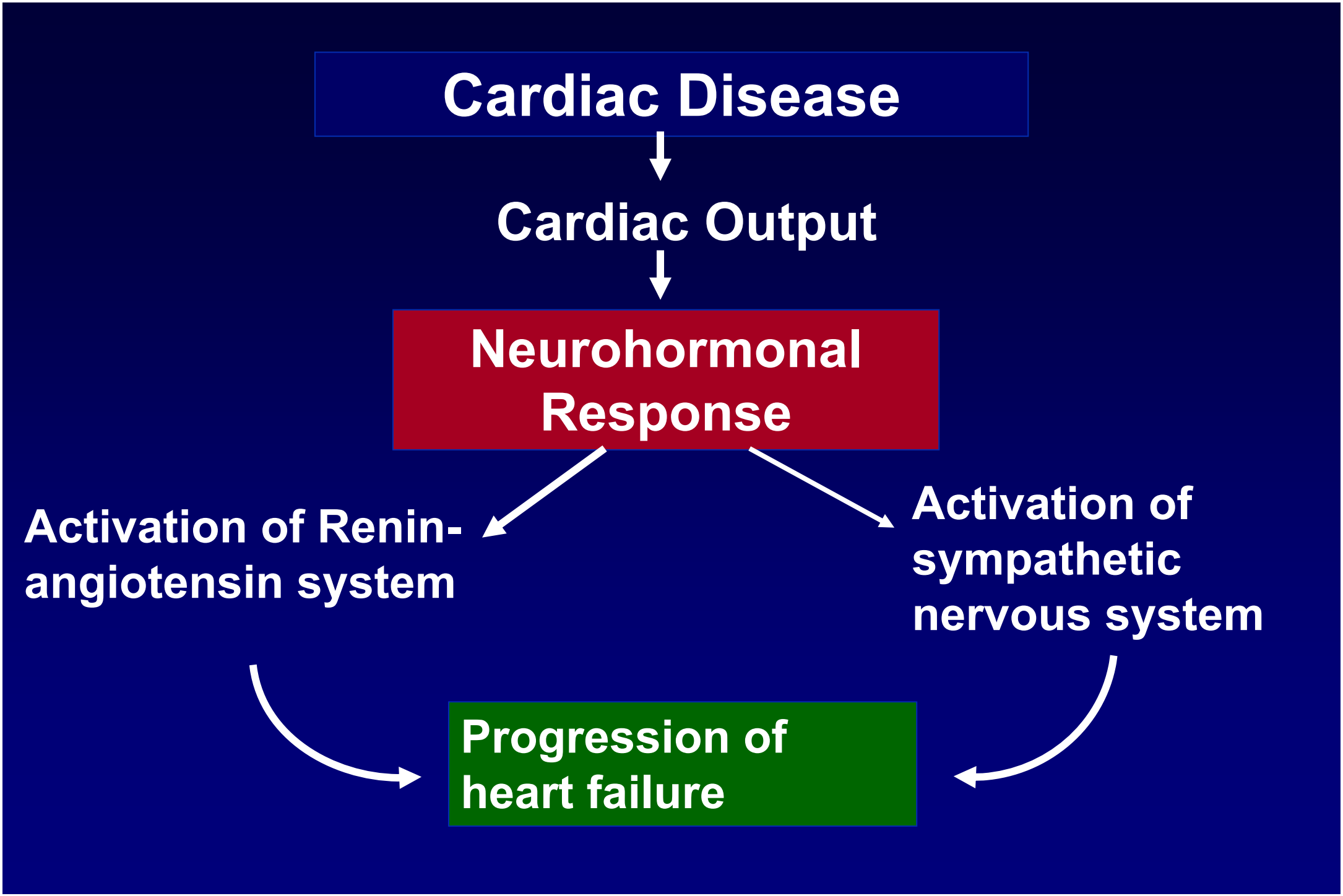
Role of Cellular Aging in Heart Failure

영남의대

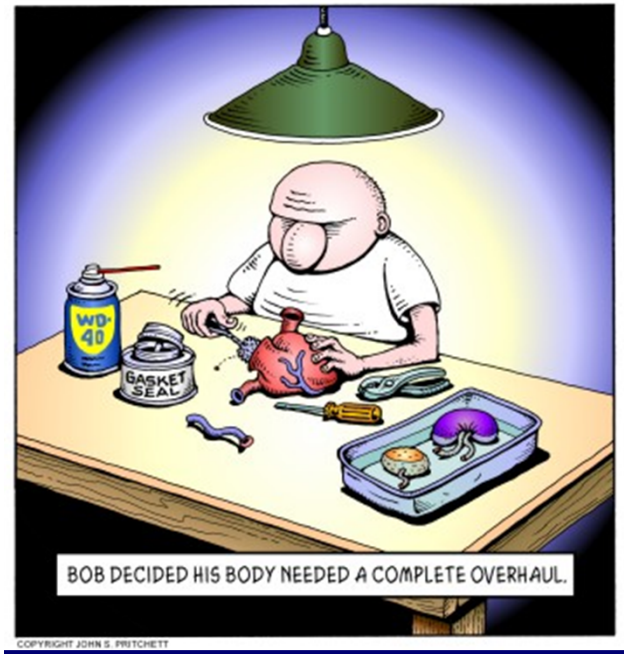
홍 그 루

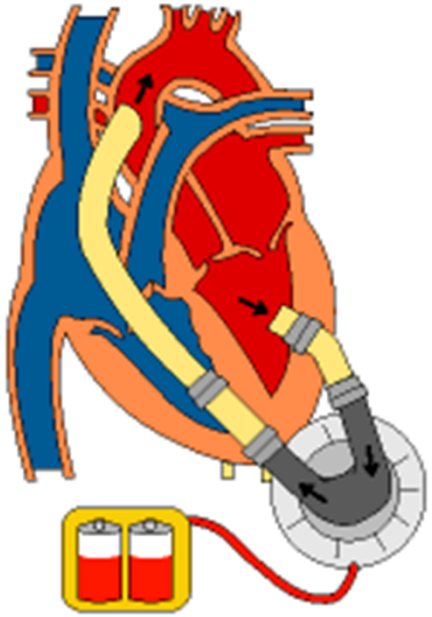
Definition of Heart Failure

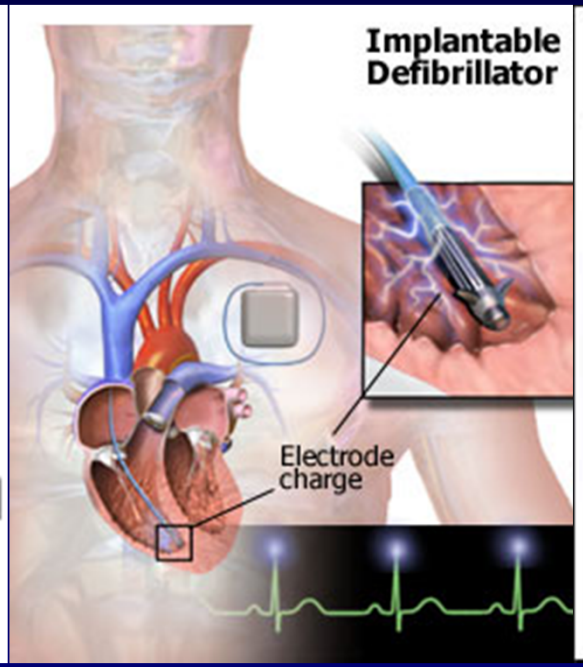
"HF is a complex clinical syndrome that can result from any structural or Functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood"

