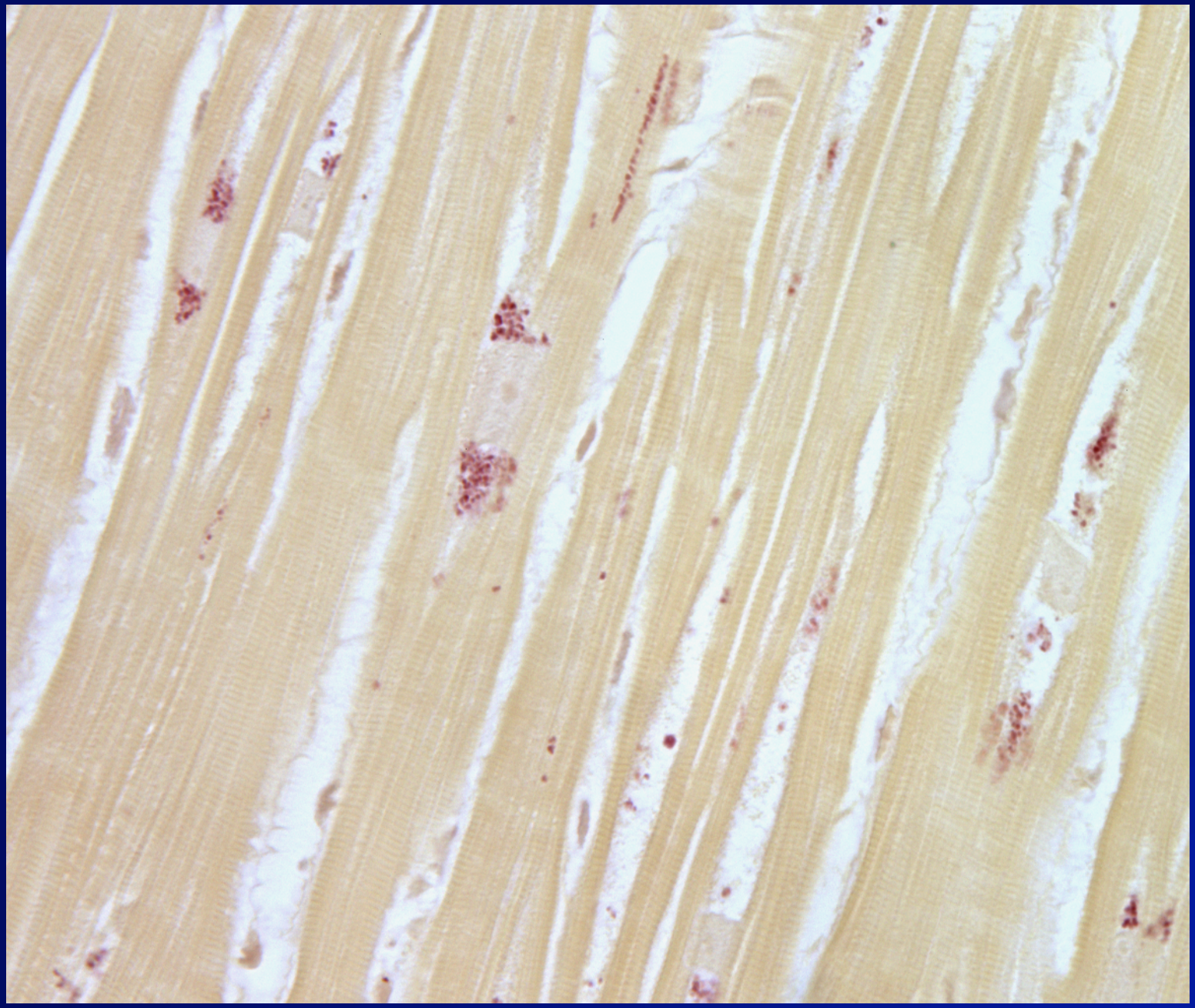
Myofibrillar Degeneration in Human MR



