In Vivo Animal Models of Heart Disease

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Why Animal Models of Disease?

- Heart Failure (HF)
  - Leading cause of morbidity and mortality in the US
  - Prevalence of associated risk factors such as diabetes, hypertension, obesity, high cholesterol, inactivity and aging is increasing
  - Current treatments only slow the progression of the syndrome
  - Thus, there is a great need to develop novel preventative and reparative therapies
  - Therefore, appropriate animals are necessary.

What is Heart Failure?

- Clinical syndrome
  - Dyspnea
  - Fatigue
  - Exercise intolerance
  - Retention of fluid in the lungs and/or peripheral tissues.
- Fundamental Defect
  - Impaired filling and/or ejection of blood from the heart

Common Causes of HF

- Valvular lesions
- Dilated cardiomyopathies
- Hypertensive heart disease
- Restrictive cardiomyopathies

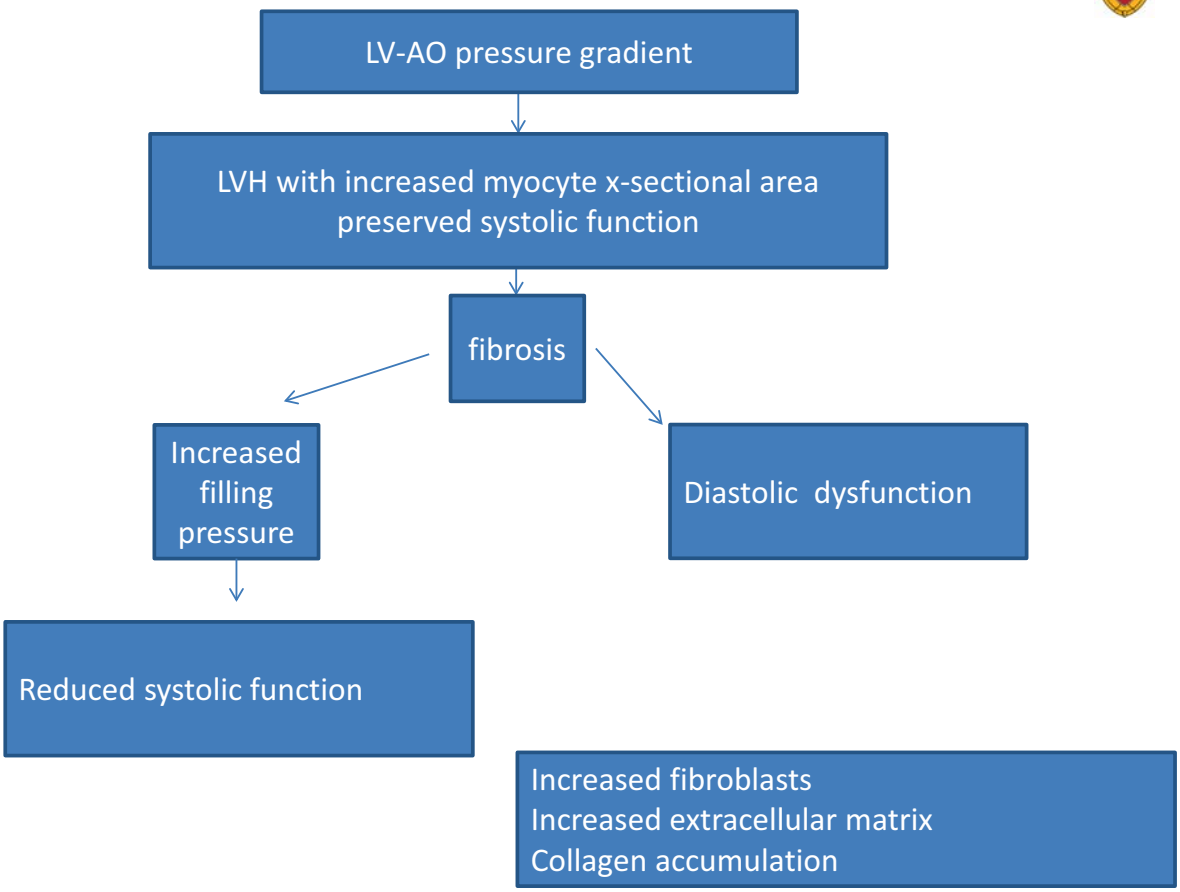
What makes a good animal model?

