

# ADVANCES IN CARDIAC ARRHYTHMIAS *and* GREAT INNOVATIONS IN CARDIOLOGY



*Heart failure with preserved left ventricular ejection fraction:  
What is the evidence ?*

## Scientific Committee

Malcolm Bell, *Usa*  
Martin Borggrefe, *Germany*  
Amir Leman, *Usa*  
Jean Francois Leclercq, *France*  
Dipen Shah, *India*

## Organizers

Carlo Budano, *Italy*  
Davide Castagno, *Italy*  
Monica Andriani, *Italy*

Turin

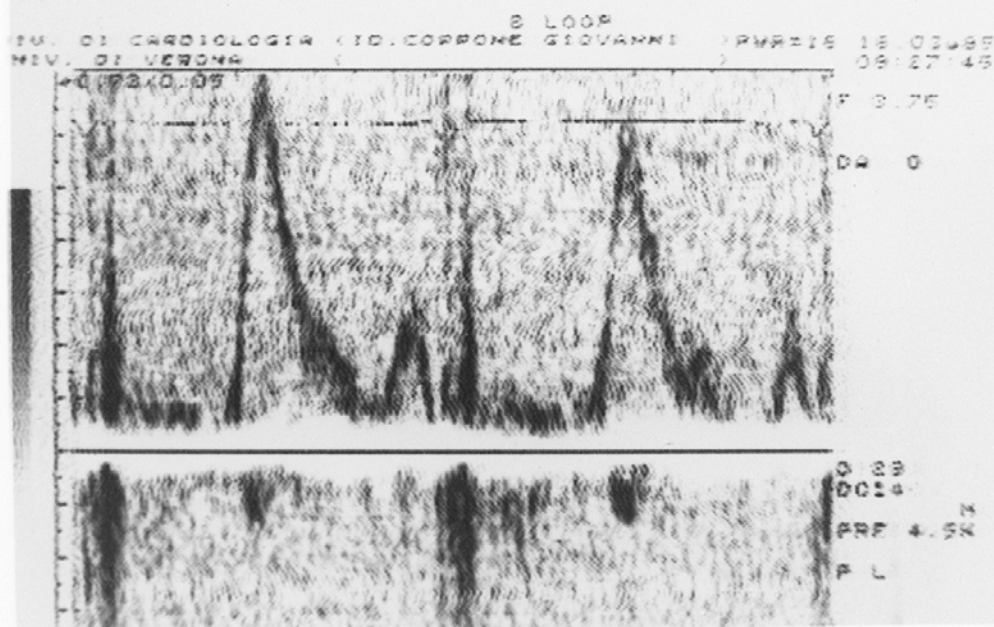
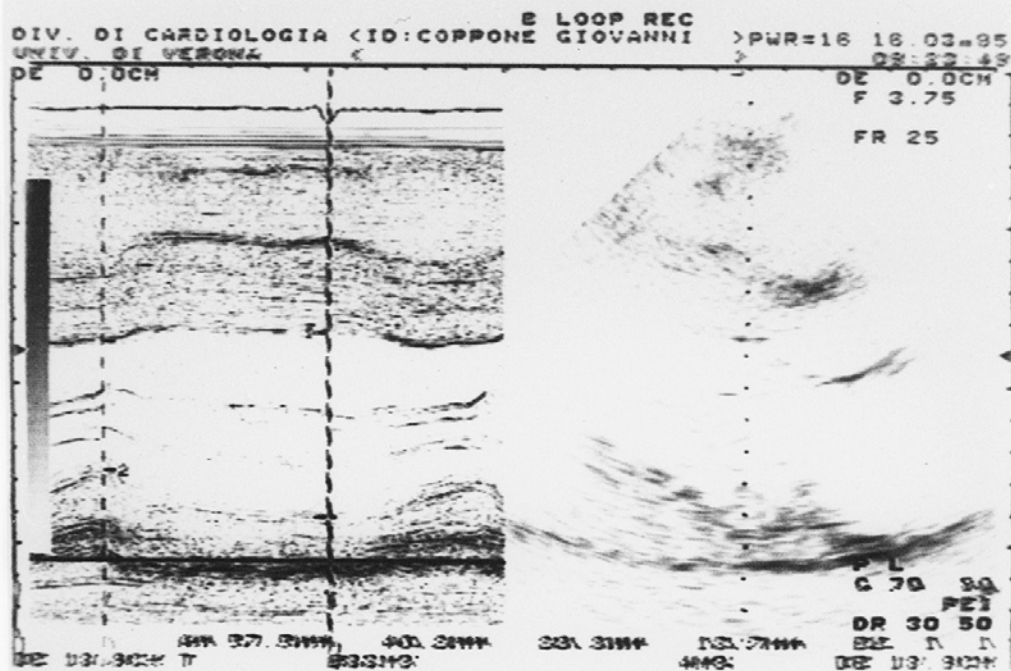
October 25-27, 2018

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Università degli Studi di Torino

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della Scienza di Torino



# Clinical features of SHF and NEFHF

|                                                  | <u>HF with reduced EF (SHF)</u>          | <u>HF with normal EF (HFNEF)</u>                                       |
|--------------------------------------------------|------------------------------------------|------------------------------------------------------------------------|
| gender                                           | M>F                                      | F>M                                                                    |
| age                                              | 50-60 years                              | 60-70 years                                                            |
| aetiology                                        | Myocardial infarction;<br>idiopathic DCM | Hypertension ± diabetes;<br>Atrial fibrillation<br>Transient ischaemia |
| Clinical progress                                | Persistent HF                            | Often episodic HF                                                      |
| Ventricular remodeling<br>(increased LV volumes) | +++                                      | 0                                                                      |
| LVH                                              | +/-                                      | +++                                                                    |
| Dyssynchrony                                     | common                                   | ? less common                                                          |
| Mitral inflow pattern                            | RFP or ARP                               | ARP                                                                    |
| Peak mitral annular<br>systolic velocity         | Markedly reduced                         | Moderately reduced                                                     |
| Peak mitral annular early<br>diastolic velocity  | Markedly reduced                         | Moderately reduced                                                     |
| LA pressure                                      | raised                                   | raised                                                                 |
| LA volume                                        | increased                                | increased                                                              |

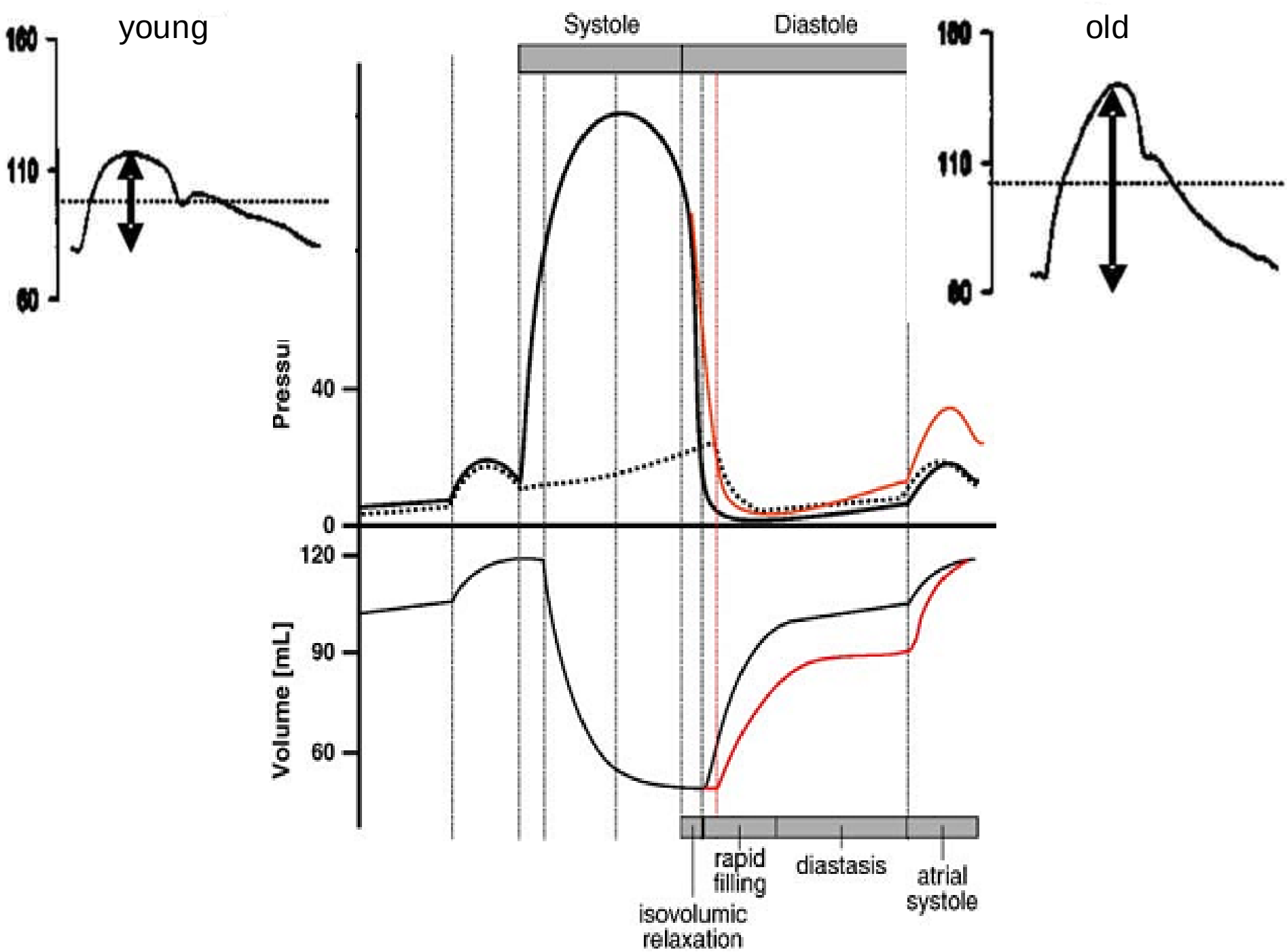
# Guideline recommendations for treatment of HFNEF

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| <i>Recommendation</i>                                                                                                             | <i>Class</i>     | <i>Level of evidence</i> |
|-----------------------------------------------------------------------------------------------------------------------------------|------------------|--------------------------|
| Control of hypertension                                                                                                           | I                | A                        |
| Rate control in atrial fibrillation                                                                                               | I                | C                        |
| Diuretics for pulmonary congestion and peripheral edema                                                                           | I                | C                        |
| Coronary revascularization in coronary artery disease with ischemia-induced cardiac dysfunction                                   | IIa              | C                        |
| Restoration and maintenance of sinus rhythm in atrial fibrillation                                                                | IIb              | C                        |
| $\beta$ -Blockers, ACE inhibitors, angiotensin II receptor blockers, calcium antagonists in patients with controlled hypertension | IIb <sup>a</sup> | C                        |

