“Let No One Without Knowledge of Geometry Enter” - 30 Years of Researching the Mechanisms of Mitral Valve Dysfunction

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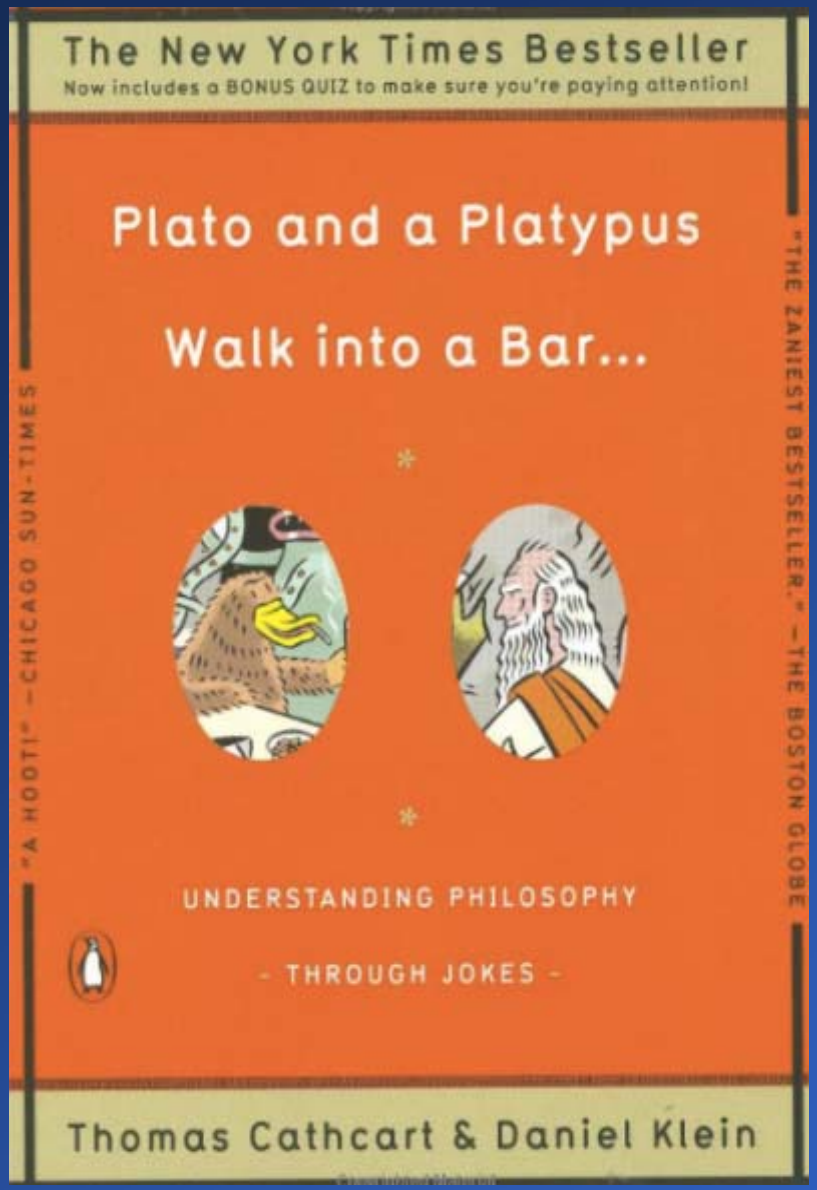
Associate Professor of Cardiology



"The construction and payoff of jokes and …of philosophical concepts … proceed from the same impulse: to confound our sense of the way things are, to flip our worlds upside down, and to ferret out hidden, often uncomfortable, truths …"

True also for scientific research

No scientific progress without questioning existing concepts, sometimes turning things upside down by kicking out problematic conventions which managed to escape rigorous testing and remained unchallenged.

“ When ideas go unexamined and unchallenged for a long time… they become mythological, and they become very, very powerful.”

EL Doctorow

Plato: ἀγεωμέτρητος μηδεὶς εἰσίτω

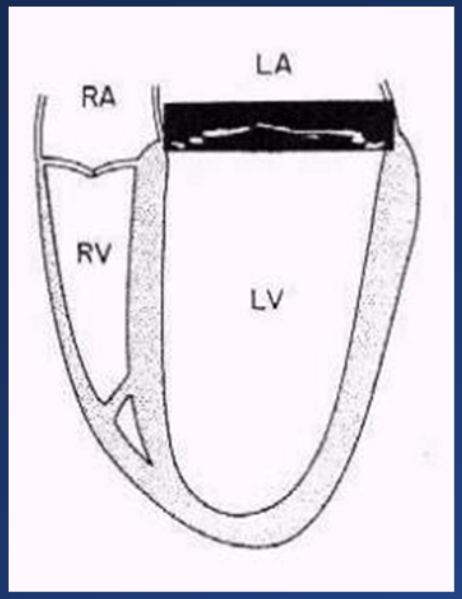
"Let no one untrained in geometry enter!”

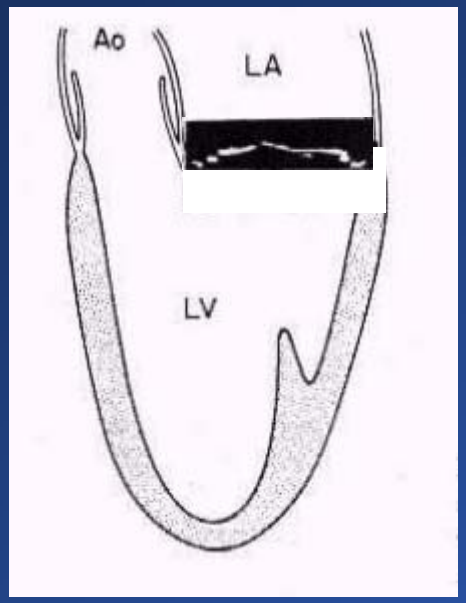
Bob: Using geometry to analyze the mechanisms of mitral valve dysfunction

Just a taste of it…

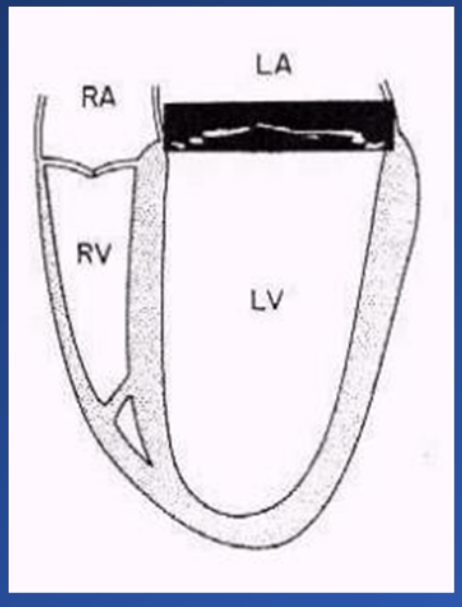
- Mitral Valve Prolapse
- Systolic Anterior Motion in HOCM
- Functional Mitral Regurgitation
- Can we put it all together into one geometric model?

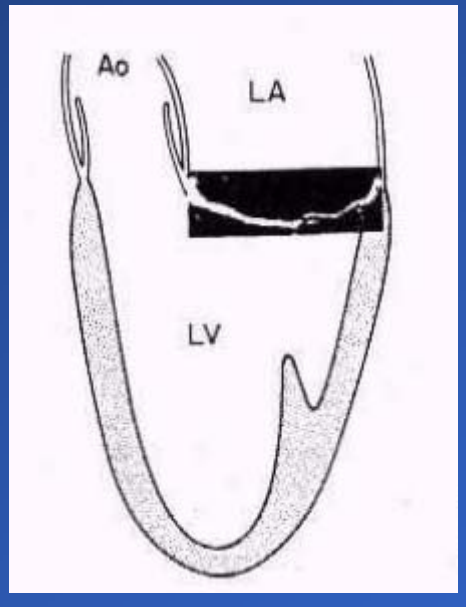
Mitral Valve Prolapse





3 decades ago: MVP was diagnosed as billowing above the mitral annular hinge-points, irrespective of the imaging plane used (4 Ch or long axis)



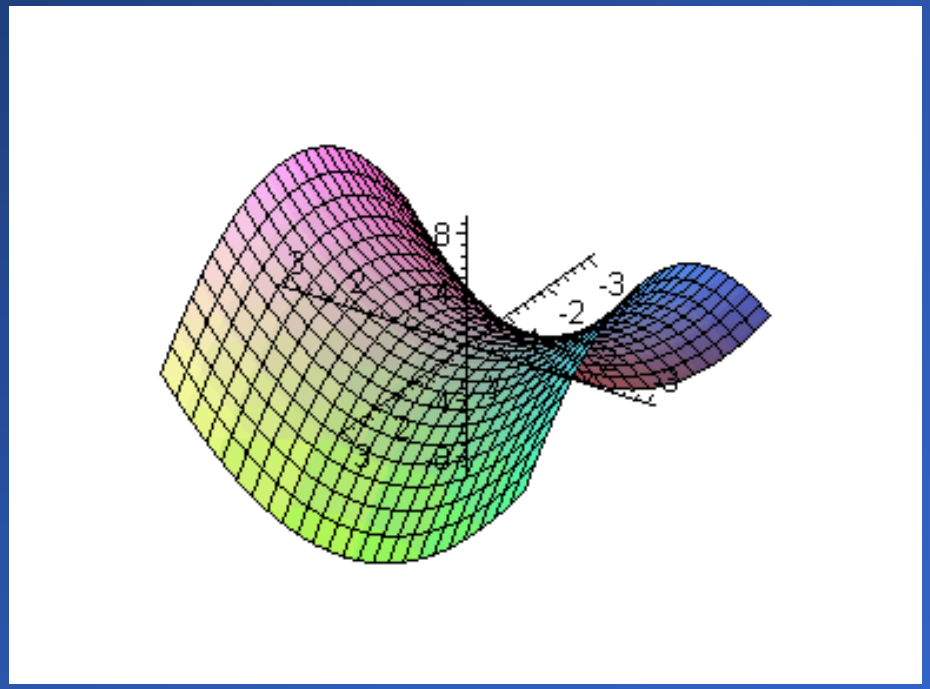


Why does prolapse go away when you switch to the long-axis view?

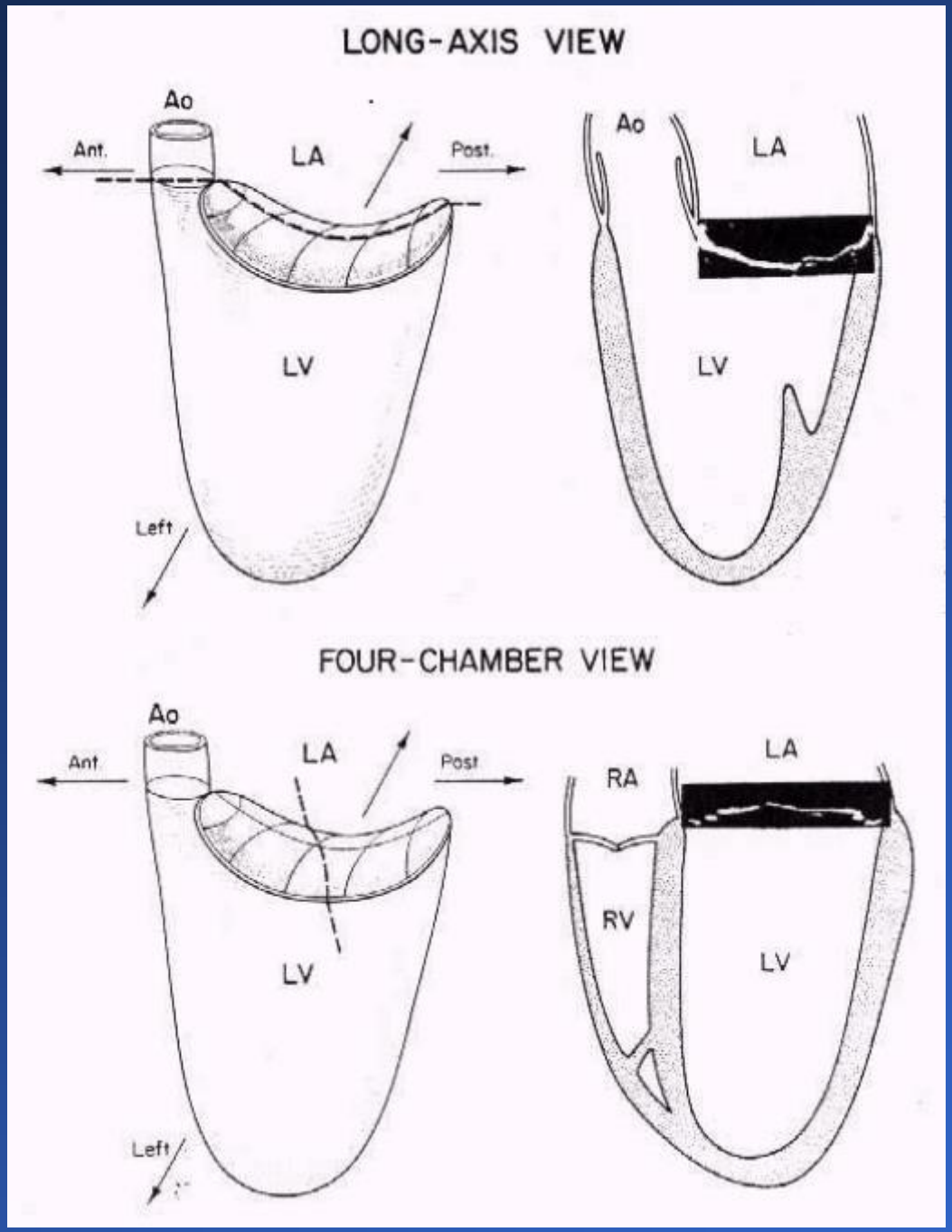
Because the mitral annular hinge points do not lie in one flat plane; the mitral annulus must be nonplanar!

Specifically: The mitral annulus has opposing curvatures in orthogonal cross-sections

The only geometric body, which has opposing curvatures in orthogonal cross-sections:



Hyperbolic paraboloid



Levine RA, et al. Circulation 1987

Levine RA, et al. J Am Coll Cardiol 1988

Levine RA, et al. Circulation 1989

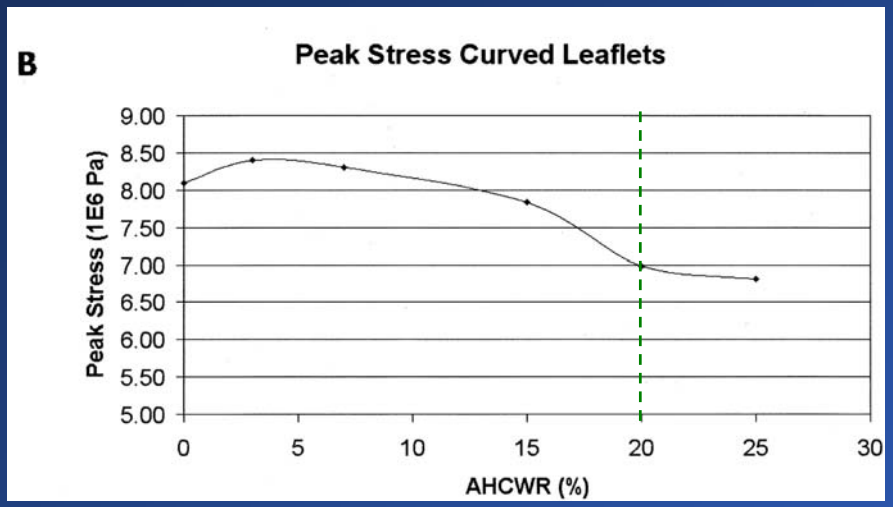
Levine RA, et al Am J Cardiol 1992

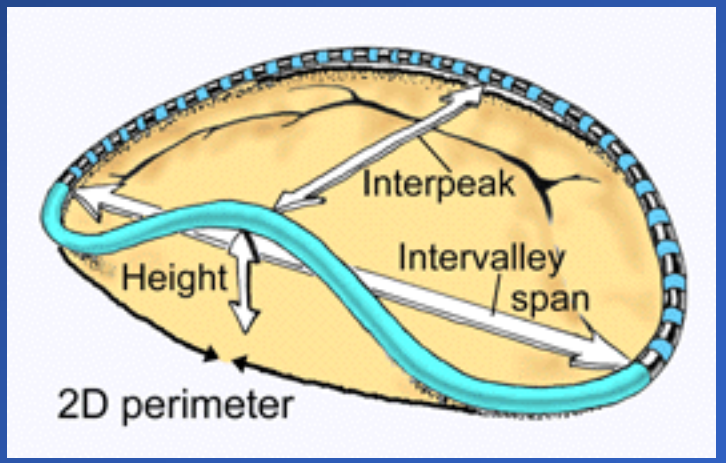
Clinical Impact

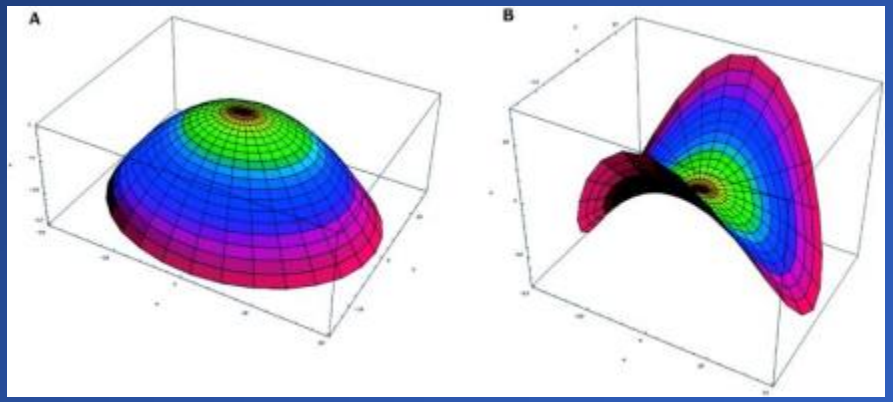
- Reduced the prevalence of MVP from 35% to less than 2% of the general population
- Reassured millions of actually healthy individuals who were wrongly given an uncertain prognosis that included sudden death, endocarditis and stroke
- Brought to an end an epidemic that was generated by its definition

Is there a mechanical advantage to non-planarity?