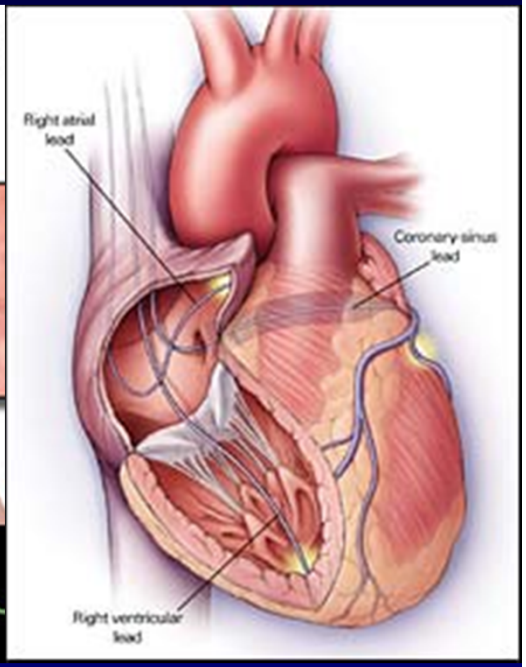

Cardiac Disease
Cardiac Output
Neurohormonal Response
Activation of Renin-angiotensin system
Activation of sympathetic nervous system
Progression of heart failure

Congestive Heart Failure
Multibillion $ Device/Tx Strategies









Transplant **LVAD** **AICD** **BiV Pacer**

Cost of CHF Therapy is Not Sustainable

Future of Cardiovascular Medicine in Heart Failure

- **Diseased based diagnosis and therapy**
  - Prevention and management of coronary artery disease, CHF, BP
  - Detection of preclinical disease/prevention strategies
- **Genomics**
  - How gene mutations and their regulation affect the development, and progression of heart disease.
- **Proteomics**
  - Expression, function and interaction of the human proteins, and their changes and effects in cardiovascular disease
- **Regenerative medicine**
  - Methods and effectiveness of strategies to regenerate heart muscle

Heart Failure & Aging

- **Congestive Heart Failure(CHF)**
  - Highly prevalent
  - Incidence & prevalence increases with age
  - Poor prognosis with 4-year survival of ~50%
  - Aging is one of the major risk factors
  - Susceptibility, age of onset, pace of progression
    : highly variable

  → conventional risk factor cannot explain this variability

Heart Failure & Aging

- **Aging**
  - – Age associated change lower threshold for the expression of HF
  - – Significant changes in diastolic function, hypertension, atherosclerosis, valve calcification, senile amyloid deposition
  - – Molecular mechanism of aging heart
    - → accumulation of DNA damage & telomere attrition
    - → senescent cell↑ with decreased function

Understanding Cellular Aging is Essential:

Disease Cell Mechanism

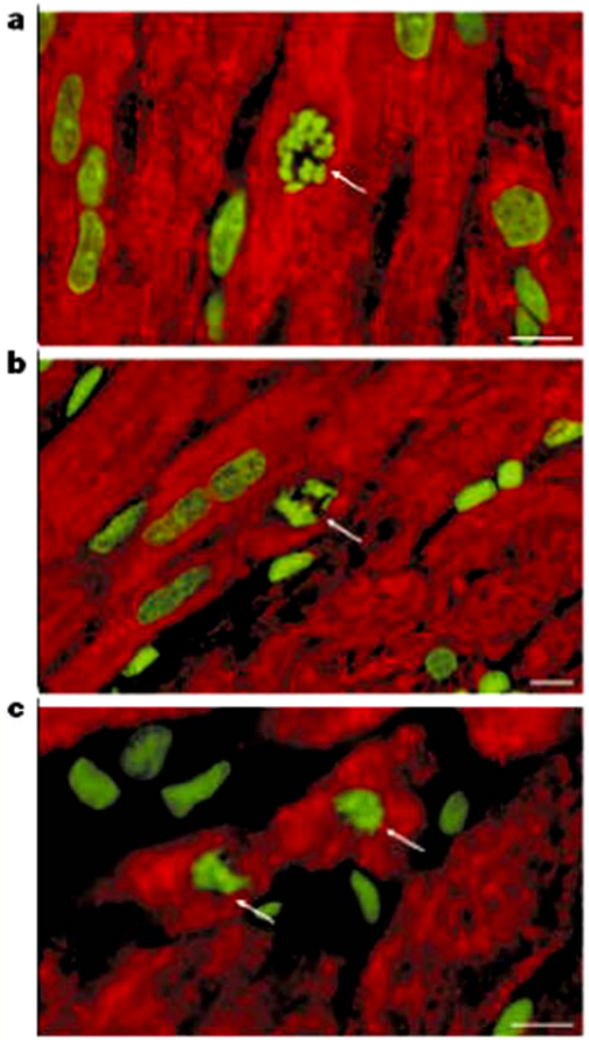
DIAGNOSTICS
- Diagnosis
- Prognosis

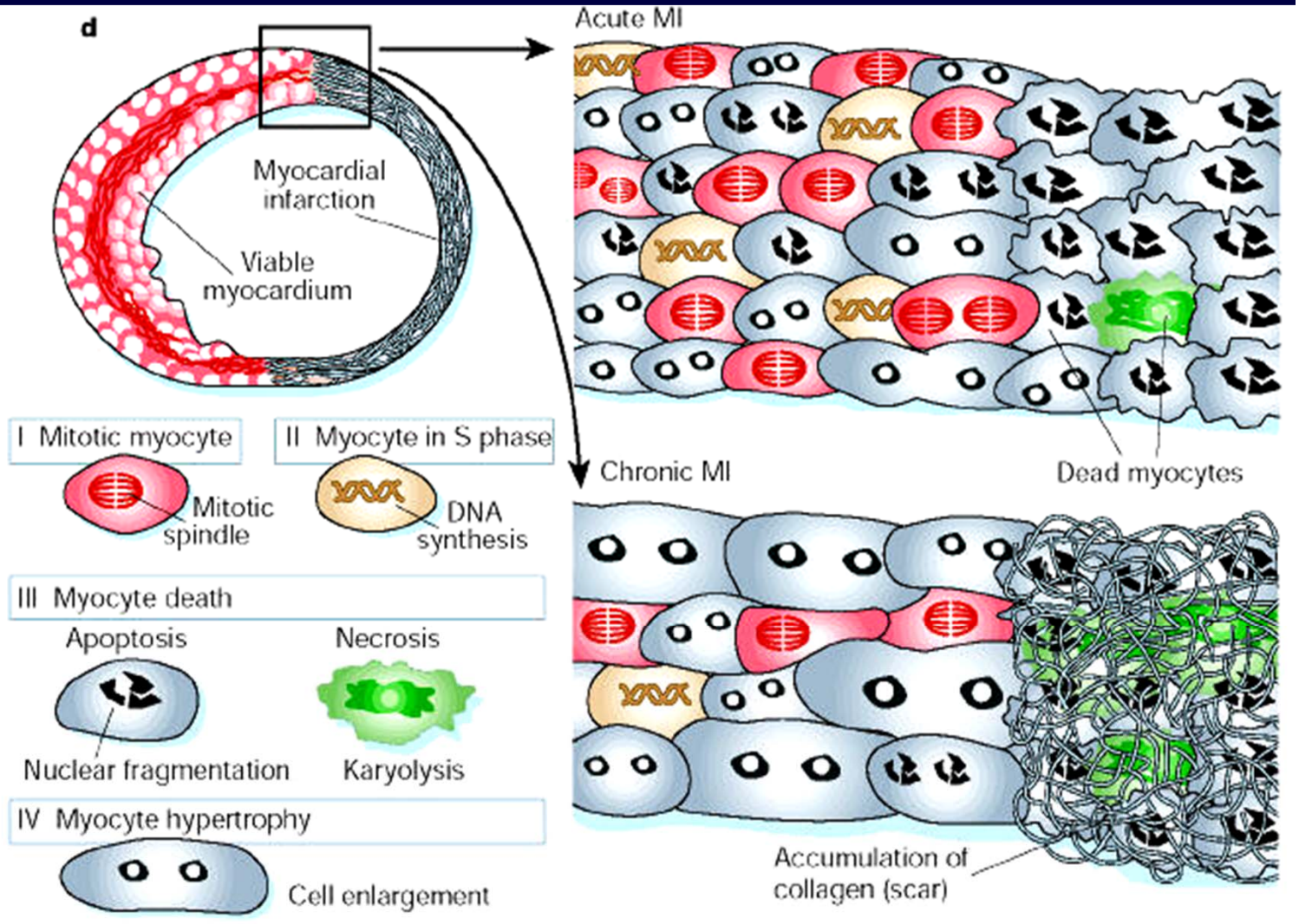
THERAPEUTICS
- Pharmaco-genomics

(Genome-based drug design)

PREVENTION
- Reverse or prevent disease

Myocytes Changes in MI
Need for Regenerative Rx



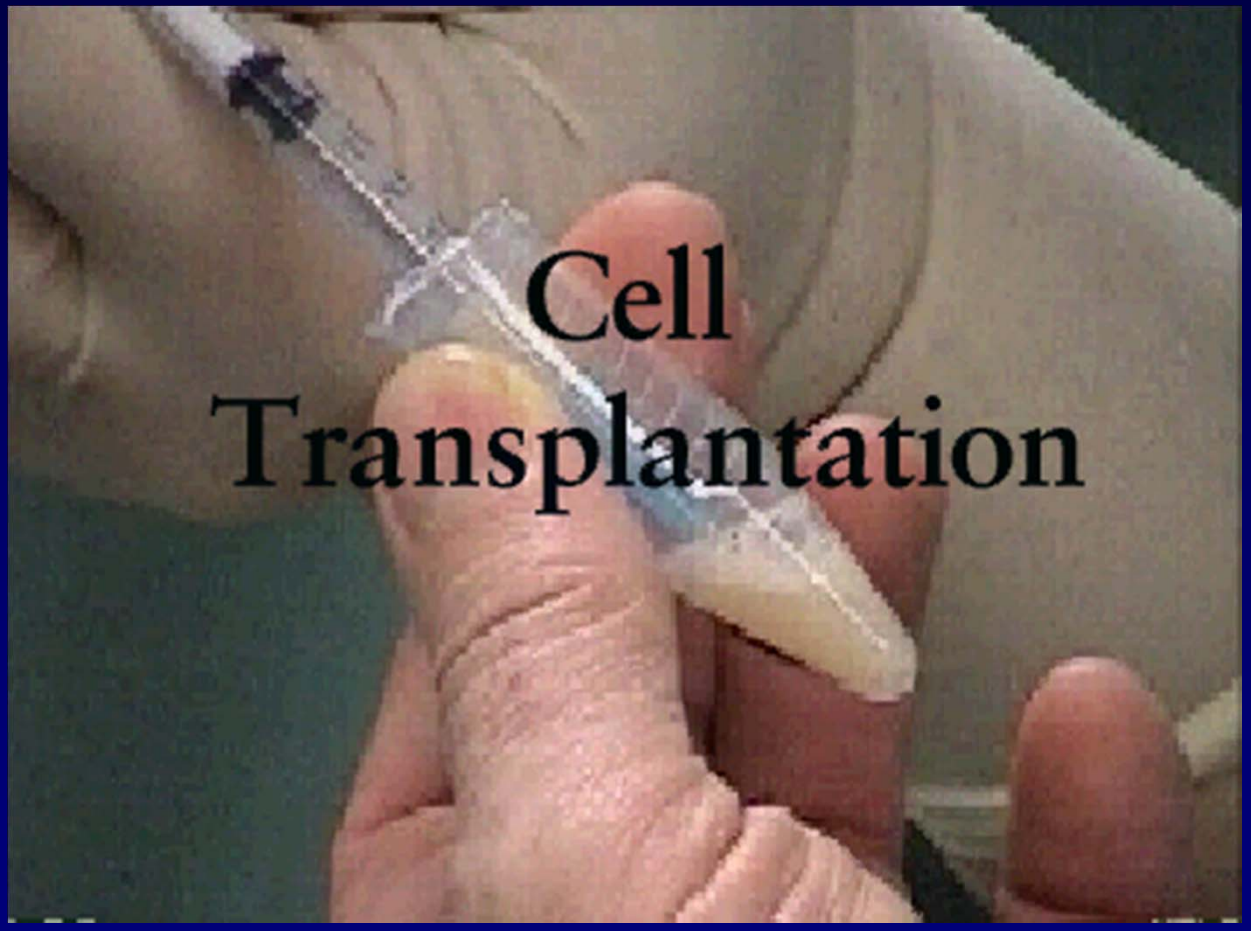


Anversa P. Nature 415; 240 2002

Cellular therapy of MI

- Transplantation of embryonic stem cells
- Human umbilical vein endothelial cells
- Adult bone marrow cells (BMC)
- Implantation of skeletal myoblasts
- Bone-marrow-derived cardiomyocytes
  - Challenge is to deliver them to the right place
  - Need to increase degree of cell survival by improving neovascularization

Porcine Model of Myocardial Infarction



Porcine Model of Myocardial Infarction

Trilogy of Aging Hearts

- Left ventricular hypertrophy
- Heart failure
- Atrial fibrillation

Functional changes of the aging heart

- Myocardial stiffness↑

  → LVEDP↑

  → Early diastolic filling↓

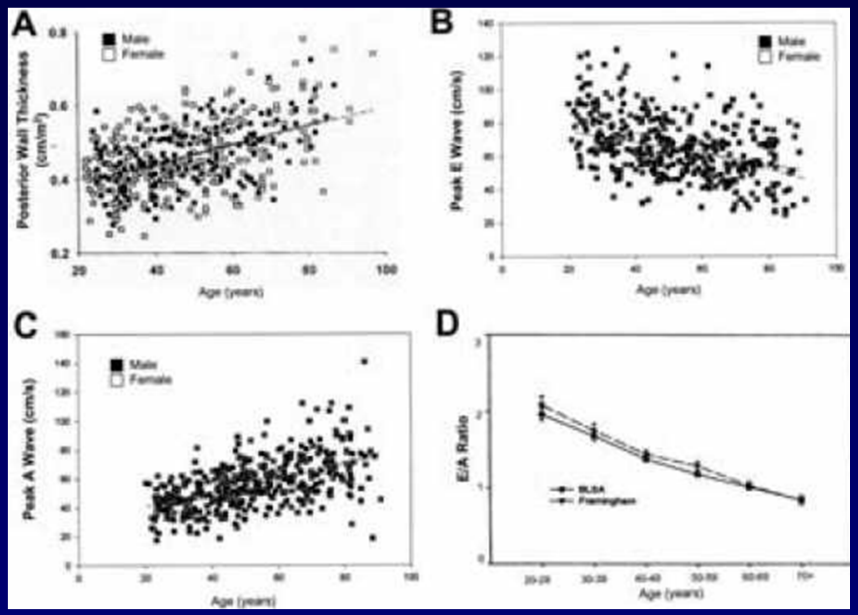
- During exercise
  - Stroke vol↑ through cardiac dilatation (EDV↑)
  - Lesser increase in HR, greater increase in BP