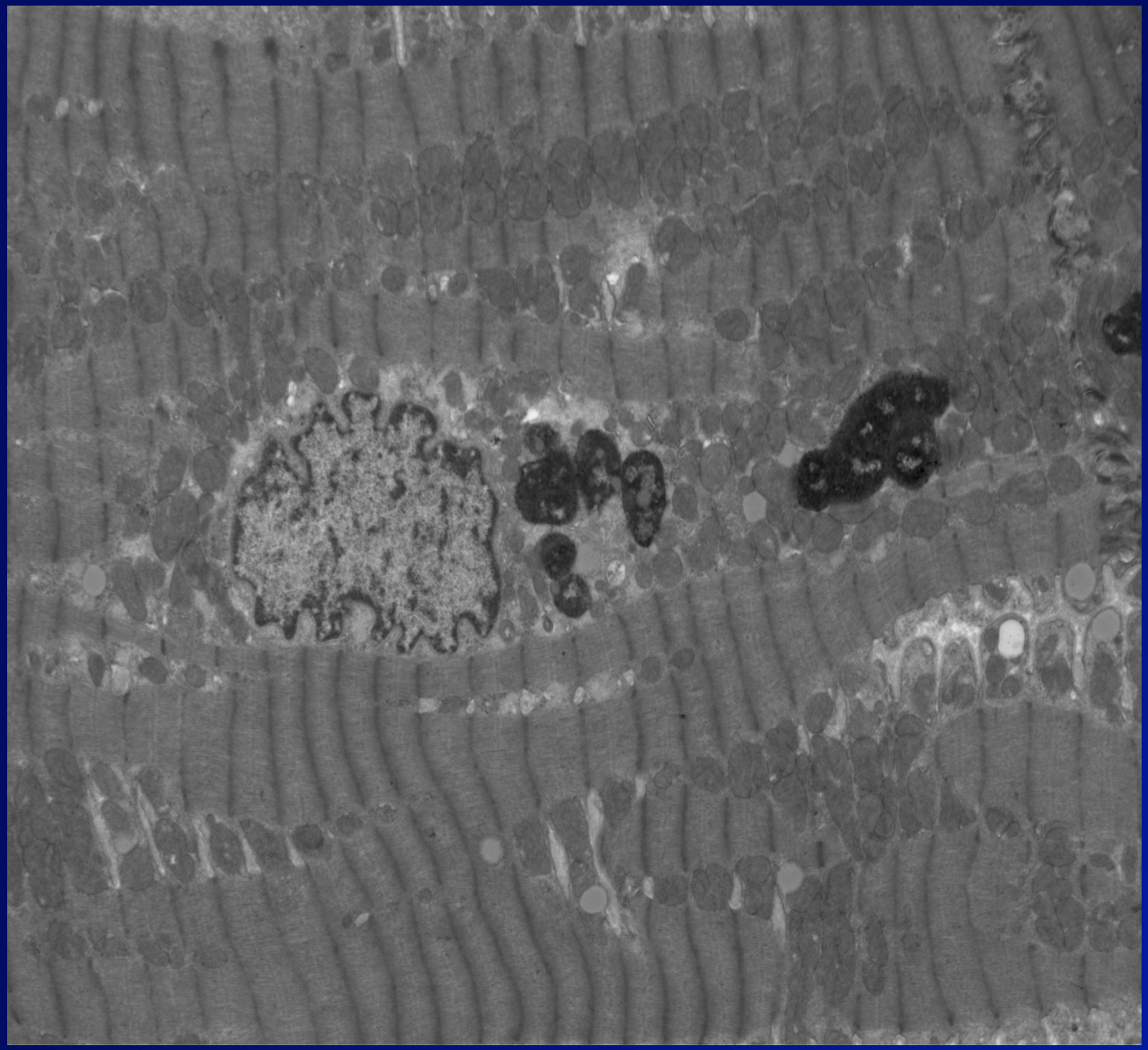
Lipofuscin in Normal Human Cardiomyocyte



