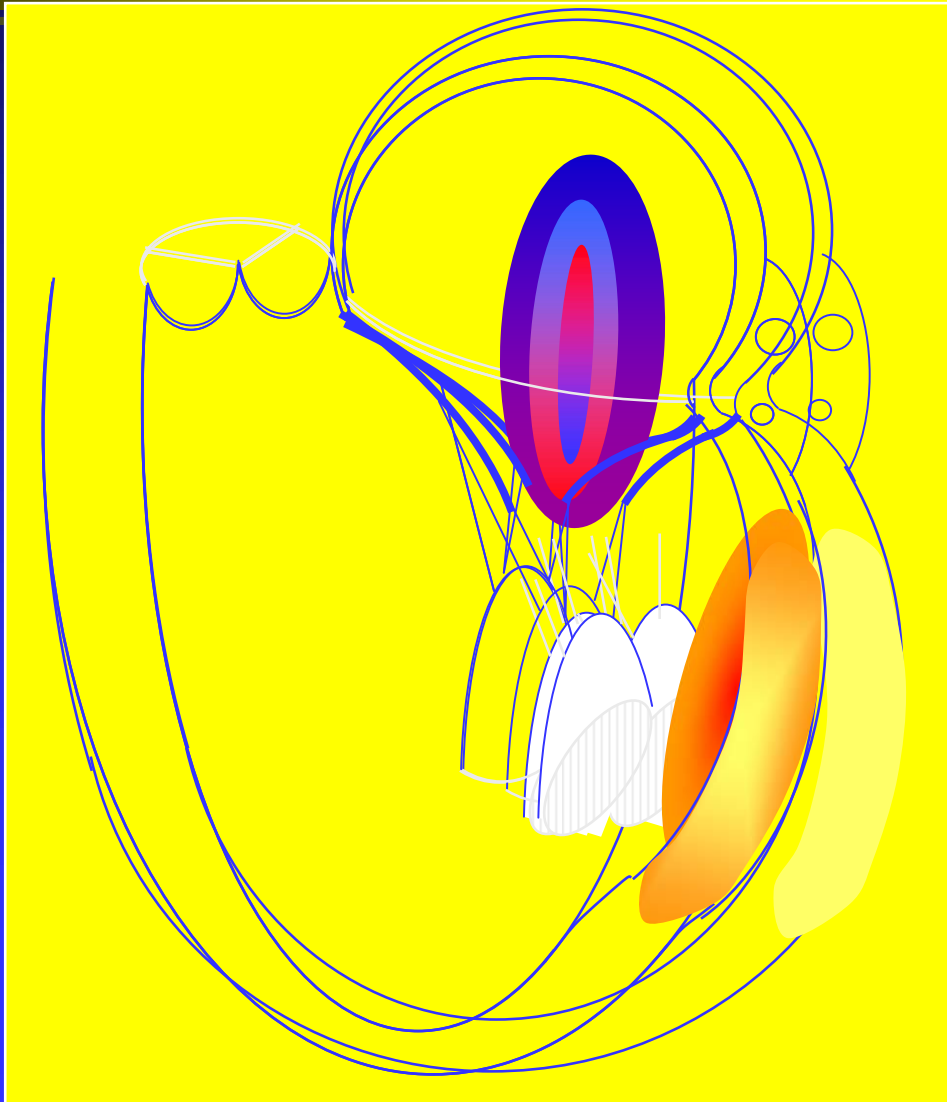


Functional Mitral Regurgitation - Current Therapies: What Determines the Future of the Ventricle?

