WHAT IS THE PHYSIOPATHOLOGY UNDERLYING HF WITH PRESERVED EJECTION FRACTION ?

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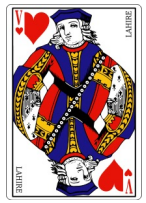

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Leader PACIFIC-preserved Project : Phenomapping, Classification and Innovation for Cardiac Dysfunction – HFpEF project

PACIFIC

Physiopathologie, classification, innovation dans l'insuffisance cardiaque

The contrast of HFpEF vs. HFrEF

Table 3.1 Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).

ESC European Society of Cardiology
European Heart Journal (2019) **40**, 2155–2163
doi:10.1093/eurheartj/ehz158

CLINICAL REVIEW
Controversies in cardiovascular medicine

The continuous heart failure spectrum: moving beyond an ejection fraction classification

Filippos Triposkiadis[1], Javed Butler[2], Francois M. Abboud[3], Paul W. Armstrong[4],

- Imprecise classification
- Arbitrary cut-offs
- Does not evaluate diastolic dysfunction
- HFpEF is defined as a non-HFrEF disease

➔ A physiopathological vision of HFpEF vs HFrEF ?
➔ If so, what are the specific mechanisms in HFpEF vs. HFrEF ?

Structural, Functional, and Ultra- structural characteristics in HFpeF and HFreF

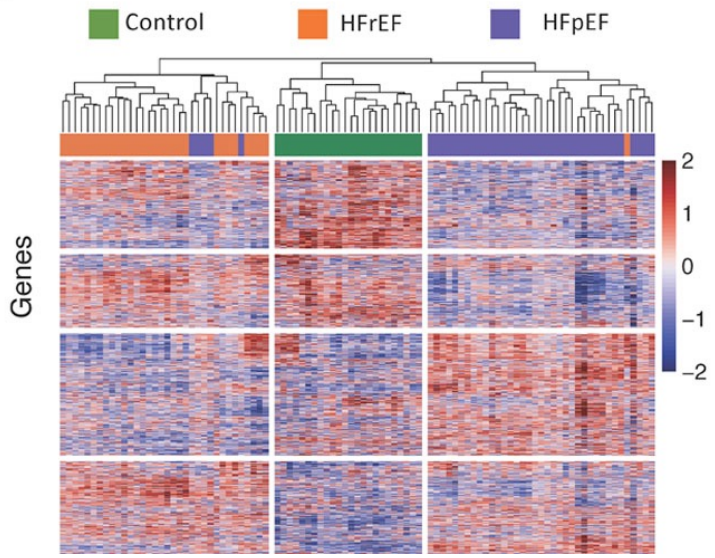
	HFpEF	HFrEF
LV structure/function		
End-diastolic volume	↔	↑
End-systolic volume	↔	↑
Wall thickness	↑	↔
Mass	↑	↑
Mass/volume ratio	↑	↓
Remodeling	Concentric	Eccentric
Ejection fraction	↔ ↑	↓
Stroke work	↔	↓
End-systolic elastance	↔	↓
End-diastolic stiffness	↑	↓
LV ultrastructure		
Myocyte diameter	↑	↔
Myocyte length	↔	↑
Myocyte remodeling	Concentric	Eccentric
Fibrosis	Interstitial/reactive	Focal/ replacement

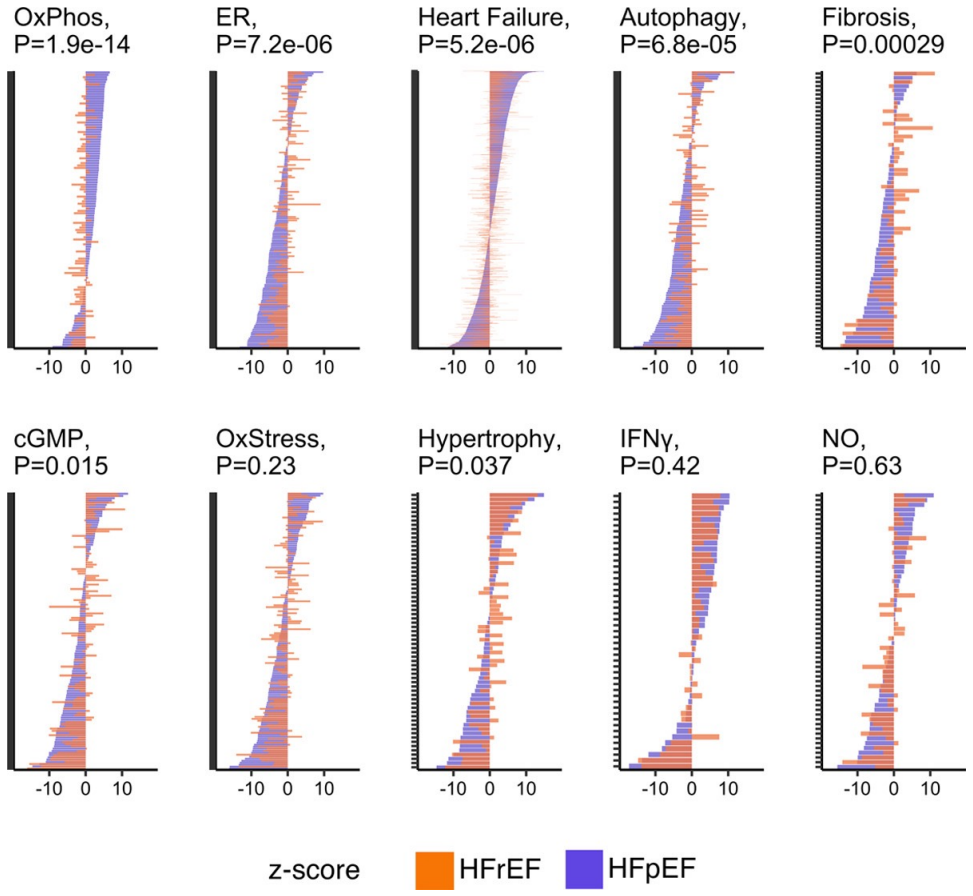
Courtesy Ariel Cohen

Gene expression signatures in HFpEF vs. HFrEF

- RNA sequencing on right ventricular septal endomyocardial biopsies in HFpEF (n=41) vs. HFrEF (n=30) vs. donor controls (n=24)

Hahn VS. Circulation 2021; 143(2):120-34





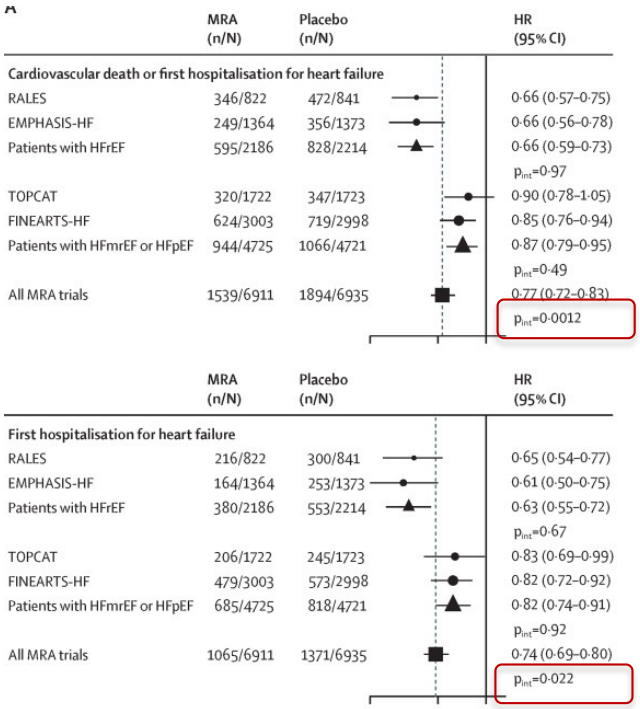
HFpEF :

⇩ ER stress / Autophagy / Angiogenesis

⇧ Mitochondrial

Major differences in response to drugs in HFpEF vs. HFrEF

- ACEi / ARAII / Beta-Blockers / ARNi are not clinically benefitial
- SGLT2i & ARM are efficient, by reducing HF hospitalization. No (or minimal) effect on CV death
- The observed benefit is globally lower in HFpEF than in HFpEF



HFrEF : -34%

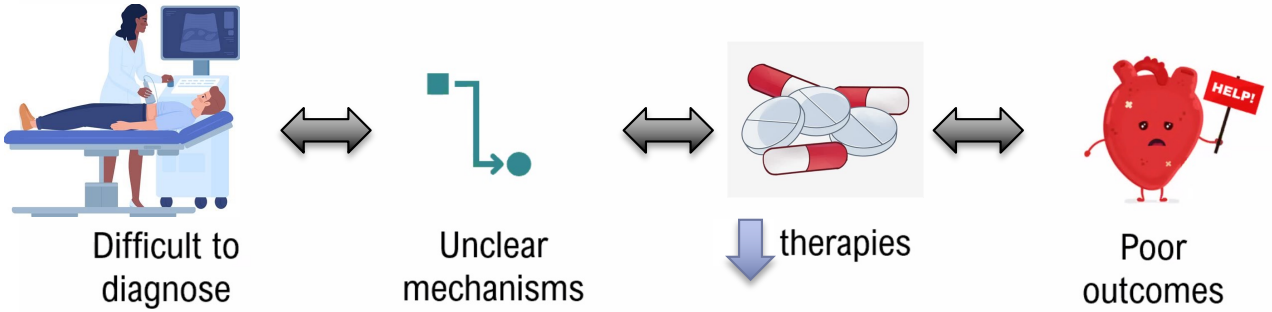
HFpEF : -13%

HFrEF : -37%

HFpEF : -18%

Jhund P Lancet 2024

Who are these patients ? What are the mechanisms ?



➔ There is not only one mechanism but probably a variety of mechanisms leading to HFpEF and potentially indicating some specific therapeutic interventions

Who are these patients ?

