

Manifestazioni Cardiovascolari e Metaboliche in Reumatologia

Approcci interdisciplinari in reumatologia

Cuore e sclerosi sistemica **Cardiopatía Restrittiva**

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Cardiologia 2

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**Azienda Ospedaliera
Città della Salute e
della Scienza di Torino**

Classification of systemic sclerosis

- 1. **Diffuse cutaneous systemic sclerosis**
 - 1) **proximal skin thickening**
 - - **distal and proximal extremity and often the trunk and face**
 - 2) **tendency to rapid progression of skin change**
 - 3) **rapid onset of disease following Raynaud's phenomenon**
 - 4) **early appearance of visceral involvement**
 - 5) **poor prognosis**

Classification of systemic sclerosis

2. Limited cutaneous systemic sclerosis

1) symmetric restricted fibrosis

- affecting the distal extremities and face/neck

2) prolonged delay in appearance of distinctive internal manifestation

3) prominence of calcinosis and telangiectasia

4) good prognosis

* CREST syndrome

- calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia



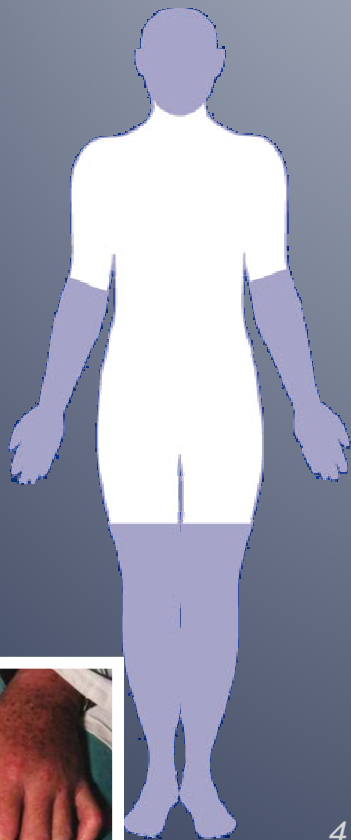


Classificazione



Limitata – **Prognosi buona**

Diffusa – **Prognosi infausta**



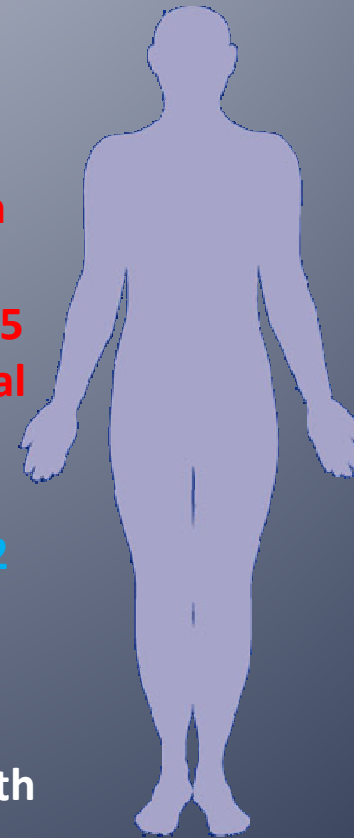
Extent of internal organ involvement influences survival in limited and diffuse forms of SSc

In diffuse SSc, mortality rate 5 to 8 times higher than general population⁴

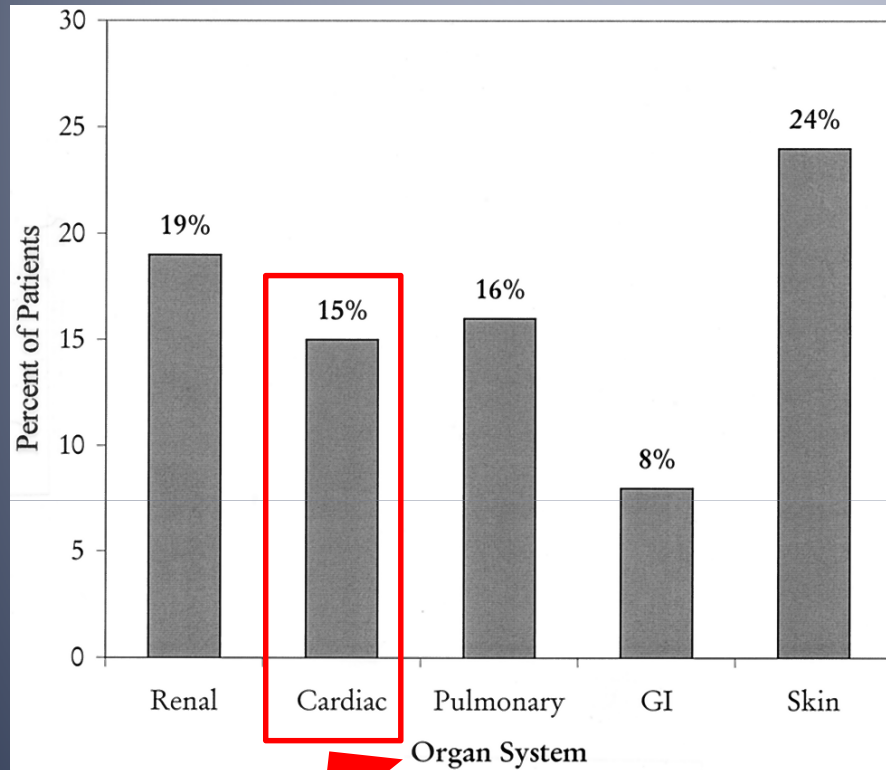
For those with limited skin involvement, mortality rate 2 times higher than general population⁴