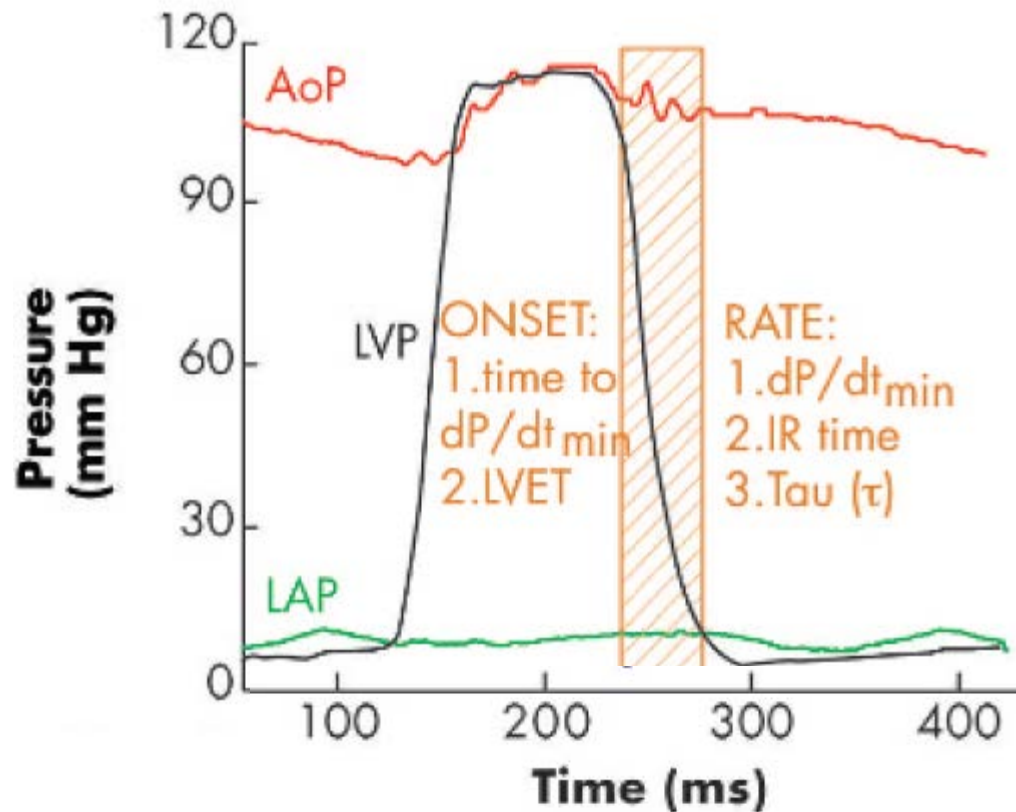
According to American College of Cardiology/American Heart Association (Hunt et al. 2005) and European Society of Cardiology guidelines (Swedberg et al. 2005).

<sup>a</sup> Differs between ACC/AHA (class IIb) and European (class IIa) guidelines.



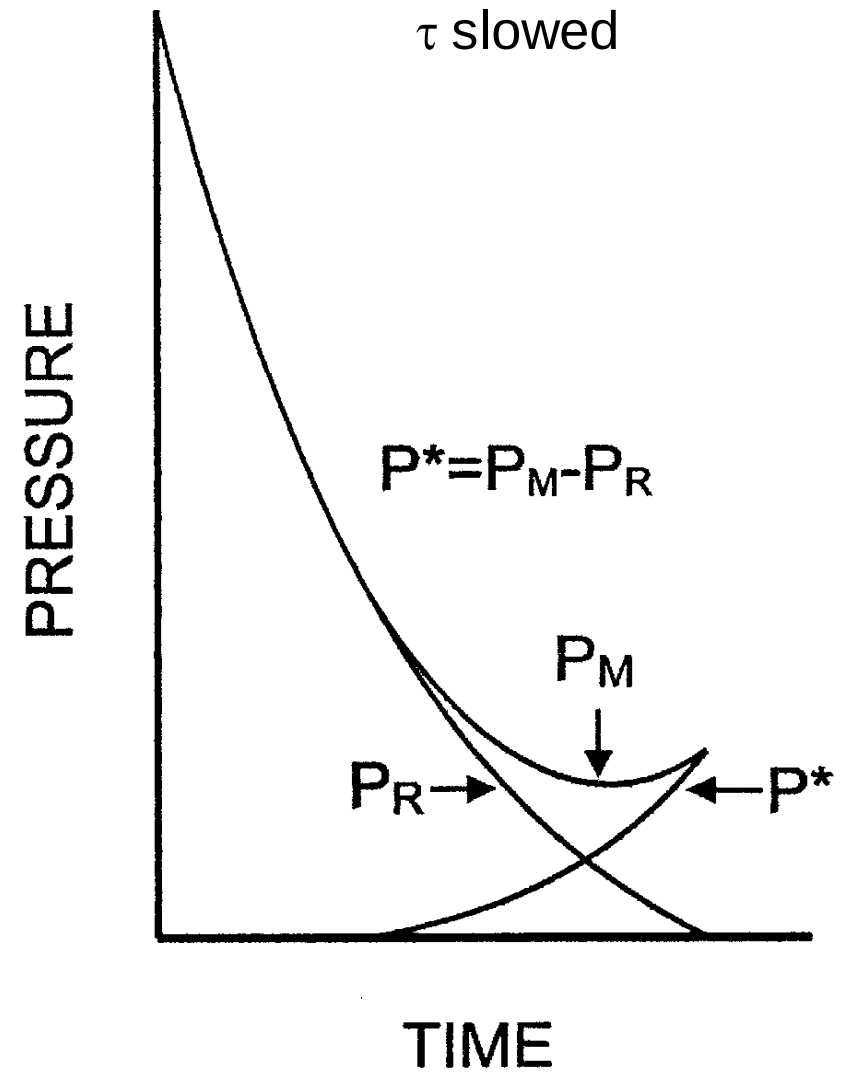
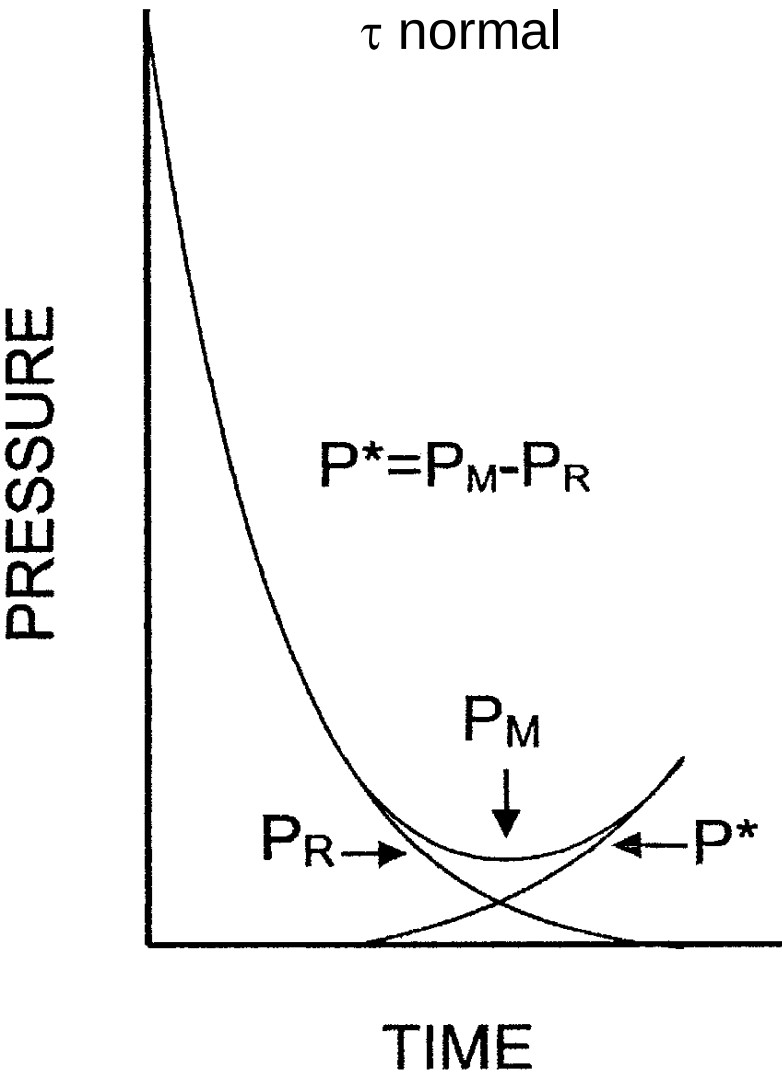
# Isovolumetric relaxation