➔ Guidelines 2021

Recommendations for the treatment of patients with heart failure with preserved ejection fraction

Recommendations	Class[a]	Level[b]
Screening for, and treatment of, aetiologies, and cardiovascular and non-cardiovascular comorbidities is recommended in patients with HFpEF (see relevant sections of this document).	I	C
Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs.[137]	I	C

➔ Multiples aetiologies can lead to HFpEF

➔ Are they sharing a same & uniform mechanism leading to HFpEF ?
➔ Is this the final expression of multiple mechanisms leading to HF ?

Etiological classification of HFpEF ?

Fayol et al. ESC Heart Failure 2021 DOI: 10.1002/ehf2.13717

2180 patients with congestive heart failure (period 2016-2019), BNP >100, need for diuretics

977 with LVEF ≤40%

275 with LVEF 41-49%

928 with LVEF ≥50%

510 (55.0%) **idiopathic HFpEF**

418 (45.0%) **secondary HFpEF**

Non-cardiac & mimickers in 45%

125 (13.5%) **abnormalities of the myocardium**

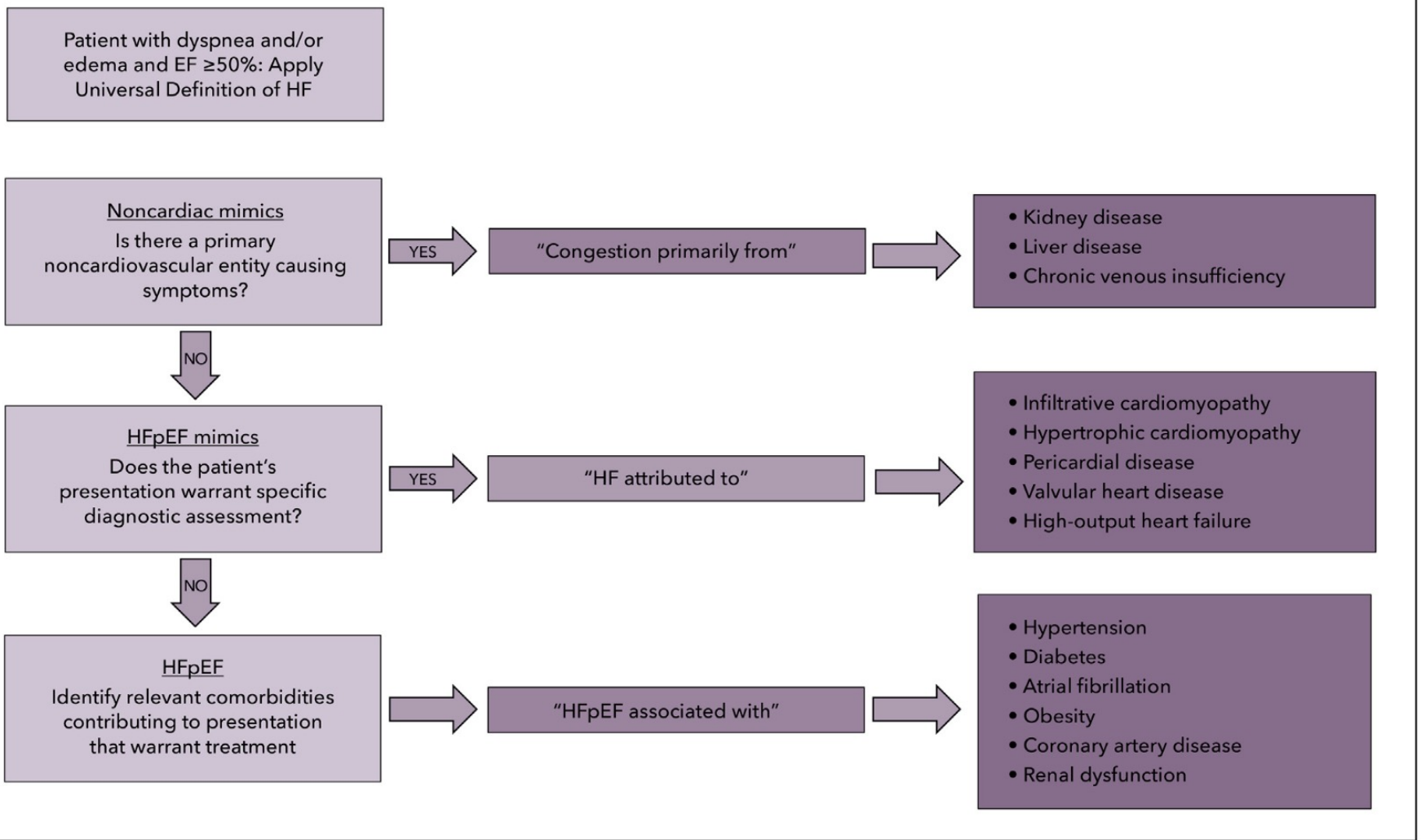
- **Ischaemic,** n=43 (4.6%)
- **Genetic,** n=44 (4.7%)
- **Toxic,** n=6 (0.6%)
- **Infiltrative,** n=28 (3.0%)
- **Immune & inflammatory,** n=3 (0.3%)
- **Metabolic,** n=1 (0.1%)

293 (31.6%) **abnormalities of the loading conditions**

- **Valvular,** n=209 (22.5%)
- **Volume overload,** n=47 (5.1%)
- **High output state,** n=14 (1.5%)
- **Pericardial pathologies,** n=6 (0.6%)
- **Hypertensive crisis,** n=10 (1.1%)
- **Structural defect,** n=7 (0.7%)

Pure HFpEF vs. HFpEF mimics ?

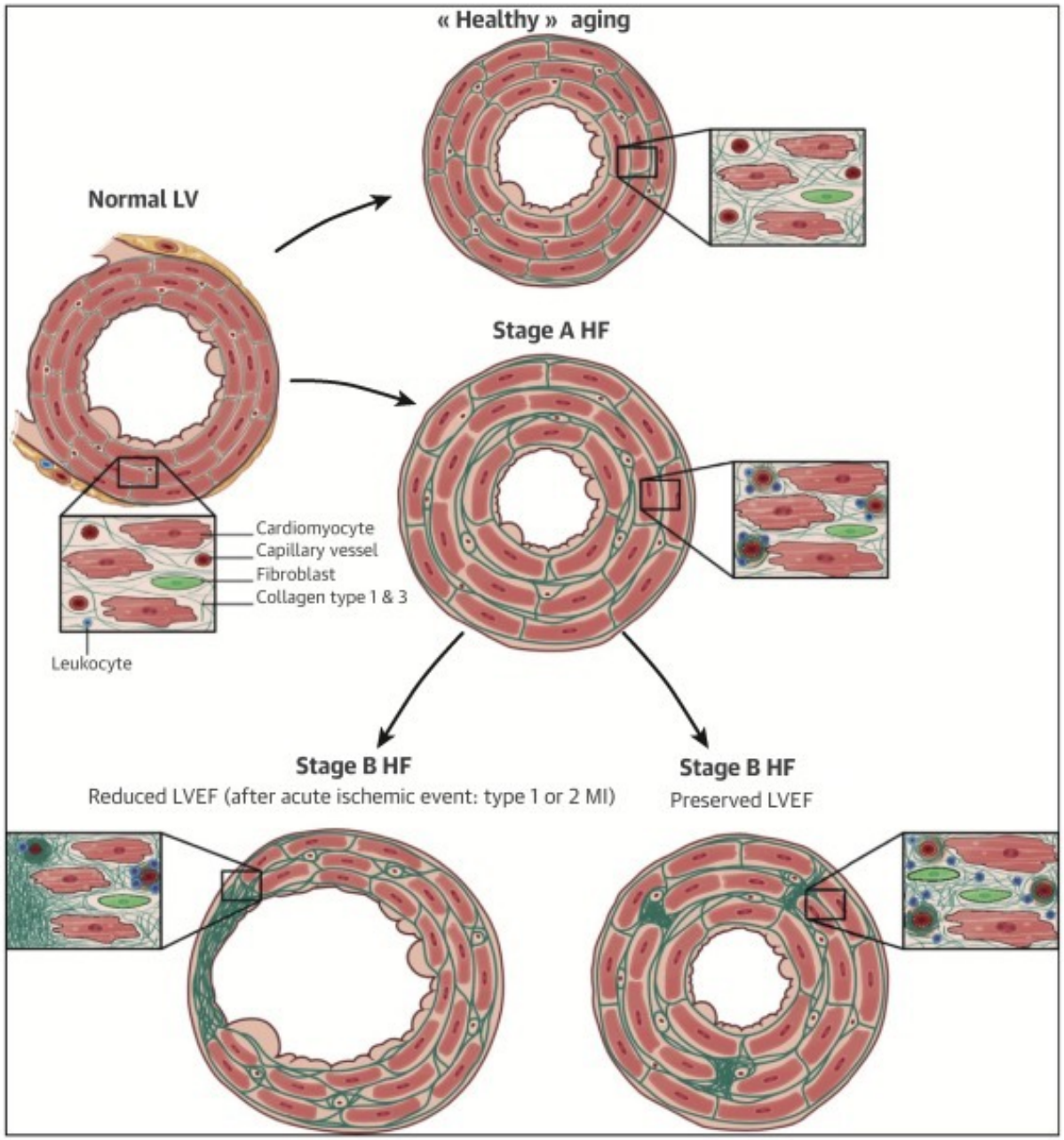
FIGURE 8 Stepwise Approach to Assessment of Individuals With Shortness of Breath and/or Edema



EF = ejection fraction; HF = heart failure; HFpEF = heart failure with preserved ejection fraction.