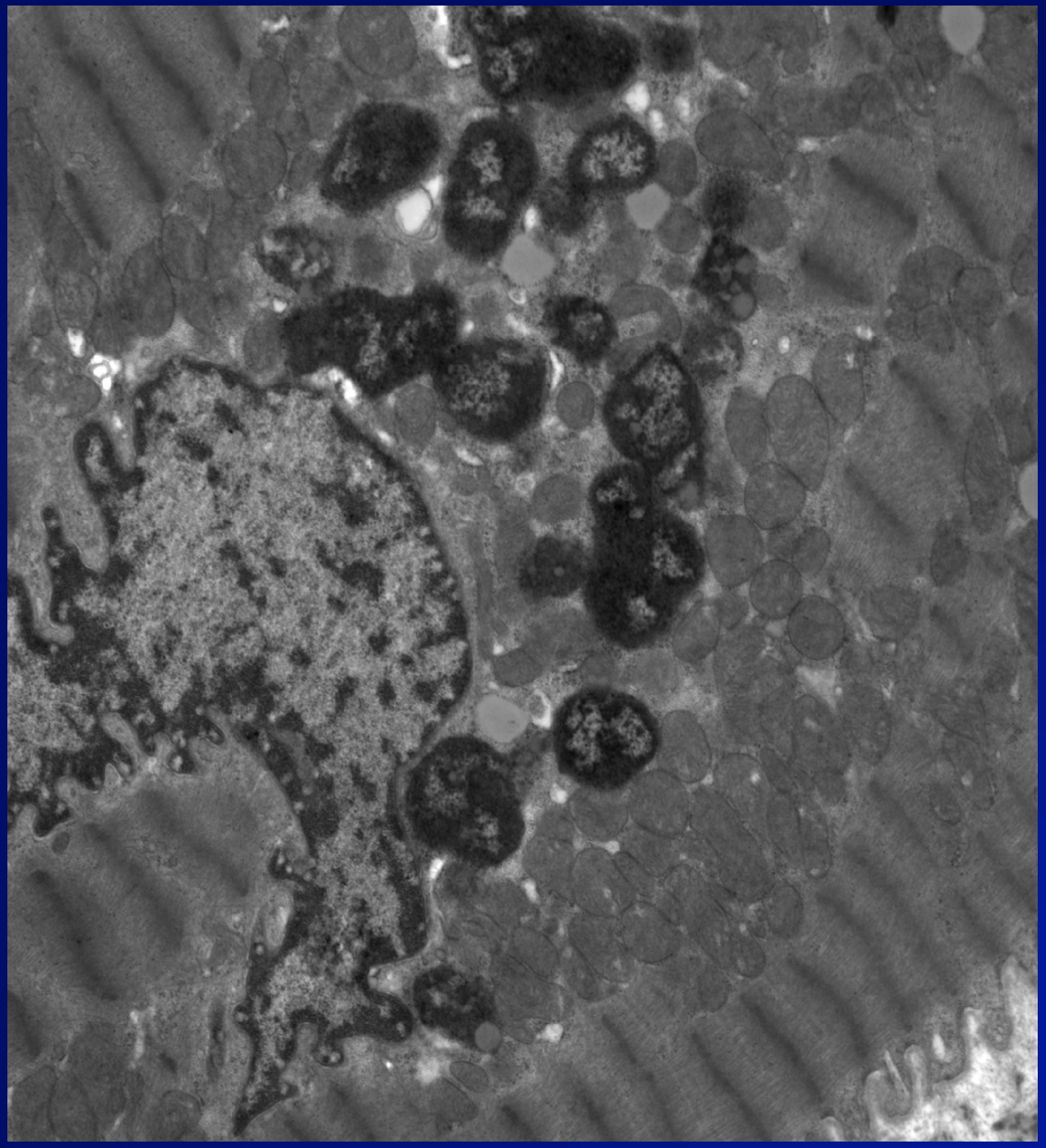
Lipofuscin in Human MR



Lipofuscin in Human MR by TEM



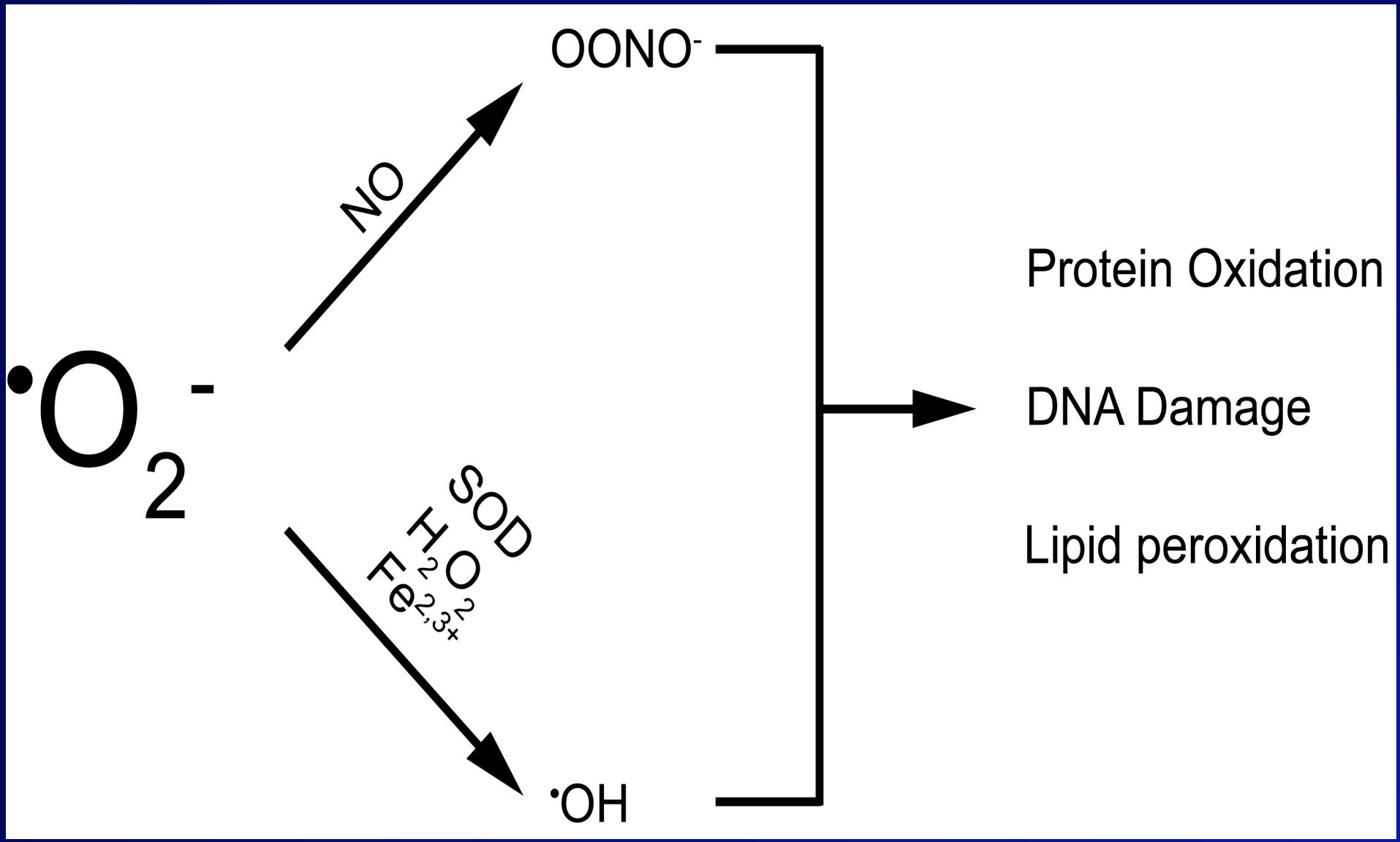
Lipofuscin in Human MR by TEM



Lipofuscin

- Nondegradable material primarily composed of oxidatively modified protein and lipid degradation residues
- Accumulation is usually seen in the aging heart and is considered to be the end product of ***excessive oxidative stress*** and overwhelmed protective mechanisms of the proteosome