Effect of MA Shape on Leaflet Curvature in Reducing Leaflet Stress







The saddle shape of the mitral annulus confers a mechanical advantage to the leaflets by adding curvature.

Salgo, et al. Circulation 2002

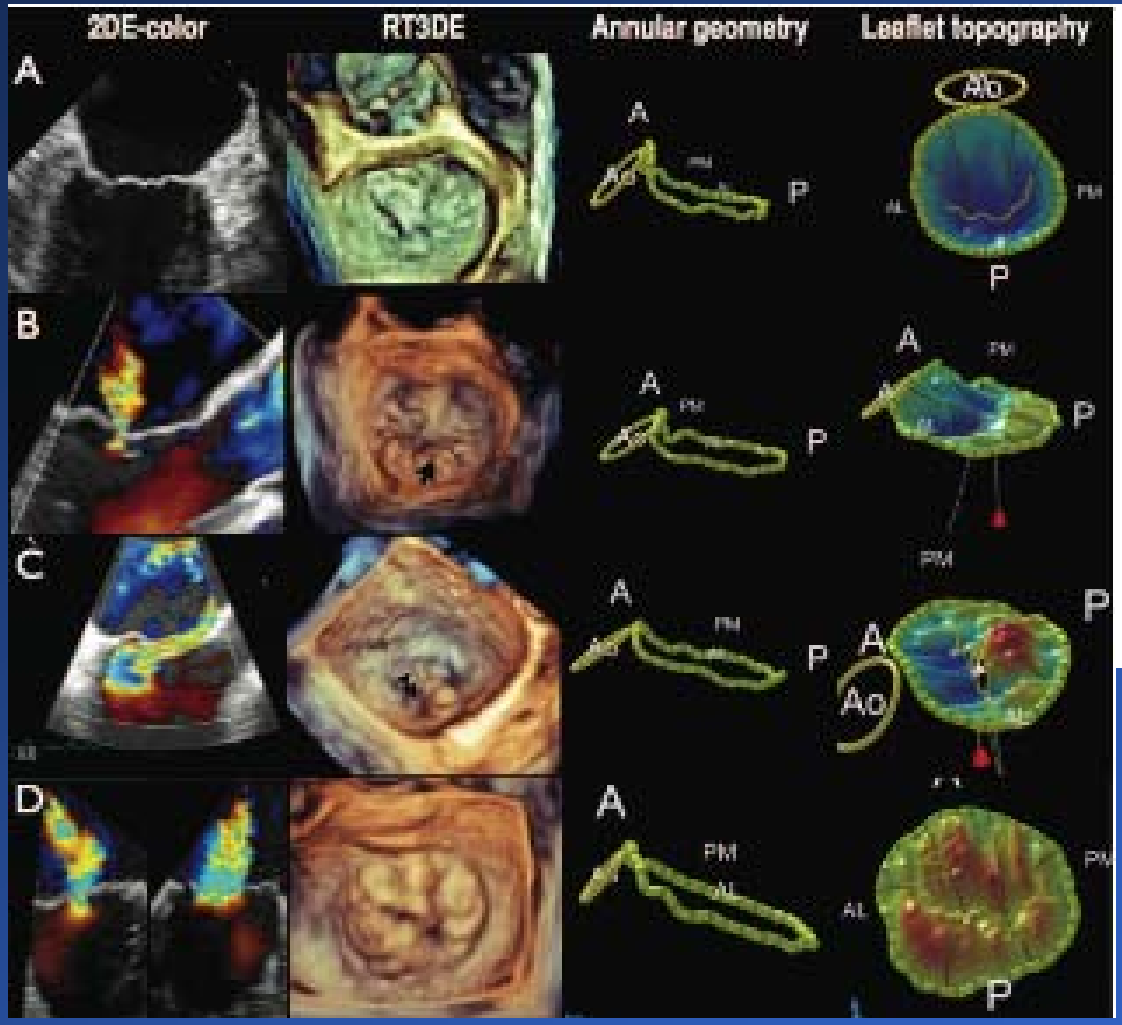
Saddle shape for stress reduction in unsupported roofs

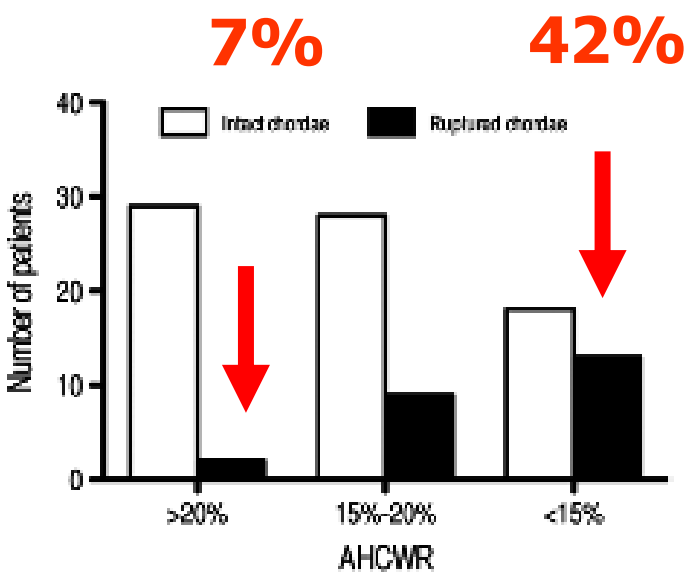
JFK Terminal 5 (TWA)

Not just for aesthetics:
If unsupported roofs were flat, they would collapse under their own weight!

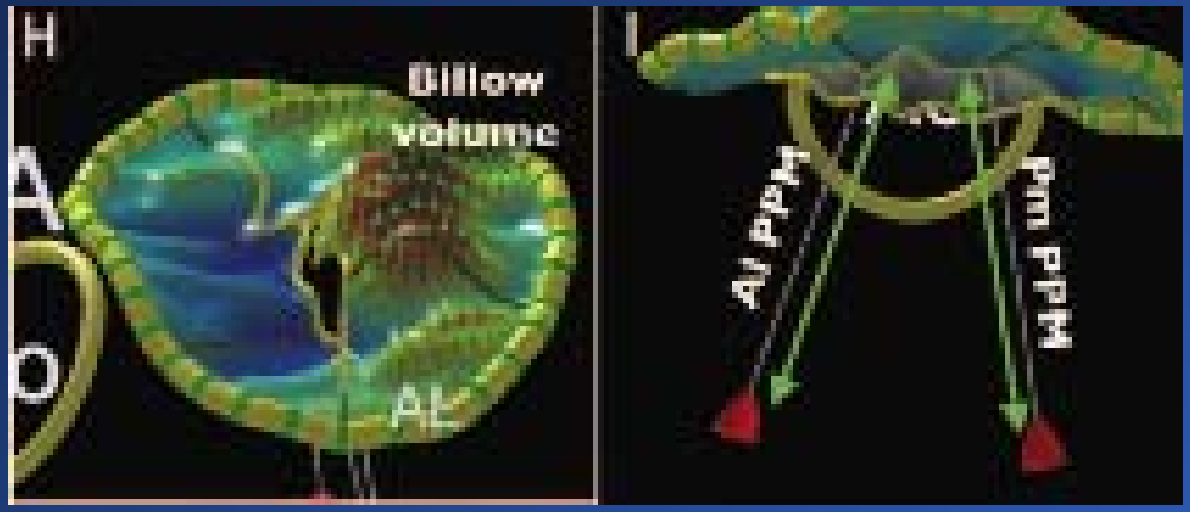
Saddle Dome Calgary

MVP: Progressive Increase in Prevalence of Chordal Rupture with Flattening of Annulus

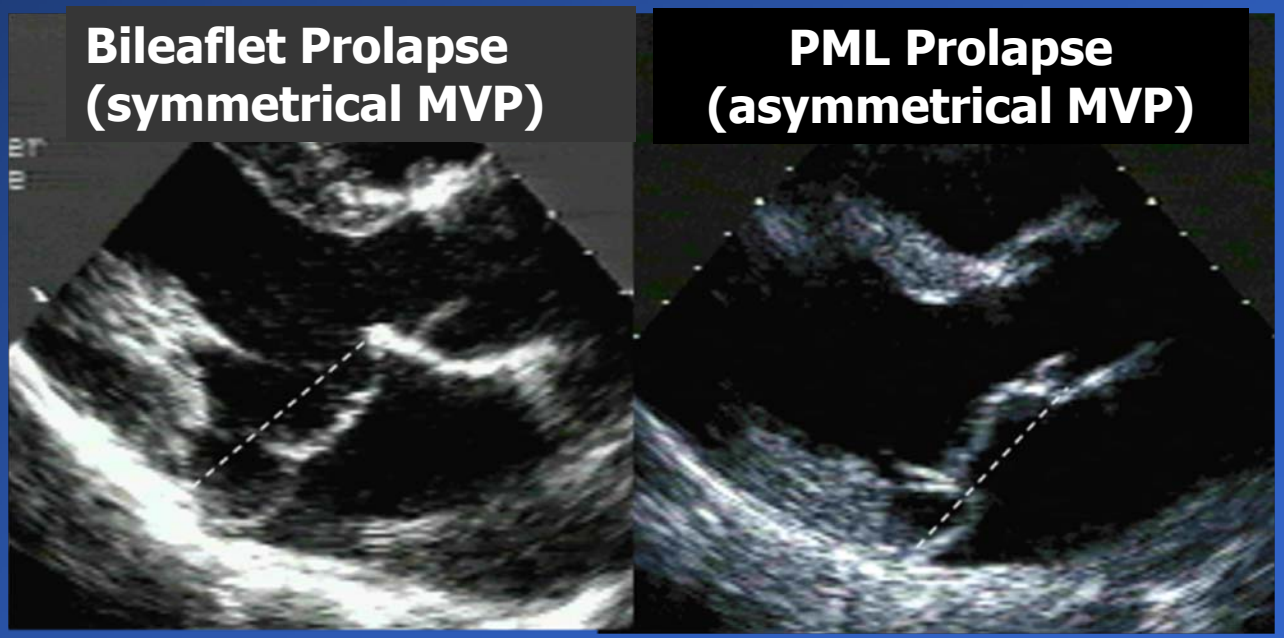




Lee et al, *Circulation*. 2012



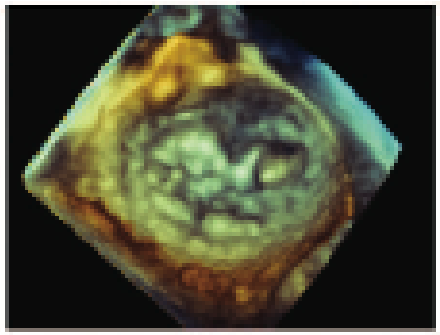
Lee et al, *Circulation*. 2012

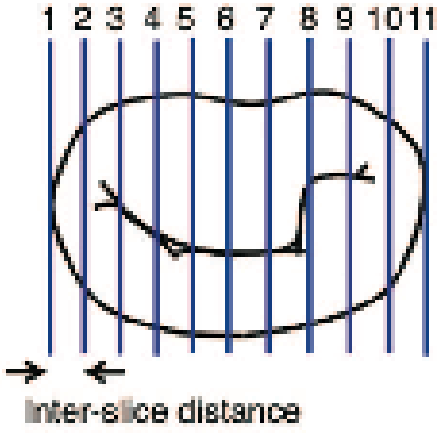


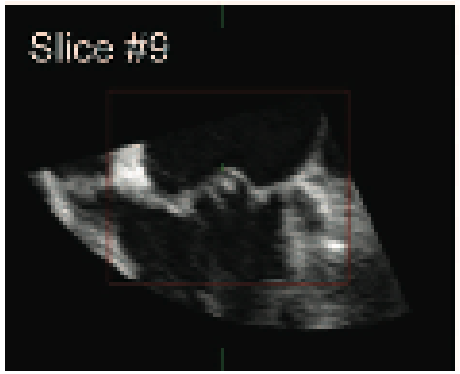
E Schwammenthal, Mitral Valve Disease, in Flachskampf (ed), Practice of Echocardiography, Thieme 2010

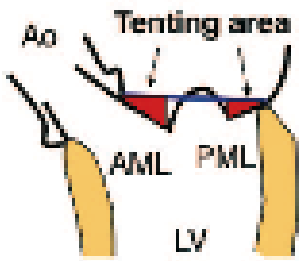
Primary posterior leaflet prolapse with MR causes secondary anterior mitral leaflet tethering

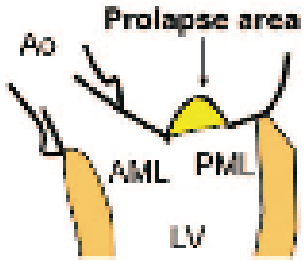
PML prolapse → MR → LV dilatation → PM displacement → AML tethering