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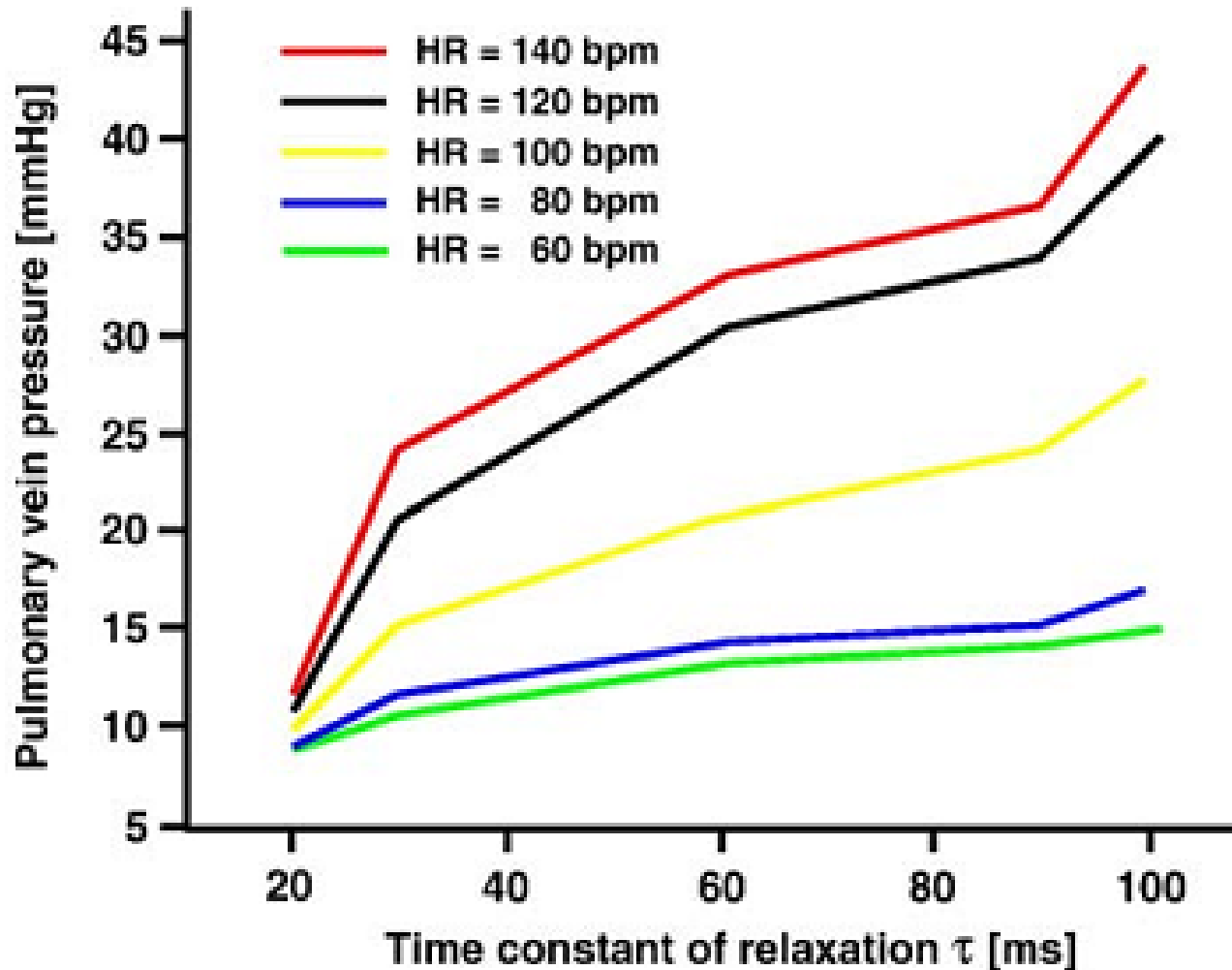
# Effects of prolonged relaxation on LV diastolic pressures

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# Interplay between $\tau$ and heart rate

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# Guideline recommendations for treatment of HFNEF

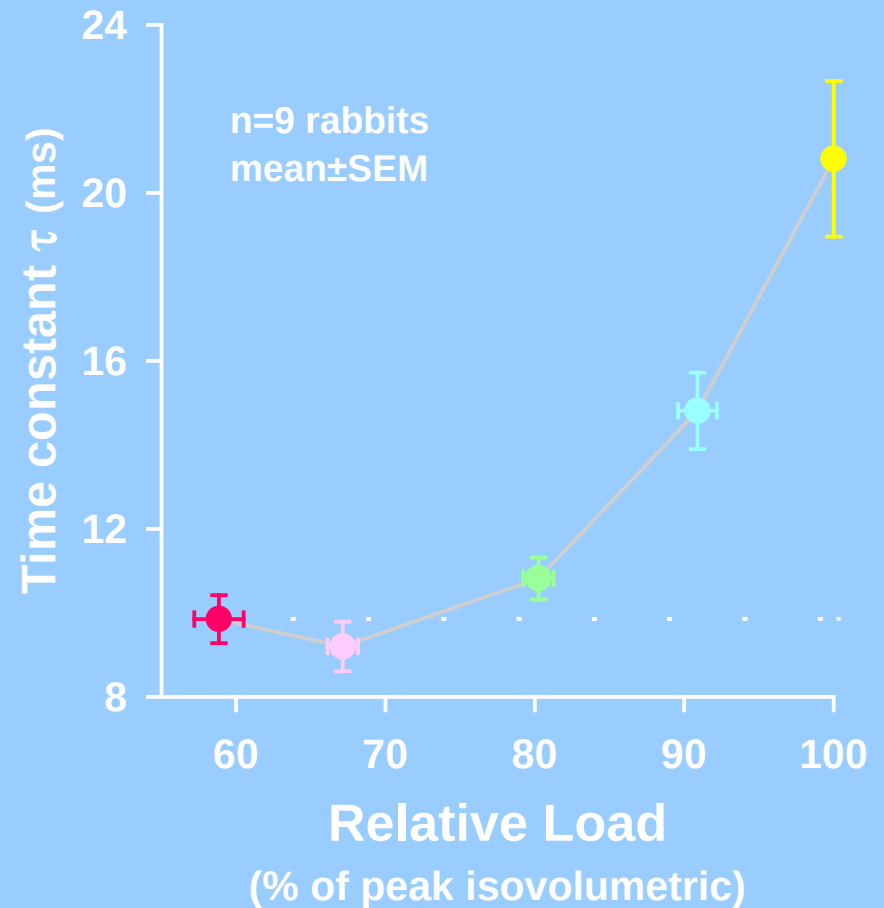
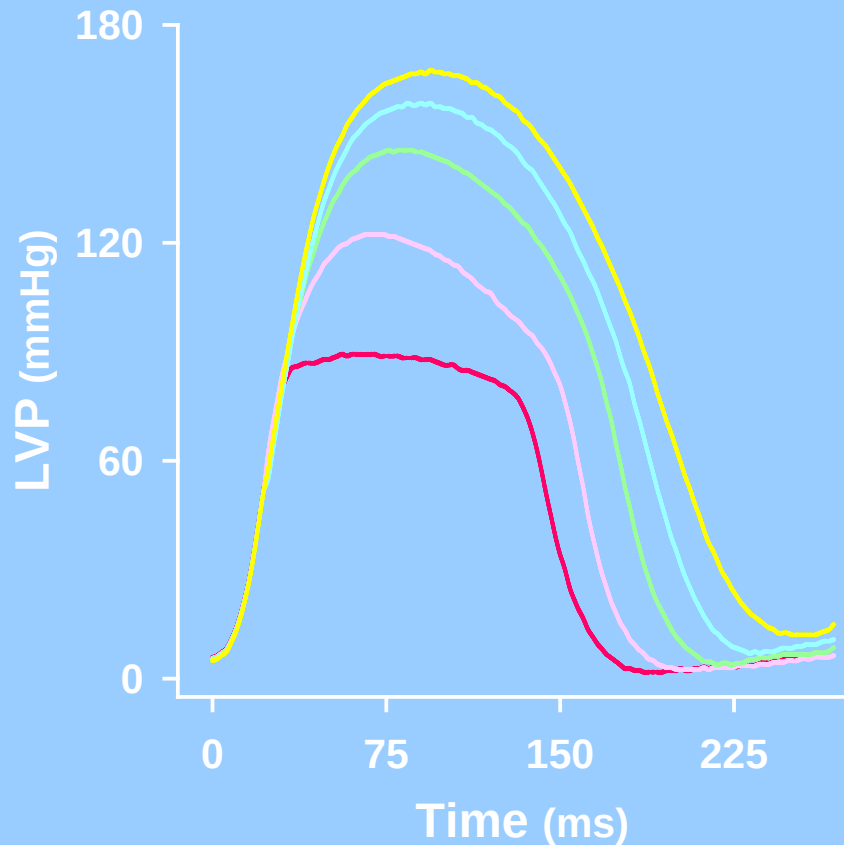
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| <i>Recommendation</i>                                                                                                             | <i>Class</i>     | <i>Level of evidence</i> |
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| Diuretics for pulmonary congestion and peripheral edema                                                                           | I                | C                        |
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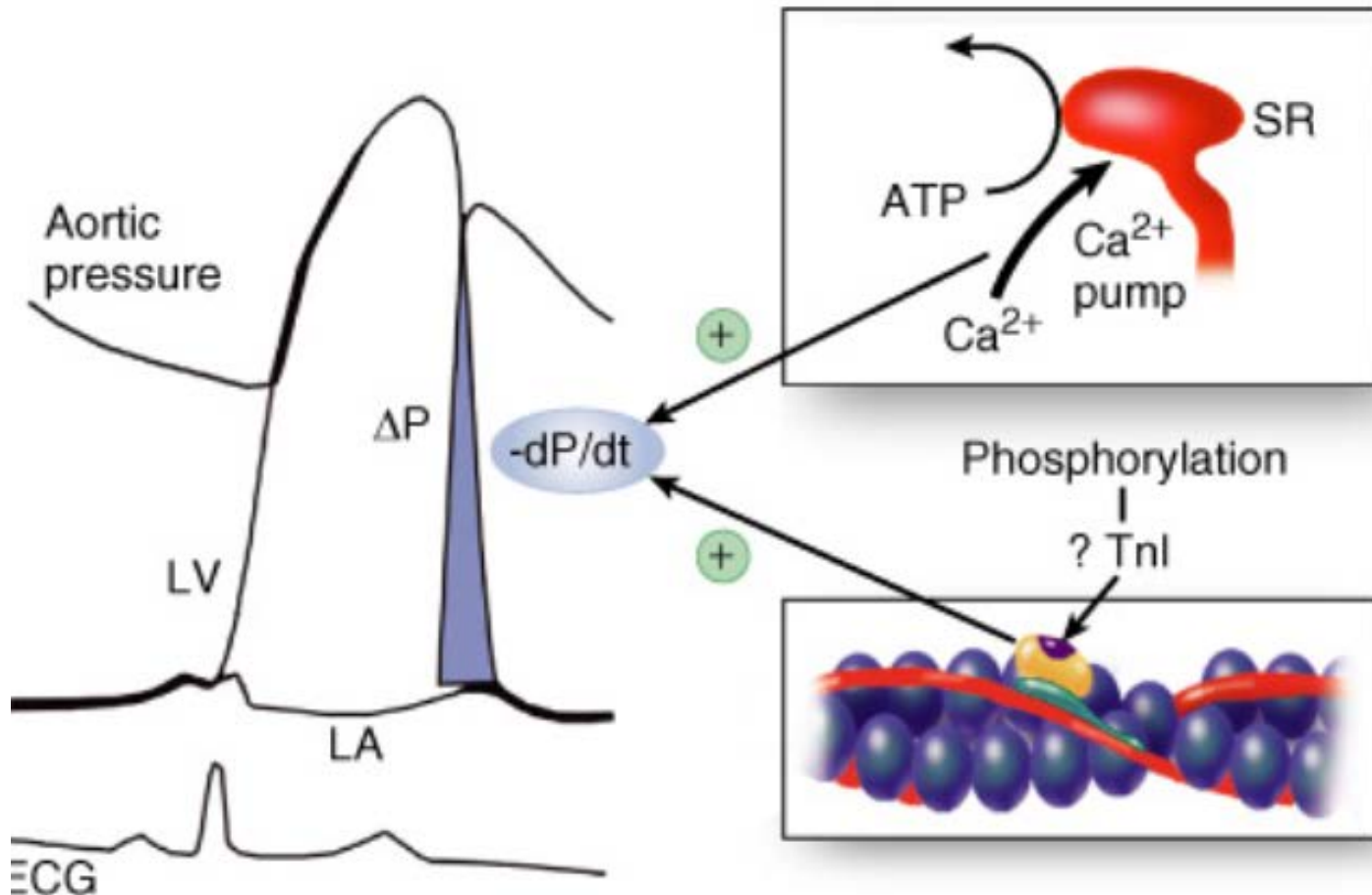
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# Load and ventricular relaxation