    : Response to catecholamine↓, SA node pacemaker cell↓

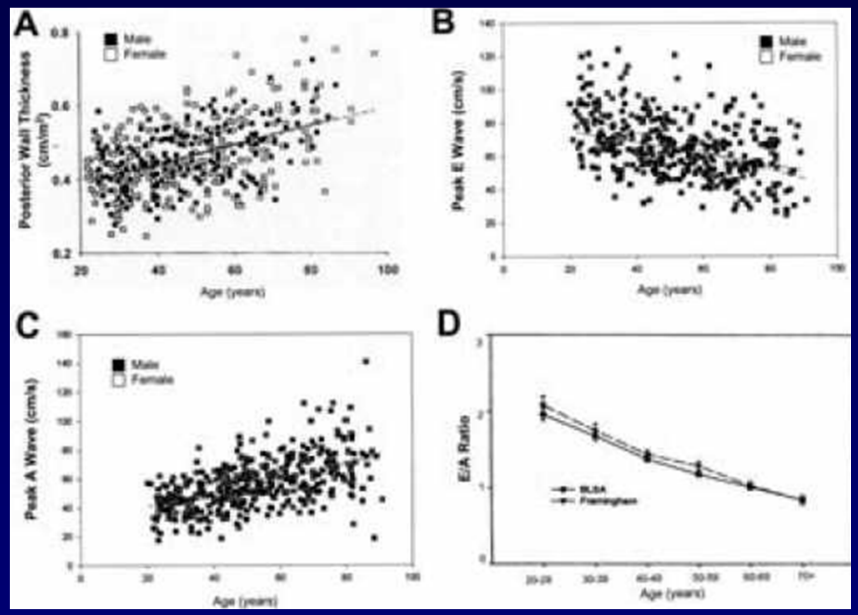
- Aortic distensibility↓

  → isolated systolic HTN

Aging on Human Heart



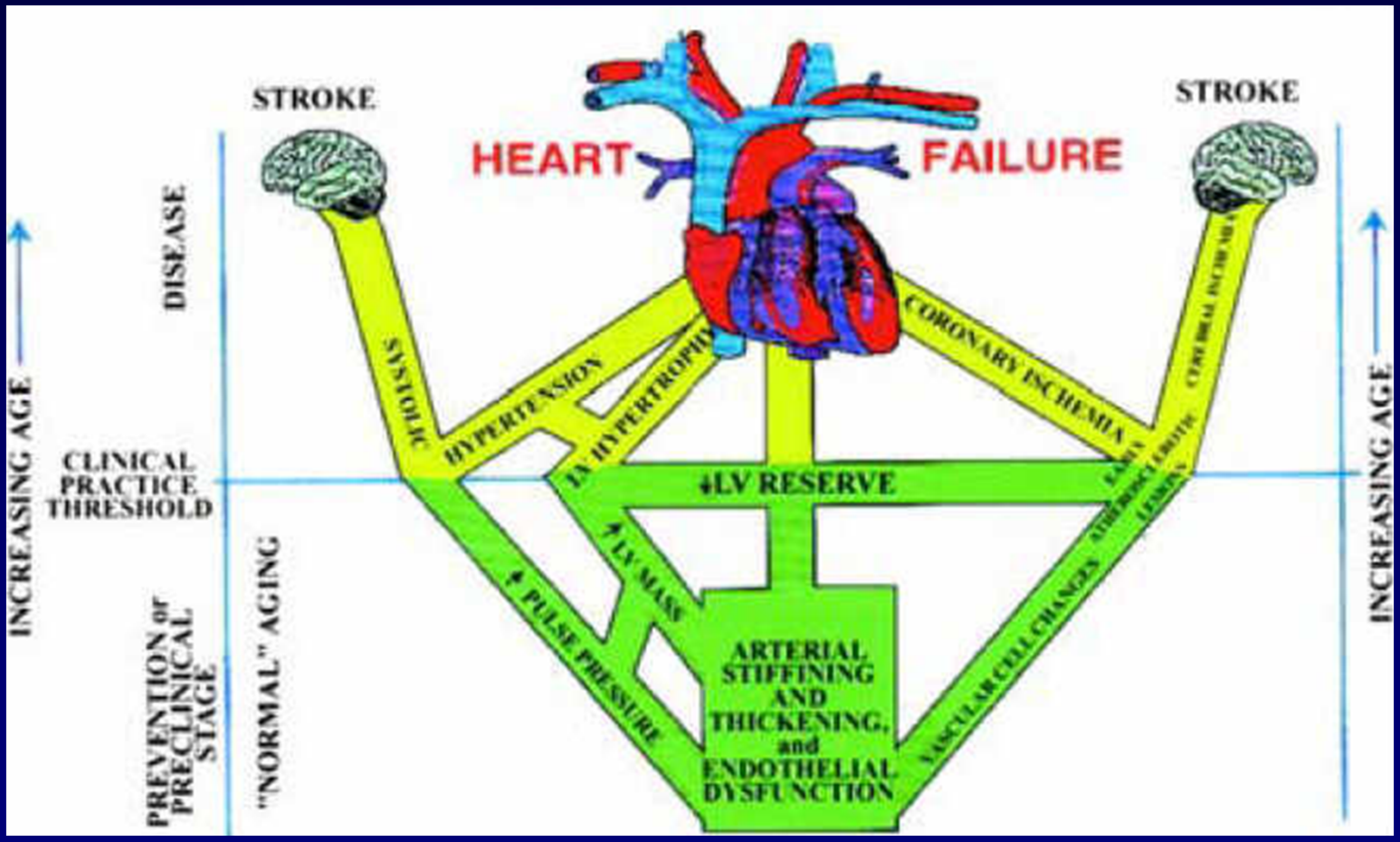
Systolic function



Diastolic function

Circulation 2003:107; 346

Aging on Human Heart



Aging on Human Heart

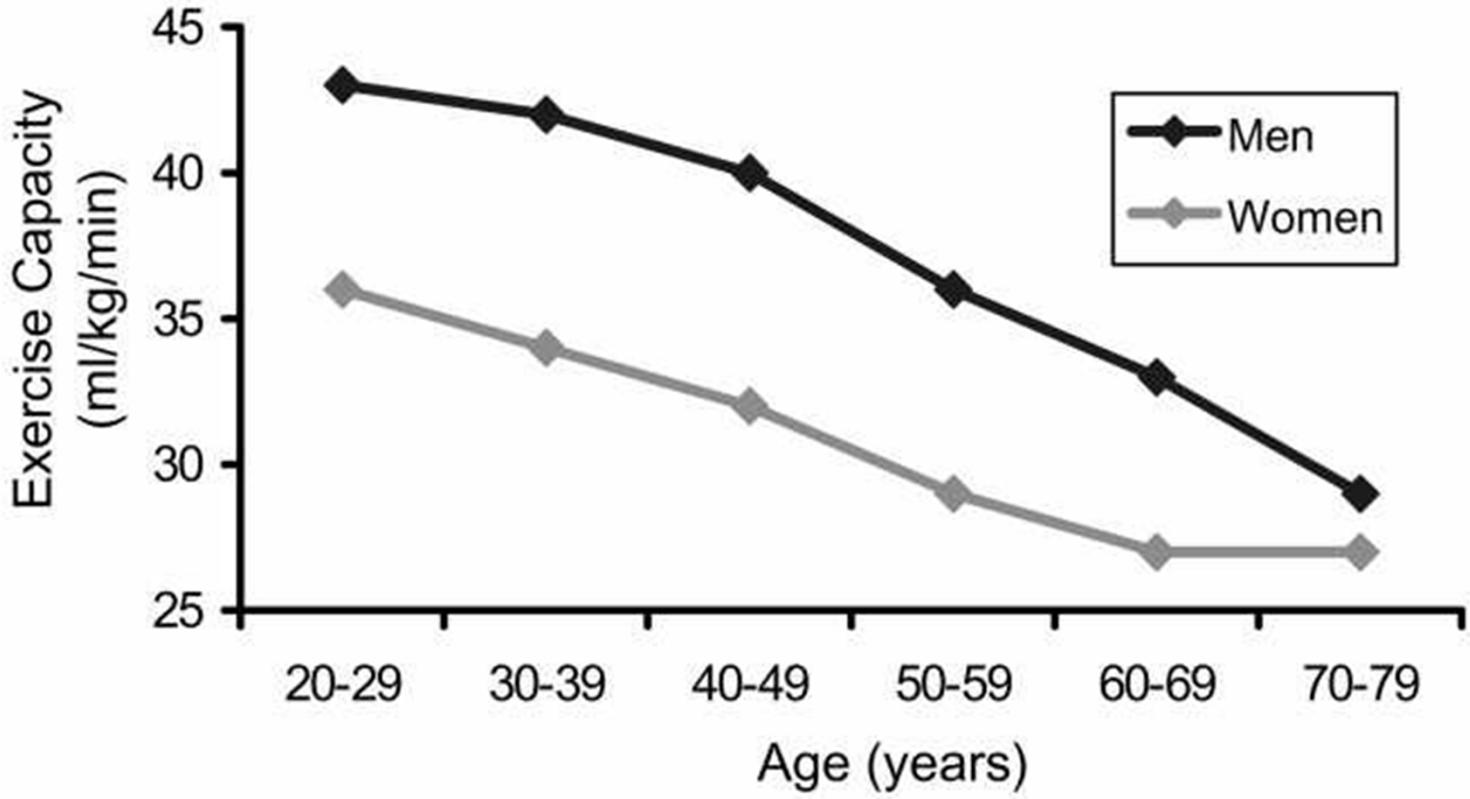
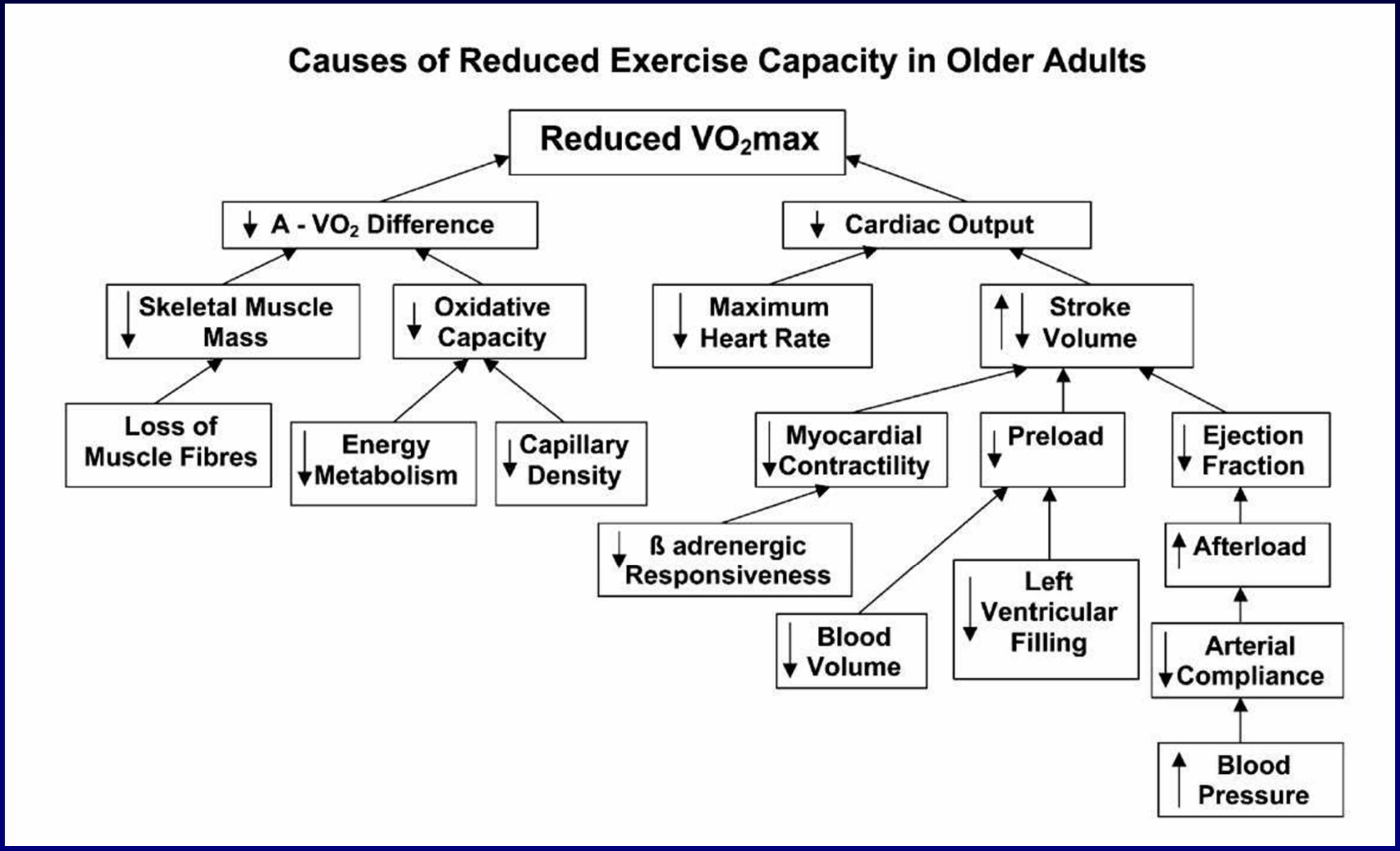


Fig. 1. Maximum exercise capacity declines with advancing age.

Aging on Human Heart



Morphological and cellular changes of the heart

- Most components of the myocardium undergo structural changes
- Myocytes loss
  - Hypertrophy of remaining myocytes
  - Apoptosis or programmed cell death
- Collagen content, fibrosis, senile cardiac amyloid deposition, lopofuscin↑

Morphological and cellular changes of the heart

- **Cellular changes**
  - Increasing age does not result in an increase in left ventricular mass
  - 35% of myocytes in ventricles is lost between the age of 30~70
  - May be related with reduction of capillary density that causes ischemic injury
  - Compensatory mechanism makes the volume of remaining myocytes increase

Morphological and cellular changes of the heart

- **Molecular changes**
  - Cellular and molecular alterations underlie the functional abnormalities of the aging myocardium
  - Represent adaptive compensatory phenomena that result in energy preservation
    - Defect in SR Ca2+ ATPase pump activity
      - control the rate of Ca2+ reuptake into the SR during relaxation
    - Significant reduction in cardiac SR Ca2+ ATPase protein concentration

    → Significant prolongation of isovolumetric relaxation occurs.

