The Cardiovascular System and Aging-
Is it Built to Fail?

Francis G. Spinale, MD, PhD
Professor of Surgery and Cell Biology and Anatomy

University of South Carolina School of Medicine
Veterans Affairs Medical Centers, Columbia, South Carolina

March 2012
OUTLINE

- Review the Causes of HF in the Elderly

- Identify Factors Causing HF in the Elderly

- Demonstrate that Enzyme Systems that Regulate CV Function Change with Age

- Report on New Blood Tests and Approaches
Normal Left Ventricle

Hypertension
Concentric Remodeling

Coronary Artery Disease
Eccentric Remodeling
AGING

Normal Left Ventricle

Hypertension

Coronary Artery Disease

Concentric Remodeling

Eccentric Remodeling
Prevalence of Hypertension and MI by Age and Sex

**HYPERTENSION**

- **Percent of Population**
  - Ages: 20-34, 35-44, 45-54, 55-64, 65-74, 75+
  - Men vs. Women

**CORONARY ARTERY DISEASE**

- **Heart Attacks (x 1000)**
  - Ages: 29-44, 45-64, 65+
  - Men vs. Women

Prevalence of Hypertension and MI by Age and Sex
CDC/NCHS and NHLBI 1999-2002
Burden of Disease: Transition of Hypertension to Failure
Aging and the Vasculature

- Central vessel wall thickening
- Endothelial dysfunction
- Smooth Muscle cell proliferation
- Changes in the Matrix

- Impaired distensibility-
  - “Stiffening of Vasculature”
Aging and the Heart

Structural Changes
- Heart Weight ↑
- Cardiomyocyte dimensions ↑
- Matrix Composition ↑
- Cardiac sympathetic nerve supply ↓
Aging and the Heart

Structural Changes

- Heart Weight
- Cardiomyocyte dimensions
- Matrix Composition
- Cardiac sympathetic nerve supply
Myocardial Collagen Matrix -2012

- Influences LV Geometry
- Coordinates Contraction
- Interface for Integrins-Intracellular Signaling
- Reservoir of Bioactive Signaling Molecules
- Dynamic Changes Following Mechanical/Biological Stimuli
The Aging Heart and Fibrosis

Structure

Increased Collagen

Normal

Function

LV Diastolic Pressure (mmHg)

LV Diastolic Volume (mL)

Increased Stiffness

Substrate

Diastolic Heart Failure

Increased Collagen

Normal
Matrix Remodeling

**Matrix metalloproteinases (MMPs)**

Family of zinc-dependent enzymes responsible for turnover of the ECM, facilitating tissue remodeling.

**Tissue inhibitors of MMPs (TIMPs)**

Endogenous inhibitors that regulate activity of MMPs by binding to their active site.
Golgi Apparatus

Pro MMPs

Serine Proteases

Pro-Peptides

Integrin

Nucleus

Golgi Apparatus
TIMPS
Active MMPs
Pro-MMPs
Serine Proteases
Pro-Peptides
Integrin
Golgi Apparatus
Nucleus
Microdialysis Instrumentation

LV

LAD
Interstitial MMP Activity

Fluorescence Emission (360 nm)

Myocardial Arrest

Myocardial Reperfusion

MMP Activity (ng/hr)

# p < 0.05 vs. Myocardial Arrest

Steady State

Cross Clamp on

Cross Clamp off

#
Dynamic changes in MMP activity occur within the human heart and is a continuous process....
Do changes in this proteolytic cascade change as a function of age?

Are these changes independent of hypertension or coronary artery disease?
Enroll subjects with a wide age range without evidence of CV disease.

Obtain measurements of left ventricular structure and function.

Measure plasma MMP/TIMP profiles.
Developing a Sensitive Blood Test for MMPs/TIMPs

Antibody Coated Fluorescent Beads

Robotics Handle and Dilute Plasma Samples

Dual Lasers Excite Coated Beads

High Sensitivity-High Throughput System for MMP/TIMP Measurements
LV Remodeling with Age

* p<0.05 vs quintile 22-29
Impaired Diastolic Filling with Age

- * p<0.05 vs quintile 22-29
TIMPs vs Age

* p<0.05 vs quintile 22-29
Changes in Collagen Turnover With Age

TIMPs with Aging
Reduce Degree of Continuous MMP Activity
Reduce Normal Collagen Matrix Turnover
Cause Increased Collagen Accumulation
The Aging Heart and Fibrosis

**Structure**
- Increased Collagen
- Normal

**Function**
- Diastolic Heart Failure (DHF)
  - Normal: $P = 2.3 \times e^{0.010V}$
  - DHF: $P = 1.5 \times e^{0.034V}$

Increased Stiffness

LV Diastolic Pressure (mmHg) vs. LV Diastolic Volume (mL)

Substrate

Diastolic Heart Failure
Prevalence of Hypertension and MI by Age and Sex

CDC/NCHS and NHLBI 1999-2002

HYPERTENSION

CORONARY ARTERY DISEASE

Men  Women

Prevalence of Hypertension and MI by Age and Sex
The Heart of The Matter in Hypertensive Heart Disease

Transverse section through ventricles

Normal
The Heart of The Matter in Hypertensive Heart Disease

Normal

Hypertensive Heart Disease

Transverse section through ventricles
Myocardial Remodeling and Hypertensive Heart Disease

Heart Wall Remodeling in Hypertensive Heart Disease
Myocardial Remodeling and Hypertensive Heart Disease
What Does Heart Failure Look Like?
Myocardial Remodeling and Hypertensive Heart Disease....

How does it happen?
(Changes in MMP/TIMPs)

Can we predict it?
PLASMA MMP-13

Control

- Detectable: 47%
- Non Detectable: 53%

LV Hypertrophy

- Detectable: 15%
- Non Detectable: 85%

\( \chi^2 = 17.89, p<0.001 \)

Circulation 113
2089-2096, 2006
TIMP-1 Identifies and Predicts Development of HF

* = p<0.05 vs Control
# = p<0.05 vs LVH without DHF

Circulation 113
2089-2096, 2006
TIMP-4 Identifies and Predicts Development of HF

P < 0.04

Mean = 1.87 ± 0.10

TIMP-4 (ng/mL)

Control without HTN
Control with HTN
LVH without CHF
LVH with CHF
Myocardial Remodeling and Hypertensive Heart Disease....

- Occurs as a function of age

- A blood test can be used to identify and predict presence and risk
Myocardial Remodeling and Hypertensive Heart Disease....

What can we do with this blood test?
- Screen
- Manage
- Test New Treatments
Cardiovascular Remodeling with Aging
Is there a meter running?