- Should mimic critical features of human HF
  - Considerations
    - Mimic the course of HF for the duration
    - Mimic for a single discrete time point
  - Limitations
    - Lack of diversity
    - Lack of co-morbidities
    - Differences between species in cell and molecular make-up

Aortic stenosis (AS)

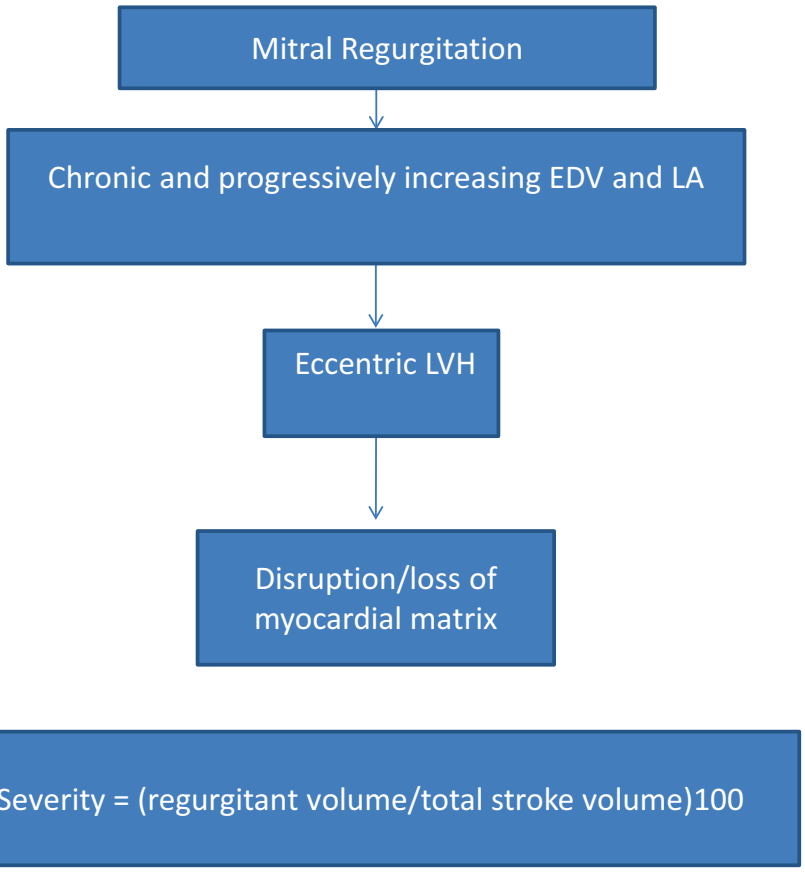
- Atherosclerotic disease w/wo calcification
- Calcification independent of atherosclerosis
- Valve malformations
- Bottom line
  - increased valve stiffness and reduced ejection orifice area leads to increased LV afterload

Critical Features of AS



Animal Models of AS

- Mouse TAC
  - Abrupt increase
    - activation of growth regulatory pathways are different
    - contractile protein are different in mice
    - extracellular remodeling is different in mice
  - Test specific molecules
- Rat TAC
  - Start with young rats to avoid the abrupt increase in pressure
- Dog/Pig
  - Ameroid constriction of aorta



Animal Models of MR

- Rodents
  - Aortocaval fistula
  - AO insufficiency
    - both lead to volume overload
    - Both feature LV eccentric hypertrophy
- Large animal
  - Severing chordae tendineae
    - Leads to volume overload
    - LV eccentric hypertrophy
    - Myocardial matrix disruption

Unresolved Issues in Valvular Lesions

- How to enhance cardiac repair after correction of the valve defects?
  - Models that correct the defect
    - Unbanding?
    - Repair of mitral valve (large animals)?
    - Repair of aortic valve (large animals)?
    - Fistula correction?