2023 ACC expert consensus JACC. 2023 May, 81 (18) 1835–1878

CENTRAL ILLUSTRATION: Left Ventricular Macrostructural and Microstructural Remodeling in Healthy Aging, Stage A and Stage B Heart Failure



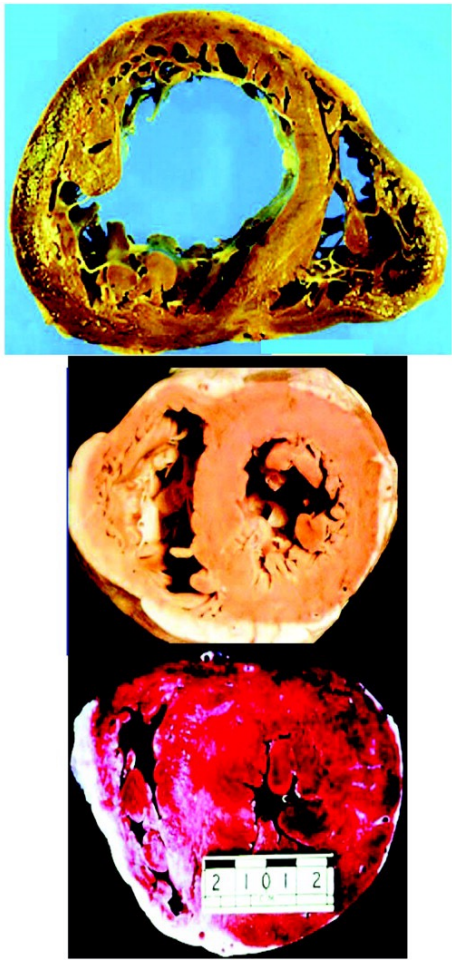
- *Conserved number of CM*
- *Hypertrophic CM*
- *Interstitial fibrosis*
- *Small vessels rarefaction*

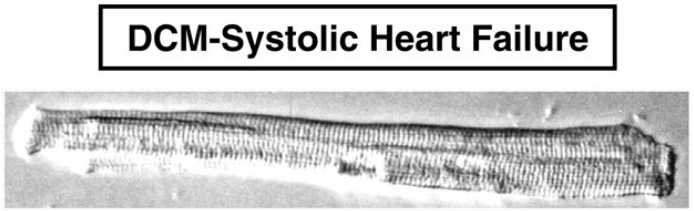
Pezel, T. et al. J Am Coll Cardiol Img. 2021;14(5):1038-52.

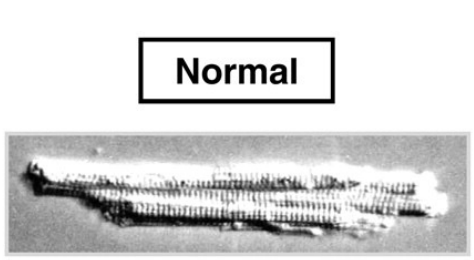
Cardiomyocytes are bigger

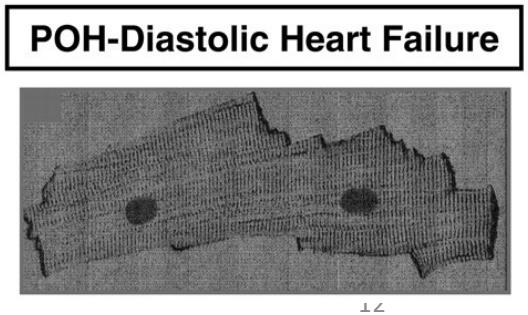
Autopsic observation ➔ Cardiac myocyte hypertrophy

Gerard P. Aurigemma et al. Circulation. 2006;113:296-304



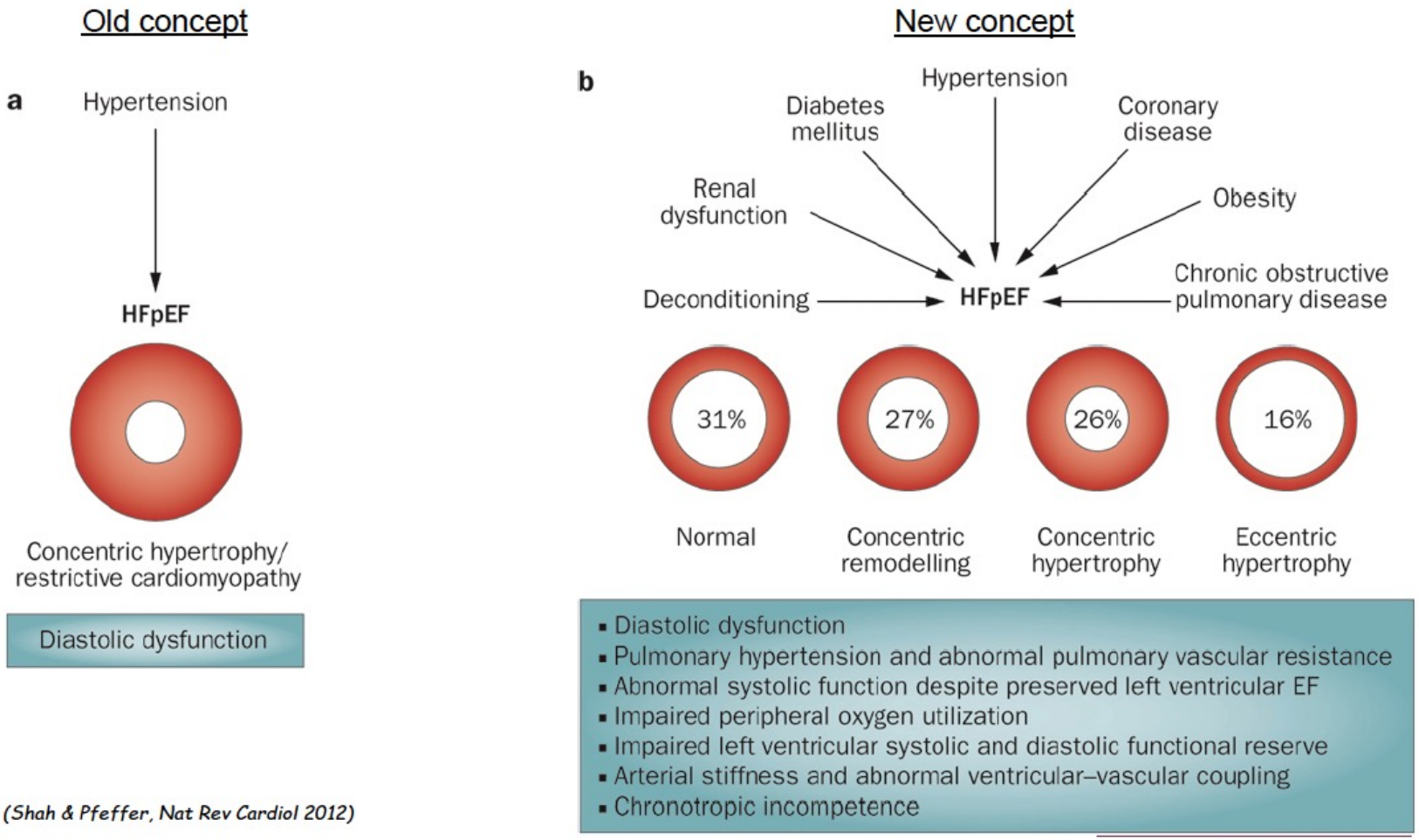






➔ Hypertrophic vs. hypertensive remodeling ?

Old and new physiopathological concepts in HFpEF

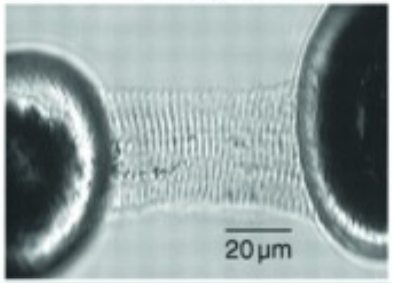


KEY MESSAGE Diastole consists of an active (myocardial relaxation) and a passive (myocardial stiffness) phase. Myocardial stiffness is determined by the cardiomyocytes and the extracellular matrix and the relative importance of each varies during the course of the disease.

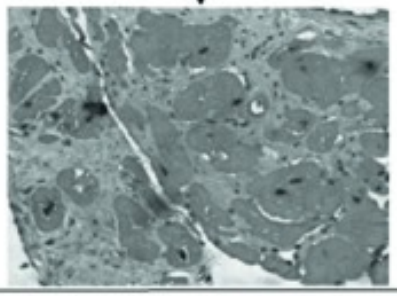
Determinants of Diastole

Myocardial Inactivation
- Ca^{2+} removal
- Cross-bridge detachment
  - ATP

Myocardial stiffness



Cardiomyocytes
- Isoform shifts
- Phosphorylation
- Oxidation



Extracellular matrix:
- Amount of collagen
- Abundance of collagen type 1
- Collagen cross-linking