Lung disease most common scleroderma-related cause of death

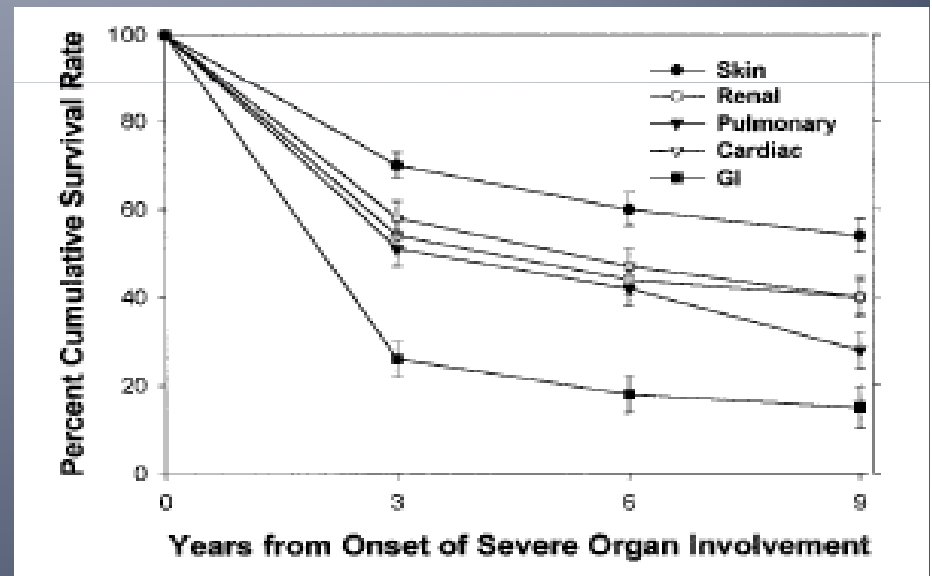
4. Denton C. UpToDate, 2004.



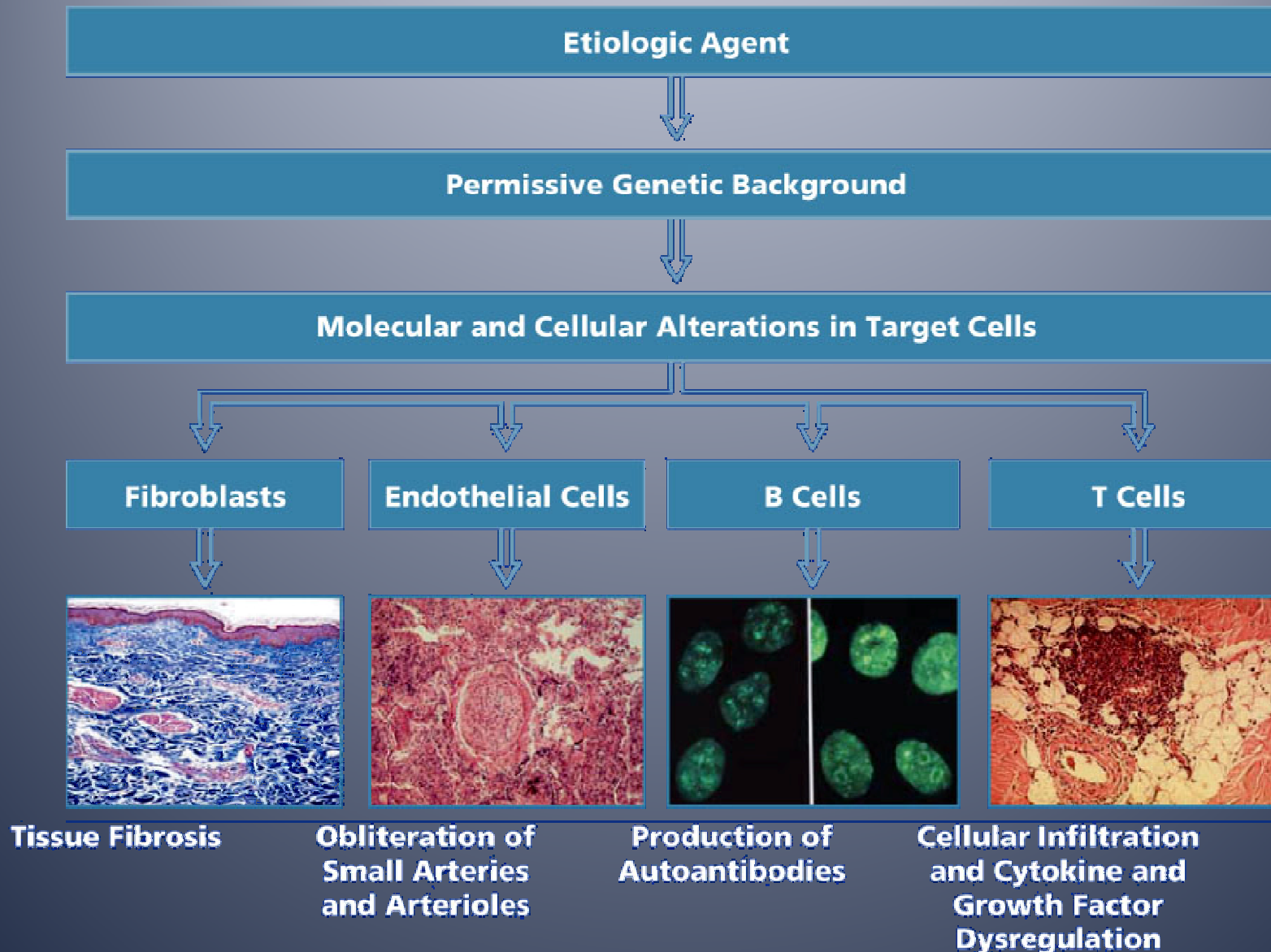
Severe organ involvement in systemic sclerosis, results from the Pittsburgh study