Dilated Cardiomyopathy

- Ventricular dilation, systolic dysfunction, abnormalities of diastolic filling, normal or reduced wall thickness (eccentric hypertrophy), increased diastolic and systolic wall stress, biventricular and biatrial enlargement, AV valve regurgitation, elevation of left and right sided filling pressures, increases in organ and chamber weight, myocyte hypertrophy, activation of neurohormonal systems

Causes

- Genetic mutations (cytoskeletal, sarcolemmal, scarcomeric , nuclear envelope proteins), MI, longstanding hypertension, CAD, myocarditis, some chemotherapeutic drugs, autoimmune disorders, excessive tachycardia, endocrine disorders, excessive alcohol consumption, nutritional deficiencies, neuromuscular disorders

Critical Similarities

- Hemodynamics
  - decreased systolic and diastolic function
  - diminished contractile reserve (catecholamine stress)
  - increase wall stress
  - depressed isovolumic ejection phase
  - slowed relaxation rate
  - depression of stretch induced force response
  - blunting of force frequency response
  - altered Ca uptake storage and release
  - altered beta adrenergic receptor function

Similarities

- Molecular hallmarks
  - activation of fetal/hypertrophic gene program
  - local and systemic inflammation
  - oxidative stress
  - upregulation of atrial natriuretic factor
  - Down regulation
    - SR calcium ATPase
    - alpha myosin heavy chain
    - Beta 1 adrenergic receptors

Similarities

- Histopathologic
  - Hypertrophy
    - myocyte length and width
    - interstitial and replacement fibrosis
    - alteration of extracellular matrix
    - progressive cardiomyocyte death (apoptosis, necrosis and autophagy)
    - relative capillary reduction.

Similarities

- Neurohormonal
  - increased adrenergic tone
  - increased renin-angiotensin–aldosterone systems
  - increased endothelin
  - increased vasopressin

Animal Models of DCM

- Rodents
  - MI in rodents
    - MI size is hard to control
  - Genetic models in mice
  - doxorubicin or isoproterenol (dilated phenotype and myocardial injury and cell death (apoptosis and oxidant stress)
  - Salt sensitive hypertensive rats
    - often little change in heart structure/function

Animal Models of DCM

- Large animals
  - MI (pigs)
  - coronary microembolization
    - contractile dysfunction
    - localized inflammatory responses
    - TNF expression
    - progressive LV dilation
    - Long time to produce, hard to titrate
  - pacing induced tachycardia
    - reliable and reproducible model
    - partially reversible over time

	Advantages	Limitations
Mouse	inexpensive genome manipulation atherosclerotic plaques similar developmental cardiac anatomy few collaterals resistant to arrhythmias rapid inflammation course transient macrophage infiltration tolerate large MI	partial resemblance to humans more atherosclerotic alpha myosin heavy chain variable coronary circulation fast HR no plateau phase in AP Na/Ca less relevant in rodents
Rat	inexpensive useful for restenosis few collaterals tolerate large MI Lewis rats (consistent coronary arteries)	No athermoa alpha myosin heavy chain
Rabbit	medium size few collaterals complex plaques restenosis fibroathermoa lesions beta myosin heavy chain similar Ca uptake	need high blood cholesterol levels no plaque rupture model more neointima formation than atherosclerosis

	Advantages	Limitations
Pig	lesions more similar to human valid for restenosis beta-myosin heavy-chain some co-morbidities useful for device testing few collaterals more consistent MI sizes angioplasty induced injury very similar to humans with high fat diet coronary vascular very similar	expensive difficult handling some genomic tools susceptible to arrhythmias
Dog	b-myosin heavy-chain	expensive many collaterals variable infarct size

Large animal models

- Preclinical validation studies
- Testing of devices
- Similar end-point measurements
  - Structural
  - Hemodynamic
  - Physiological assessments
  - Histopathologic, biochemical, cellular, molecular studies should be used to document DCM and improvements

General Considerations

- Cost
- Housing/maintenance
- How to measure end-points?
  - Imaging (echo, MRI, CT, PET, x-ray, molecular)
    - Volumes, function
  - Invasive and implantable physiology
    - PV loops, ECG, pressures, pacing wires, flows,
- Surgical methods (open chest, closed chest)
- Cell delivery methods
- Multiple animal models
- Co-morbidities
- Age
- Male vs. Female

Conclusions

- Randomization
- Blinding
- No one size all fits models
- Careful experimental design
- Choose your models carefully
- Multiple animal models, use Co-morbidities, ages

Conclusions

- Beta-adrenergic receptor antagonists are a great success story that have been translated from animal models of heart failure to humans
- Cell therapies will follow this same path