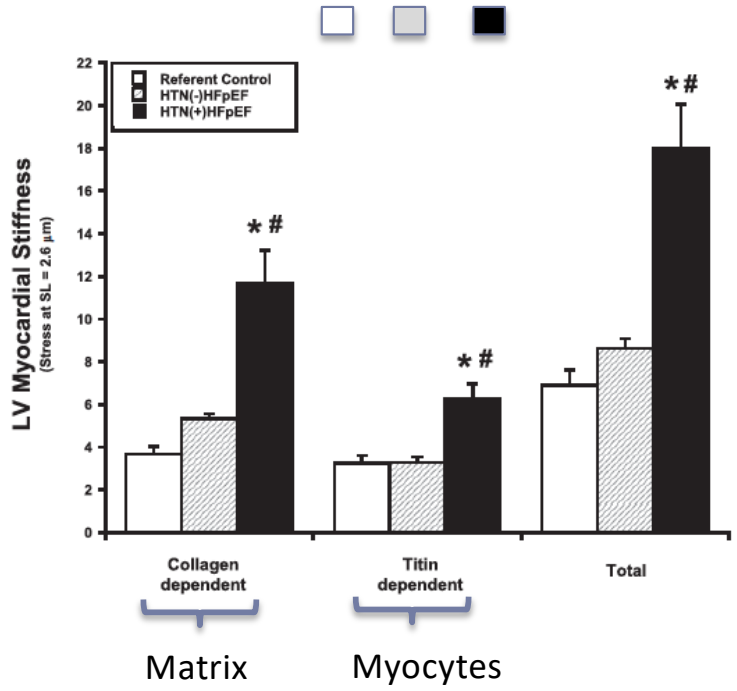
The stiff heart in HFpEF

Increased myocardial tissue passive stiffness

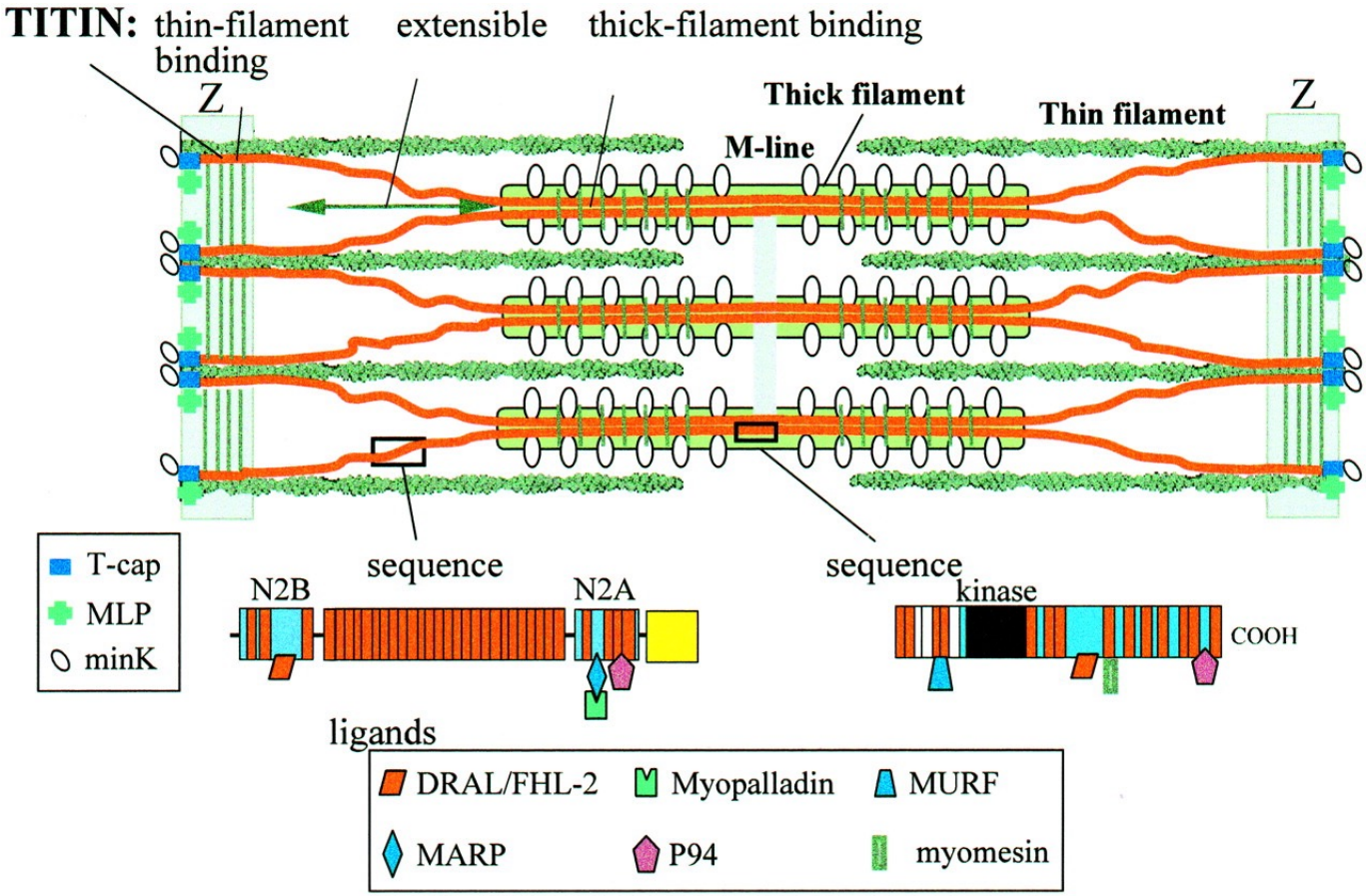
From Circulation 2015, 131, 1247-59

➔ 70 patients undergoing cardiac surgery (bypass) with LV biopsy

Hypertension	-	+	+
HFpEF	-	-	+
N=	*17*	*31*	*22*

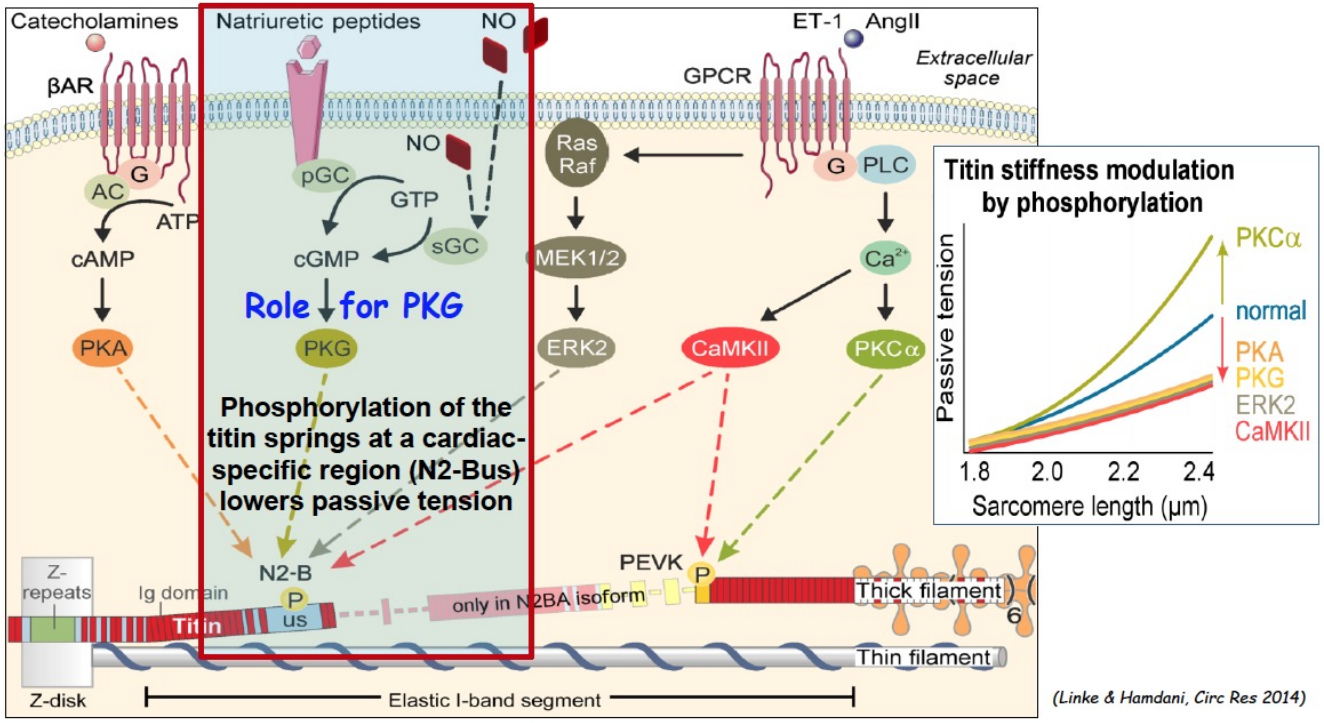


Titin : the key regulator of cardiac myocyte stiffness

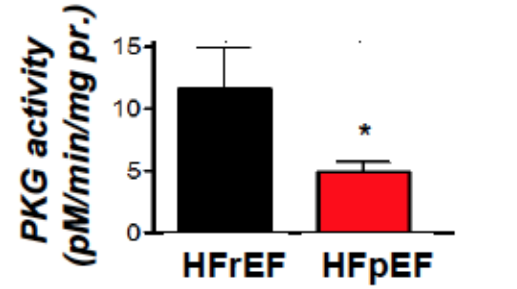


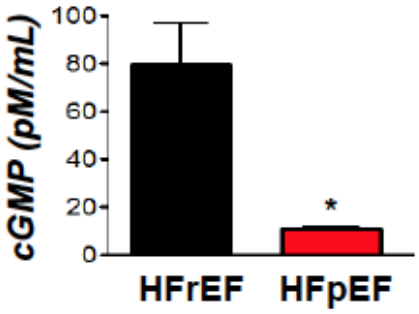
Henk L. Granzier, and Siegfried Labeit Circ Res. 2004;94:284-295

Titin phosphorylation & diastolic passive stiffness



Linke & Hamdani, Circ Res 2014





➔ Titin N2-B PKG-dependent phosphorylation : decreased stffness by 20%

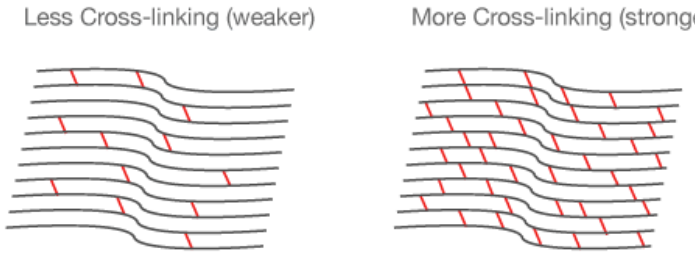
➔ Titin PKCalpha phosphorylation: increased stiffness

Myocardial collagen in HFpEF ?

	Control subjects (N=20)	HFpEF patients (N=39)	*P*
Constant of pressure stiffness [1] (mm Hg)	11.4±1.9	16.1±1.4	<0.05
LV end-diastolic pressure (mm Hg)	8±1	12±1	<0.05
E : e' ratio	8.2±2.3	14.9±8.0	<0.001
Total collagen content (%)	5±4	16±9	<0.0001
Collagen type I content (%)	6.43±0.65	8.34±0.23	<0.01
Collagen cross-linking [2]	0.9±0.4	1.7±0.8	=0.03

(Values are expressed as mean±SD)

Perez del Villar, Cardiovasc Res 2017



➔ Changes in collagen turn over ?

How to measure myocardial stiffness ?