- CHF
- symptomatic pericarditis
- arrhythmia requiring treatment



Fisiopatologia



Fisiopatologia

- **Danno di arteriole e capillari**
 - - cellule endoteliali
 - - adesione e attivazione delle piastrine
 - - rilascio di ET, trombossano A2
 - - vasocostrizione & crescita di cellule endoteliali e fibroblasti
 - - stenosi o occlusione, aumentata permeabilità capillare
- **Fibrosi**
 - - alterata regolazione del fattore di crescita dei fibroblasti
 - - aumentata produzione della matrice extracellulare (collagene, fibronectina, and glicosaminoglicani)
 - - ispessimento della cute & fibrosi di organi interni

Alterazioni cardiovascolari

- **In generale**
 - Versamento pericardico
 - Aritmie
 - Disturbi del sistema di conduzione
 - Alterazioni valvolari (rare)

Alterazioni cardiovascolari

Microcircolazione

- **Vasospasmo**
 - Precoce
 - Reversibile
- **Ridotta riserva coronarica**
 - Tardiva
 - Irreversibile

Fibrosi

- **Deposito di collagene nella matrice intracellulare**
 - Tardiva
 - Disfunzione sistolica e diastolica
 - Entrambi i ventricoli



Causes of restrictive cardiomyopathy

Infiltrative disorders

Amyloidosis

Haemosiderosis

Sarcoidosis

Endomyocardial fibroelastosis

Scleroderma

Radiotherapy

Idiopathic

CARDIOMIOPATIA RESTRITTIVA

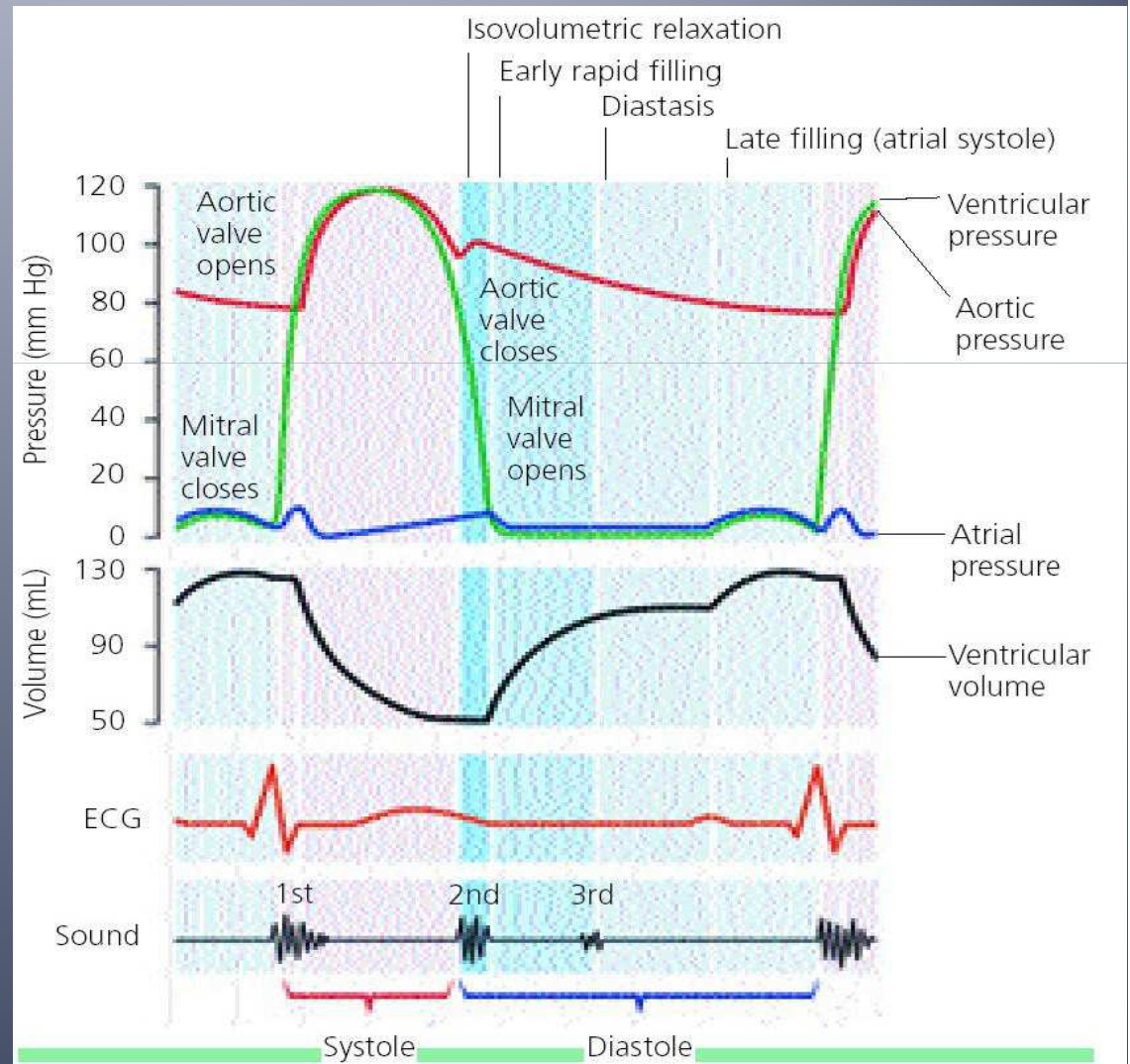
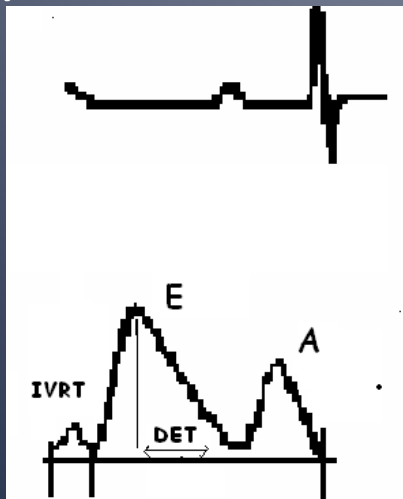
- meno comune
- funzione sistolica normale o solo lievemente ridotta
- normali spessori o aumentati
- normali volumi
- dilatazione di entrambi gli atri
- classificazione funzionale
- alterazione della funzione diastolica

Diastole

E' un processo attivo che si estende dalla chiusura della valvola aortica al termine dell'afflusso mitralico

E' divisa in 4 fasi:

- 1) RILASCIAMENTO ISOVOLUMETRICO (RI)**
- 2) RIEMPIMENTO RAPIDO (RR)**
- 3) RIEMPIMENTO LENTO (diastasi)**
- 4) SISTOLE ATRIALE**



Definizioni

- **Anormalità diastolica:**

alterazione del rilasciamento ventricolare identificata da \uparrow IVRT o E/A patologico ma senza segni di aumentata PTD