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Myocardial Infarction



LV Remodeling



Mitral Annular Dilatation

+

Papillary Muscle
Displacement



Mitral Valve Tethering



Functional MR

Volume
Overload

Remote
Apoptosis

Neuro-
endocrine
Activation

SCHOOL OF
MEDICINE



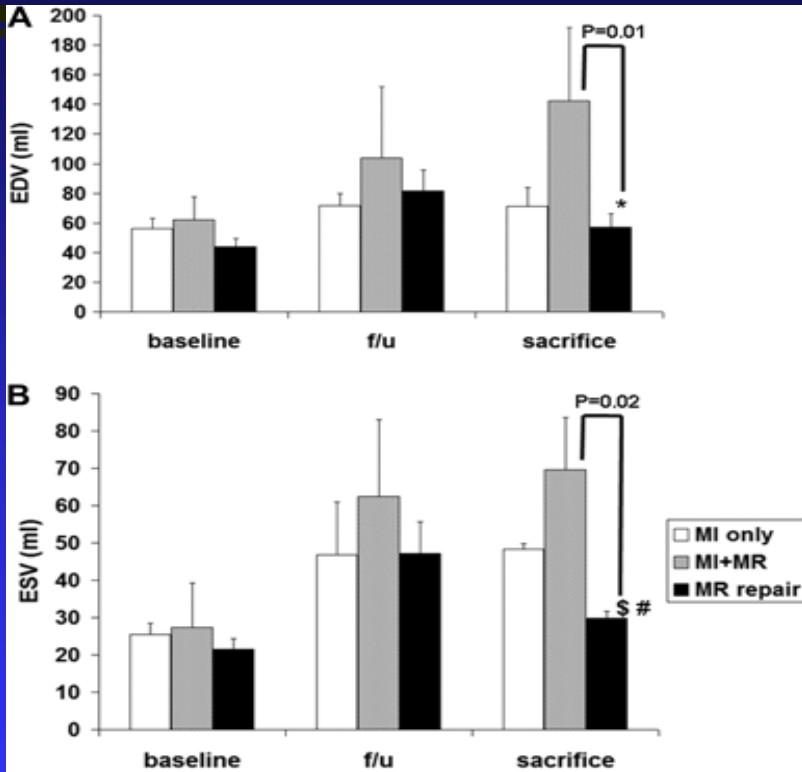
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Which Factors Determine the Future of the Ventricle?

Known that LV remodeling:

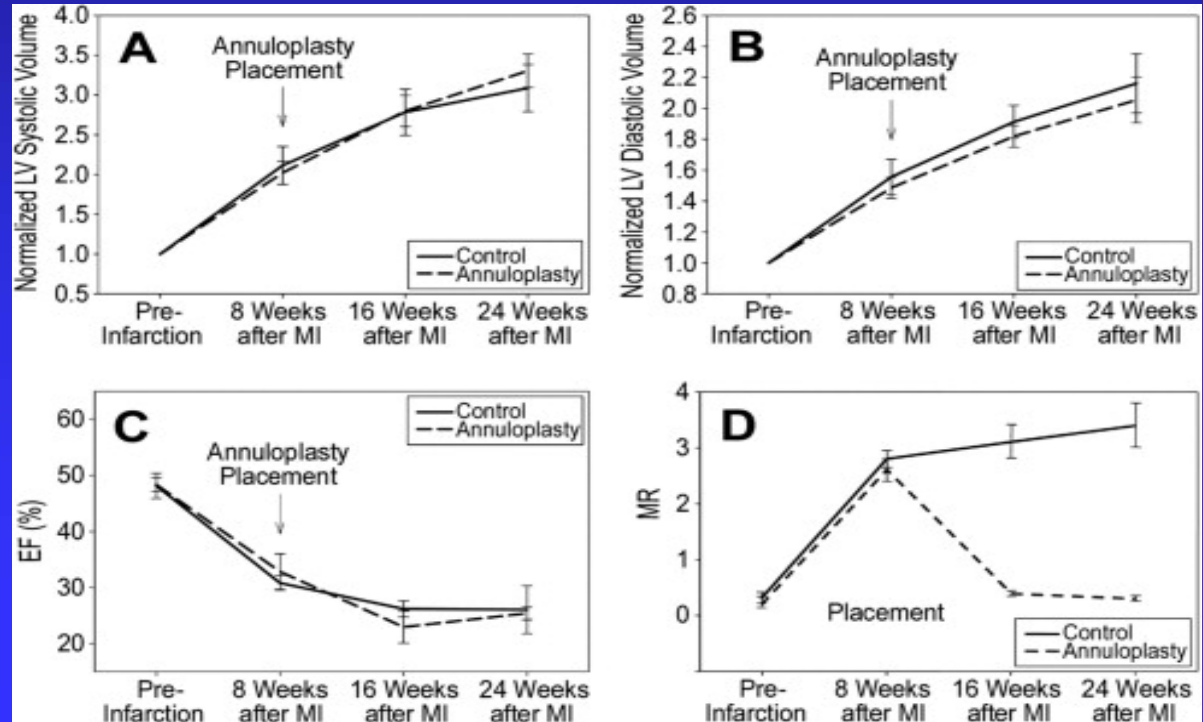
- Relates to myocardial mass lost & amount of scar replacement
- Due to intrinsic increase of cardiomyocyte length & decrease of end-diastolic wall thickness via chronic volume overload
- Increases LV dimension with remote cardiomyocyte apoptosis (stress/strain?)
- Activates neuroendocrine systems including activation of adrenergic cardiac nerves, activates the renin-angiotensin-aldosterone system, and releases atrial natriuretic peptide
- Unanswered Questions- Which of the above mechanisms dominates the remodeling response? When is a negative response pattern irreversible in the setting of FMR?