# The LV pressure decay



*Modified from Opie LH: Heart Physiology, from Cell to Circulation. Philadelphia, Lippincott Williams & Wilkins, 2004*

# Determinants of myocardial inactivation

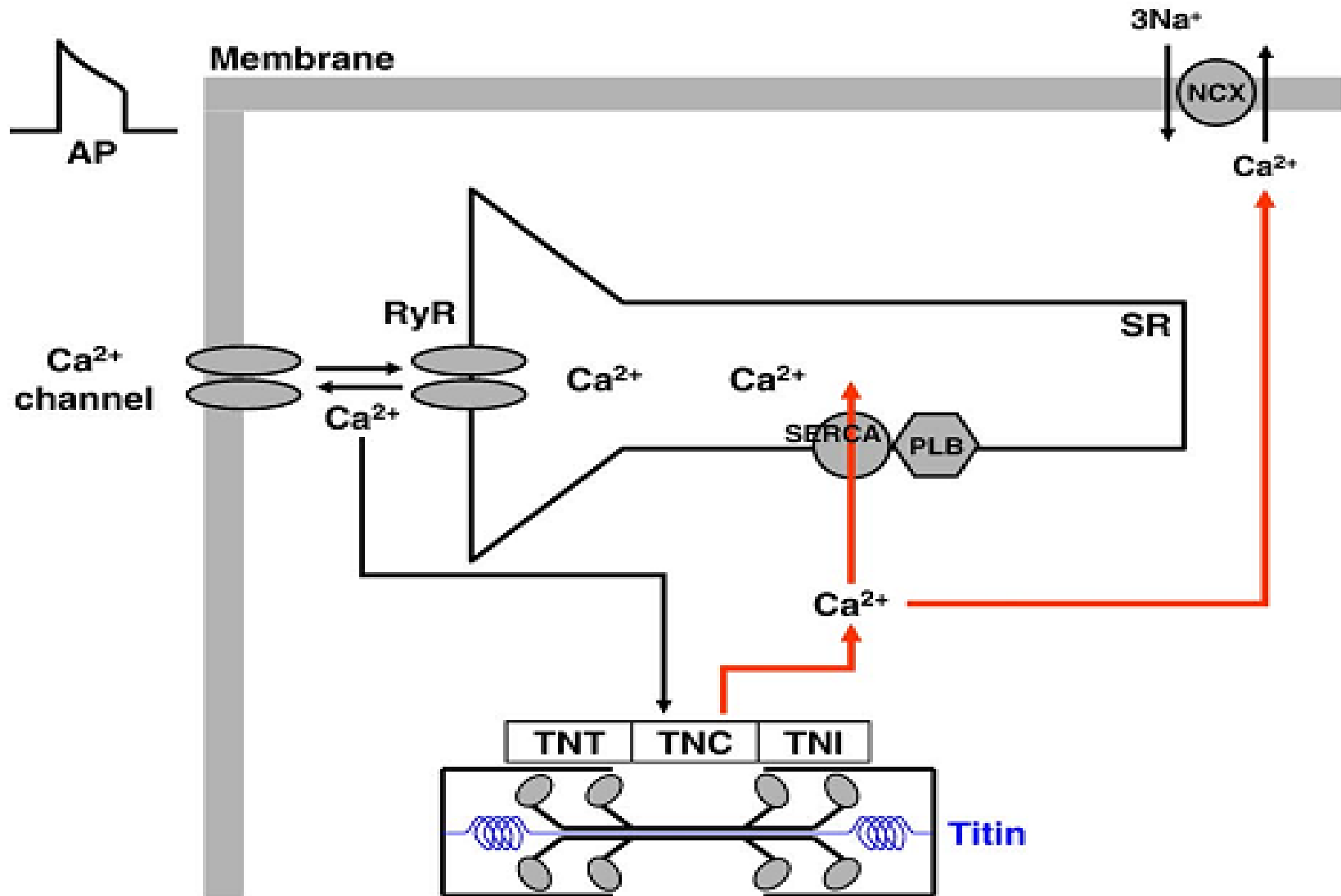
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- ▶  $\text{Ca}^{2+}$  homeostasis
  - $\text{Ca}^{2+}$  concentration
  - sarcolemmal and SR  $\text{Ca}^{2+}$  transport
  - modifying proteins (phospholamban, calmodulin, calsequestrin)
- ▶ Myofilaments
  - Tn-C  $\text{Ca}^{2+}$  binding
  - Tn-I phosphorylation
  - $\text{Ca}^{2+}$  sensitivity
  - $\alpha/\beta$ -MHC ATPase ratio
- ▶ Energetics
  - ADP/ATP ratio
  - ADP and Pi concentration

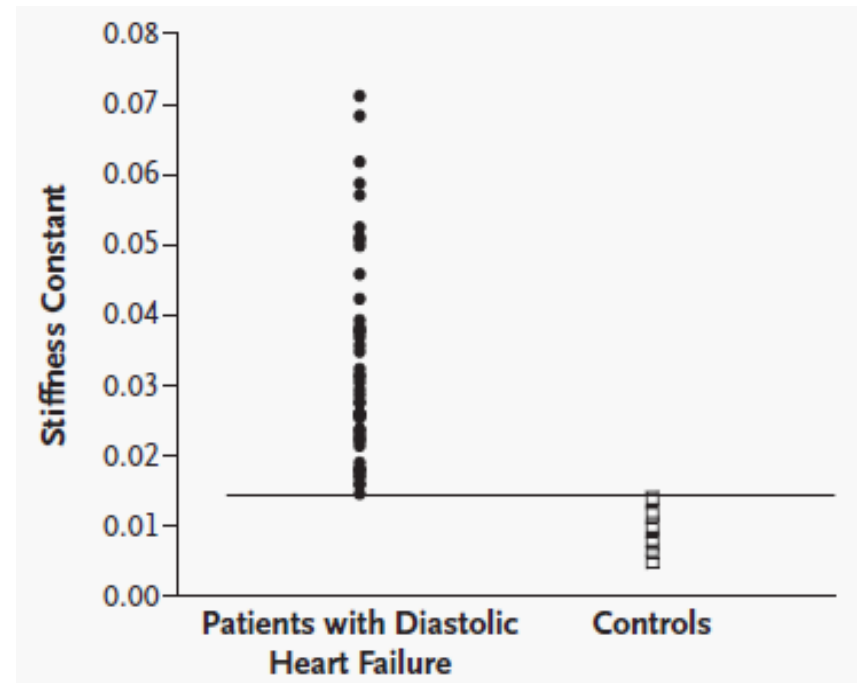
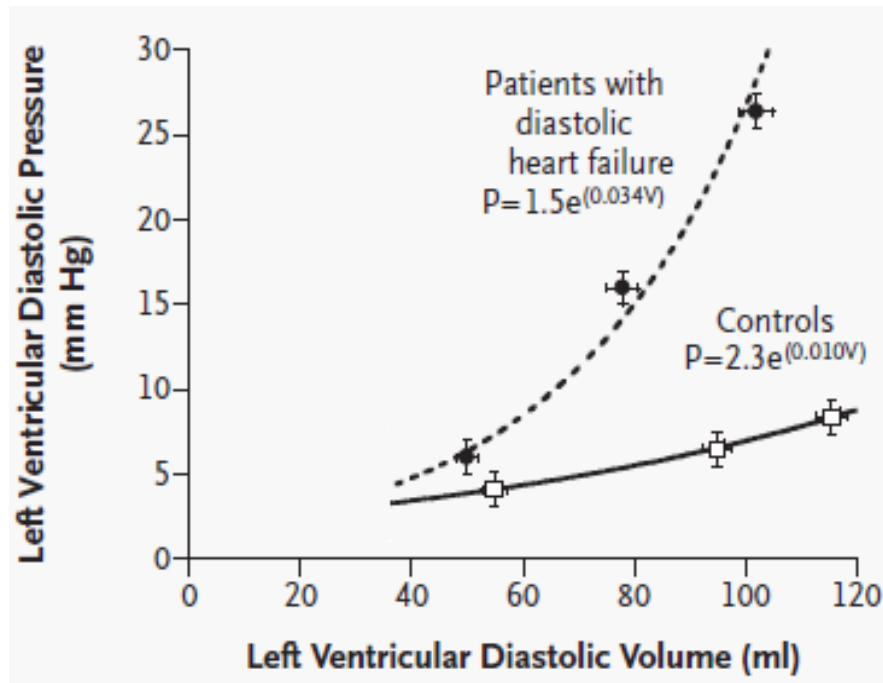
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ADP, adenosine diphosphate; ATP, adenosine triphosphate; MHC, myosin heavy chain; SR, sarcoplasmic reticulum; Tn, troponin.