→ **pattern diastolico**

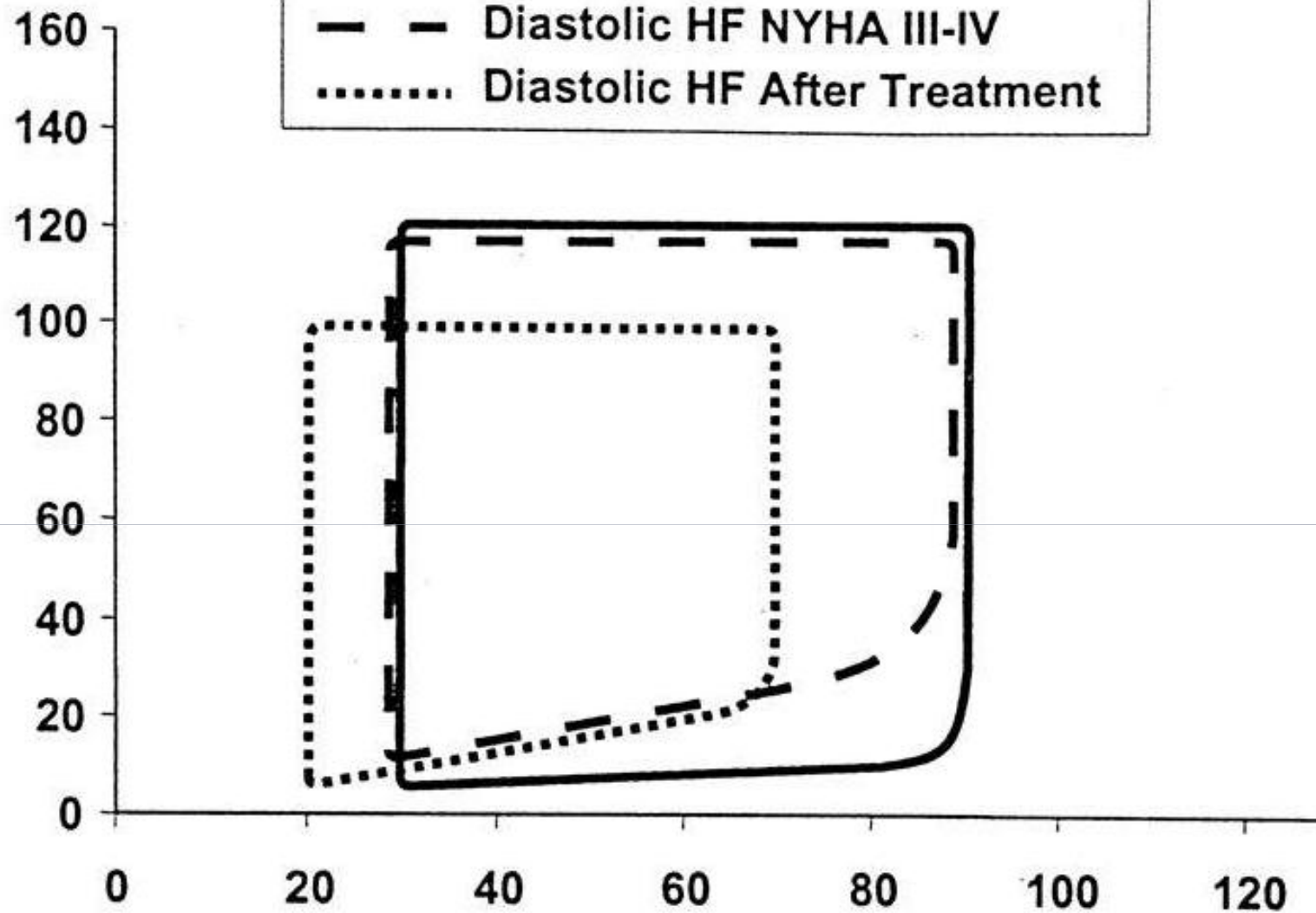
- **Disfunzione diastolica:**

viene identificata dai segni Doppler di un aumento della PTD o PA → **disfunzione diastolica I,II,III-IV grado**