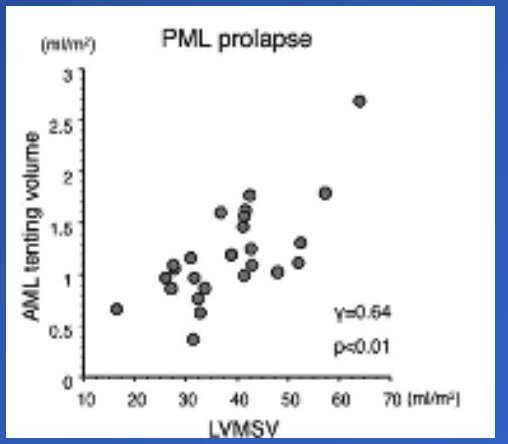


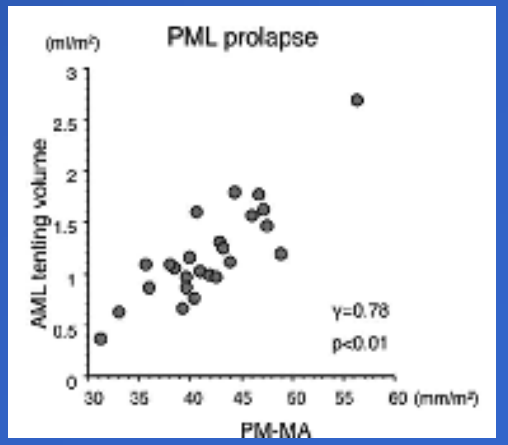








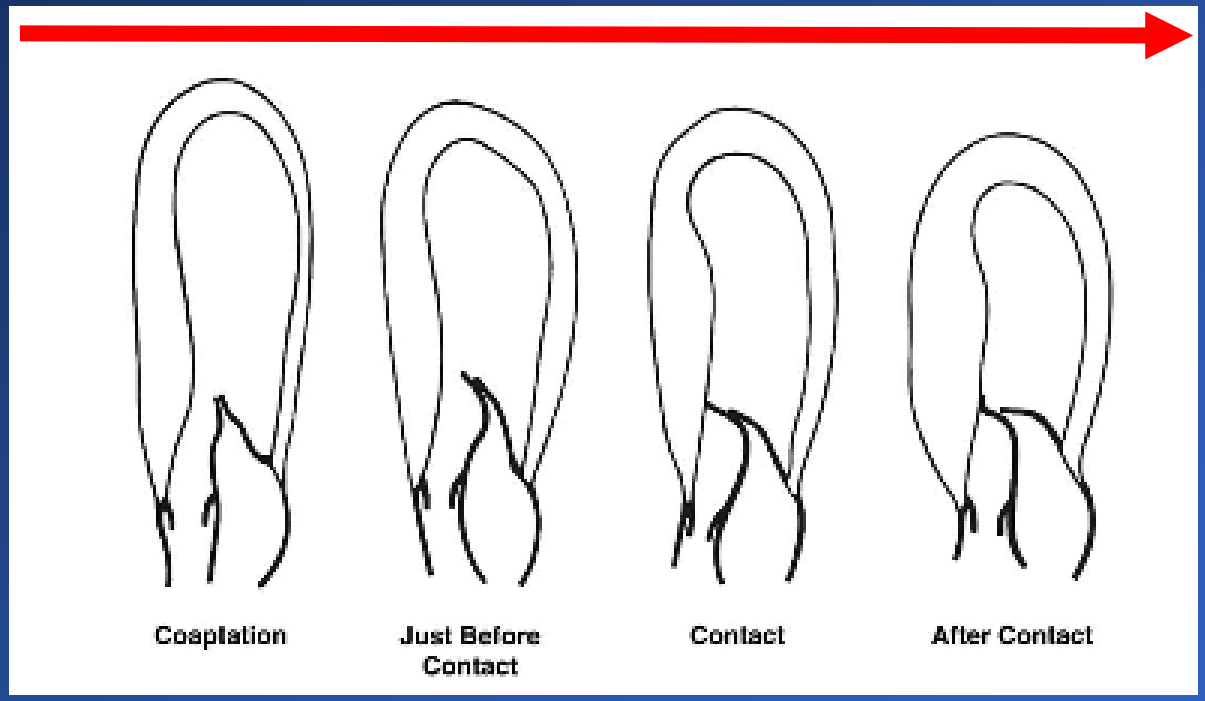




Otani, Levine, Otsuji (et al). Circulation 2012

Systolic Anterior Motion

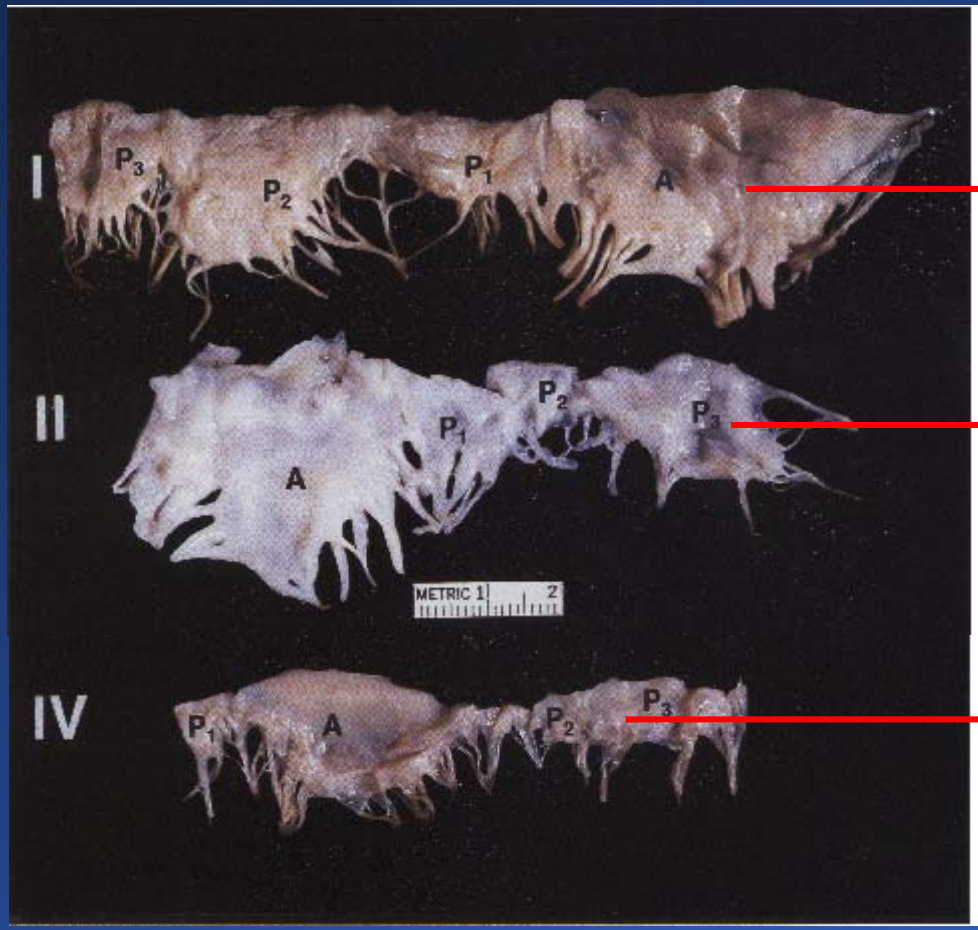
What causes this systolic leaflet motion?

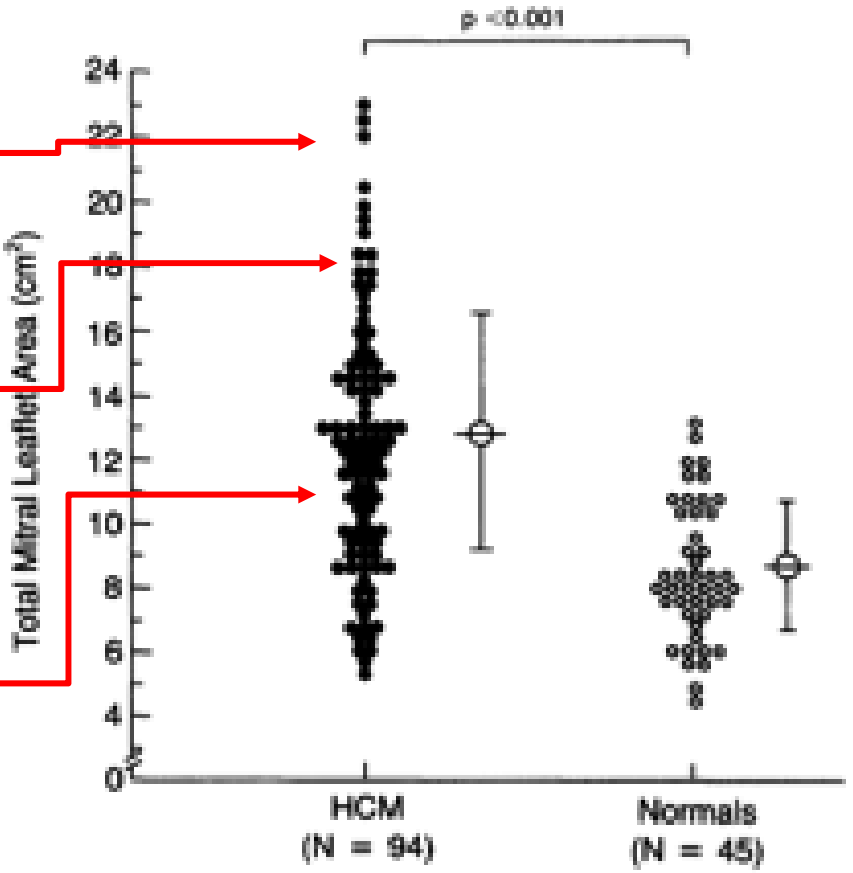


Leaflets move in response to the forces acting on them,

But for the leaflets to be able to follow a force, leaflet slack is required to provide at least one degree of freedom

Structural Mitral Valve Alterations in HOCM

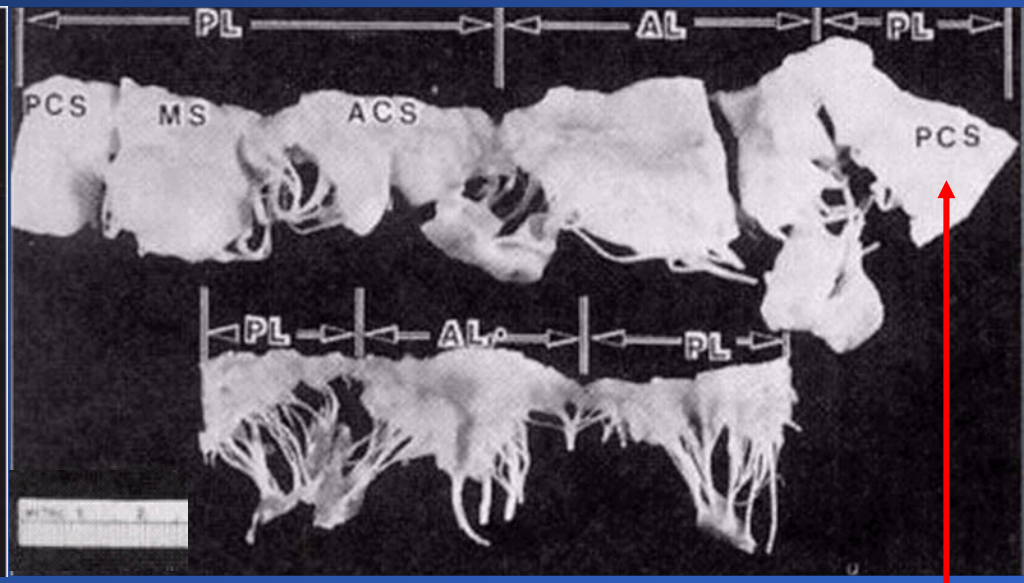


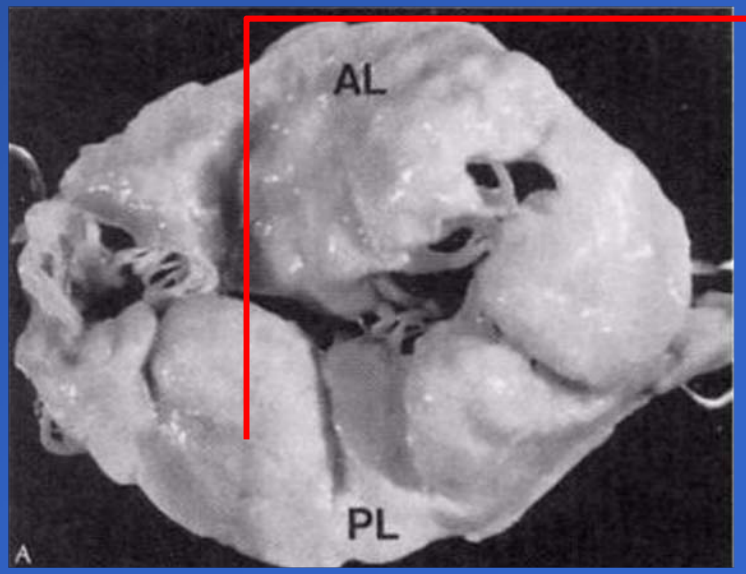


Klues, Maron, Dollar, Roberts. Circulation 1992

HOCM

Myxomatous

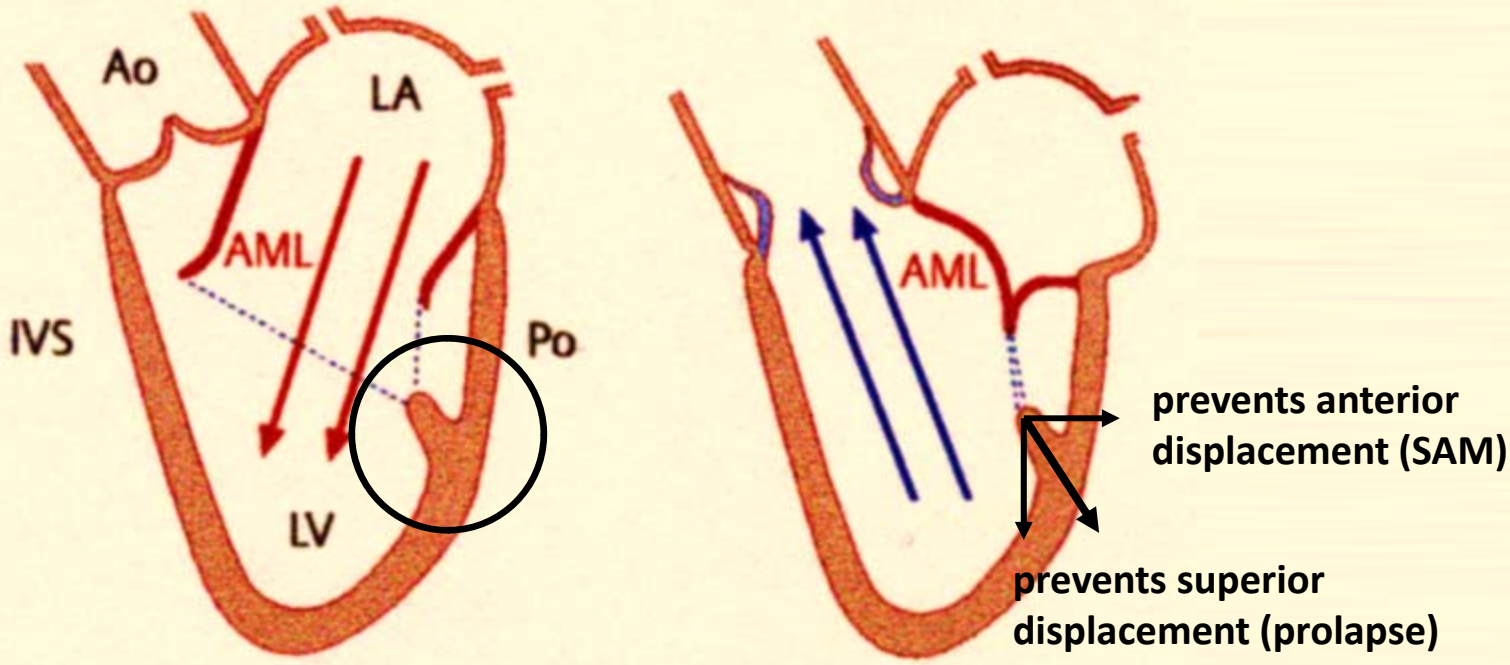




If mitral leaflet area is enlarged in HOCM similar to myxomatous disease, why SAM and not MVP?

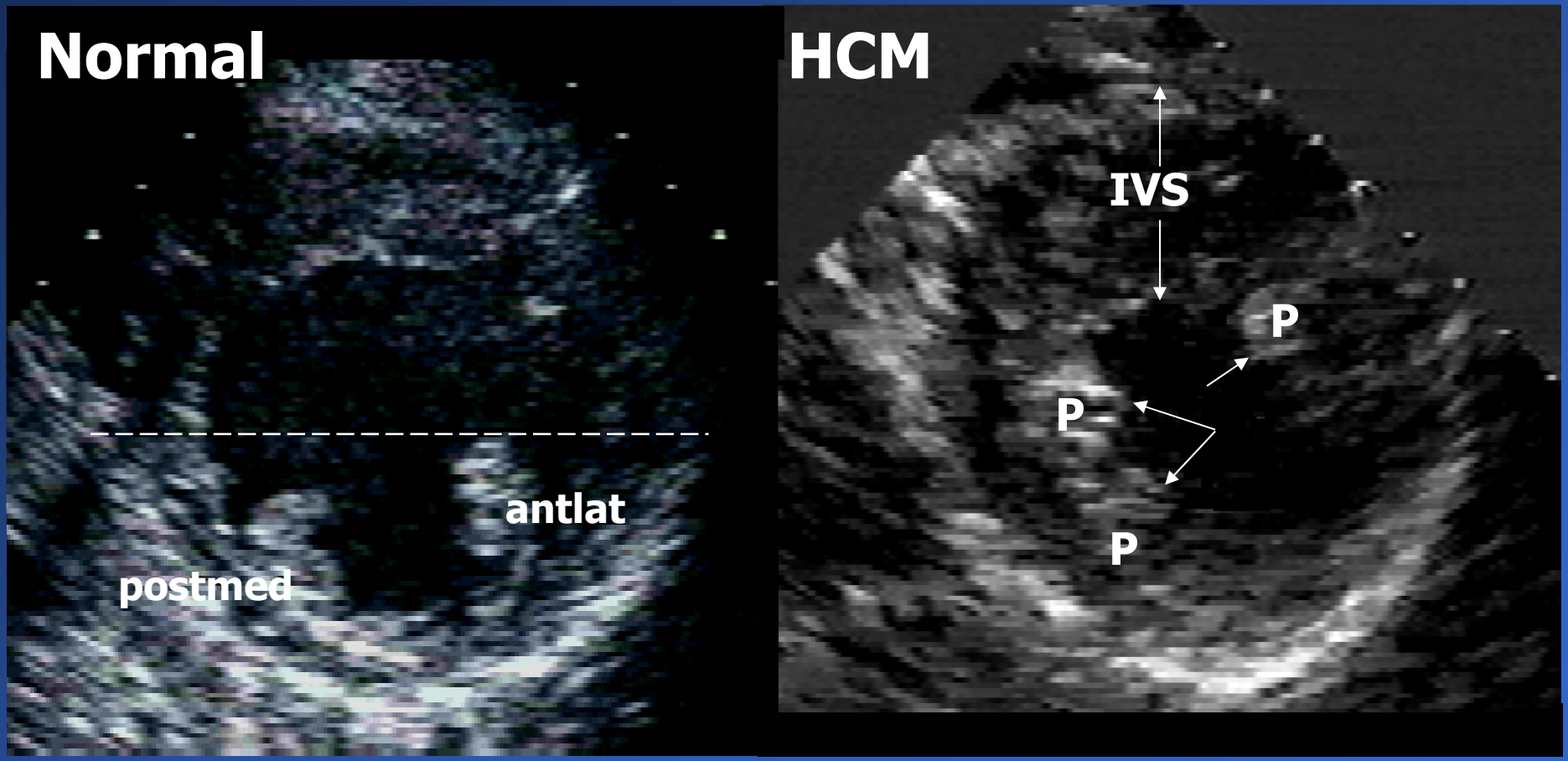
Position of papillary muscles

Conversion of Left Ventricle from an Inflow Chamber (diastole) into an Outflow Chamber (systole) by AML