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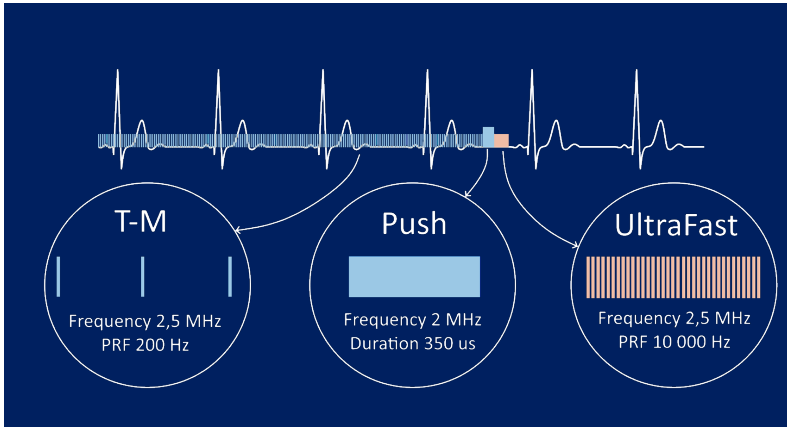
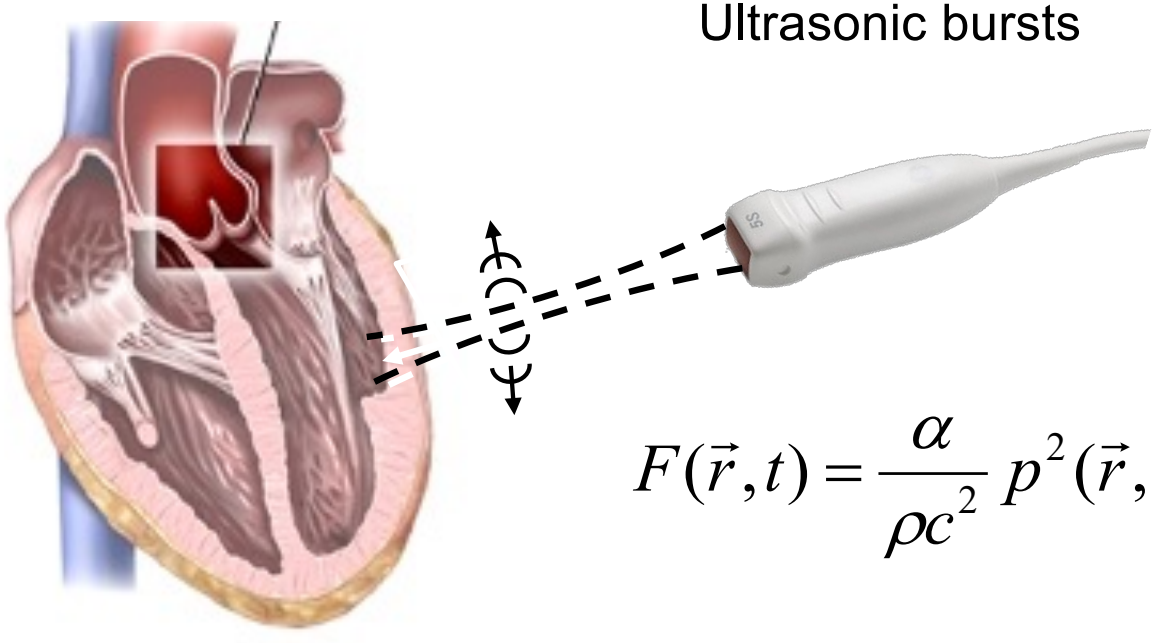
Physiopathologie, classification, innovation dans l'insuffisance cardiaque

➔ Ultrafast elastrography technology



Shear wave generated by the Acoustic Radiation Force

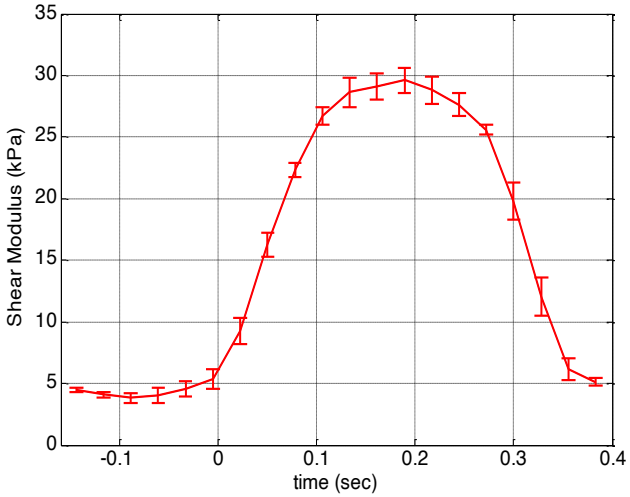
Ultrasonic bursts



$$F(\vec{r},t) = \frac{\alpha}{\rho c^2} p^2(\vec{r},t)$$

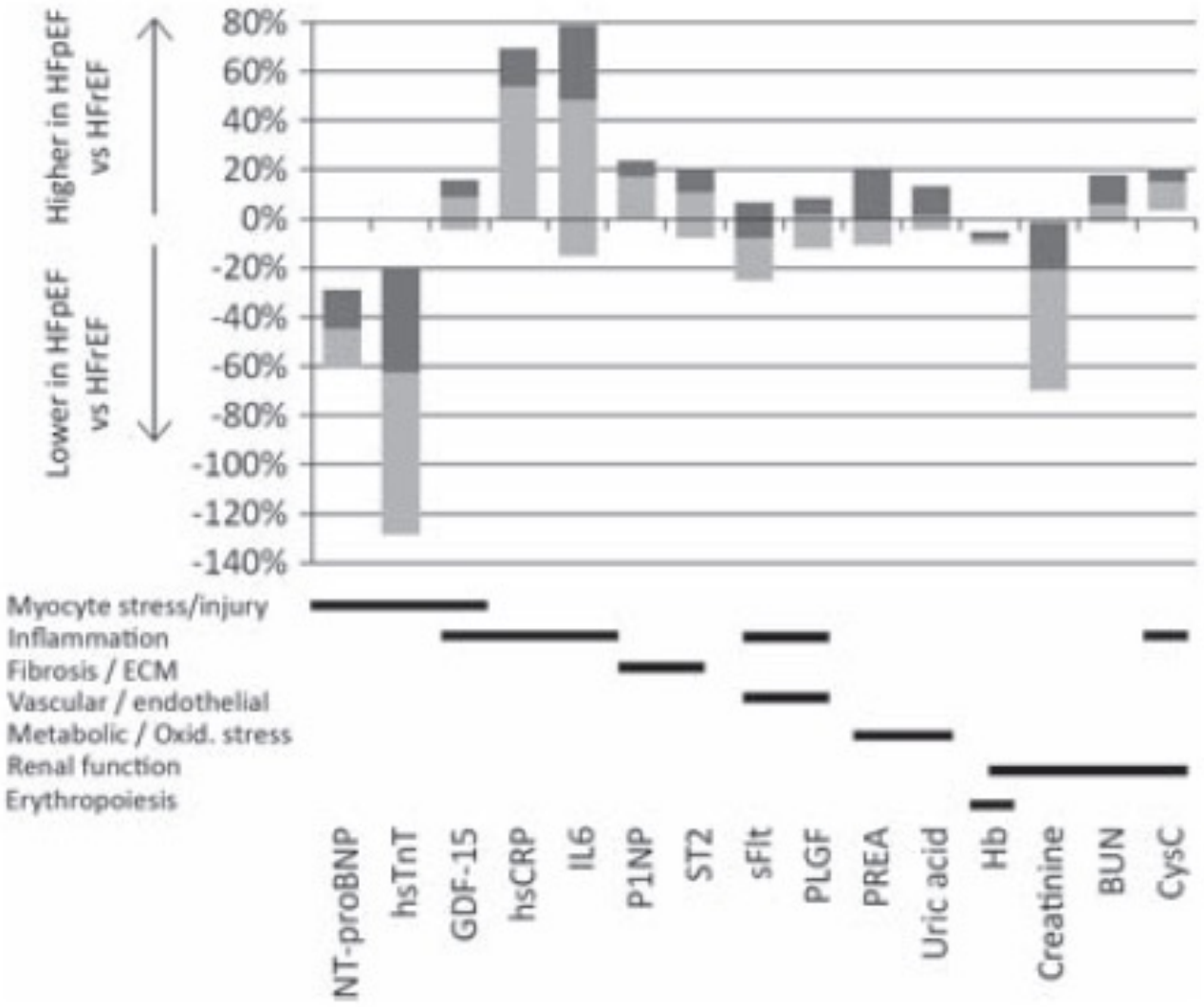
Couade et al. IEEE transactions on medical imaging, 2011, 30, 2, 295-305

Myocardial stiffness during one cardiac cycle



Evaluation Of Myocardial Stiffness Change Over Age In Healthy Adult And Hypertrophic Cardiomyopathy Populations Using New Noninvasive Ultrasound Shear Wave Imaging. *O Villemain, M Correia, E Mousseaux, J Baranger, G. Soulat, A. Hagège, S. Zarka, , E Messas, M Pernot.* **Submitted**