Morphological and cellular changes of the heart

- Prolonged contraction and relaxation

  - changes in calcium homeostasis

- Troponin, myosin production↓
  - Prolonged contraction with decreased force of myofilaments
  - Down regulation of genes involved in contractile activity
- Mitochondria
  - Larger but less efficient , ATP production per cell↓

Deficient Regulation Mechanisms

- Deficits in sympathetic modulation of heart rate and LV contractility
- Elaboration of catecholamines
- Impaired responses to beta-adrenergic receptor stimulation
- Impaired vascular-ventricular load matching
- Decreased heart rate variability

Aging on Human Heart

Cardiovascular changes associated with aging and their clinical consequences

	Change associated with aging	Clinical consequences
Arterial wall	Increased thickness	Increased systolic blood pressure, afterload, and pulse wave velocity
	Reduced compliance	Widening of pulse pressure
Myocardium	Loss of myocytes Increased ratio of left ventricular wall thickness to chamber size	
Cellular changes	Reduced sarcoplasmic reticulum $Ca2^{+}$ATPase protein concentration Reduced reuptake of $Ca2^{+}$ into sarcoplasmic reticulum	Prolongation of myocardial relaxation Increased isovolumetric relaxation time
Systolic function	Preserved	
Diastolic function	Reduced early diastolic filling Increased late diastolic filling Reduced myocardial diastolic velocities	Reduced E velocity Prolonged E deceleration time Increased A velocity Reduced E′ and E′/A′

Characteristics of Aging Heart

- **Reduce cardiovascular reserve and increasing the risk of heart failure**
  - Age related changes in cardiovascular function plus the high prevalence of hypertension and CAD
- **Increase in the prevalence of heart failure with normal left ventricular systolic function**
  - Significant reduction in early left ventricular filling

Characteristics of Aging Heart

- **Increase in left atrial size and pressure**
  - High prevalence of atrial fibrillation
  - Further impairs LVdiastolic filling by reduced atrial contraction
- **Reduced b-adrenergic responsiveness**
  - Limits heart rate and the contractile response to stress
  - Non-compliant left ventricle is unable to accommodate increases in intravascular volume
  - Pulmonary edema occurs when receiving intravascular fluid or left ventricular function is impaired

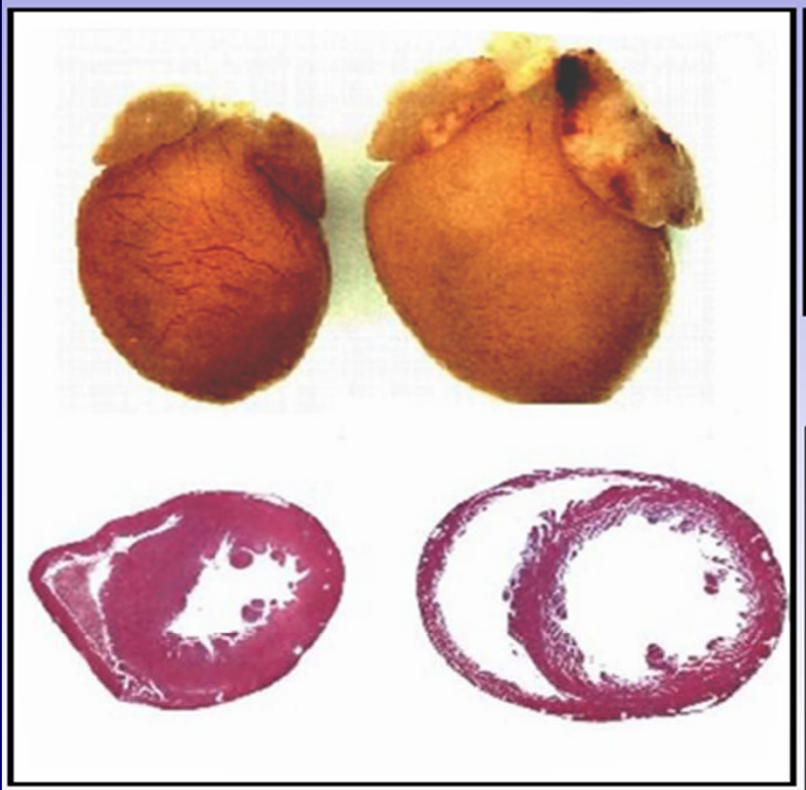
Cardiomyocyte Turnover During Aging

- DNA of cardiomyocytes continues to be synthesized many years after birth
  - Cardiomyocyte DNA synthesis decreases with age
  - Cells in human heart renew well into adulthood
  - ~1% cardiomyocyte renewal rate at the age of 25 and 0.45% at the age of 75
  - At the age of 50 years, 55% of the cardiomyocytes remain from the time around birth

Validated Animal Models of HF: Test Genomic Rx

Morphology

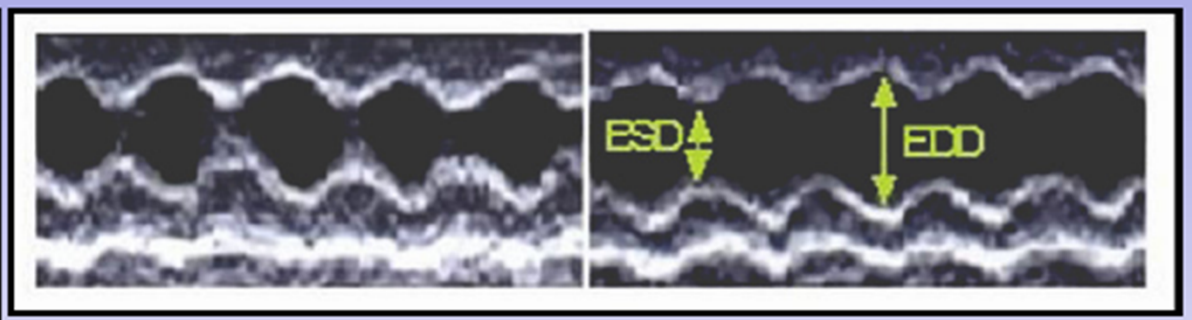
WT Mouse HF Mouse



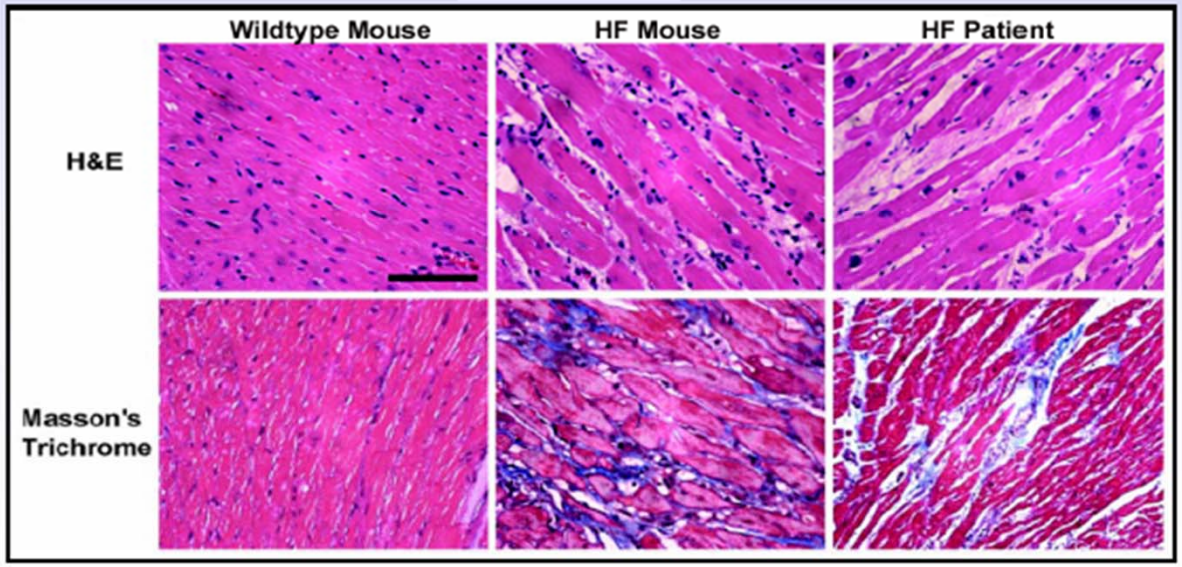
Mutant mouse hearts exhibit similar phenotype to human disease