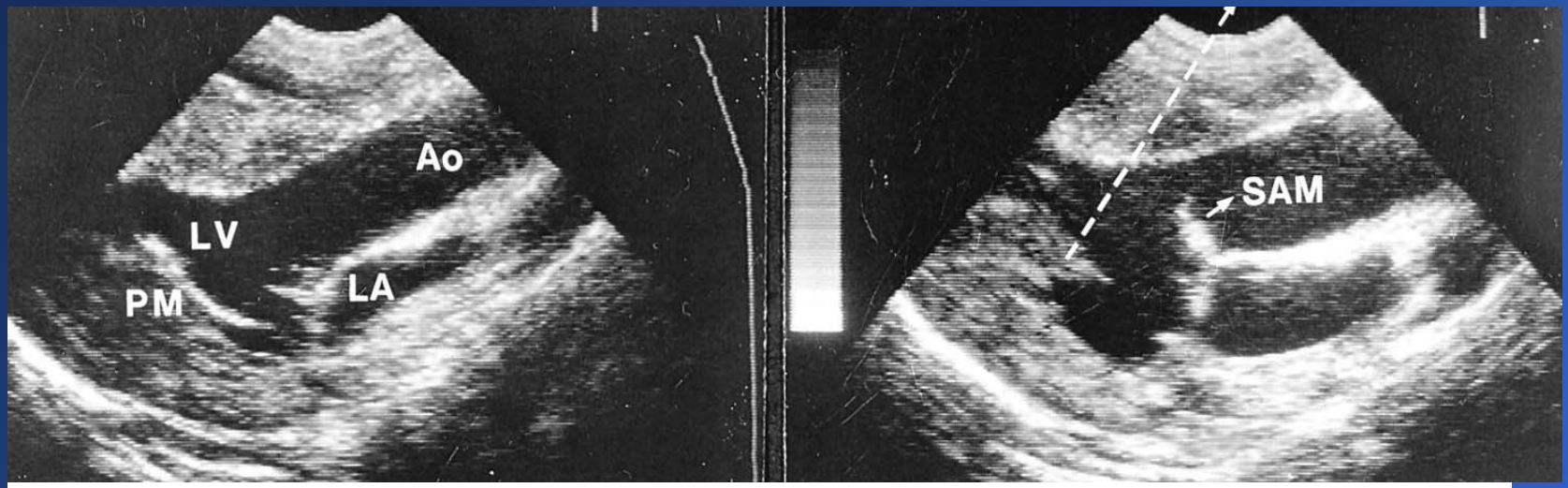


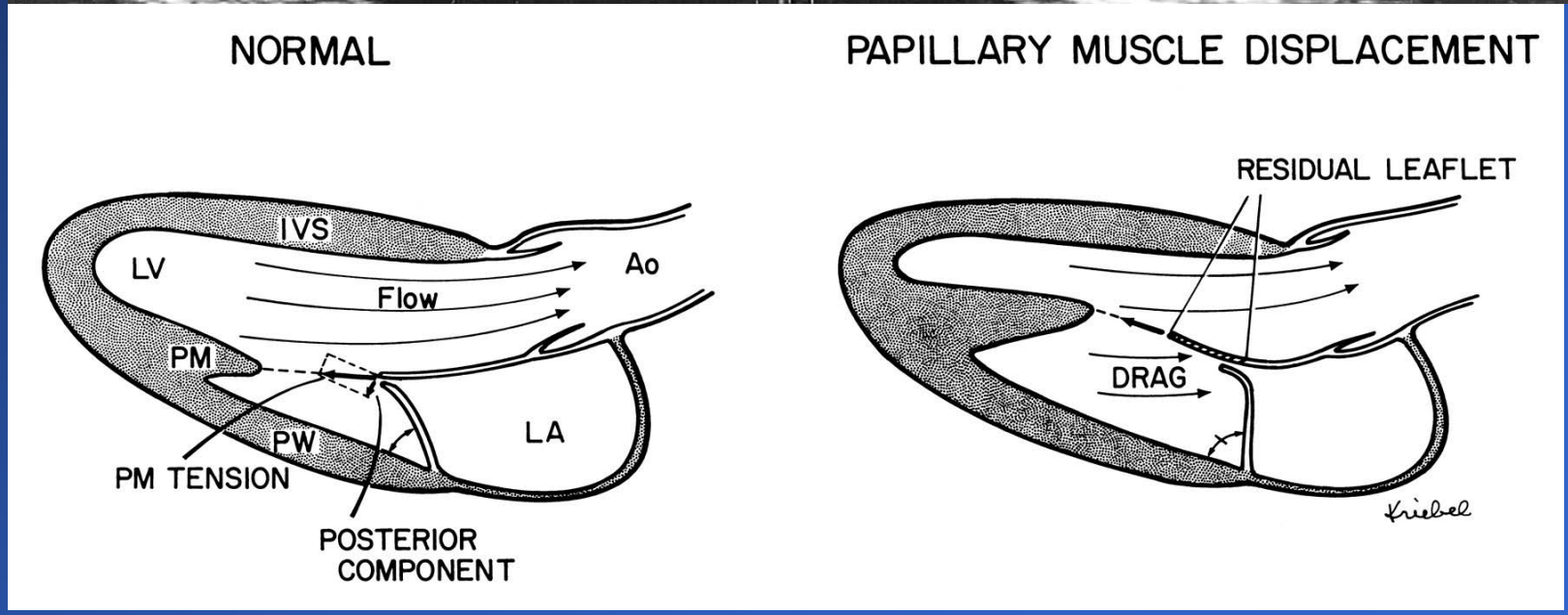
E Schwammenthal, Mitral Valve Disease, in Flachskampf (ed), Practice of Echocardiography, Thieme 2010

Anterior papillary muscle displacement in hypertrophic cardiomyopathy → loss of posterior leaflet restraint



Anterior Papillary Muscle Displacement Causes SAM (acute dog model)

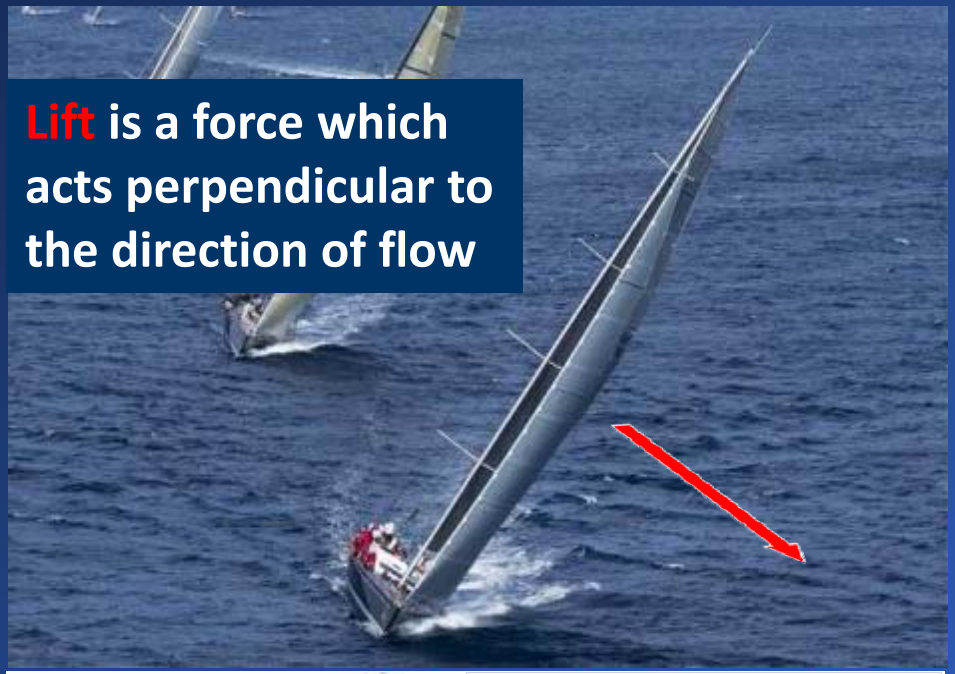




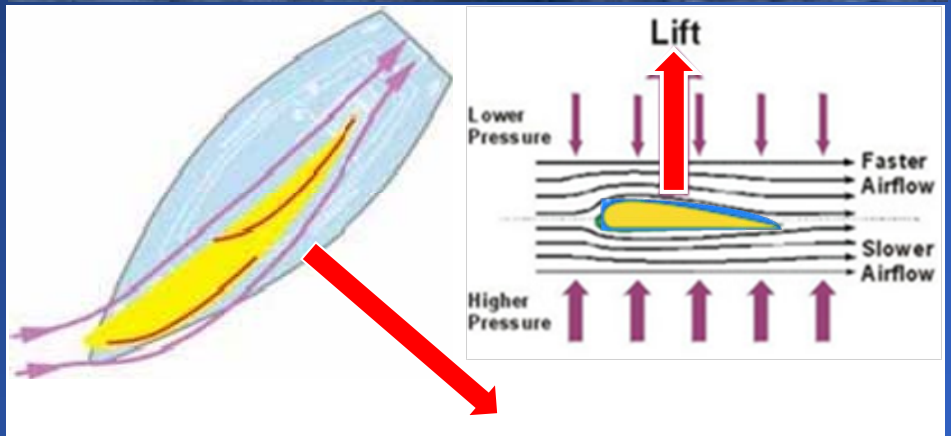
Levine et al, Circulation 1995

Lift (Pull)

Sailing upwind (close-hauled)



Lift is a force which acts perpendicular to the direction of flow

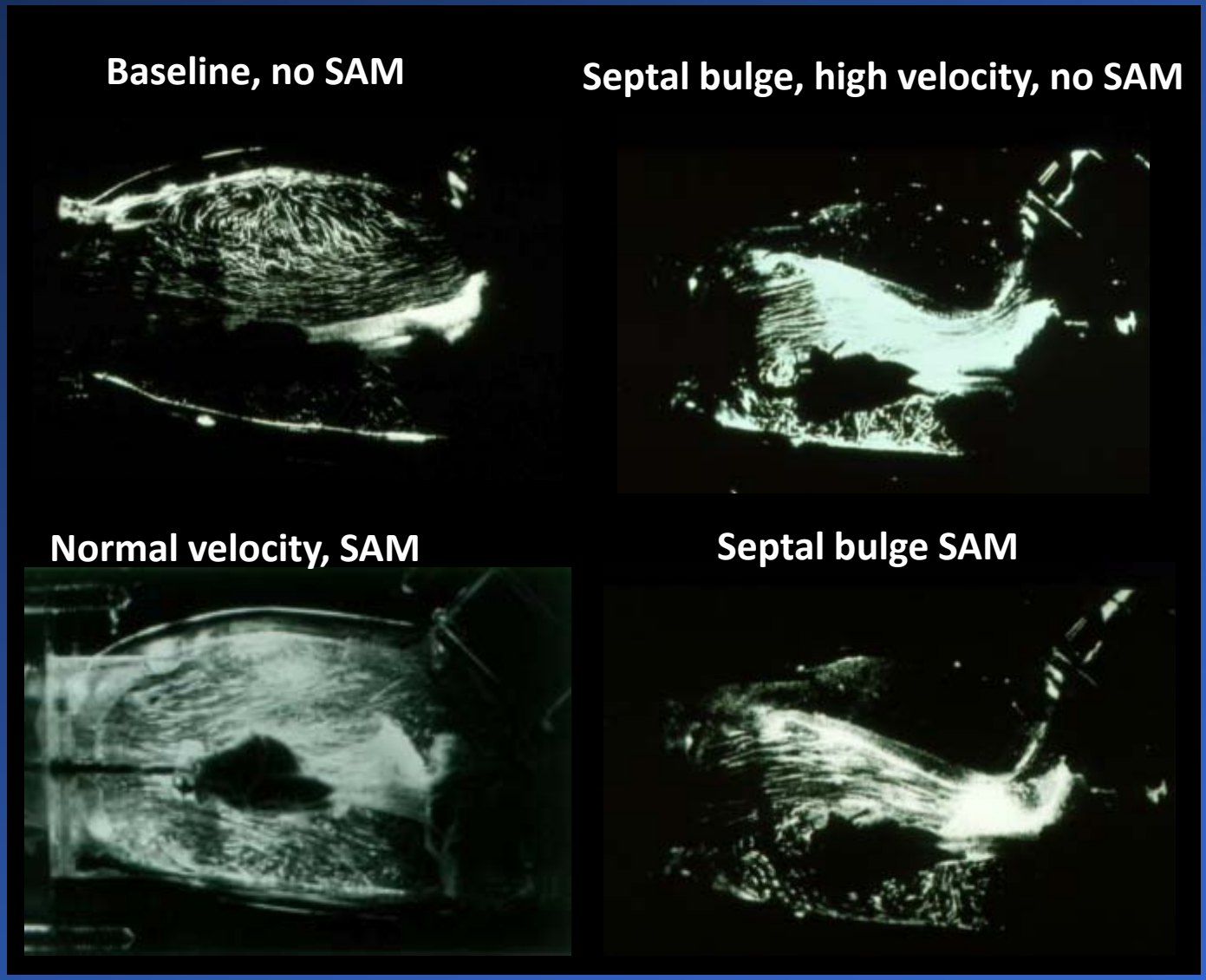


Drag (Push)

Sailing downwind (broad-reach)

Drag is a force which acts in the direction of flow

Lift does not explain most features of SAM, Drag explains all of them

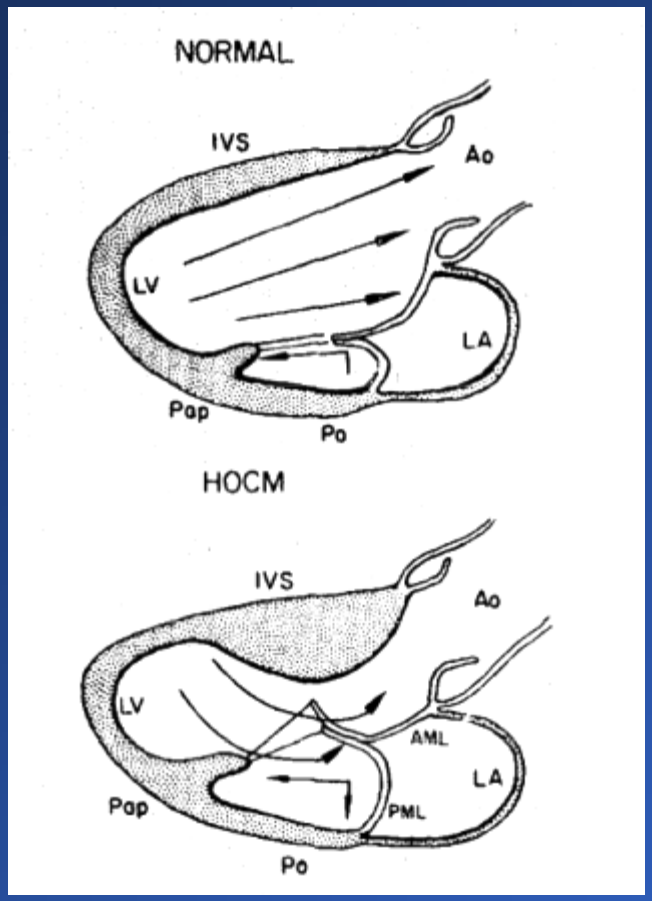


Particle flow visualization studies in a pulsatile flow model

Levine, Lefebvre, Guerrero, Vlahakes, Cape, He, Yoganathan, Levine 1994, Lefebvre, He, Levine, Yoganathan 1995

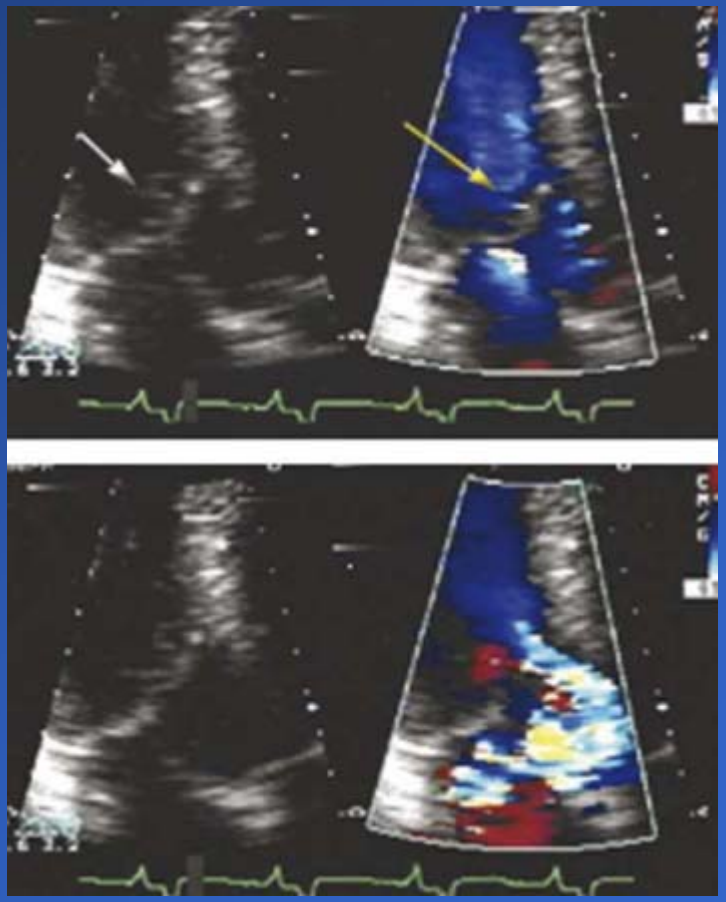
SAM in HCM: Result of an abnormal mitral apparatus exposed to an abnormal flow field

Septal bulge forces streamlines of flow to push anteriorly displaced MV from below



Schwammenthal, Levine
J Am Coll Cardiol 1996

SAM occurs at low velocities; SAM generates high velocities, not vice versa



t_0

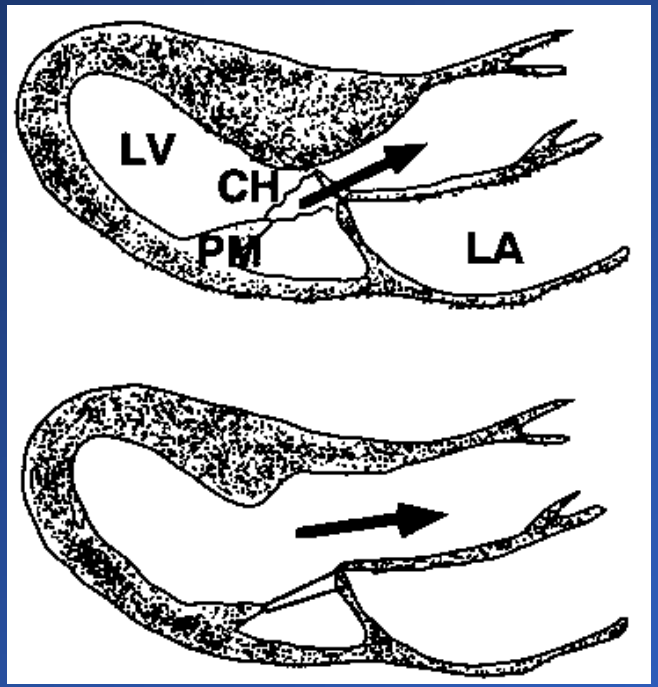
t_1

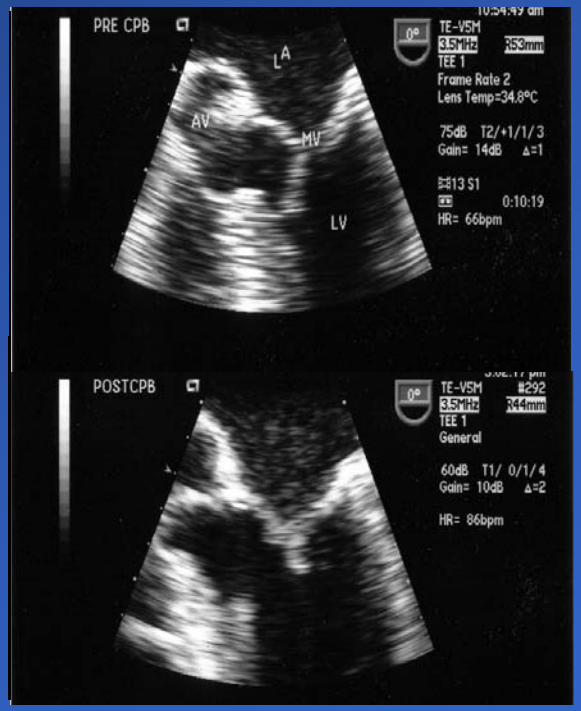
Sherrid MV. Progr
Cardiovasc Disease 2006

If it is not lift, how come myectomy abolishes SAM?