Systemic inflammation in HFpEF

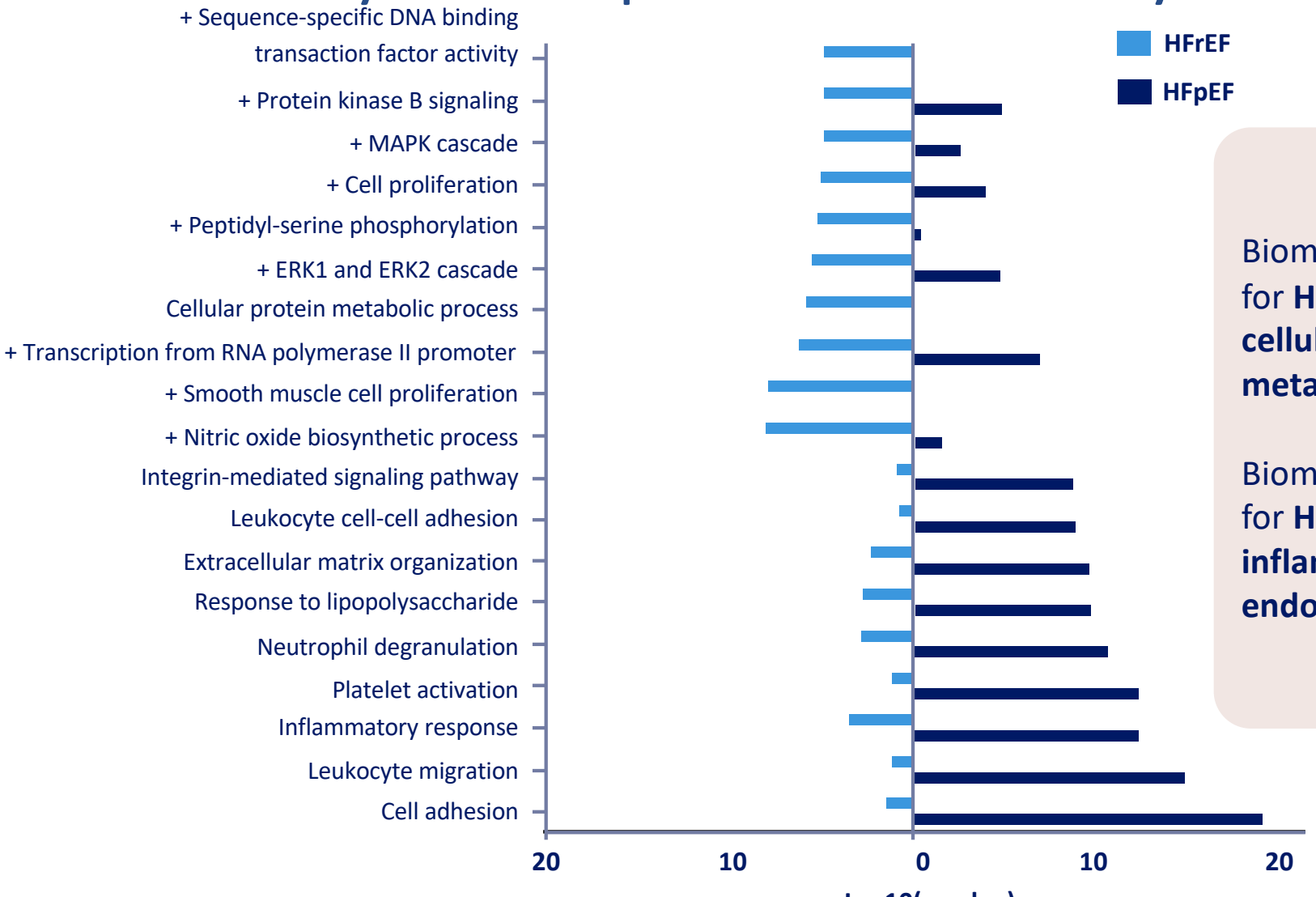


Inflammation
➔ Endothelial dysfunction ?

Sanders-VanWijk et al, Eur J HF 2015

Systemic inflammation in HFpEF: BIO-STAT Analysis

Pathway over-representation analysis[1]



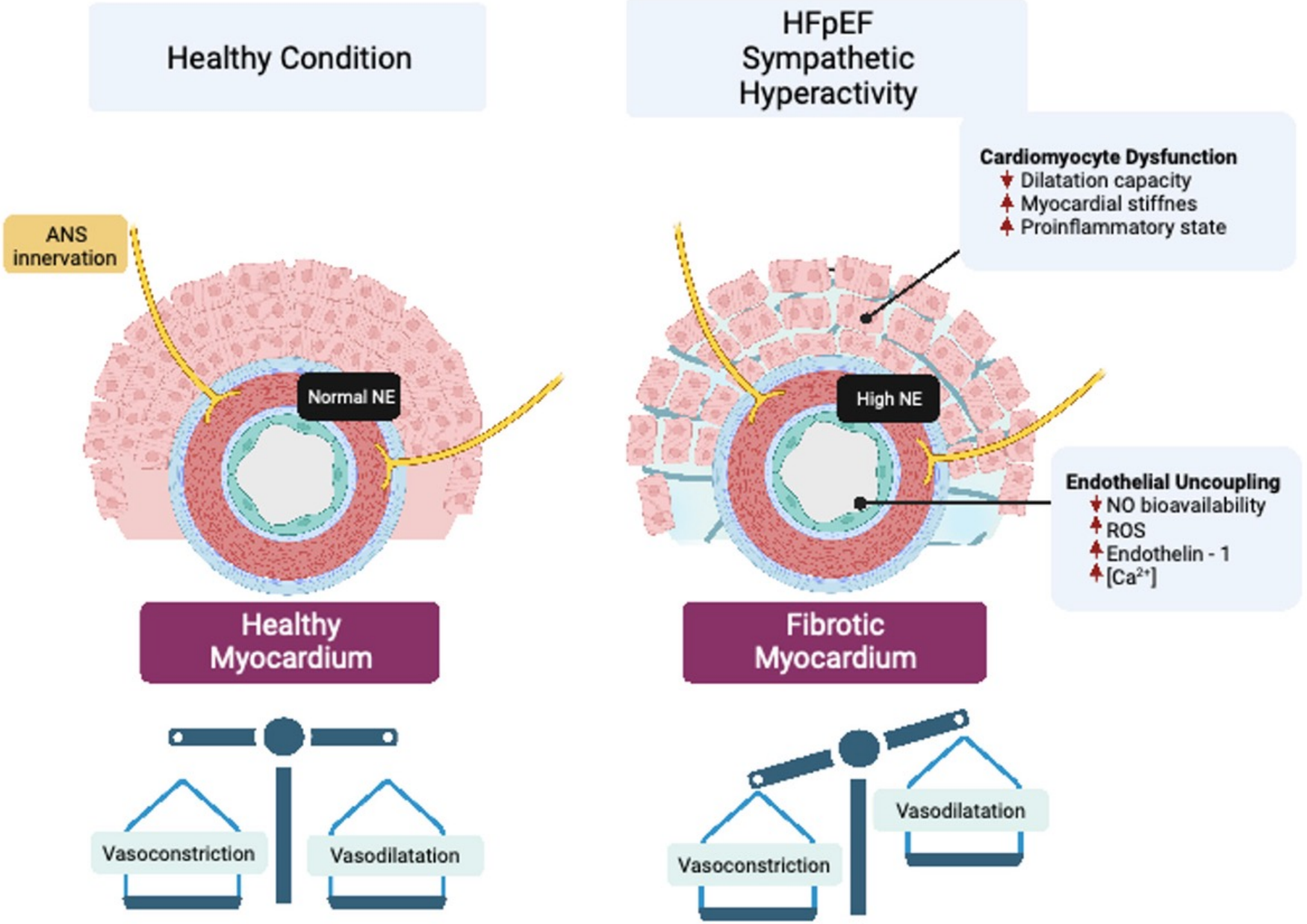
Biomarker profiles specific for **HFrEF** are related to **cellular proliferation and metabolism**

Biomarker profiles specific for **HFpEF** are related to **inflammation and endothelial function**

ERK, extracellular signal-regulated kinase HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MAPK, mitogen-activated protein kinases

1. Tromp et al. J Am Coll Cardiol 2018;72(10):1081–90

Endothelial dysfunction in HFpEF



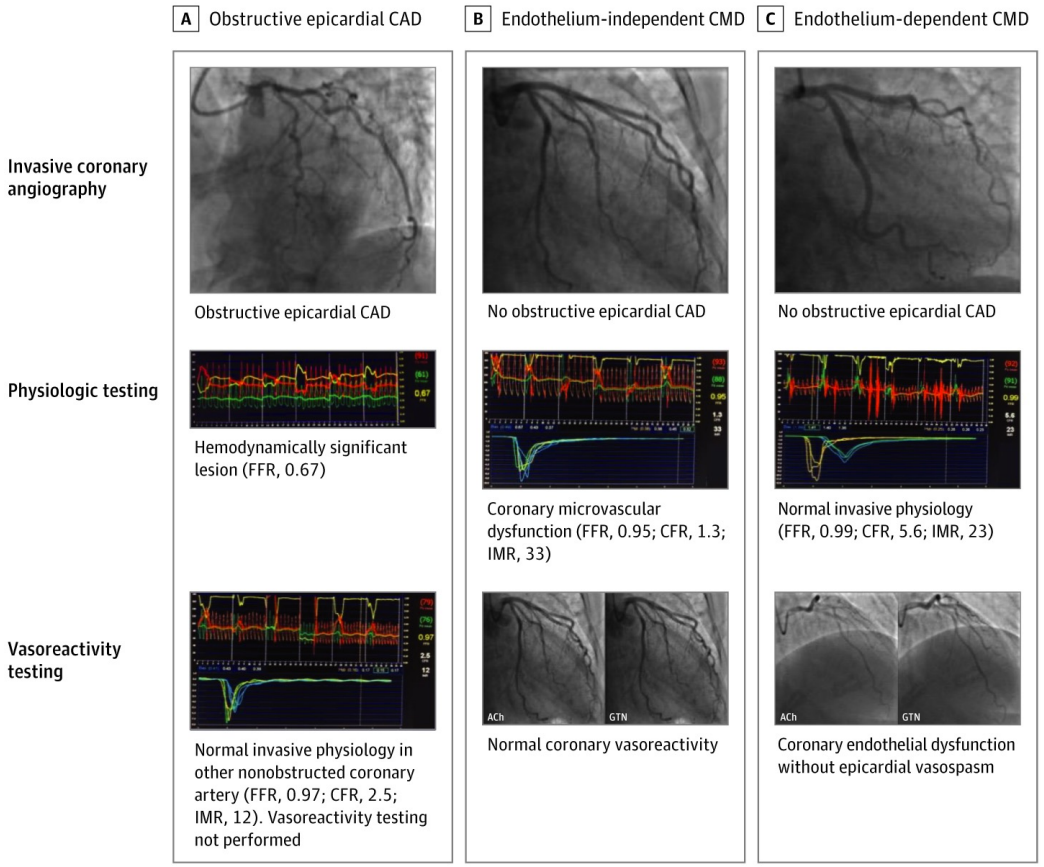
JAMA Network™

Paris Cardiovascular research Center PARCC

From: **Prevalence of Coronary Artery Disease and Coronary Microvascular Dysfunction in Patients With Heart Failure With Preserved Ejection Fraction**