Echocardiography

WT Mouse HF Mouse



Histology



Schmitt JP, MacLennan DH, et al. Science 2003; 299:1410-3

Cardiomyocyte Turnover During Aging

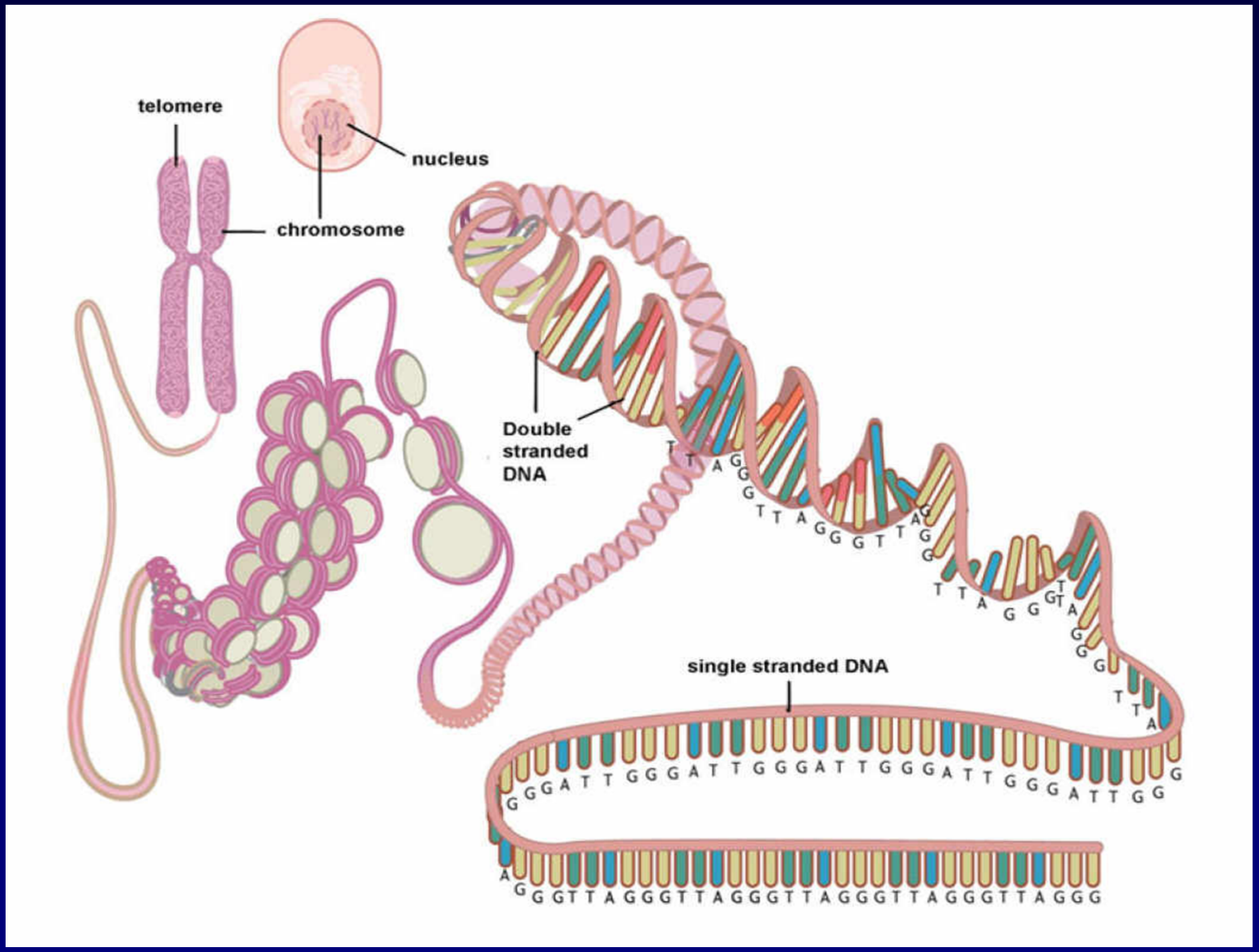
- Stem cells do not replace adult mouse cardiomyocytes during at least 1 year of aging
- If at a later stage, stem contribute to cardiomyocyte renewal or regeneration
- Precursor cells participate in the formation of new cardiomyocytes after injury

  - In the setting of myocardial infarction or pressure-overloaded hearts
- Bone marrow and adipose tissue are pool of multiple type of progenitor cells

Telomeres and heart failure

- **Telomeres**
  - DNA structures made up of tandem repeats (TTAGGG in humans)
  - Located at the end of chromosomes
  - Critical function as protective cap, preventing the chromosomal ends
- **Telomere length**
  - Measure from leukocyte or cardiac tissue
  - Cumulative replicative history, exposure to environmental factors
  - Strongly associated with date of birth (chronological) age
  - Biological / cellular aging
  - Highly variable among individuals of the same age
  - Hereditable from parents