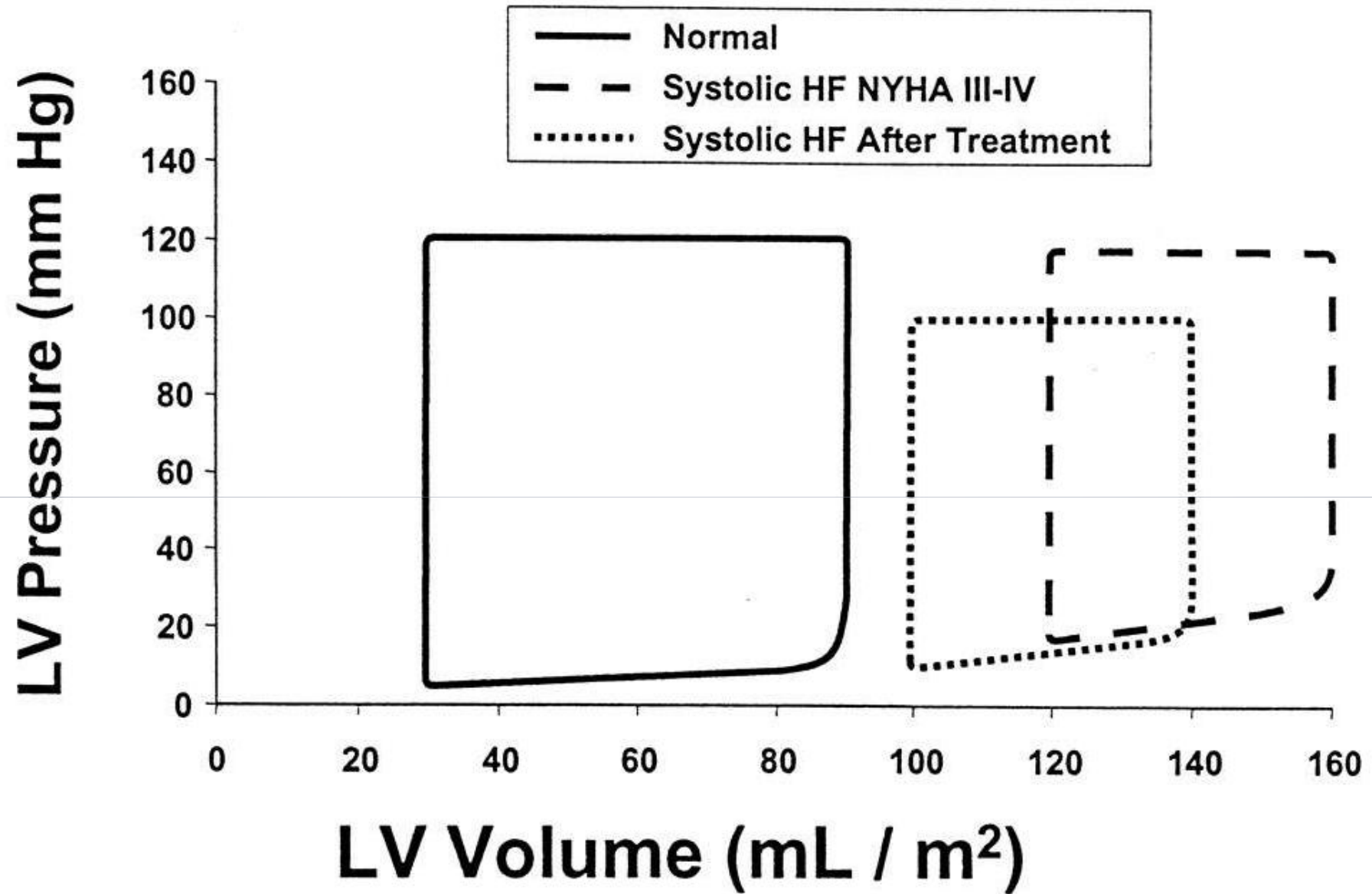
- **Scompenso diastolico:**

disfunzione diastolica + sintomi