# Cellular mechanisms of diastolic dysfunction



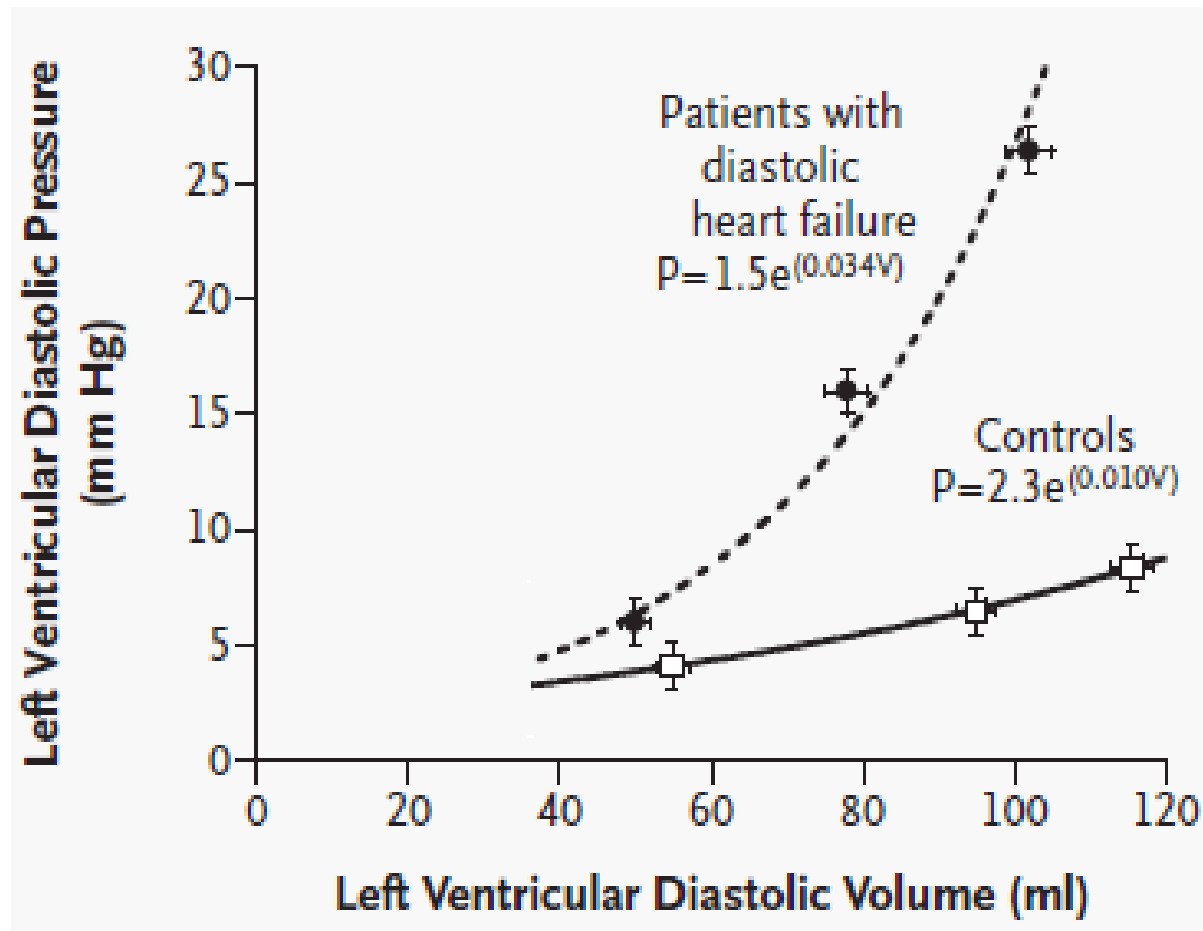
# Passive properties in diastolic heart failure



Zile NEJM 2004

# Passive properties in diastolic heart failure

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# Mechanisms that interfere with structural/functional abnormalities in HFPEF

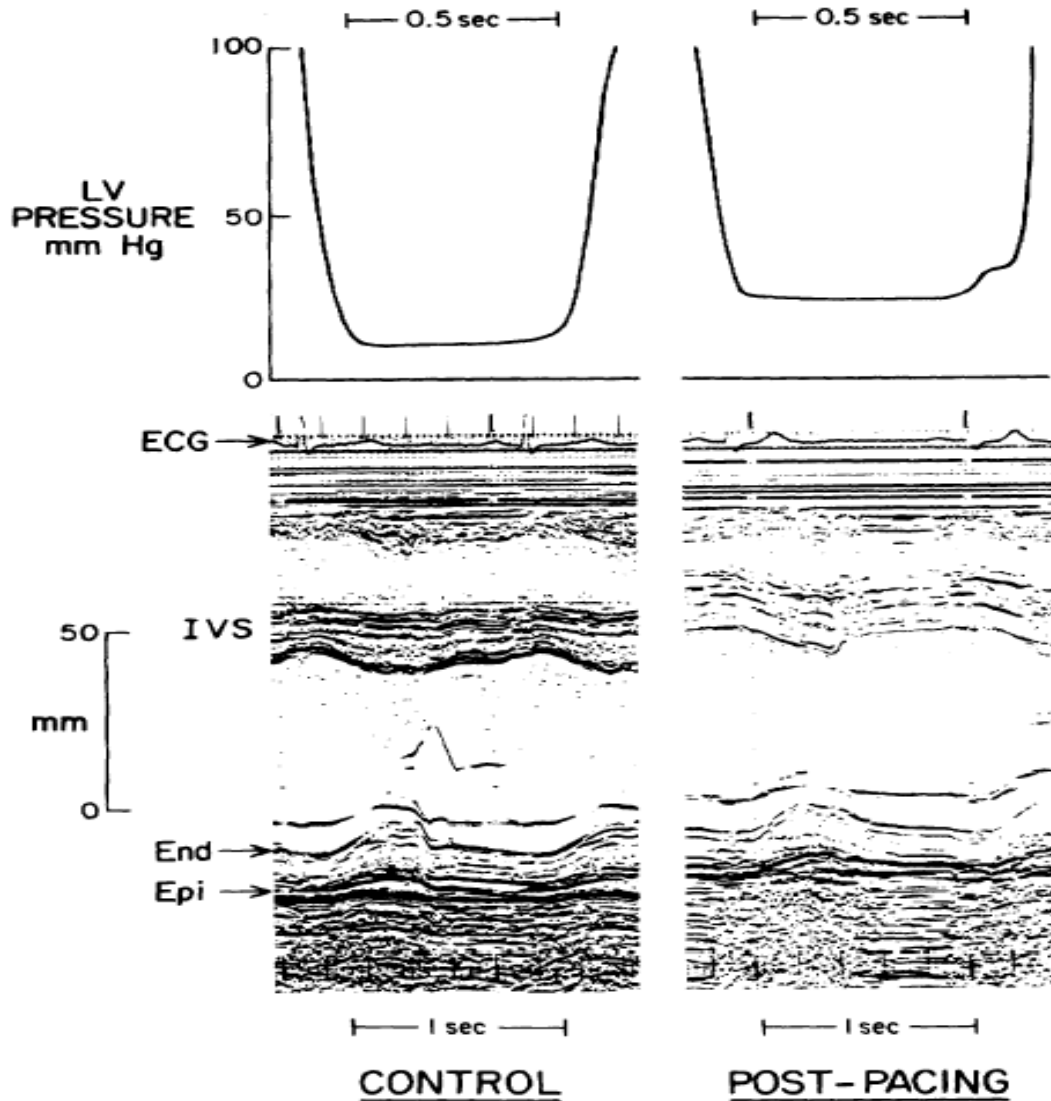
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- Prominent cardiomyocyte hypertrophy
- Breakdown and turnover of ECM which leads to concentric hypertrophy
- Elevated cardiomyocyte resting tension and less phosphorylation of the stiff N2B titin isoform
- Shift in myocardial metabolism from glucose to free fatty acids use because of diabetes and obesity

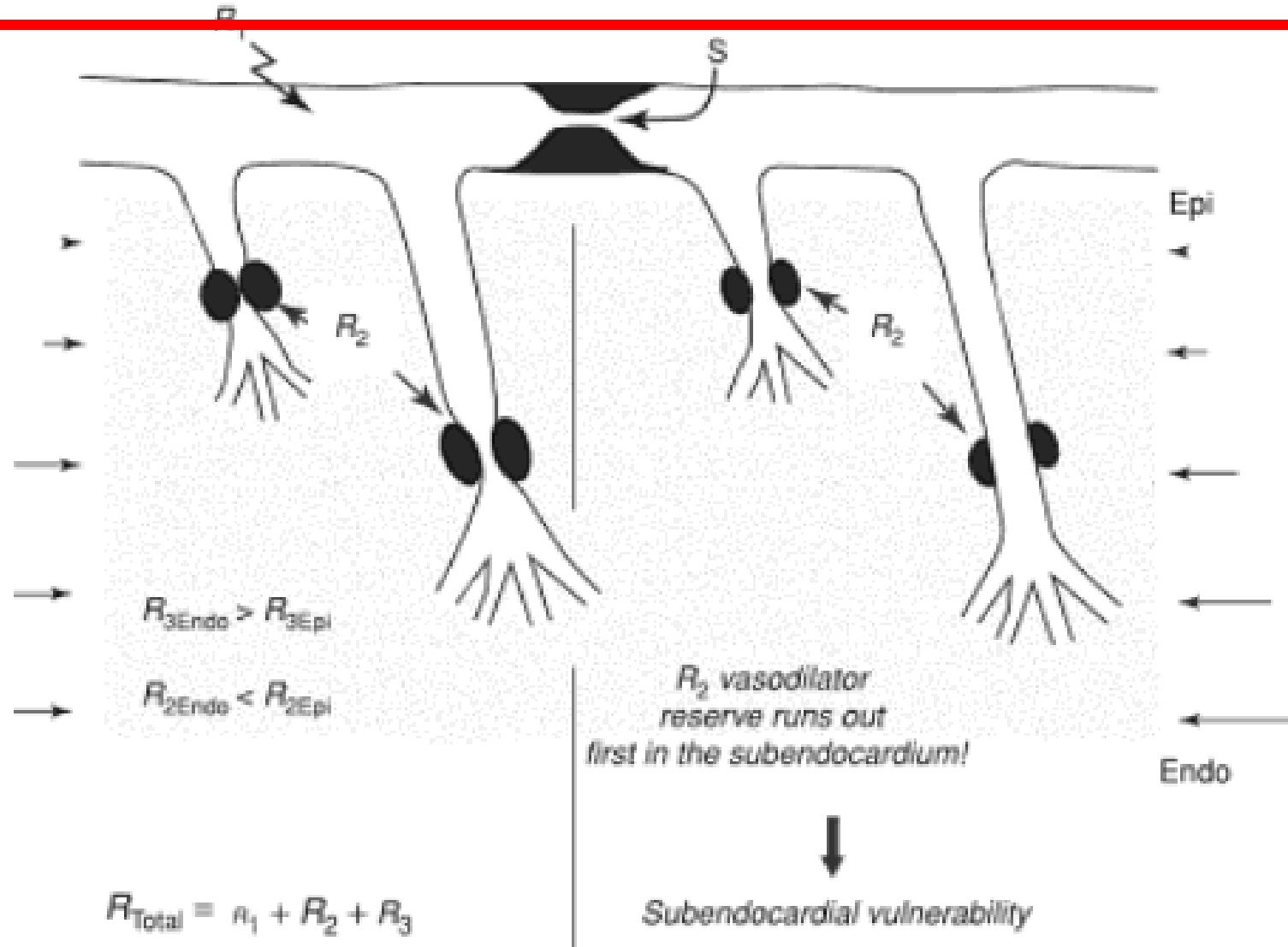


# Effect of ischemia on LV diastolic pressure

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# Transmural differences in perfusion and effects of a coronary stenosis