- Deleterious effects on cellular function include triggering of mitochondrial pro-apoptotic pathways in cardiomyocytes and fibroblasts
- Oxidative stress enhances lipofuscin formation while administration of antioxidants decreases its formation

Why is XO Important?



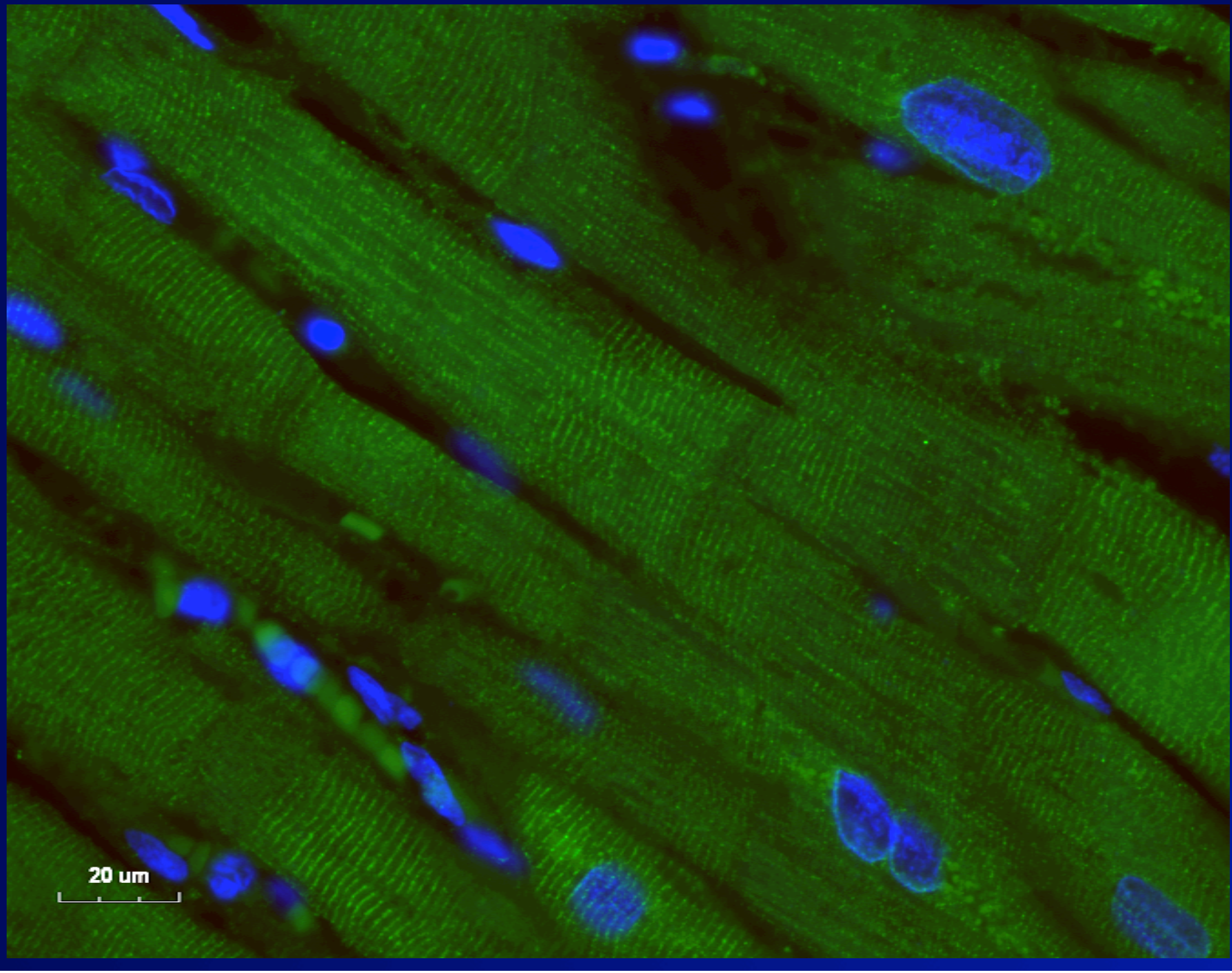
Xanthine Oxidase

- Xanthine oxidase is widely distributed: liver, gut, lung, kidney, heart, brain, and plasma
- XO is capable of producing superoxide and hydrogen peroxide
- XO may have profound effects on the myocardium