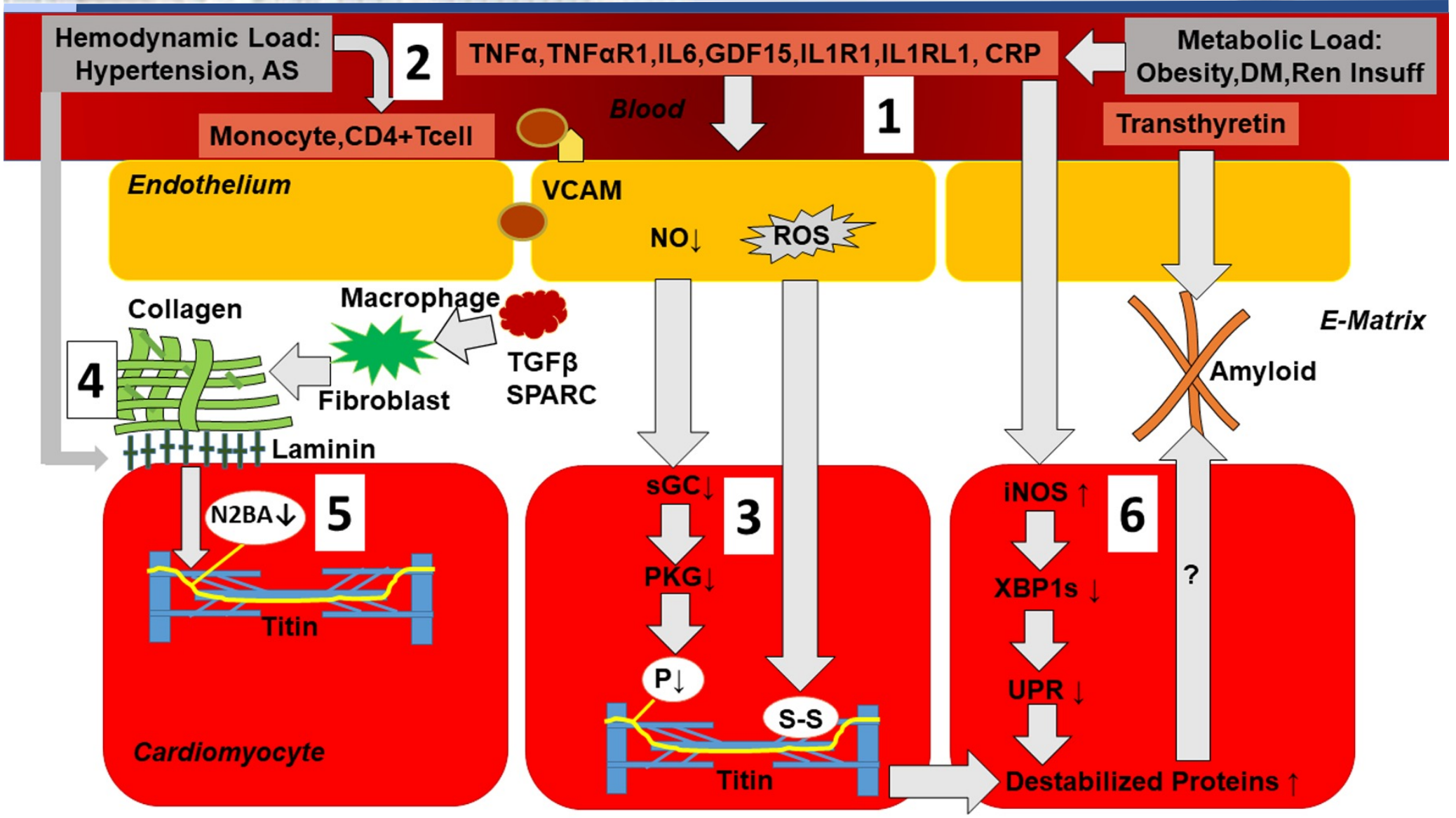
JAMA Cardiol. 2021;6(10):1130-1143. doi:10.1001/jamacardio.2021.1825

N=106 HFpEF patients with evaluation of CAD and CMD



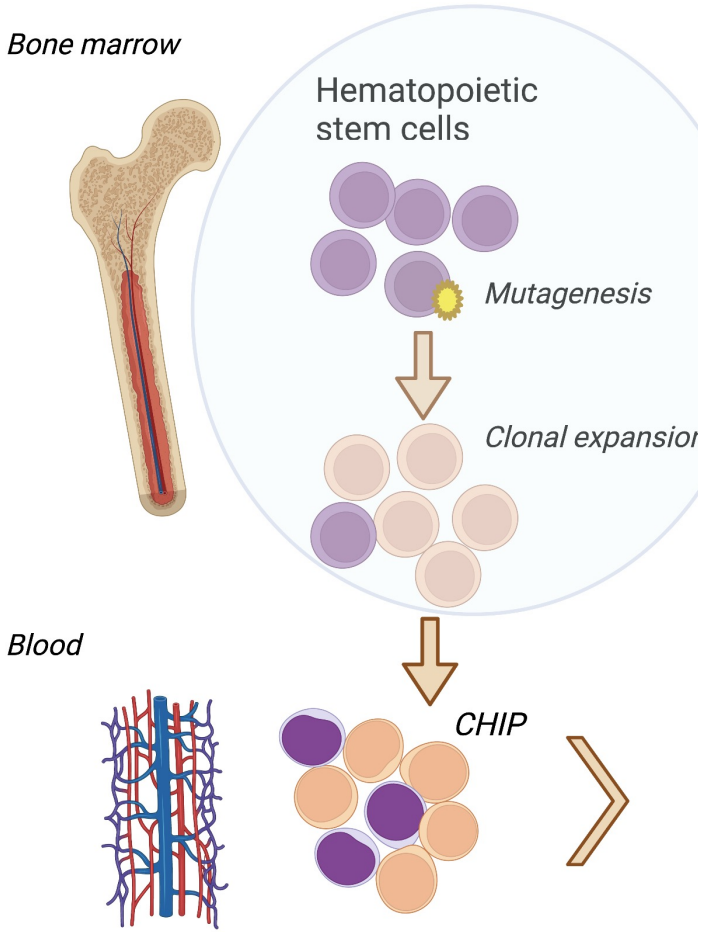
51% 66% 24%

➔ 91% with CAD, CMD or both



Paulus W. Zile M, Circ res 2021

What are CHIPs mutations ?



CHIPs = acquired mutations in hematopoetic stem cells that create an indeterminate potential

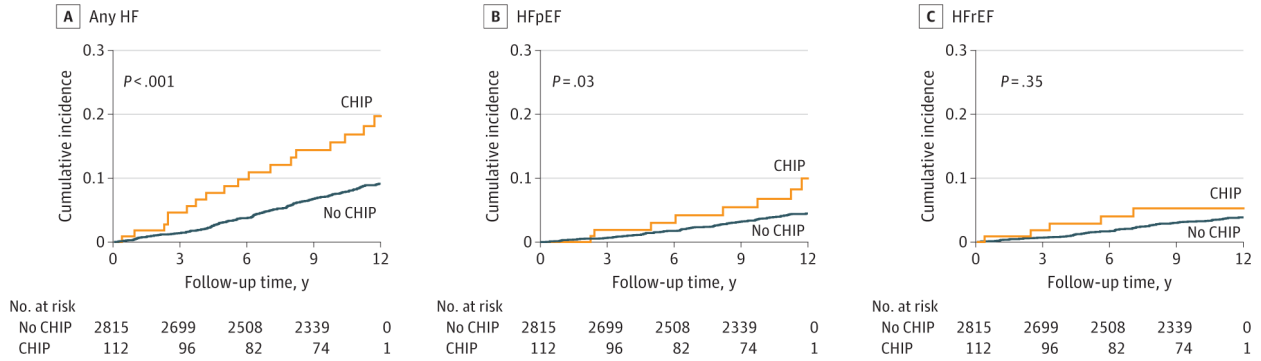
No clonality and proliferation leading to a cancer

But these mutations induce an abnormal reactivity = low-grade inflammation ? Inflamm aging ?

From: **Clonal Hematopoiesis and Incident Heart Failure With Preserved Ejection Fraction**