della congestione venosa polmonare

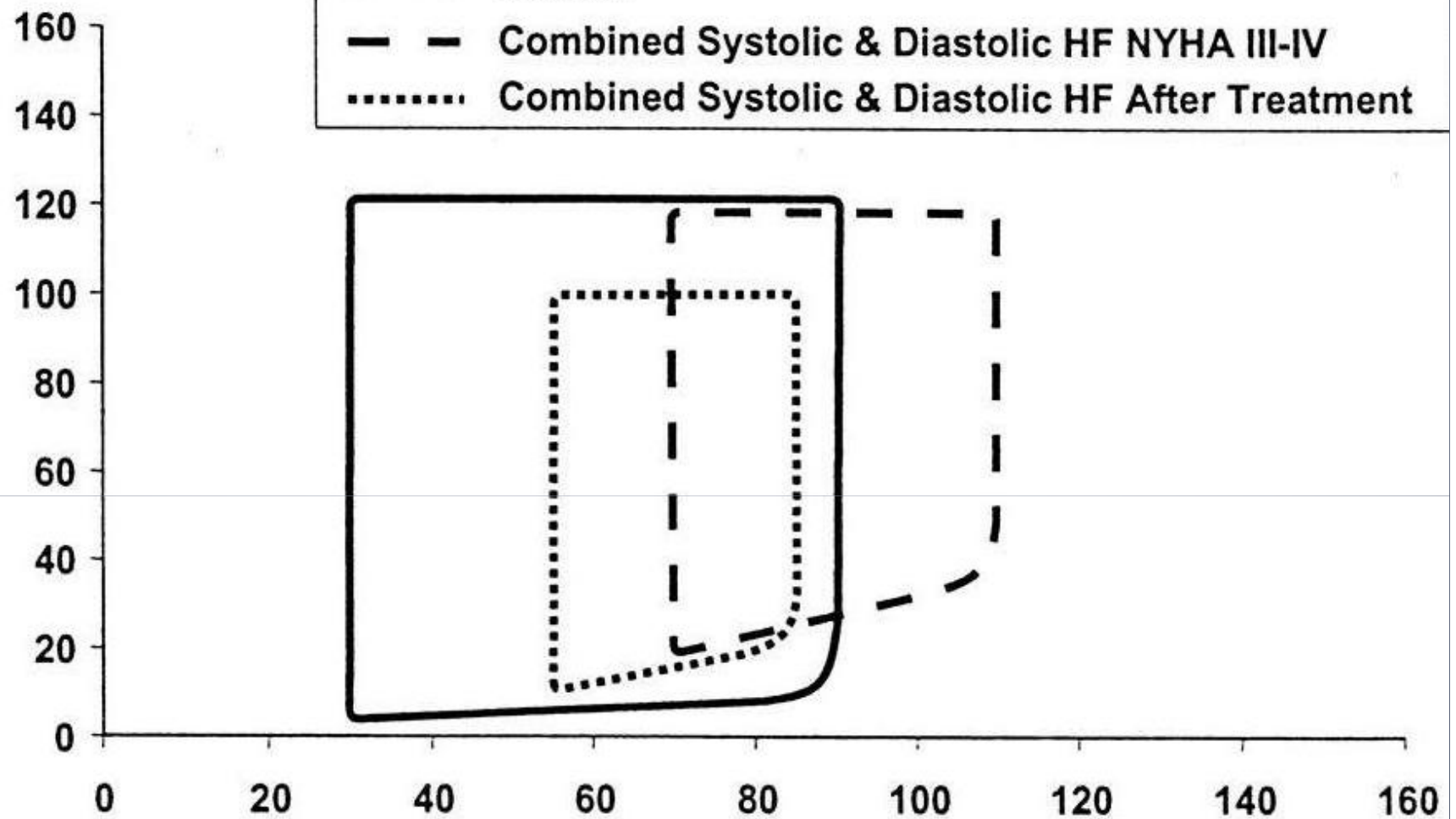
LV Pressure (mm Hg)