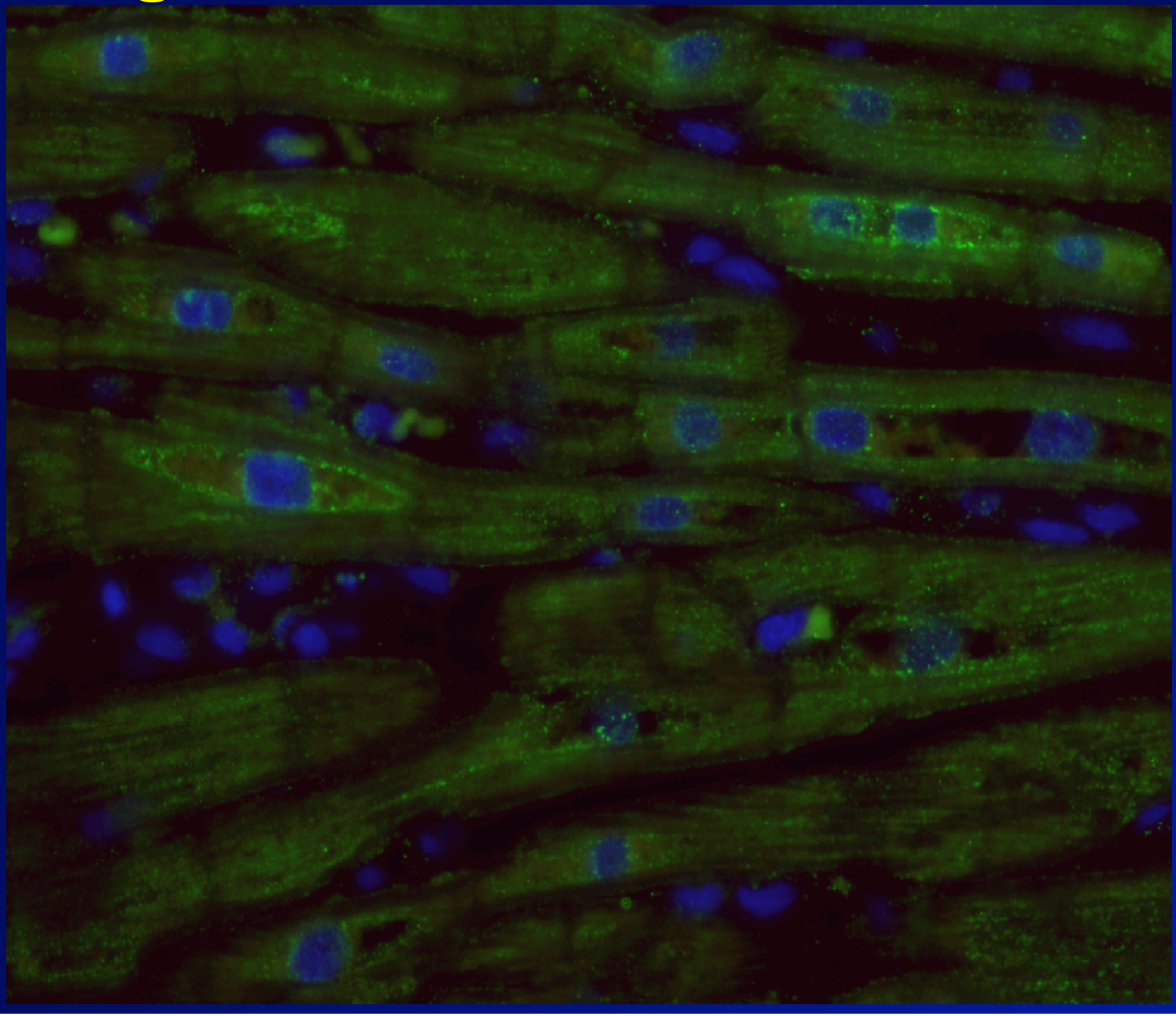
  - XO depresses myofilament sensitivity to calcium

  - co-localises with nitric oxide synthase in SR and can cause oxidative myofilament damage