Myectomy allows flow "to take the straight path - above the valve rather than below - pushing the valve back

In addition to rectifying streamlines of flow, the change in outflow geometry positions the mitral valve more posteriorly with respect to the outflow tract





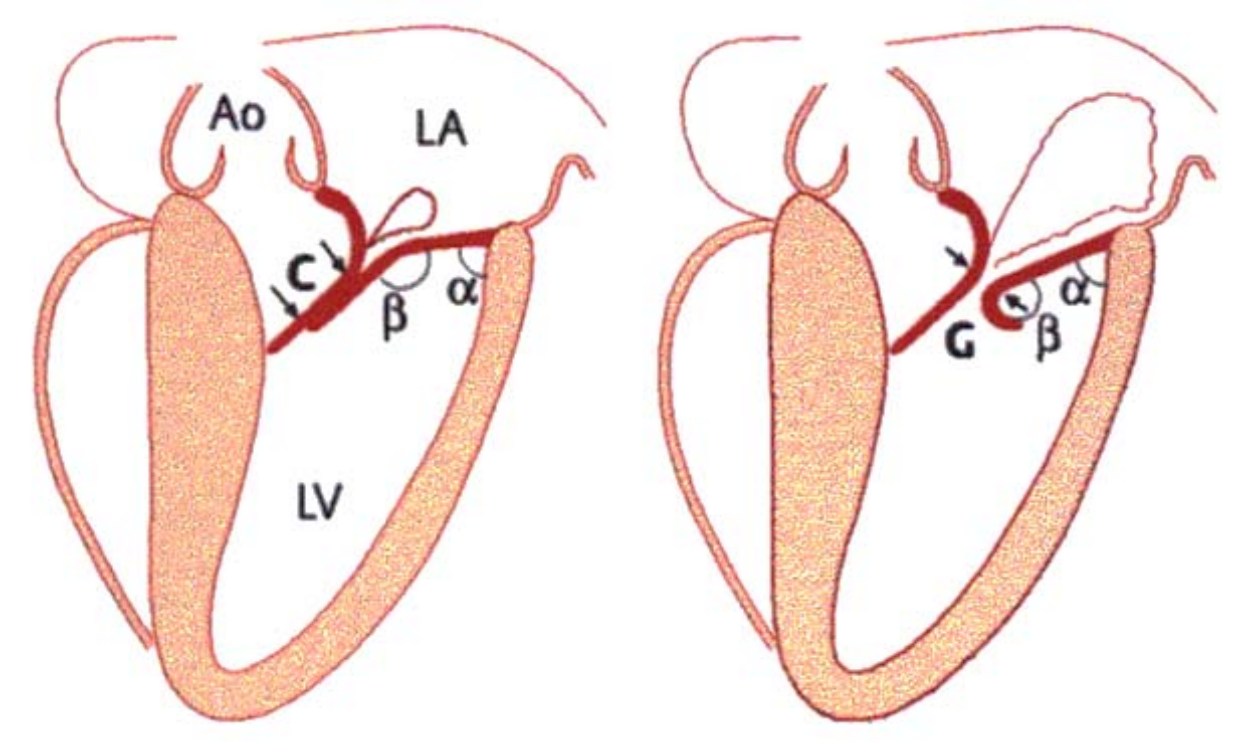
Nakatani, Schwammenthal, Lever, Levine, Lytle, Thomas. Am Heart J 1996

St. Luke's – Roosevelt Hospital

Mechanism of MR in SAM:

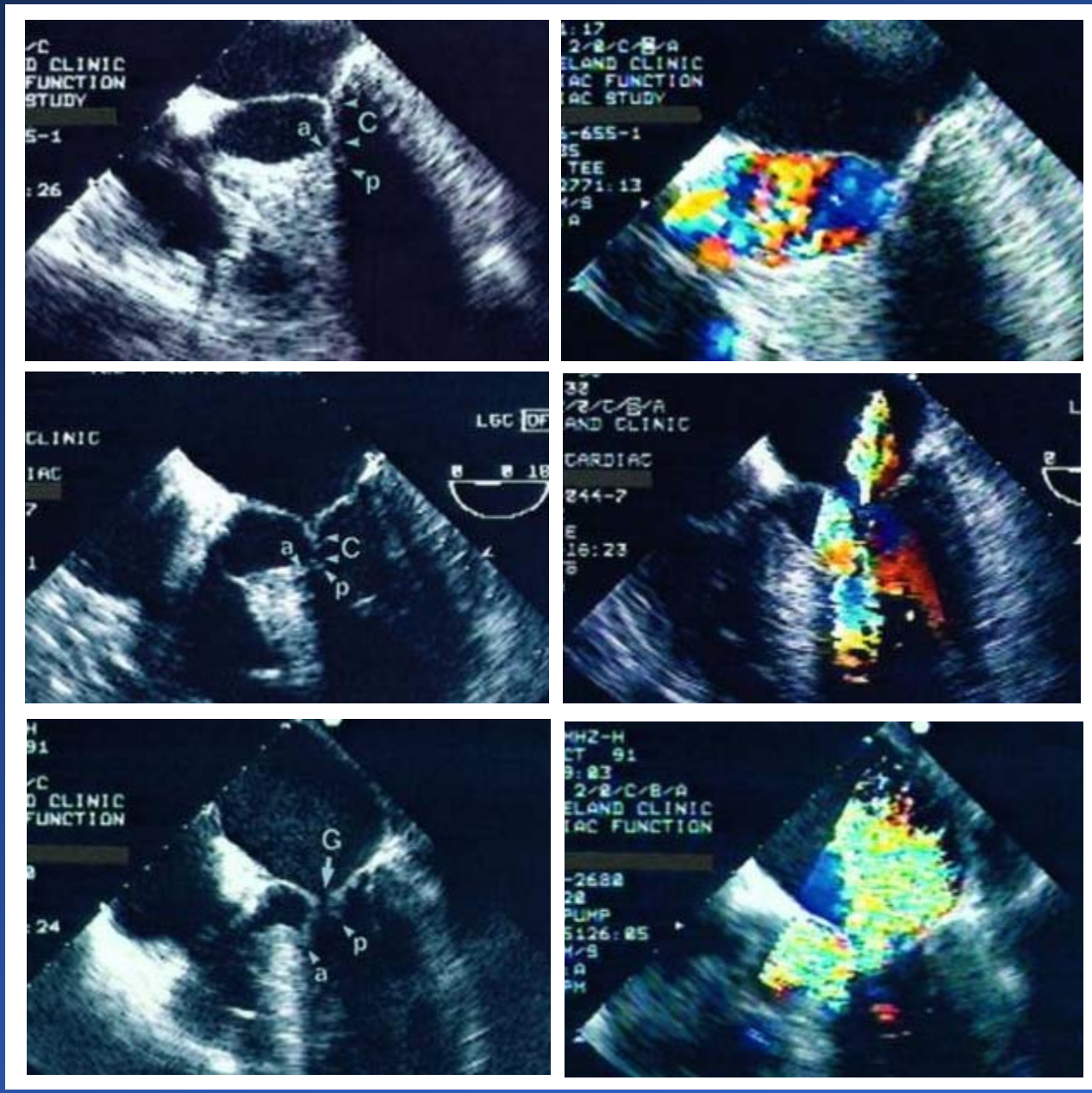
Why do patients with the same gradient have different degrees of MR?

Hypothesis: Coaptation length, and thus MR, depend on posterior leaflet length and mobility



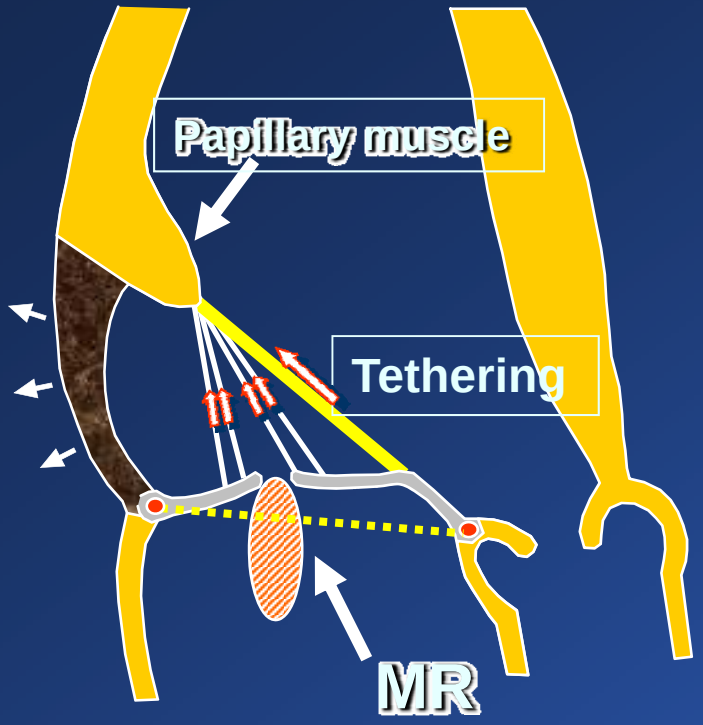
Left: Outflow tract obstruction without MR
Right: Obstruction with MR

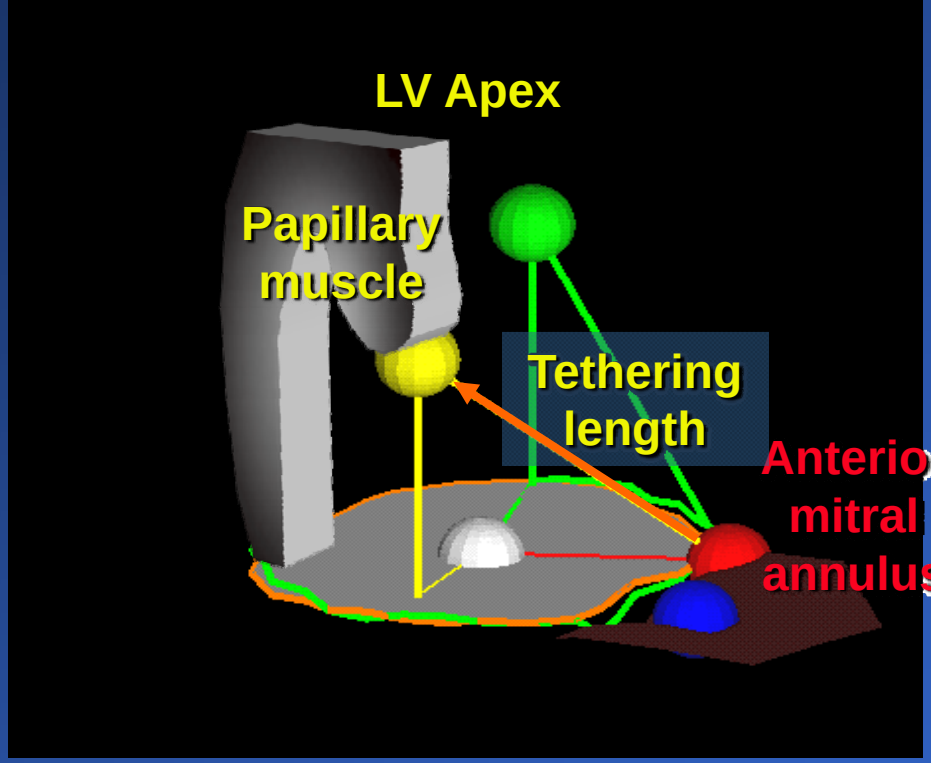
Schwammenthal, Nakatani, He, Hopmeyer, Sagie, Weyman, Lever, Yoganathan, Thomas and Levine. *Circulation* 1998



Schwammenthal, Nakatani, He, Hopmeyer, Sagie, Weyman, Lever, Yoganathan, Thomas and Levine. *Circulation* 1998