JAMA Netw Open. 2024;7(1):e2353244. doi:10.1001/jamanetworkopen.2023.53244

Cohort 1



Cohort 2

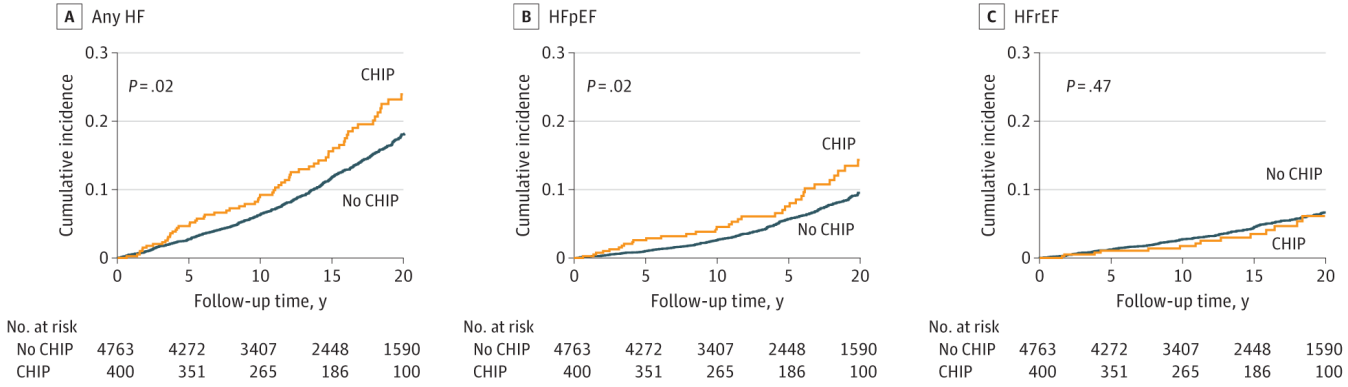
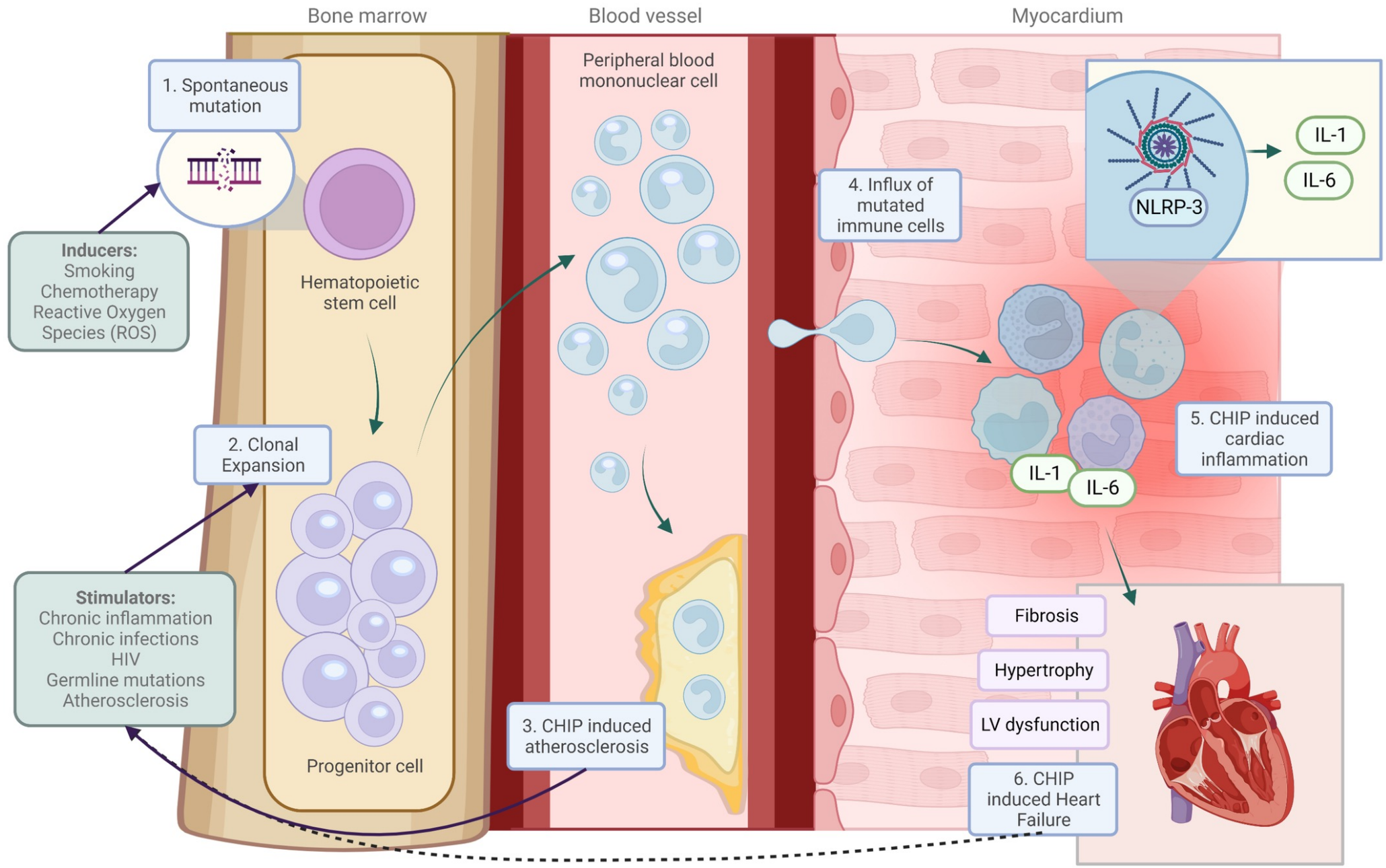


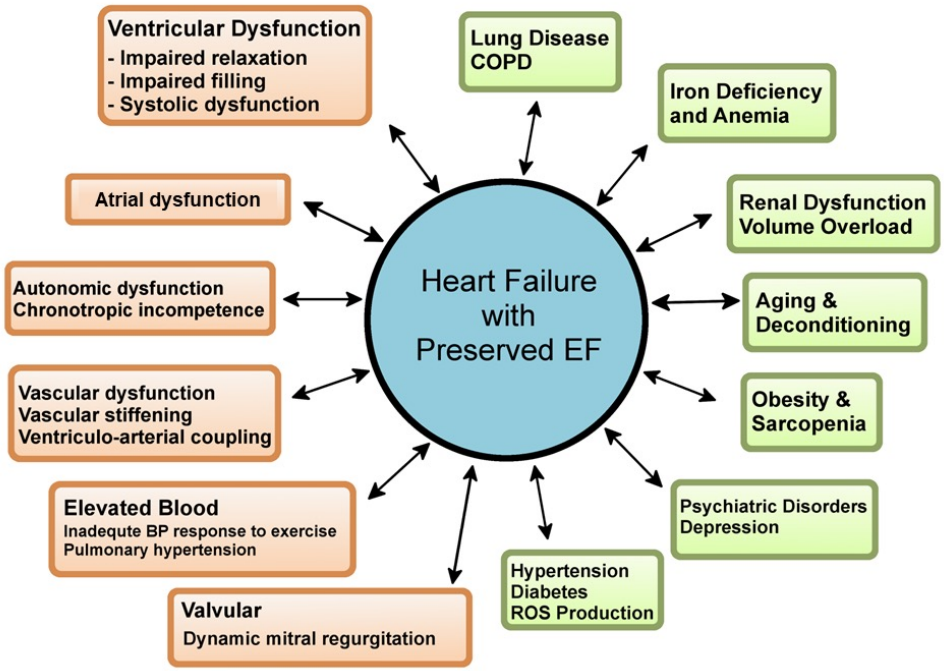
Figure Legend:

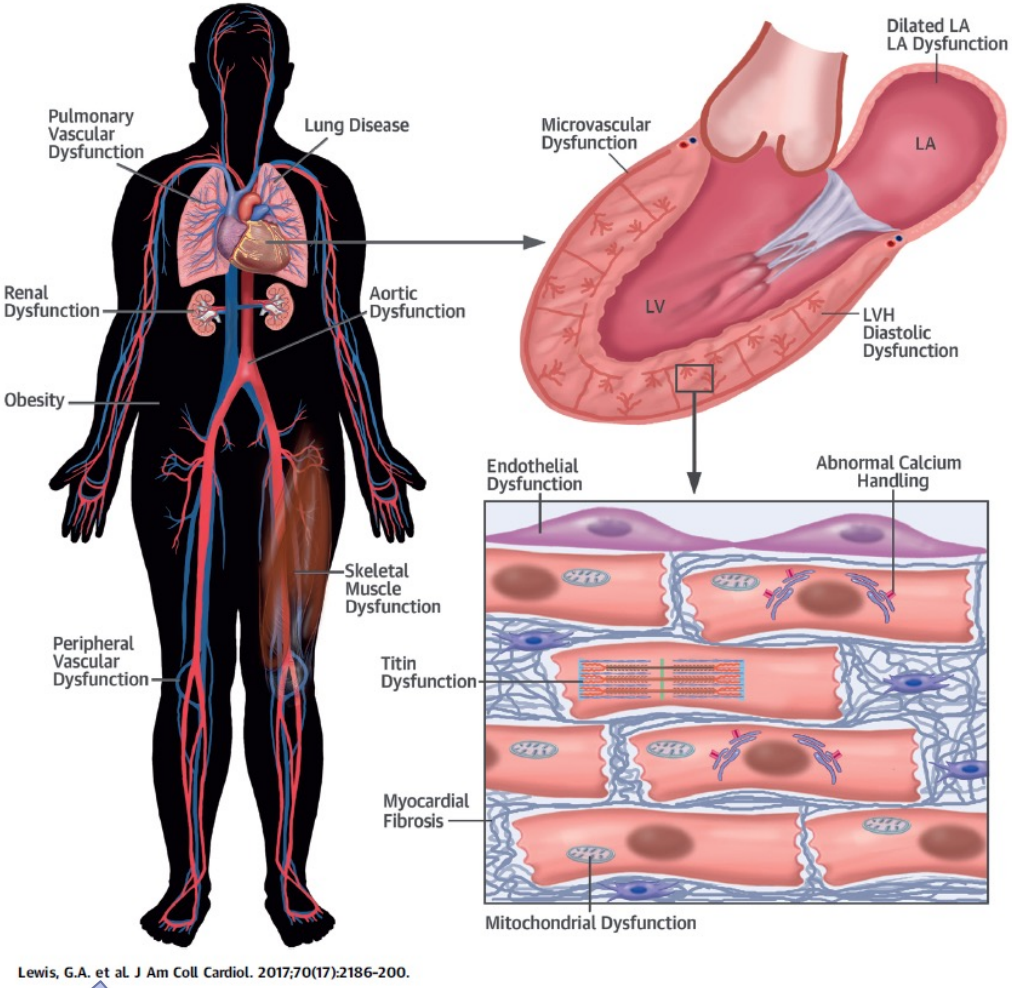
Cumulative Incidence of Heart Failure (HF) and HF Subtypes by Clonal Hematopoiesis of Indeterminate Potential (CHIP) Carrier Status in the Jackson Heart Study (JHS)Cumulative incidence curves for any HF, HF with preserved ejection fraction (HFpEF), and HF with reduced ejection fraction (HFrEF) were constructed using the Kaplan-Meier method and compared using the (unadjusted) log-rank test. Any HF was defined as a composite outcome including HFpEF, HFrEF, and HF with unknown ejection fraction. Follow-up occurred over a median (IQR) of 12.0 (11.0-12.0) years.

Can we link all together ?



HFpEF : a multi-organ disease ?





Ponikowski P, et al. *Eur Heart J.* 2016; **37**:2129–200. Supplementary Appendix;
Senni M, et al. *Eur Heart J.* 2014; **35**:2797–811.

Thank you for your attention

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Physiopathologie, classification, innovation dans l'insuffisance cardiaque

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