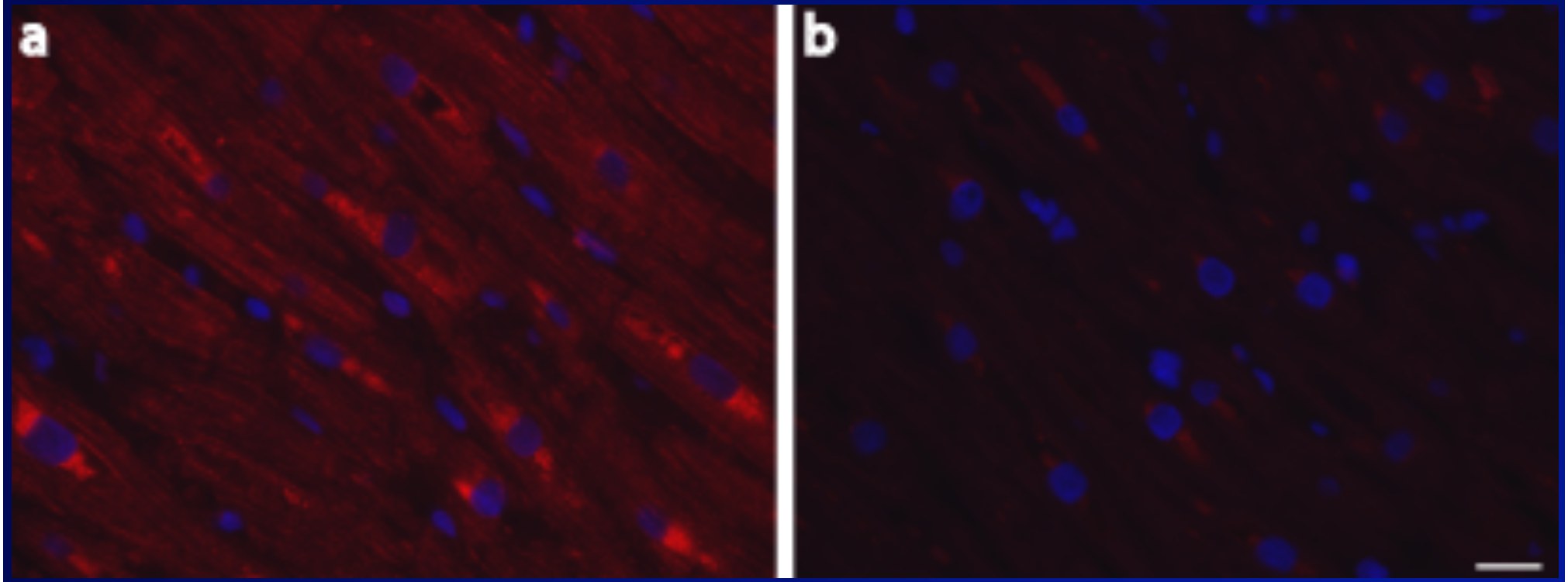
XO in Normal Human Cardiomyocyte



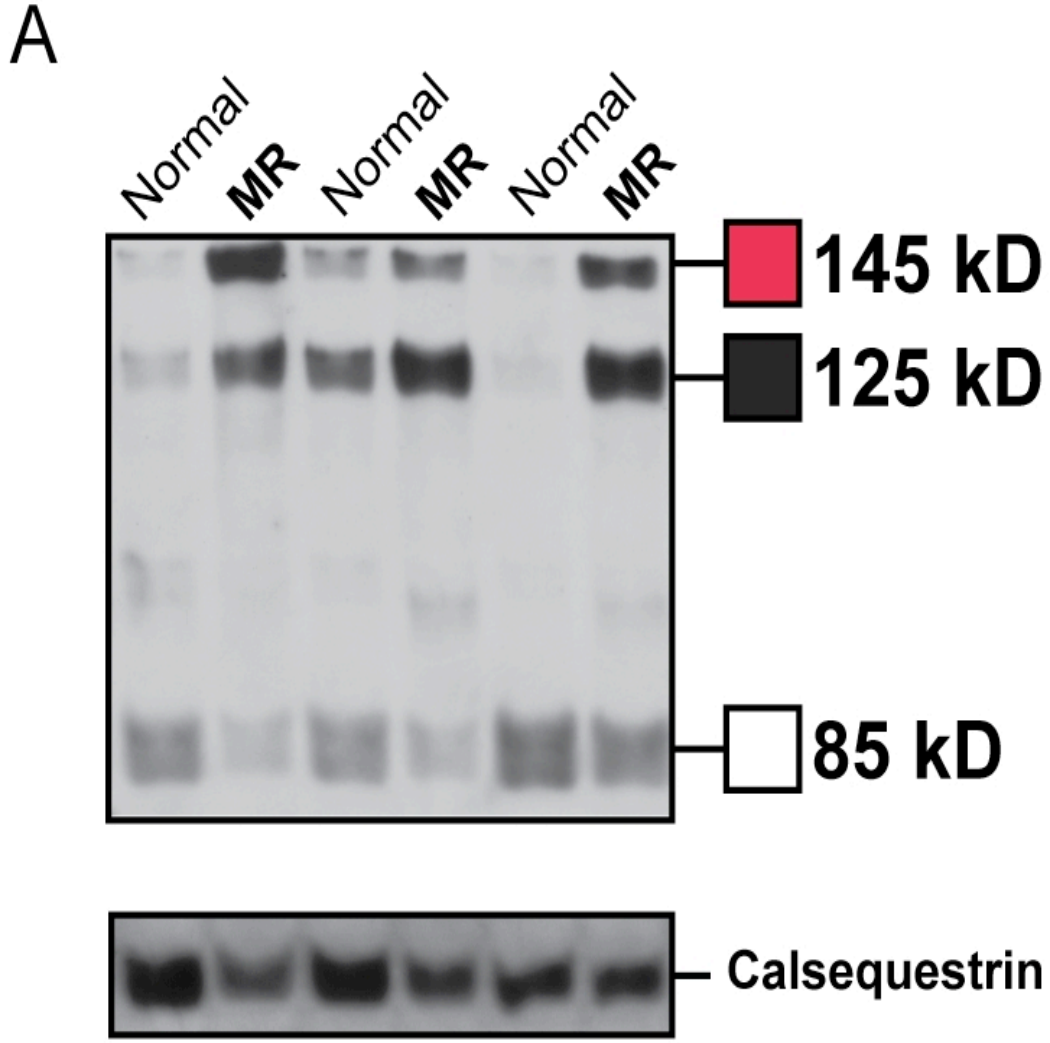
XO in Cardiomyocytes with Myofibrillar Degeneration in Human MR LV