Functional MR and Ventricular Remodeling: Conflicting Animal Models



Levine et al. (A) End-diastolic and (B) end-systolic LV volumes (EDV, ESV) of MI-only (white bars), MI+MR (gray bars), and MR repair groups (black bars) at baseline, 1-month follow-up, and 3-months sacrifice. The volumes at 1 month are significantly higher than at both baseline and 3-month sacrifice ($P < 0.01$ for both EDV and ESV) (* $P = 0.003$ versus 1-month follow-up; \$ $P = 0.008$ versus 1-month follow-up; # $P < 0.001$ versus MI only).

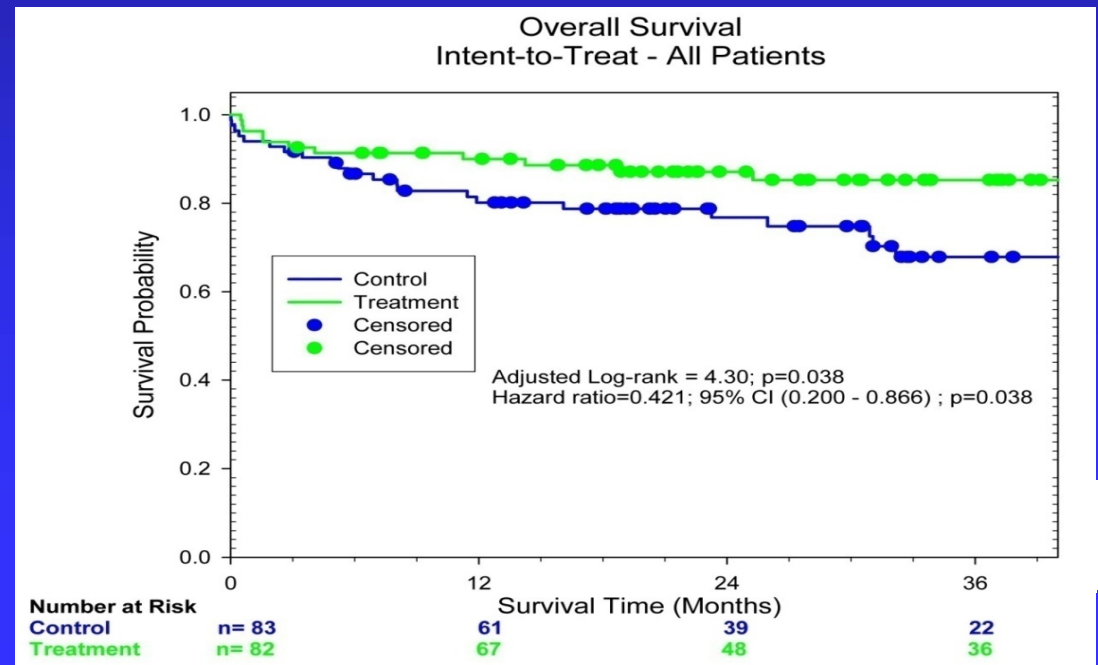
Gorman et al. Echocardiographic data for annuloplasty group (dashed line) and control group (solid line): (A) Serial LV end systolic volume normalized to preinfarction value. Annuloplasty was placed 8 weeks after myocardial infarction (MI) in the annuloplasty group. The control group received no treatment. (B) Serial left ventricular end diastolic volume normalized to preinfarction value. (C) Serial ejection fraction (EF). (D) Degree of mitral regurgitation (MR) on standard 0 to 4 scale. The only statistically significant difference between groups was the degree of mitral regurgitation at 16 and 24 weeks after myocardial infarction.



Functional MR and Ventricular Remodeling: Conflicting Clinical Results

- Dion- LV reverse remodeling was sustained with time for $LVEDD \leq 65$ mm: Diastolic reverse remodeling occurred in 52%; Systolic reverse remodeling occurred in 74%
- Hung, Duran, Qin- LV often continues to remodel & dilate, which renders initial repair ineffective
- STICH Trial- perhaps beyond interpretation due to issues of study execution

• RESTOR-MV Trial- Ventricular shape change device for FMR. Compared reduction annuloplasty to ventricular shape change. Reduction annuloplasty showed discrepancy between degree of MR reduction and improved survival/ better symptom relief.



What is our Research Gap and Where is the Opportunity?

What are the driving mechanisms for ongoing cardiac remodeling (positive and negative) when FMR is treated? Which patients will benefit from repair/ replacement alone and which patients will benefit from ventricular repair?

- ~ Where is the cutoff for a 'valve-only solution' in patients with FMR?
- ~ Is there a differential between the remodeling mechanism of ischemic and non-ischemic etiology? Why/why not?
- ~ How can we uncouple pathophysiologic responses to break the cycle of negative ventricular remodeling?
- ~ How can we determine the optimal timeframe post- MI to intervene, and what treatment is most appropriate (revascularization, remodeling, etc.)?
- ~ Current CTSN protocols incorporate the study of moderate and severe IMR, however, they fail to stratify by LV end-diastolic dimension.