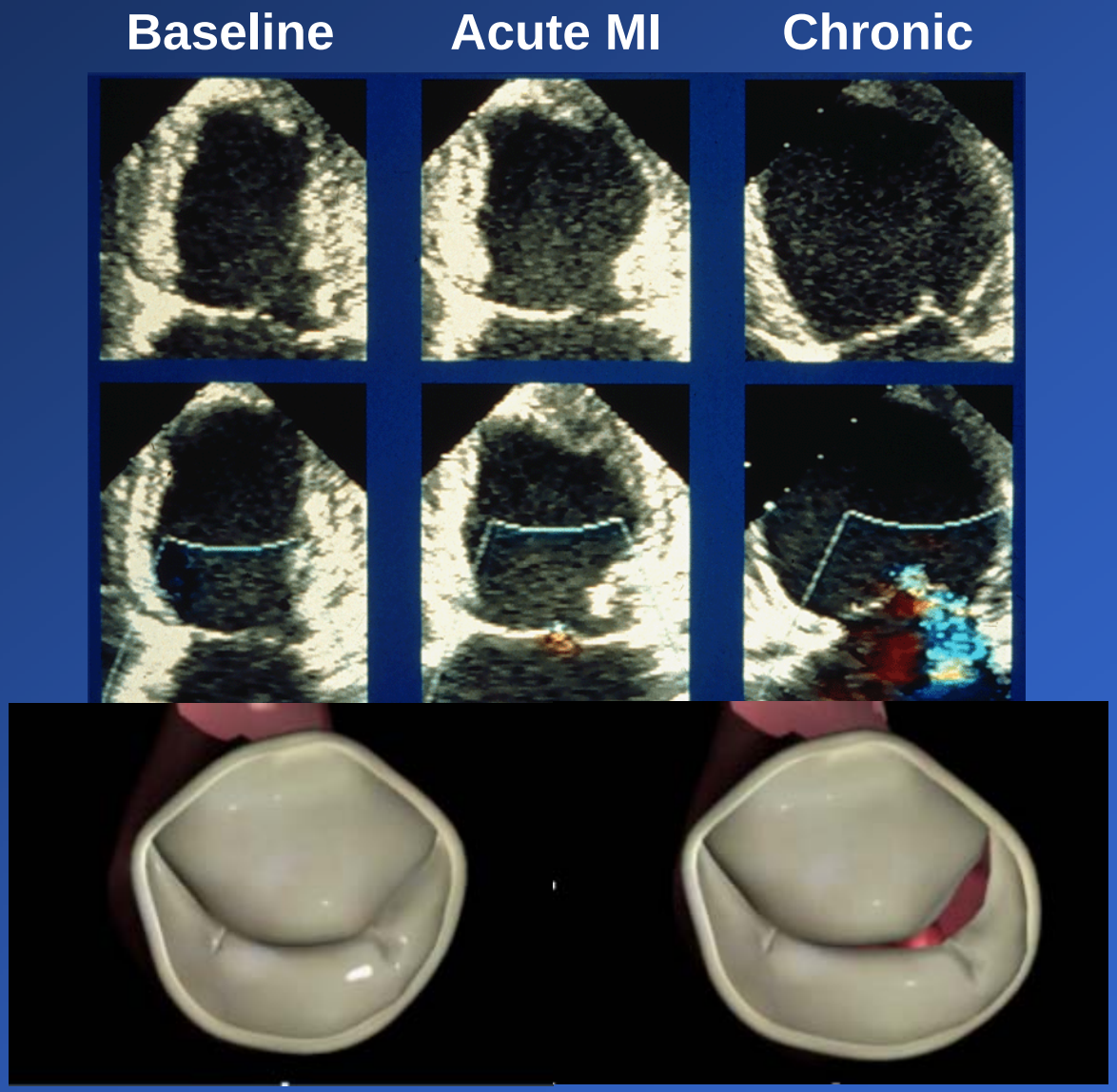
Functional Mitral Regurgitation



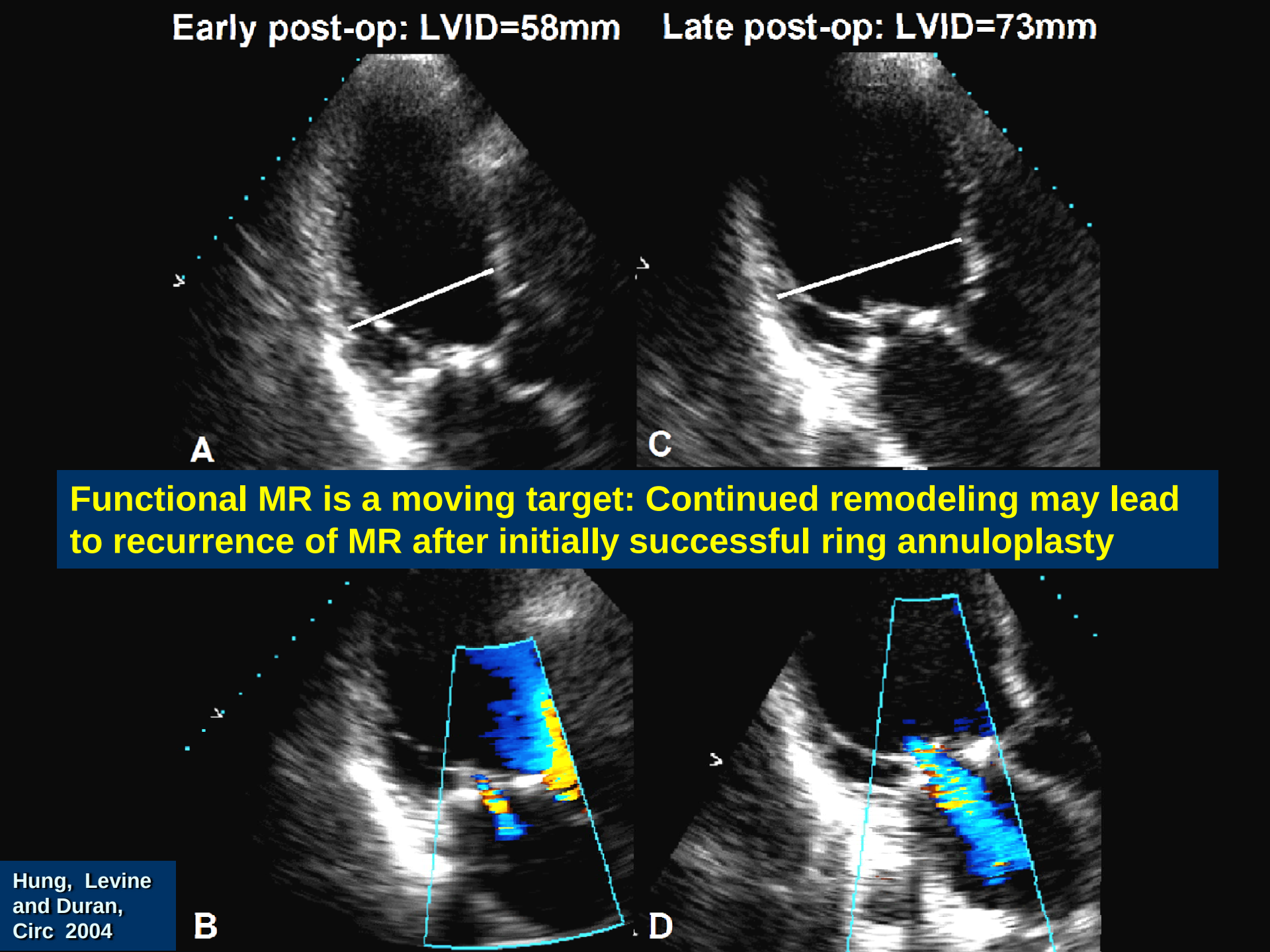


Functional MR is caused by papillary muscle displacement, increasing the tethering distance between the pap. muscles and the anterior mitral annulus as well as between the pap. muscles themselves

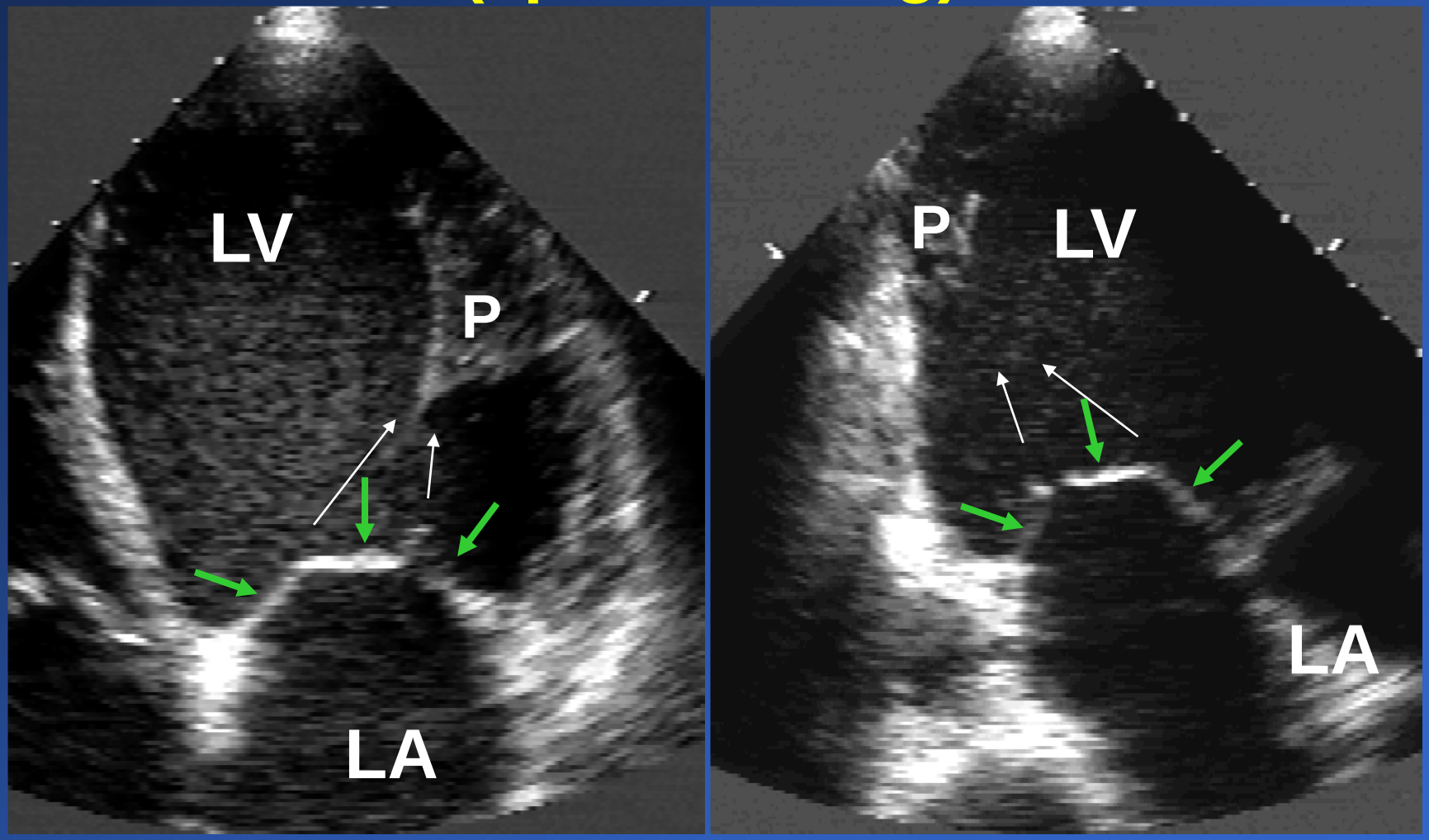
Ischemic MR is a special case of functional MR, asymmetrically effecting the posteromedial PM



Liel-Cohen, Levine, et al. Circulation 2000


Early post-op: LVID=58mm
Late post-op: LVID=73mm
A
C
Functional MR is a moving target: Continued remodeling may lead to recurrence of MR after initially successful ring annuloplasty
B
D
Hung, Levine and Duran, Circ 2004

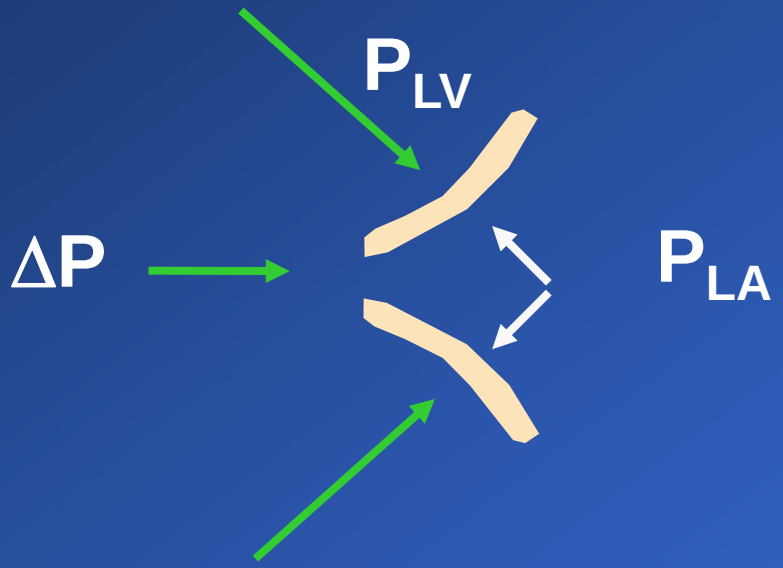
Shape of mitral valve in functional MR (apical tenting)



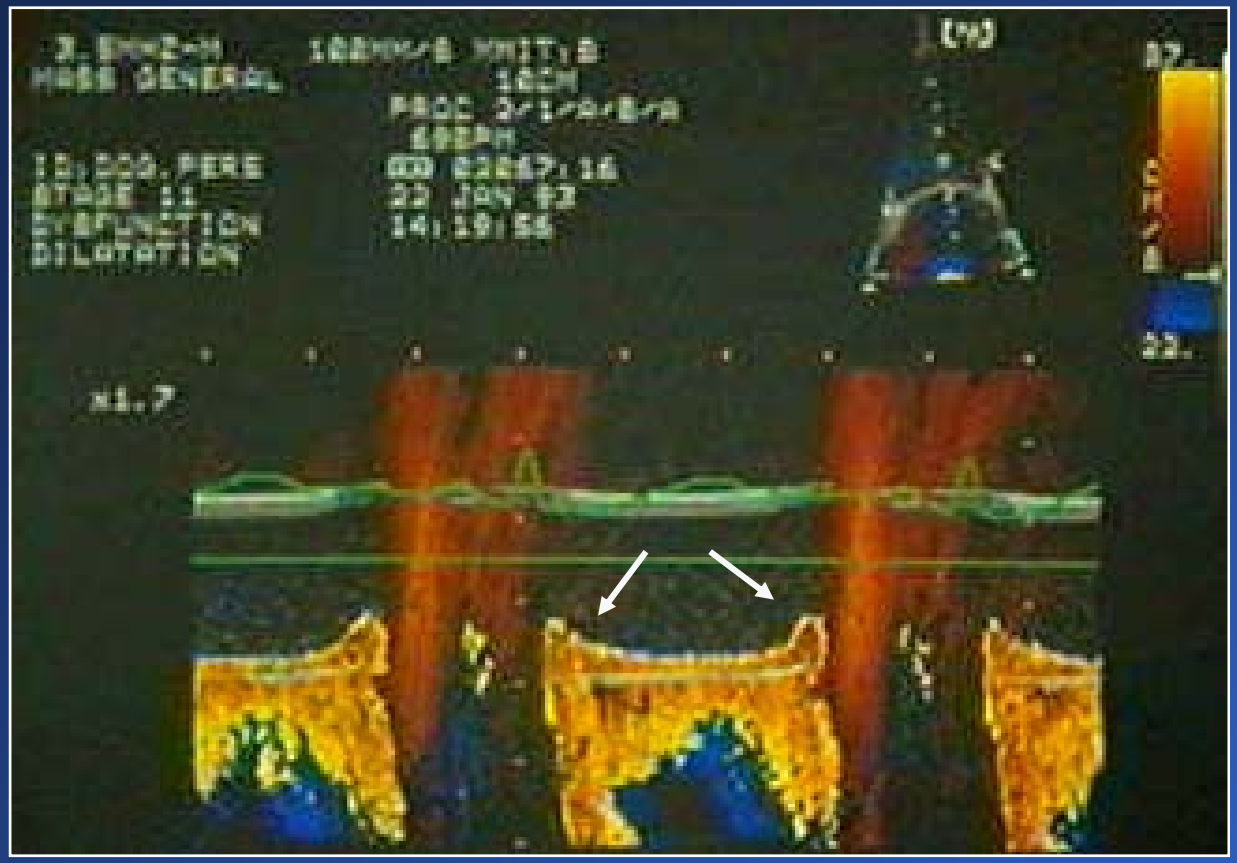
Implies that increased tethering forces are opposed by less effective closing forces

Tethering sets the stage for the pressure-sensitive orifice!

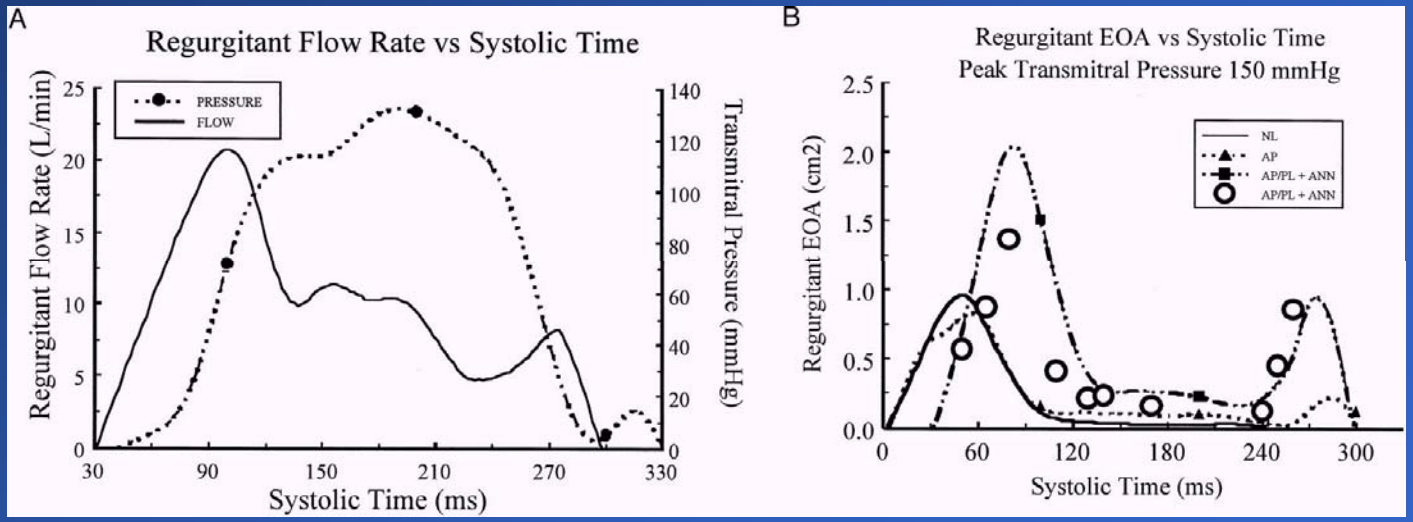
DYNAMIC ORIFICE



1. Increased tethering requires more force to close the mitral valve
2. The LV-LA (transmitral) pressure difference is the (only) closing force



Schwammenthal, Levine et al Circulation 1994



He, Fontaine, Schwammenthal , Levine al. Circulation 1997

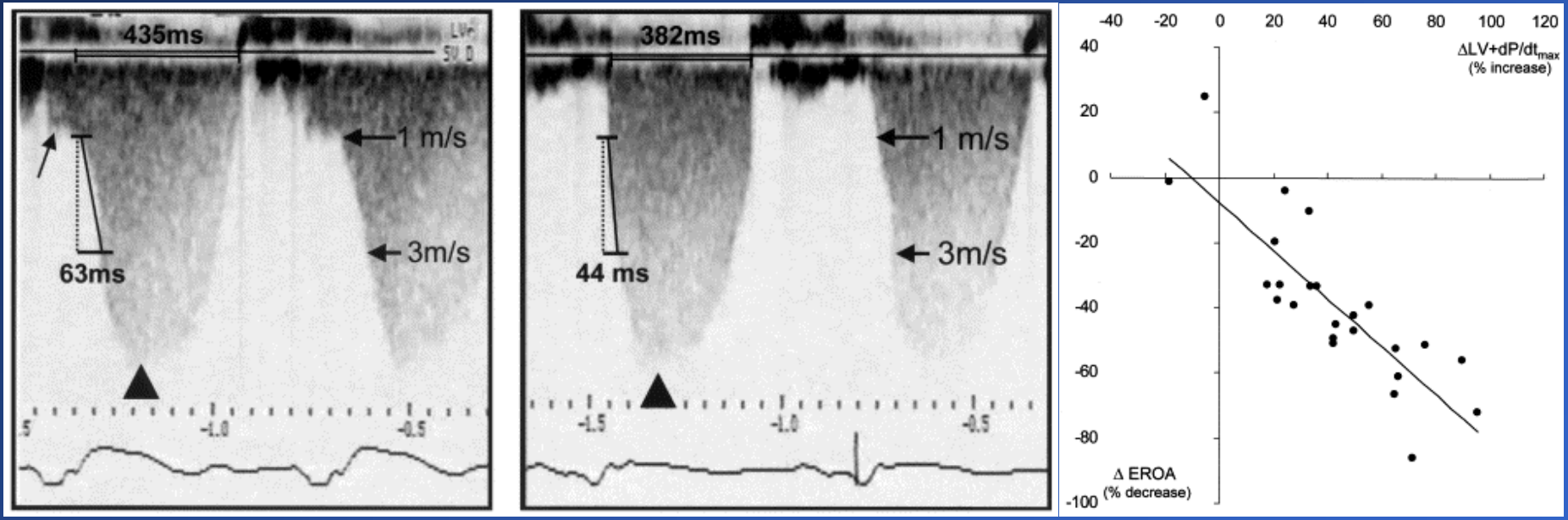
In order to treat ischemic MR: Address the mechanisms