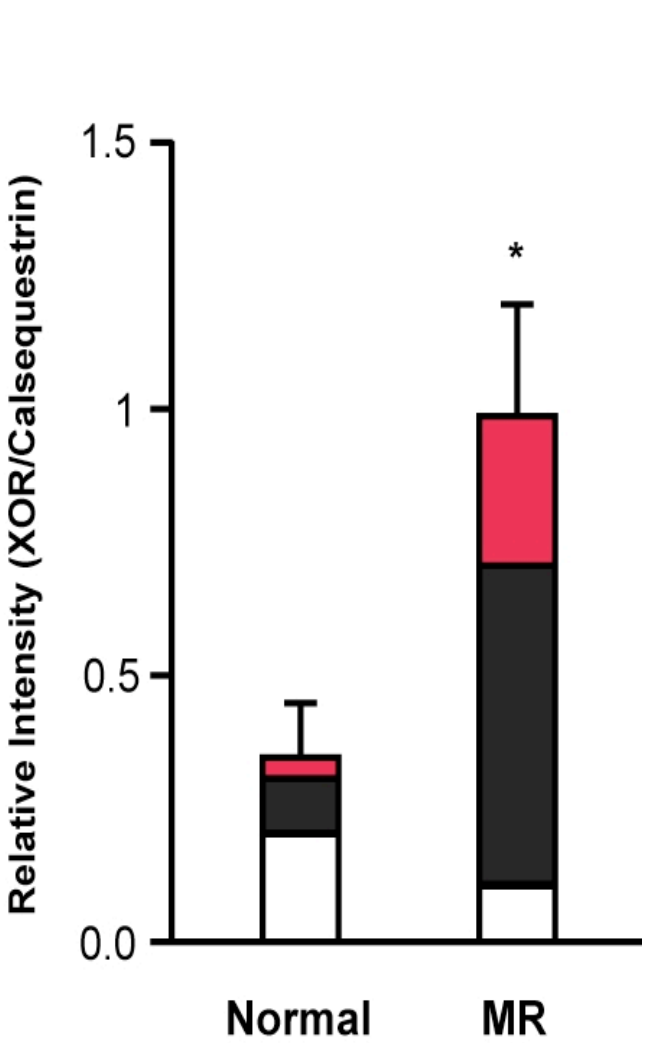


Increased Nitrotyrosine Staining in Areas of Lipofuscin Accumulation (a) with Corresponding Image With Immunoabsorbed Antibody (b) in MR LV



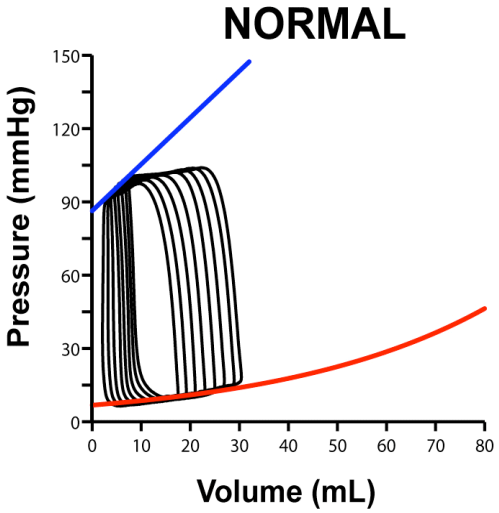
Increased Xanthine Oxidase in Human MR Left Ventricle