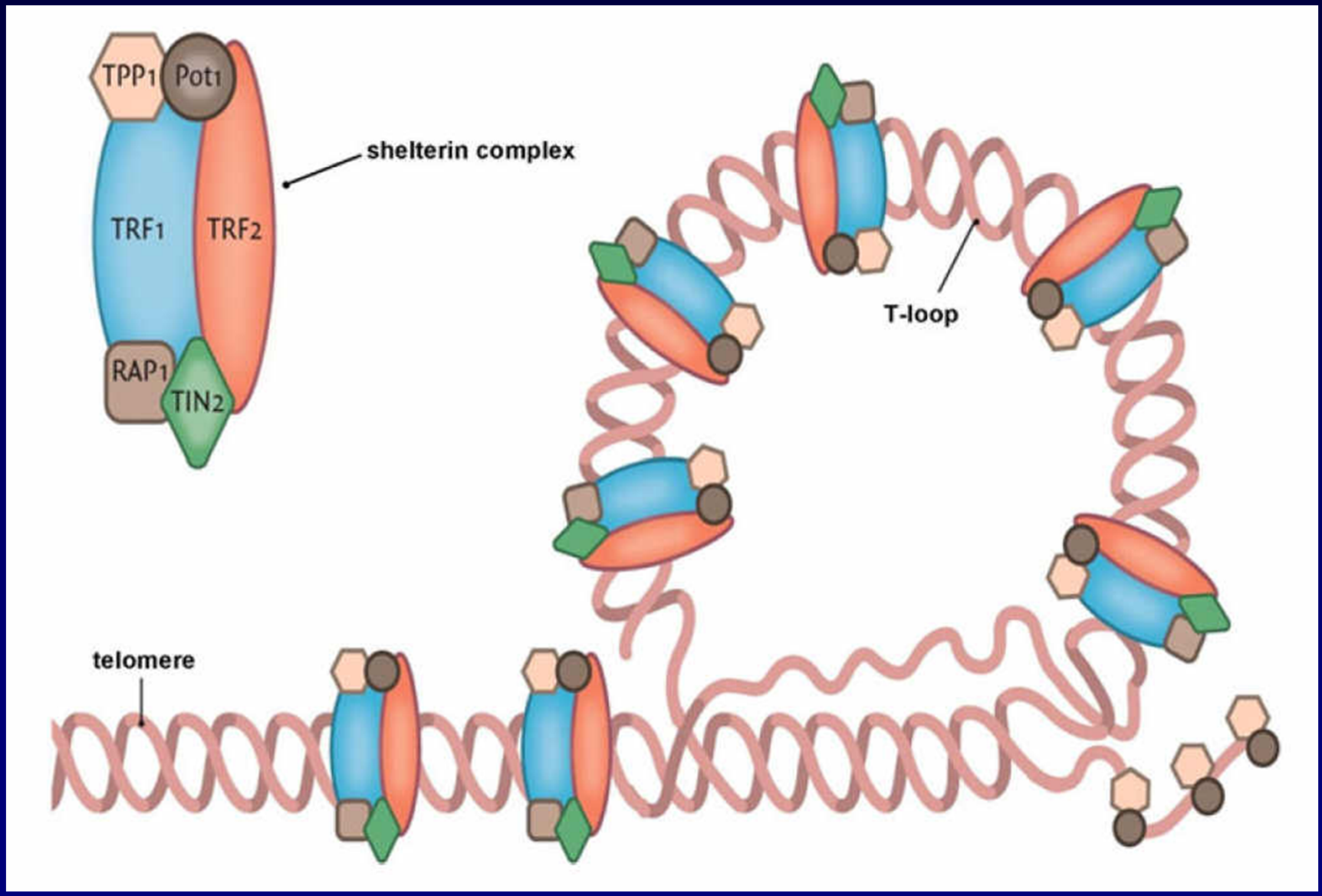
Telomeres


telomere
nucleus
chromosome
Double stranded DNA
single stranded DNA

Telomeres and heart failure

- **If telomere reach critical short length**
  - Cell will no longer divide, become dysfunctional or senescent
- **Environmental factors associated with telomere length**
  - Oxidative stress (smoking, UV radiation)
- **Disruption of telomere binding-binding protein**
  - Chromosomal instability, senescence, apoptosis
- **Telomerase**
  - Ribonucleoprotein enzyme
  - Elongation of telomere sequence by addition of nucleotides to their ends
  - Detectable in stem cell, germline cell, malignant cell, epithelial and lymphoid cells

Telomeres


TPP1
Pot1
shelterin complex
TRF1
TRF2
RAP1
TIN2
T-loop
telomere

Telomeres and heart failure

- **Telomere length is associated with CHF, HTN, DM, premature MI, RAAS activation**
  - Shorter telomeres (25% shorter than controls)
  - Associated with severity of CHF symptoms
  - Worse renal function(powerful predictor of outcome in CHF)
  - Associated with 5% reduced LV ejection fraction
- **Cardiomyocytes with shortened telomeres**
  - positive for p16INK4a

  (marker for cellular senescence : large in aged diseased heart)

Telomeres and heart failure

- **Dose short telomere length directly contribute to the development and progression of heart failure?**

  - Telomere dysfunction is a common pathway of cardiomyocyte senescence and dysfunction

  - Diminished regenerative capacity (exhaustion of progenitor pool with repair capacity)

  - Fifth-generation telomerase knockout mice → severely reduced telomere length → severe LV failure

  - Stabilize telomeres by over expression of TRF2 prevent doxorubicin –induced cardiac apoptosis

- **However, convincing evidence in humans for a causal role of telomere is lacking.**

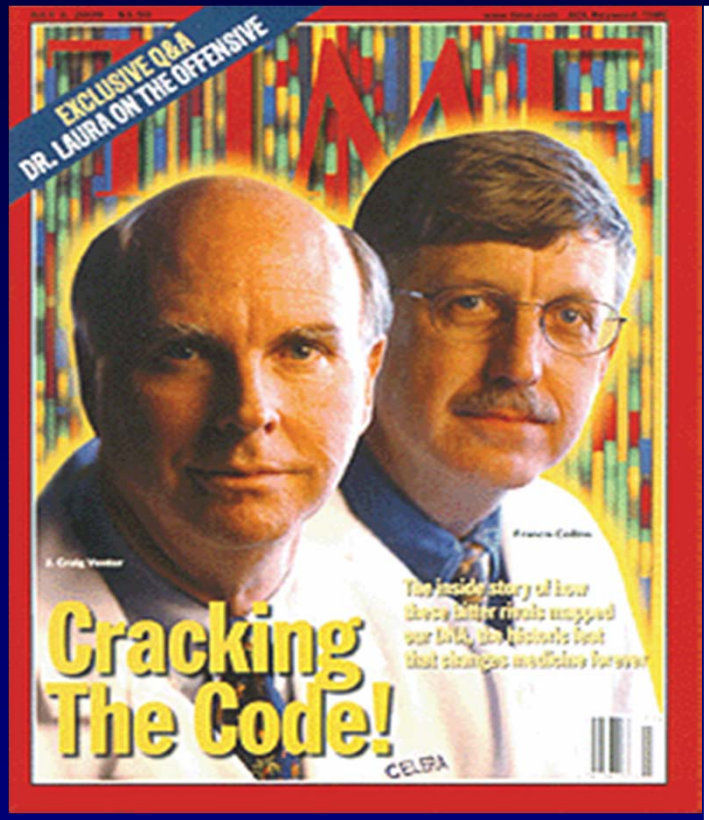
Conclusions and Future Perspectives

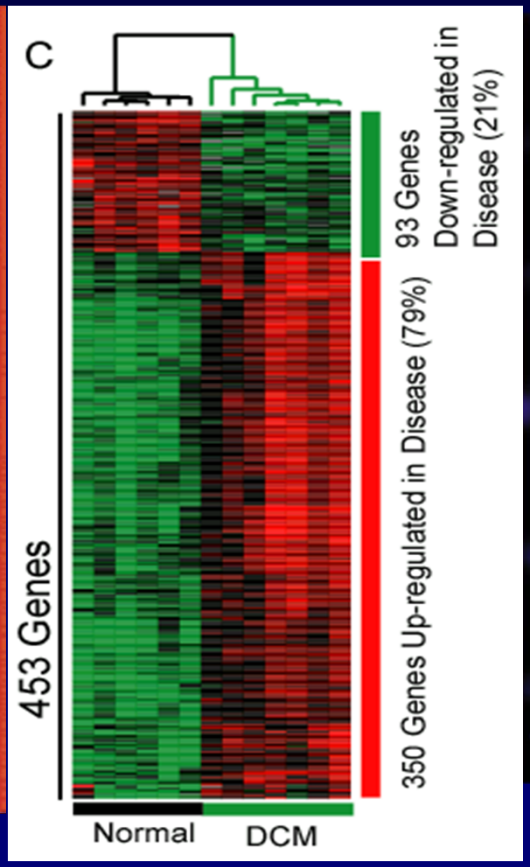
- Therapeutic strategies to improve myocardial function and outcome in CHF are urgently needed
- Cellular aging process including telomere biology might be involved aging and age-associated pathology

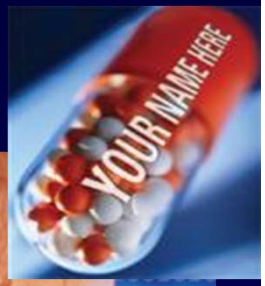
Conclusions and Future Perspectives

- Large, prospective, longitudinal studies to provide the association between telomere length and CHF are needed
  - To develop novel strategies in the treatment and prevention of CHF, for example stem-cell modifying

The Future: Cellular, Genomics, Proteomics and Personalized Rx







Human Genome, Gene chips, Tailored therapy