LV Volume (mL / m²)



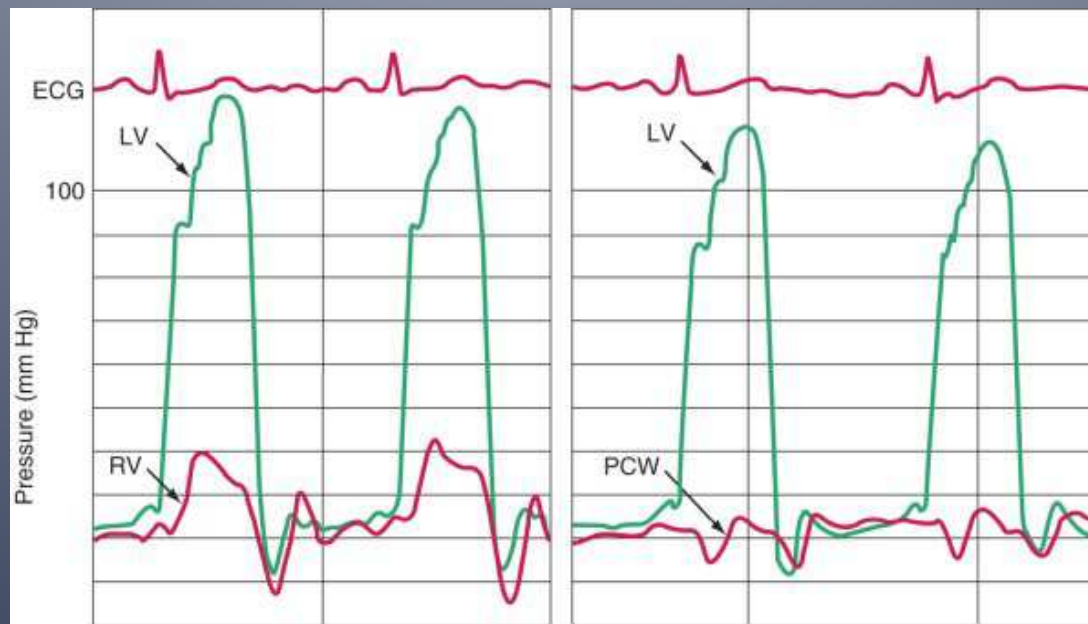
LV Pressure (mm Hg)



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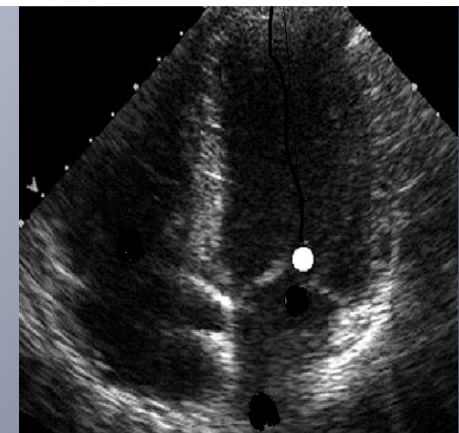
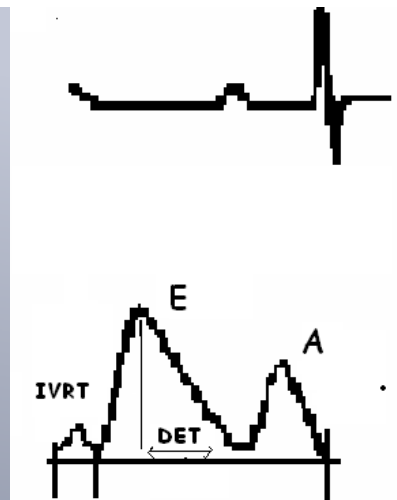
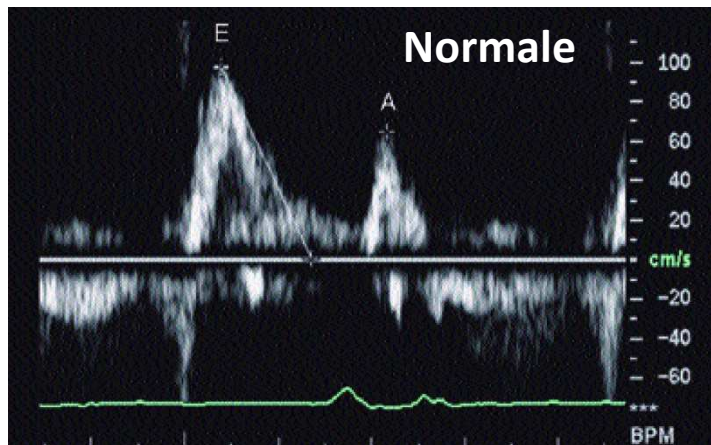
Valutazione della Funzione Diastolica