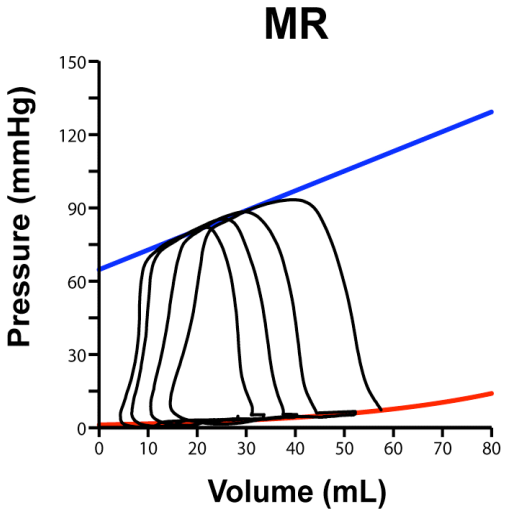




Ahmed and Gladden *JACC*, In Press, Feb 16, 2010

The Vicious Cycle of XO-Mediated Oxidative Stress in VO





Increased ATP Demand of Volume Overload

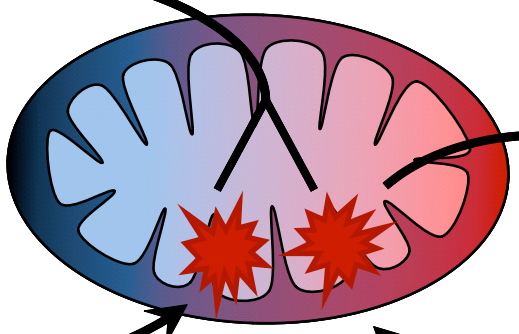
Increased catabolism of ATP/ADP

↓ATP/ADP Ratio

HX

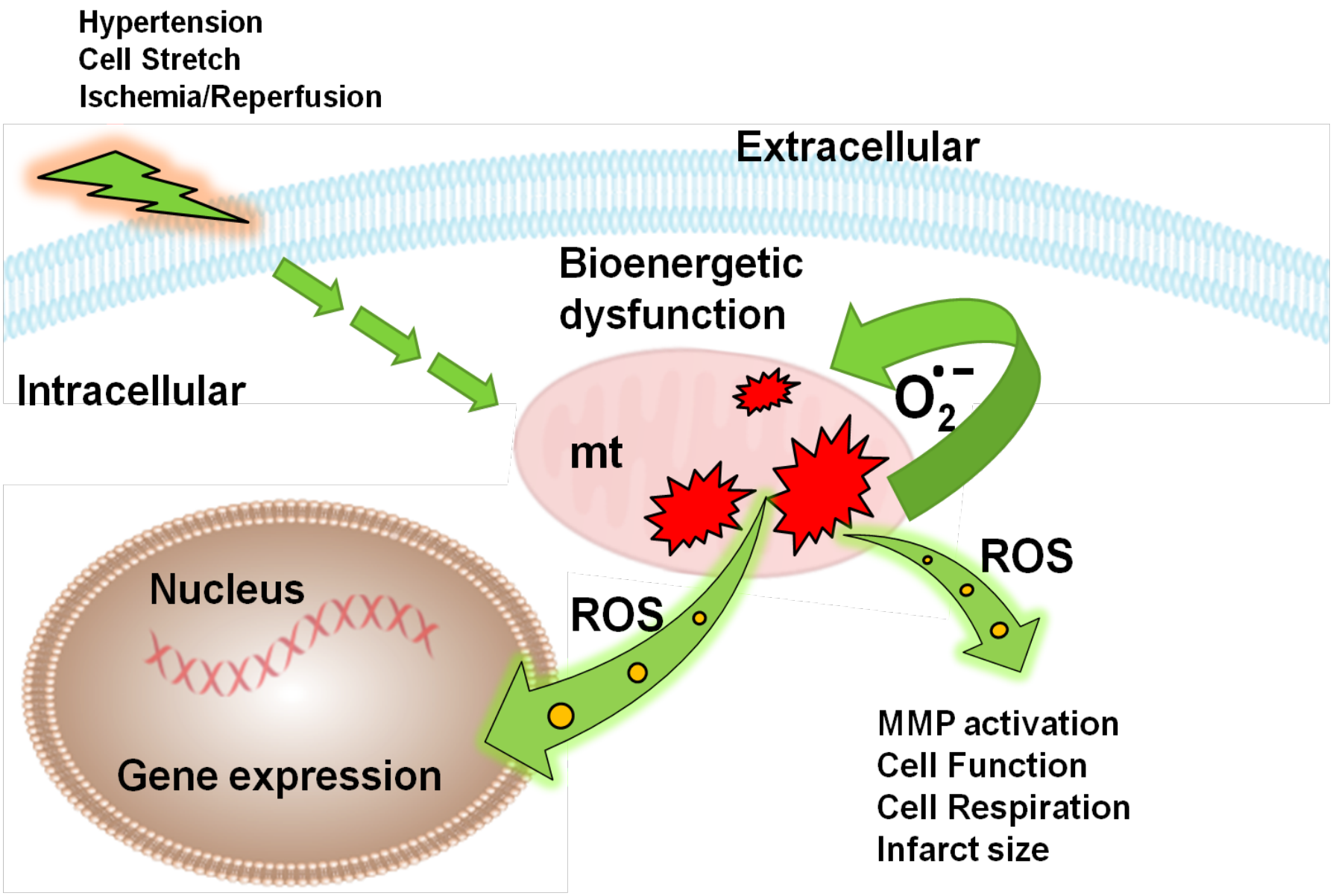
Xanthine Oxidase

$O_2^{\bullet -}$



$O_2^{\bullet -}$

Mitochondria as Targets and Sources of Oxidative Stress In Cardiovascular Disease



Future Directions in VO

- Determine the connection
  - –Increased oxidative stress
  - –Mitochondrial dysfunction and reserve capacity
  - –LV contractility

Translational Research

Translational Research