- **Increasing closing force**
- **Decreasing tethering force**

Mechanism → **Therapy**

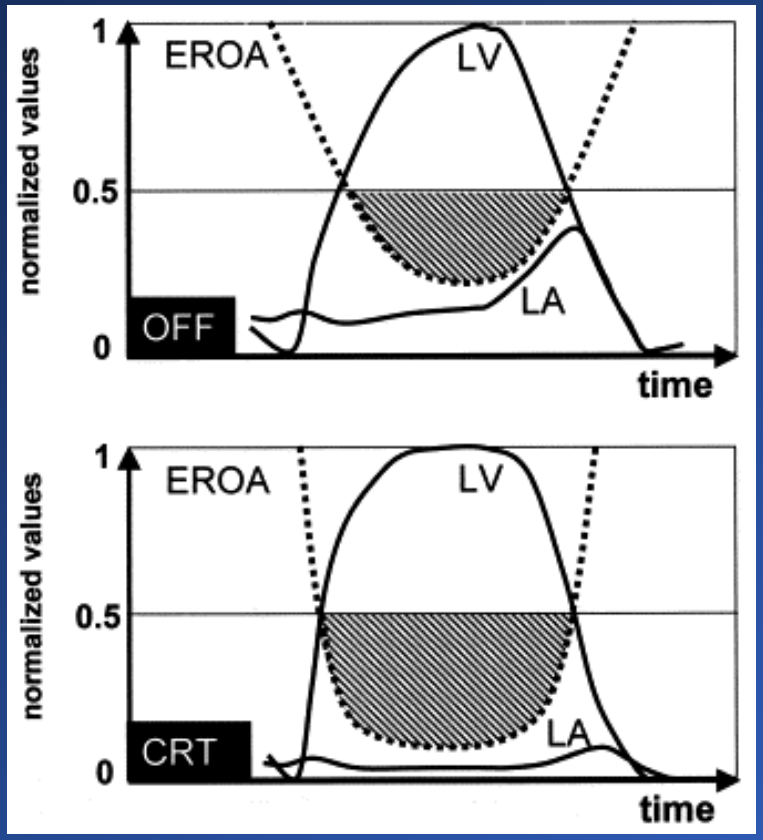
Acute increase of the closing force by CRT reduces functional MR in advanced systolic heart failure

Δ LV dp/dt correlates inversely with EROA



Breithardt, Sinha, Schwammenthal et al. JACC 2003

Acute effects of CRT on functional MR in advanced systolic heart failure



Shaded area represents time in systole during which EROA is below 50% of its initial value

OFF

Slow LV pressure rise, delayed development of an effective transmitral closing force, EROA remains large for a relatively long period.

CRT

Faster rise in LV pressure, so steeper rise in transmitral closing force. Consequently, the reduction in EROA occurs earlier, EROA reaches lower values and for a longer period of time

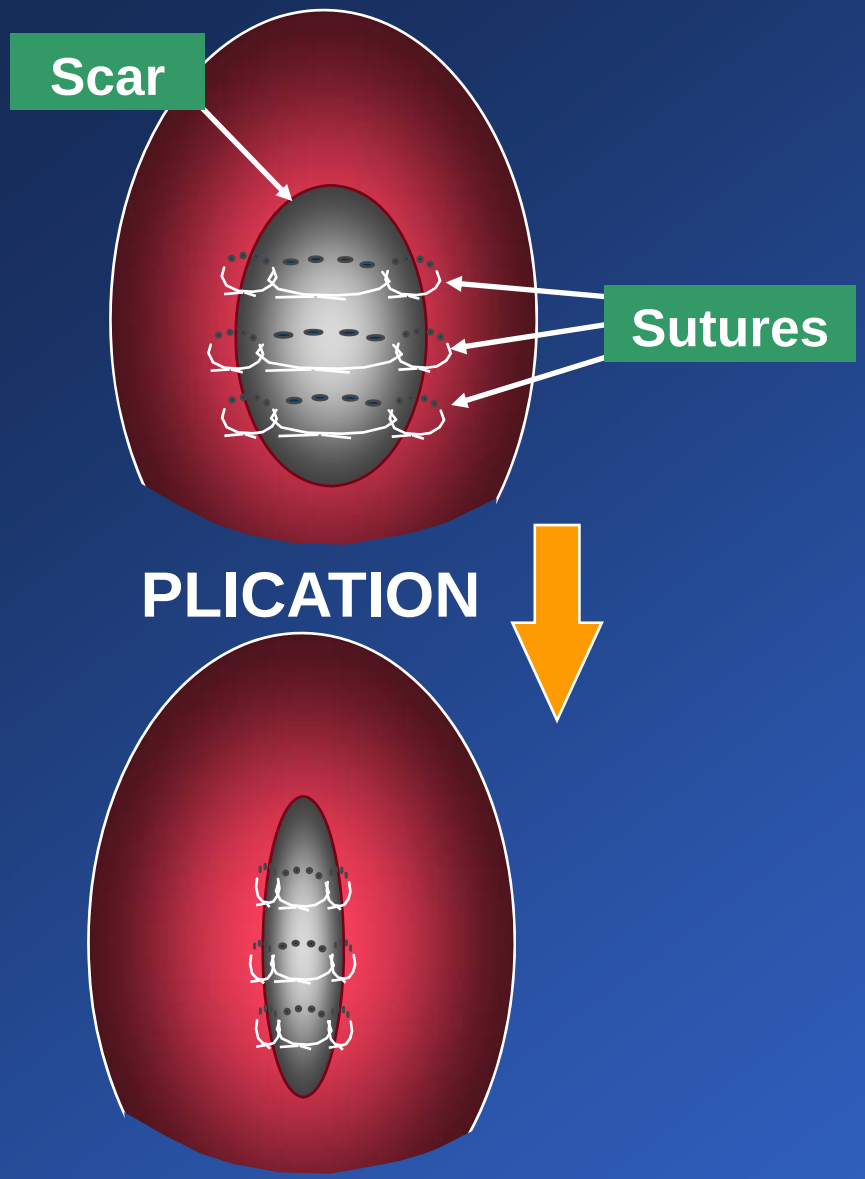
Breithardt, Sinha, Schwammenthal et al. JACC 2003

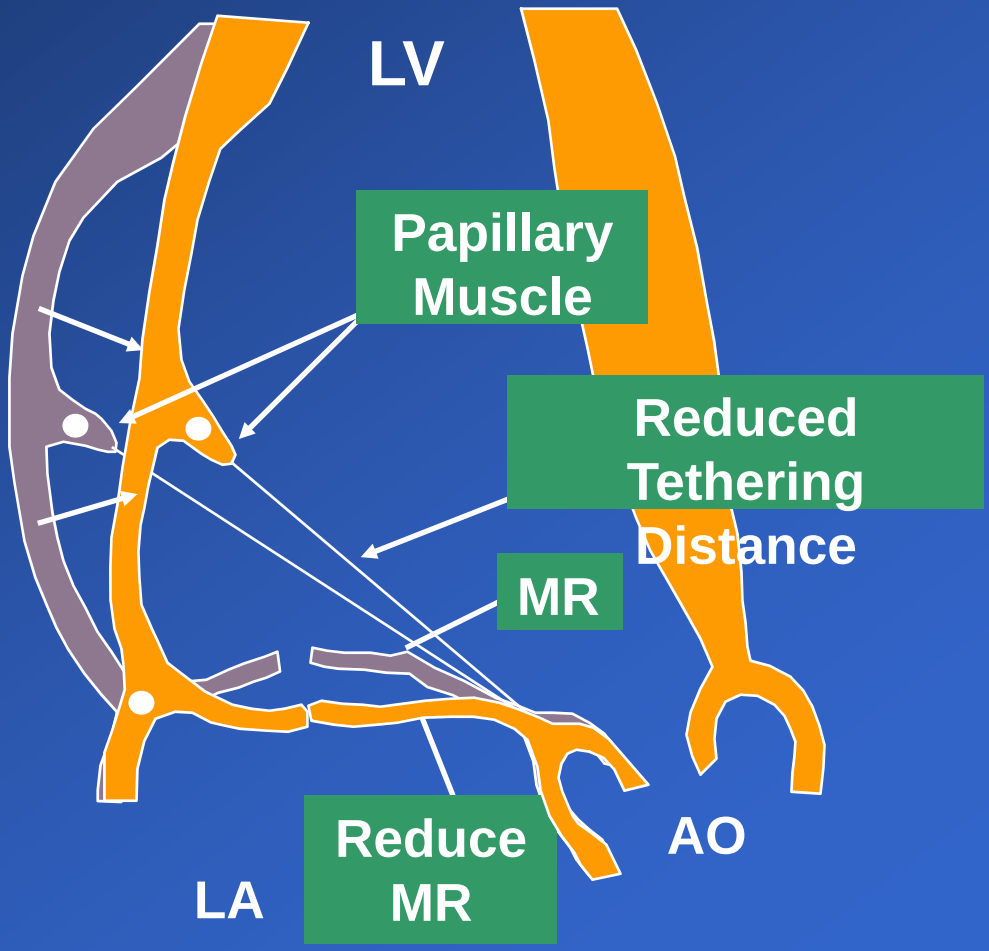
In order to treat ischemic MR: Address the mechanisms