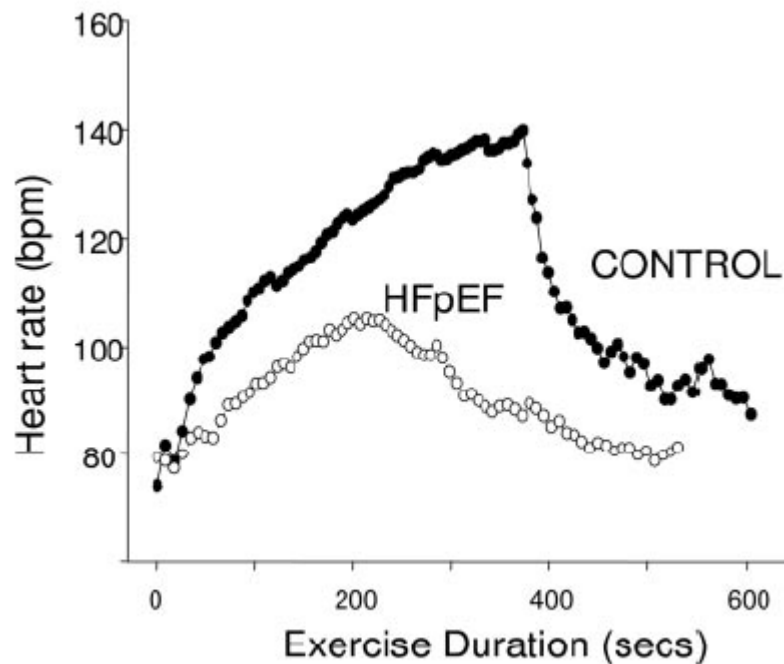
after Klocke FJ

# Mechanisms that interfere with structural/functional abnormalities in HFPEF

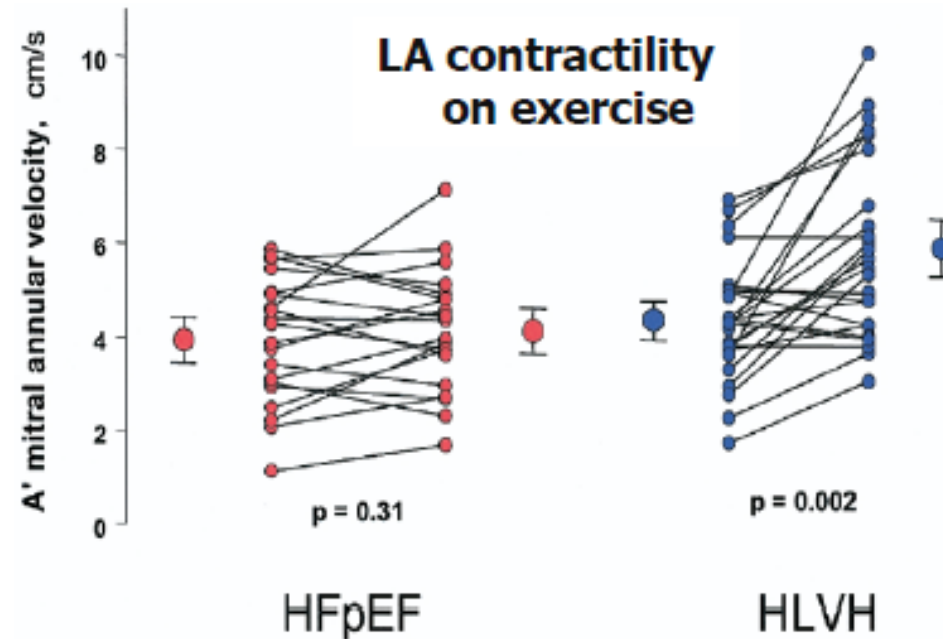
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# Cardiovascular response, at low and equivalent workload, in subjects with diastolic dysfunction vs. control patients

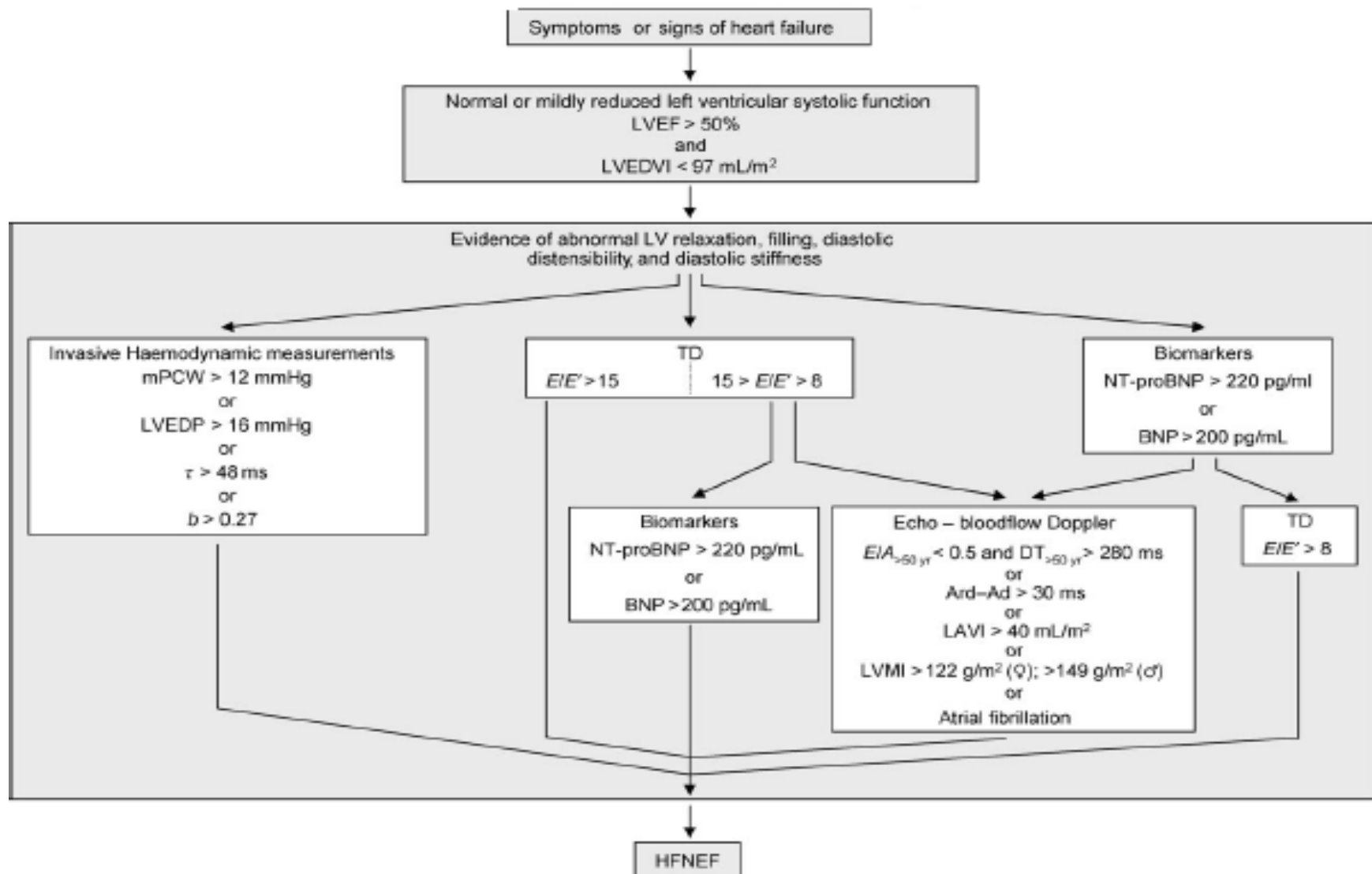


Borlaug et al, Circulation 2006



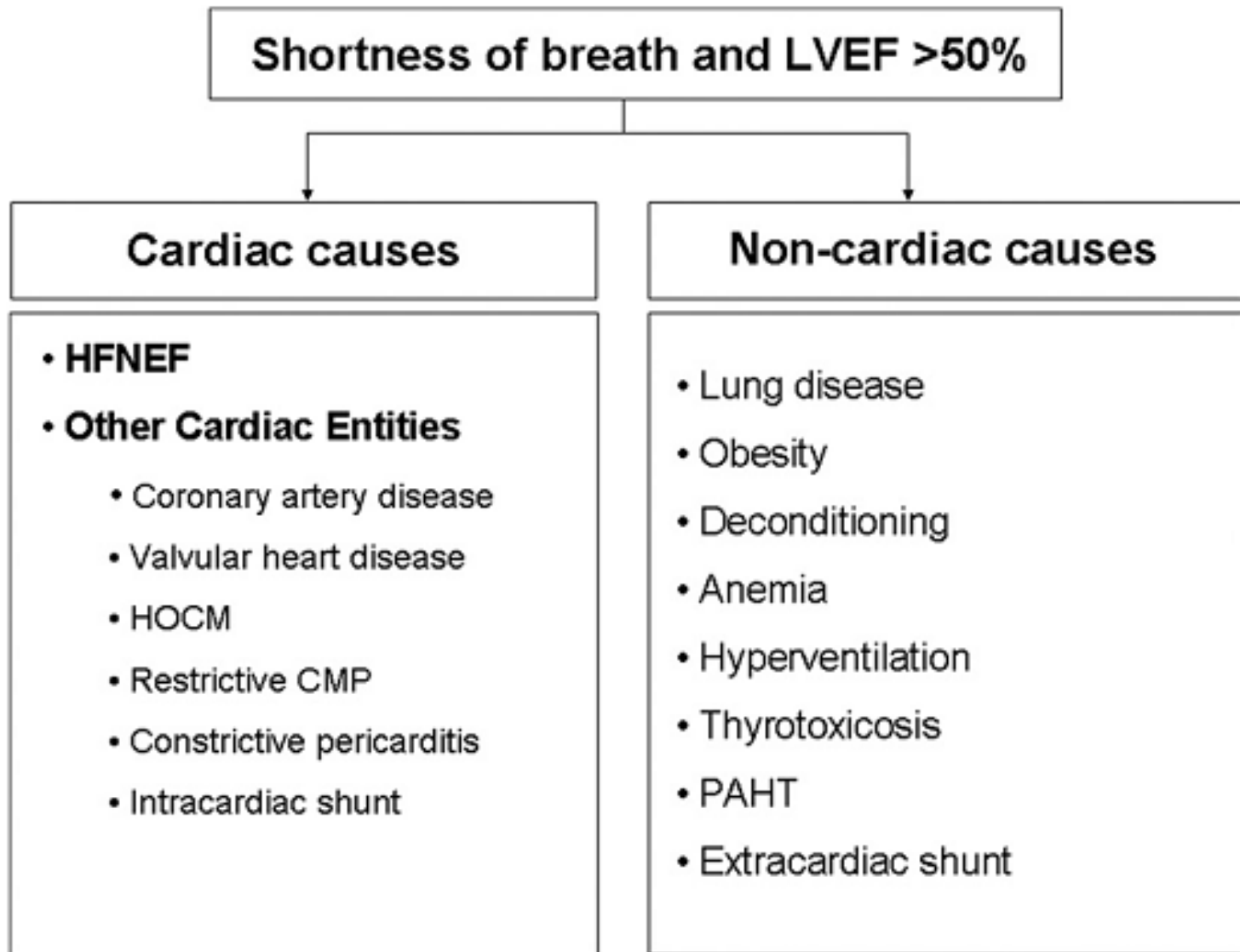
Melenovsky et al, JACC 2007

# How to diagnose HFPEF



# How to diagnose HFPEF

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JM   
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ORIGINATOR

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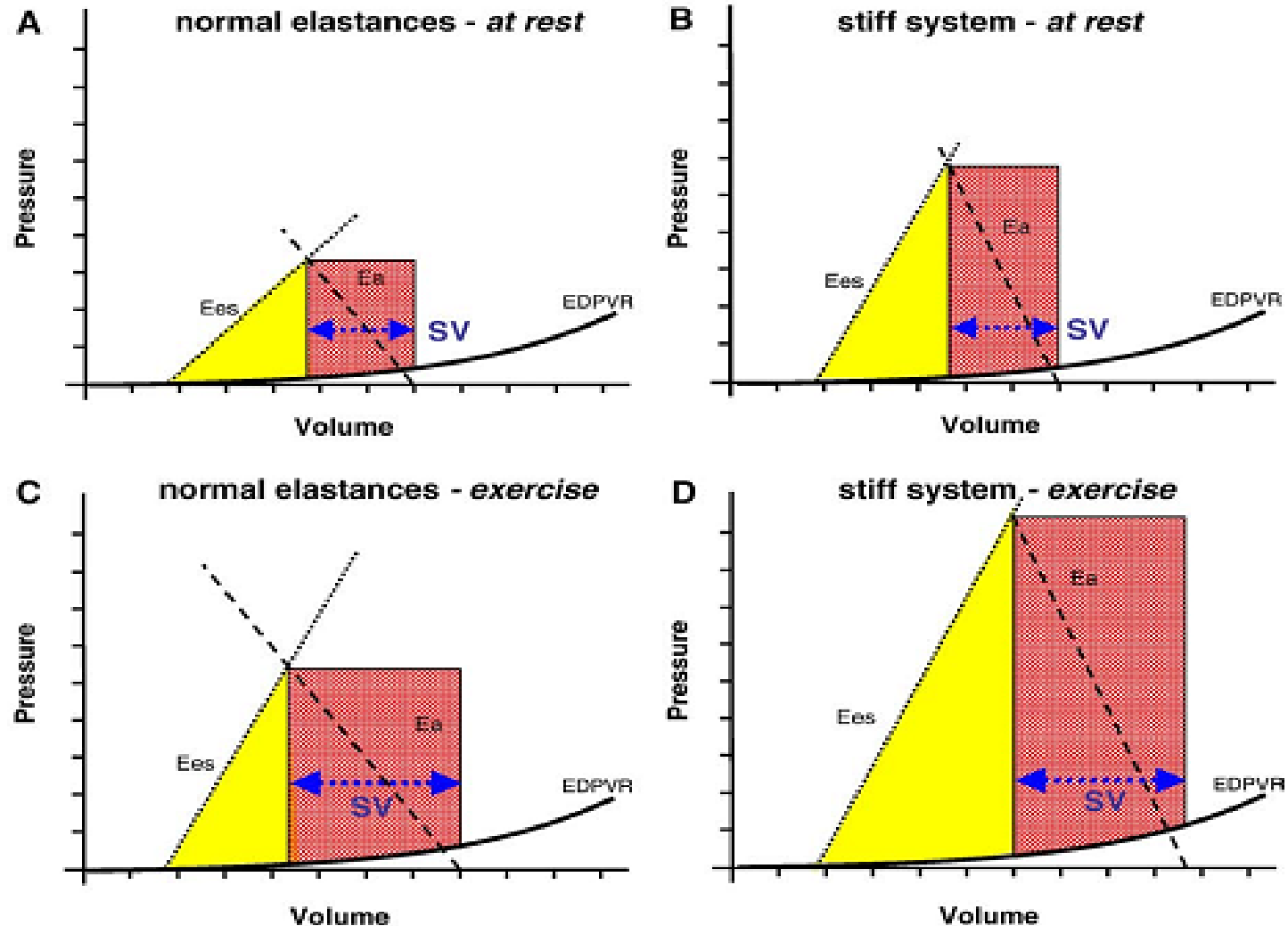
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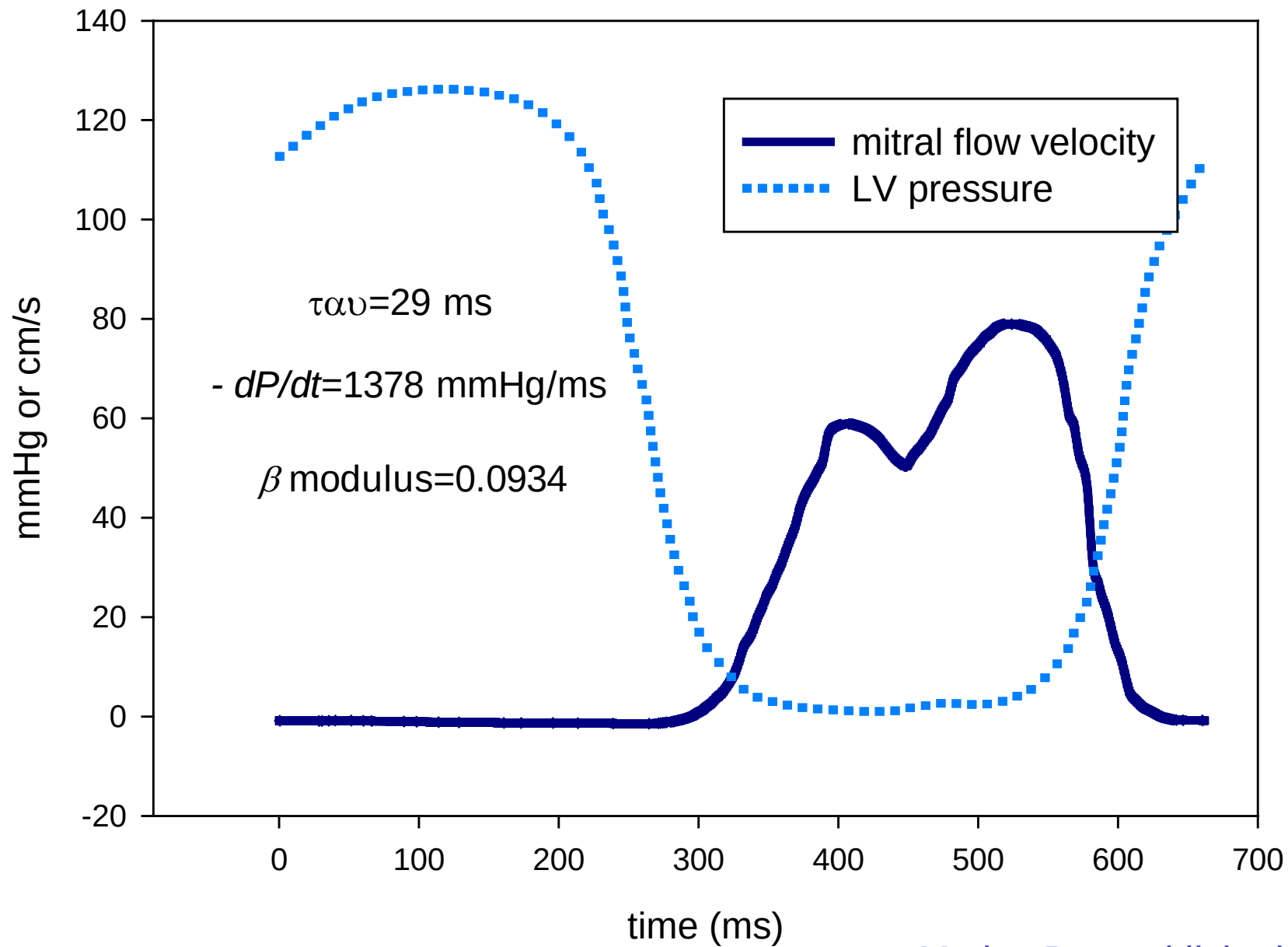