- Increasing closing force
- Decreasing tethering force

Mechanism → Therapy

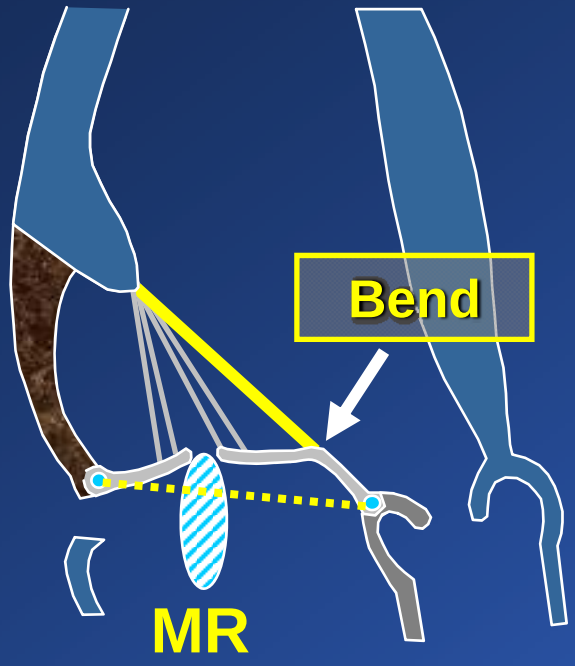
Reversing the Bulge

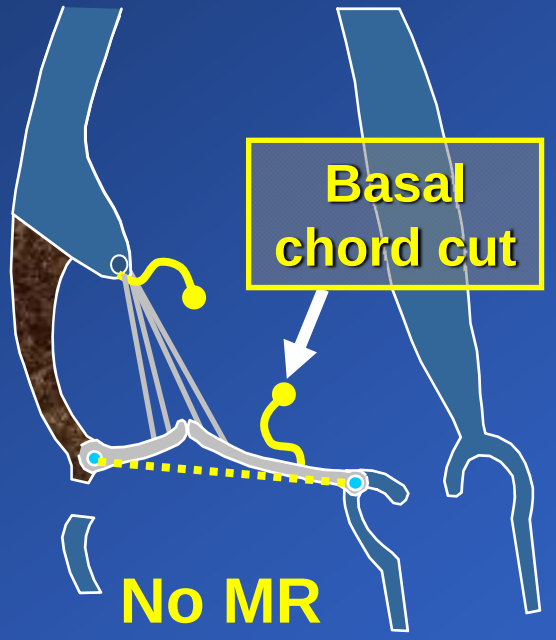


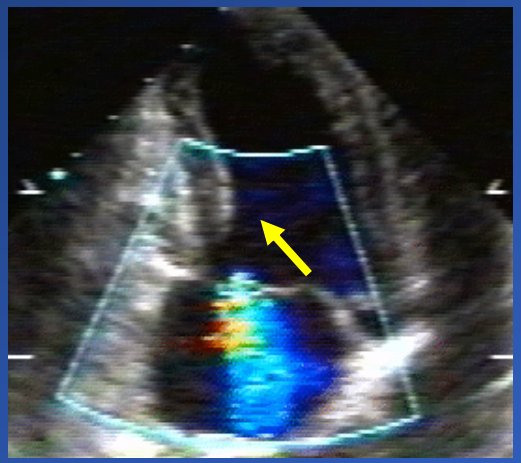


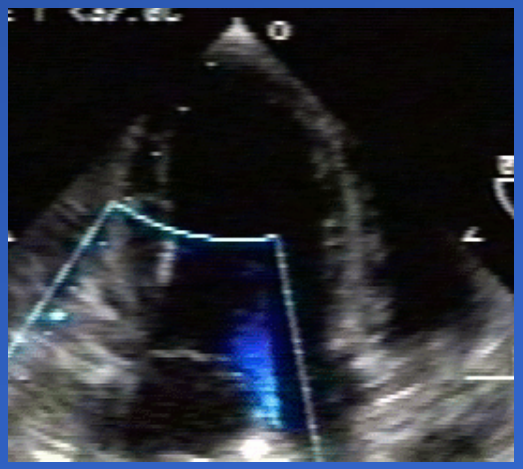
Liel-Cohen, Guerrero, Levine 2000

Chordal Cutting





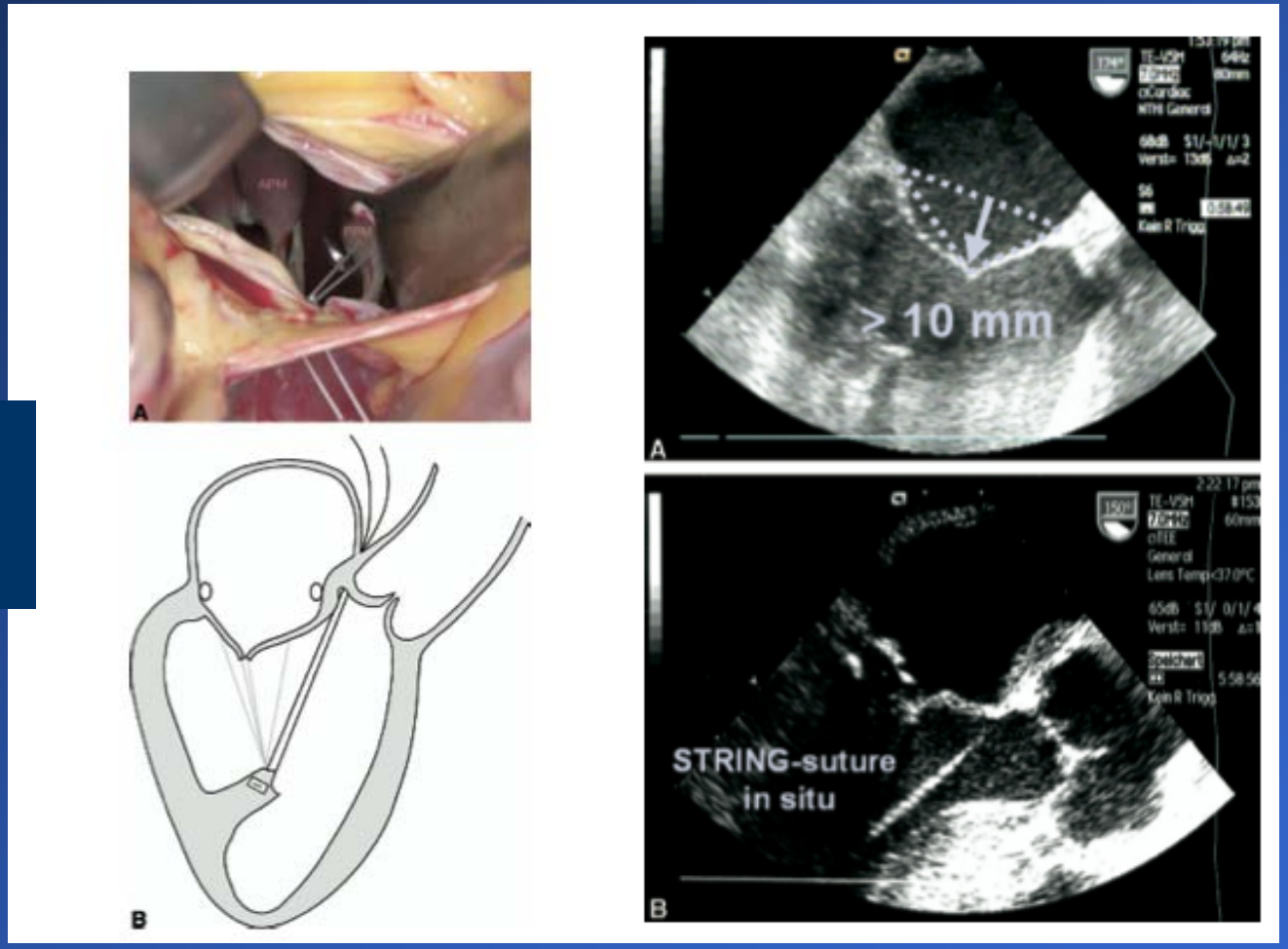




Messas, Levine, et al. Circulation 2002

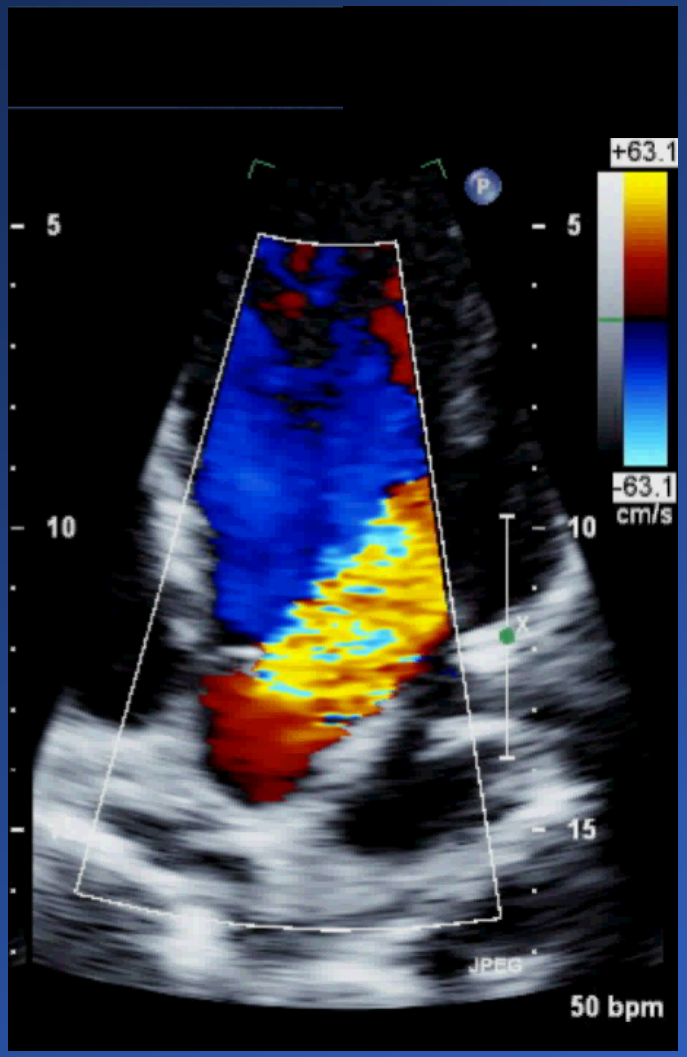
RING plus STRING: Papillary muscle repositioning as an adjunctive repair technique for ischemic MR

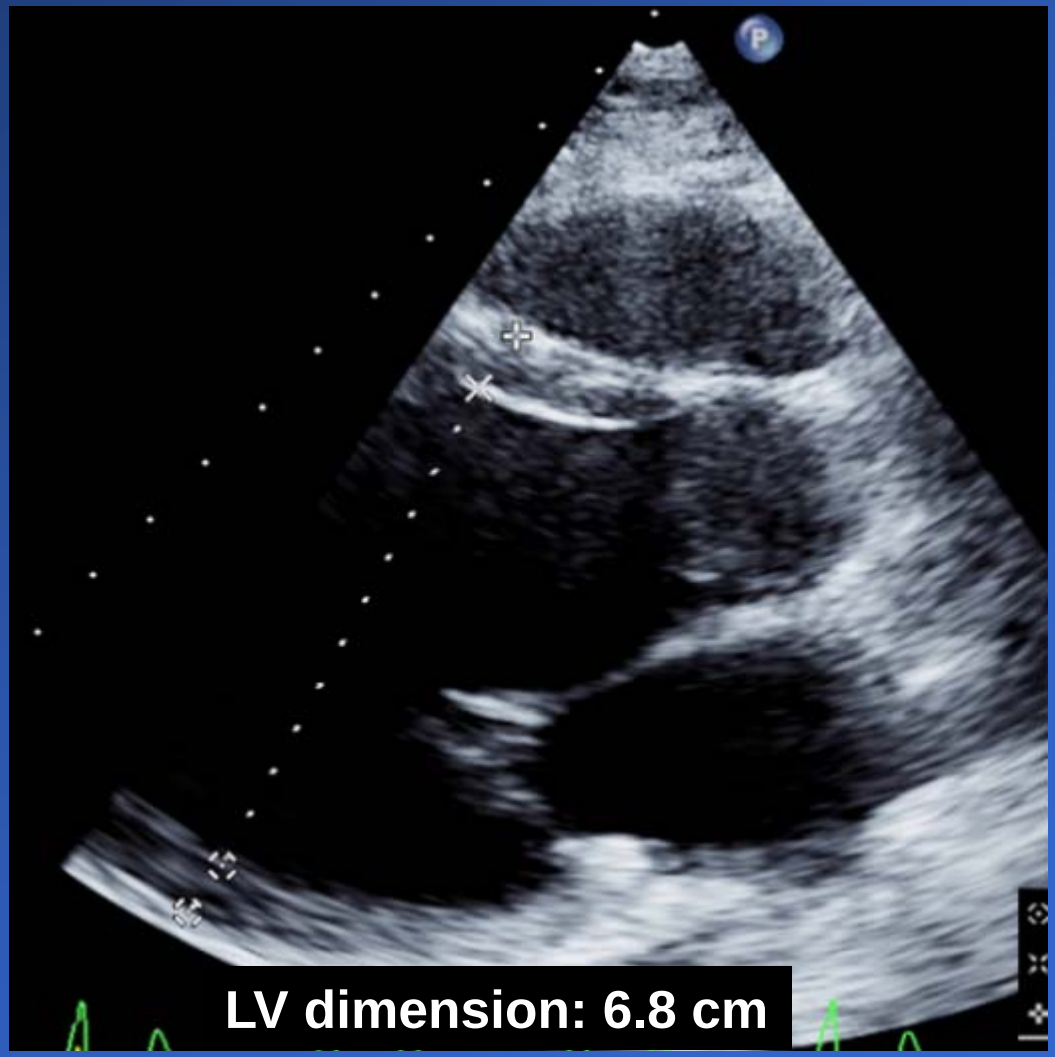
String adjusted off-pump



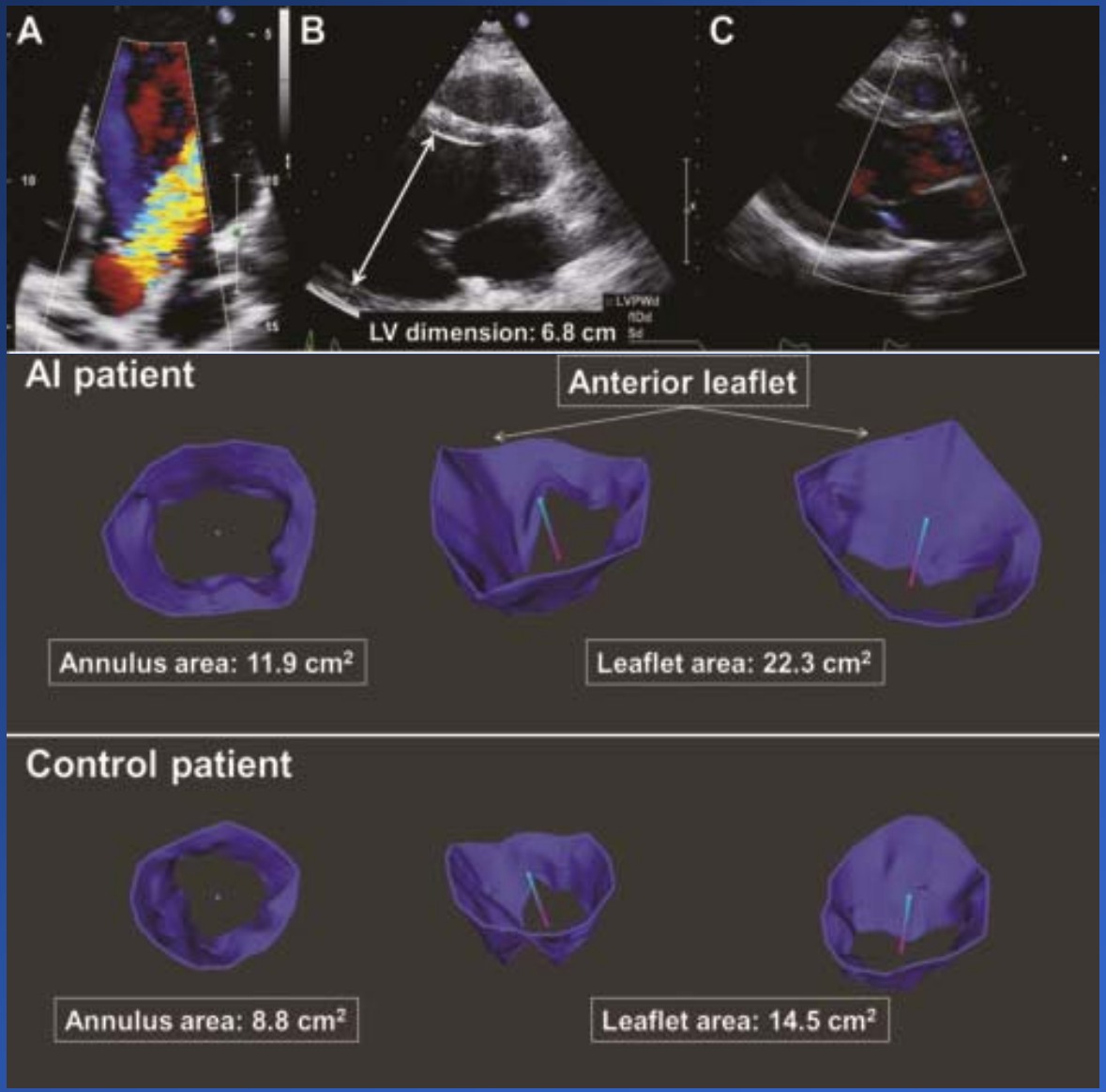
Langer, Schäfers J Thorac Cardiovsc Surg 2007

If LV dilatation causes functional MR, how come AR patients, those with the largest LVs, rarely have significant MR?



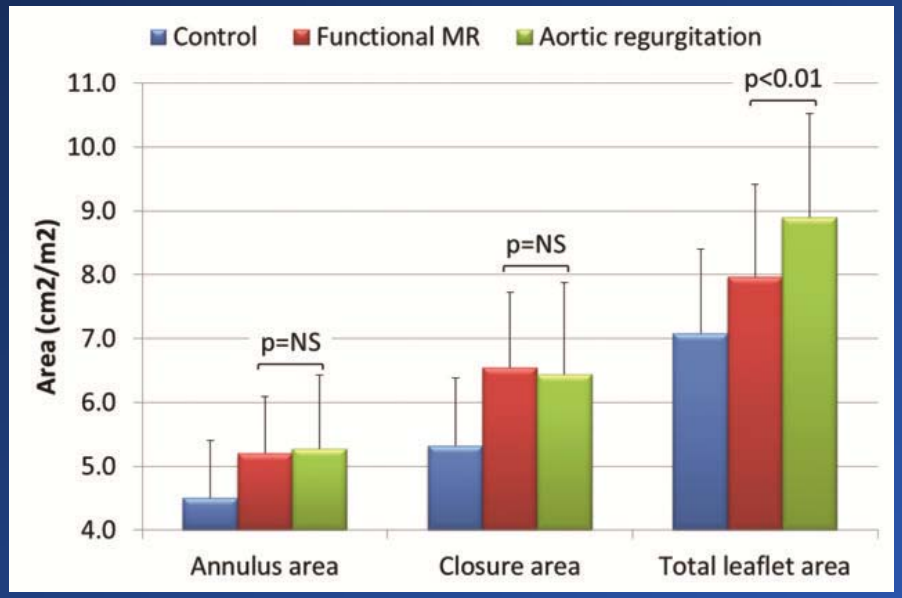


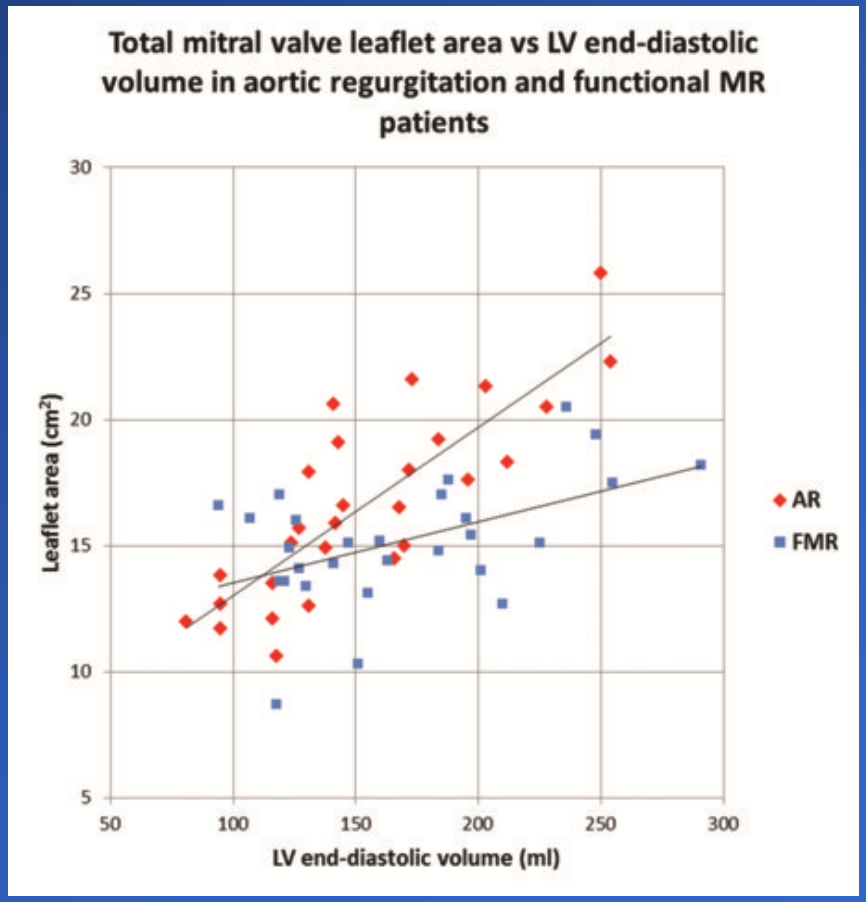
Hypothesis: Compensatory mitral valve enlargement!



Beaudoin , Handschumacher, Zeng , Hung, Morris, Levine, Schwammenthal. *J Am Coll Cardiol* 2013 (in press)

Mitral Valve Enlargement in Chronic Aortic Regurgitation as a Compensatory Mechanism to Prevent Functional Mitral Regurgitation in the Dilated Left Ventricle





Beaudoin, Handschumacher, Zeng, Hung, Morris, Levine, Schwammenthal.
J Am Coll Cardiol 2013 (in press)

Functional MR may result from inadequate compensation of tethering by an insufficient degree of compensatory MV enlargement

A Unified Geometric Model

There are only 2 mechanistic-geometric principles of systolic mitral valve dysfunction:

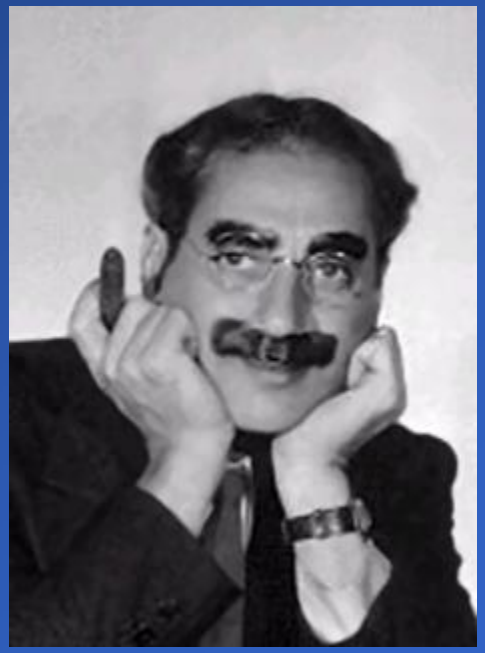
- **Reduced Tethering**
- **Increased Tethering**

(Even the Carpentier classification collapses into these two)

Geometric Principles of Systolic Mitral Valve Dysfunction

Prinicple mechanism	Length of mitral leaflets/chordae	Papillary muscle position	Symmetry	Result
Reduced leaflet tethering (decreased leaflet tension)	Elongated (increased)	Anterior displacement	Symmetric	SAM without significant MR
	Elongated	Anterior displacement	Asymmetric	SAM with significant MR
	Elongated	Superior (or no) displacement	Symmetric	MVP without significant MR
	Elongated	Superior (or no) displacement	Asymmetric	MVP with significant MR
Increased leaflet tethering (increased leaflet tension)	Normal	Posterior, lateral, apical displacem.	Symmetric/ asymmetric	Incomplete mitral valve closure (functional MR)
	Shortened (reduced)	Normal (apical/lateral)	Symmetric/ asymmetric	(incomplete mitral valve closure) organic MR

“These are my principles;
if you don’t like them - I have others”



Groucho Marx
1890-1977