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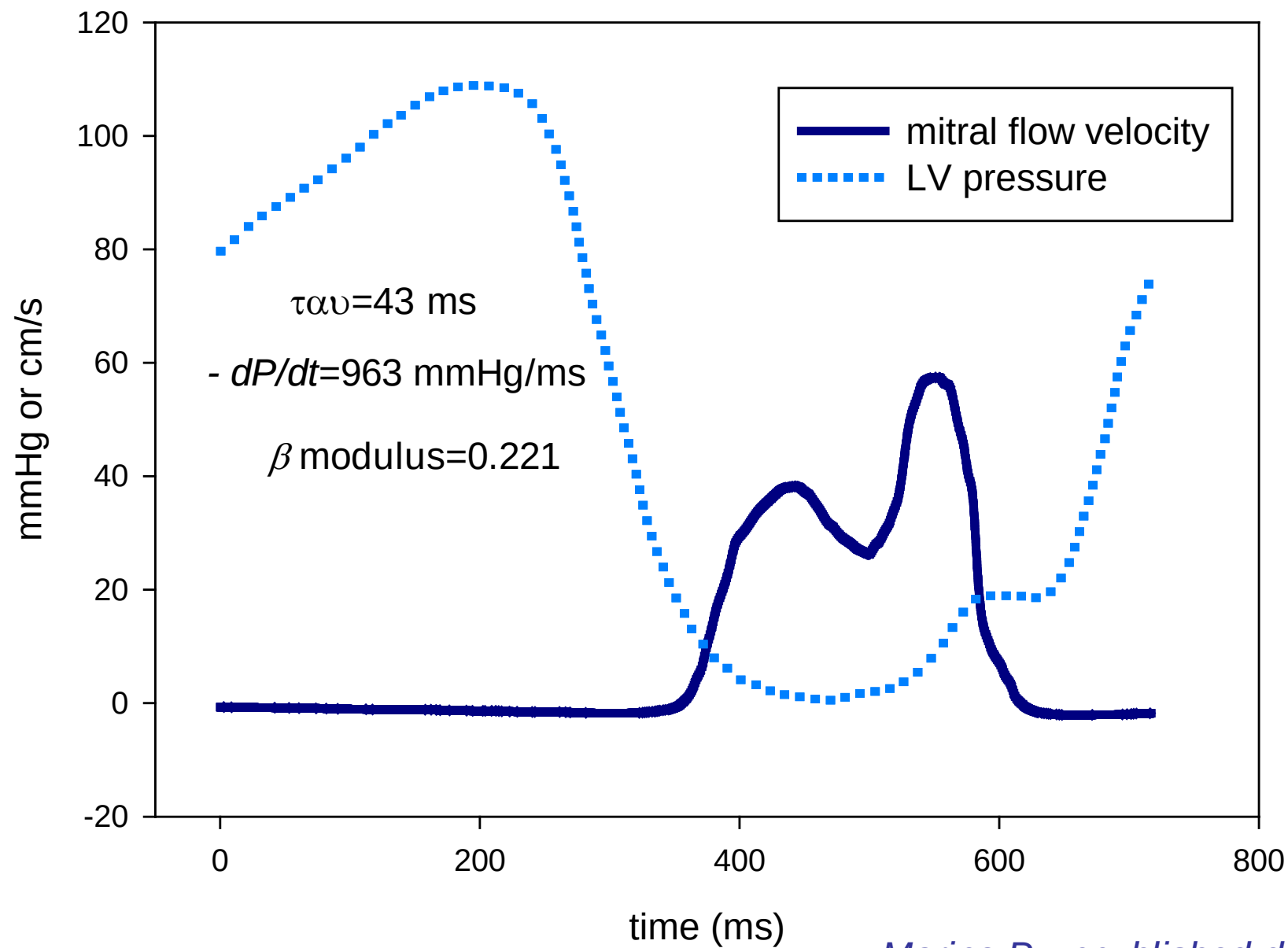
# PV analysis of ventricular-vascular coupling





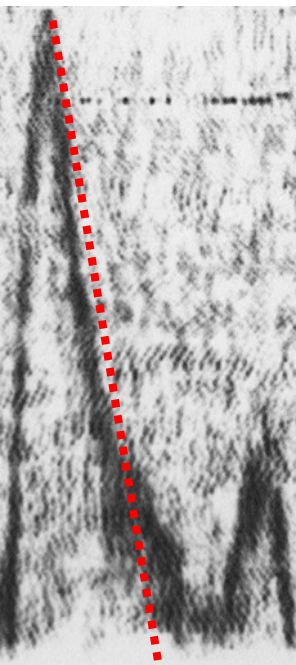
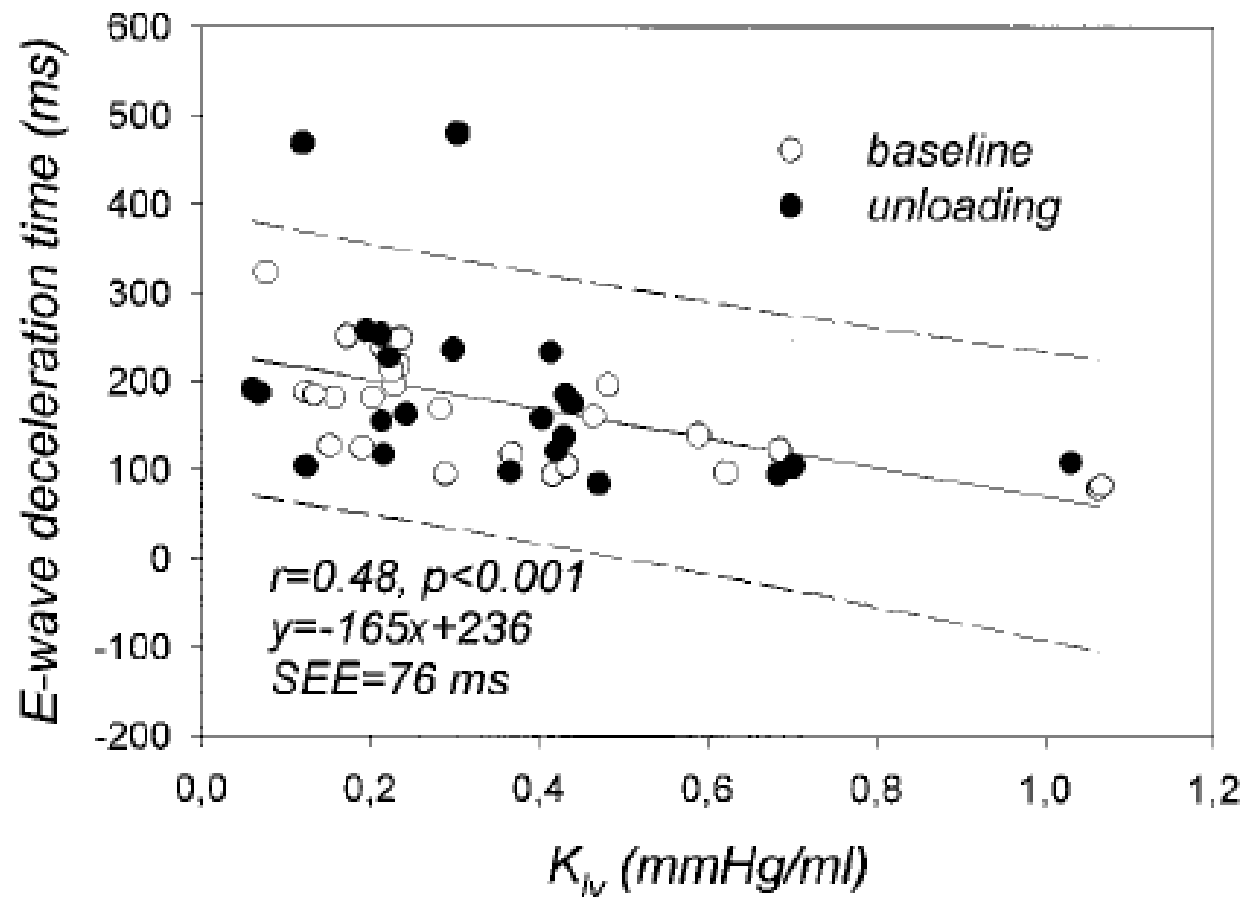


*Marino P, unpublished data*



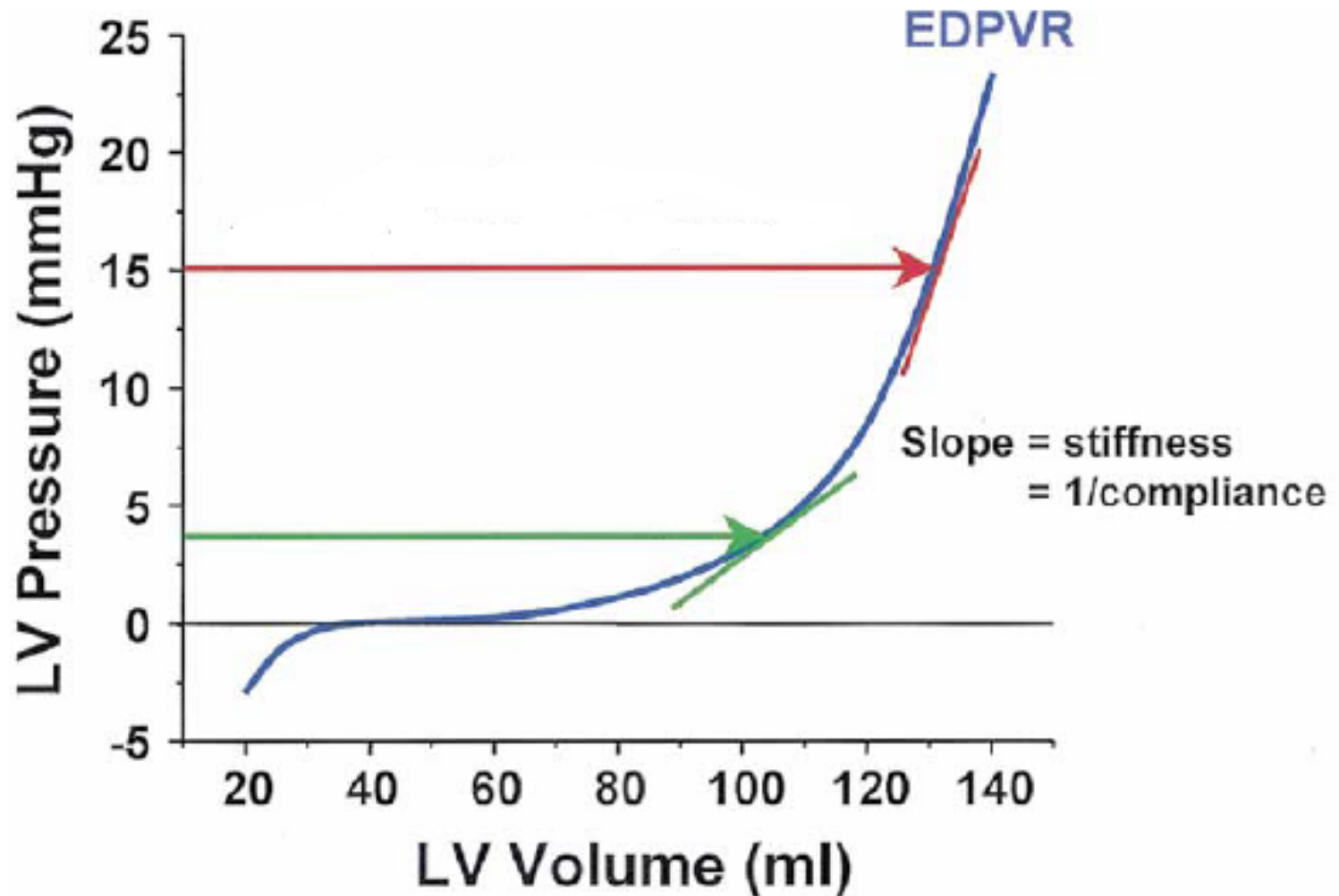
*Marino P, unpublished data*

# E-wave deceleration e stiffness ventricolare



# Nonlinearity of end-diastolic P-V relationship

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# Ventricular properties via P-V analysis

## *End diastolic pressure-volume relationship*

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