- **Cateterismo cardiaco** (gold standard): misura in maniera diretta la pressione diastolica ventricolare

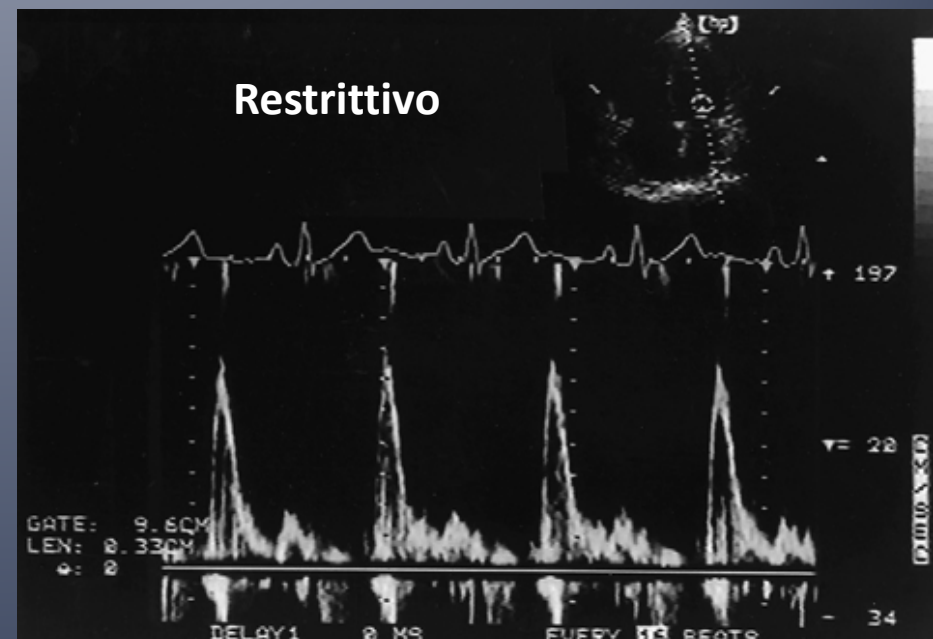
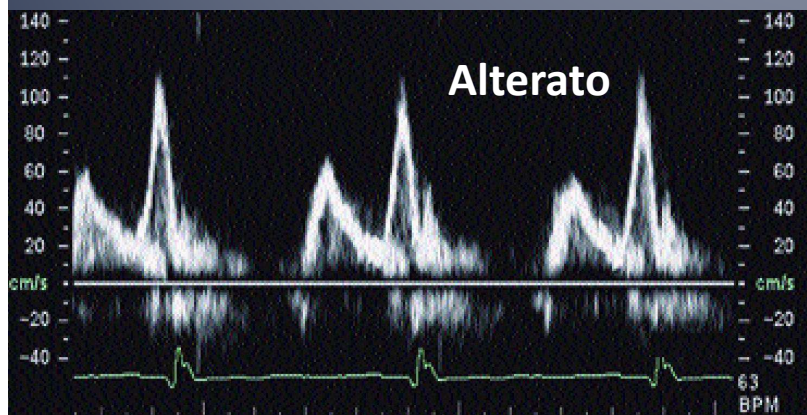


Valutazione della Funzione Diastolica

- **Ecocardiografia** (volumi, cinesi, spessori, funzione ventricolare, cavita' atriali, apparati valvolari, flussimetria, pericardio)
 - **Doppler pulsato**
 - Doppler Tessutale TDI
 - Flusso Venoso Polmonare
 - Color Doppler Mmode transmitralico
 - Speckel Tracking

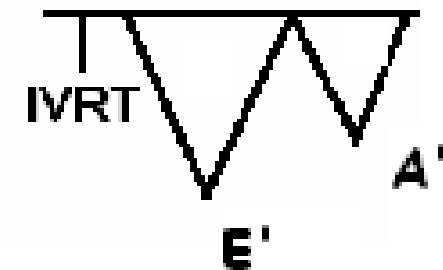
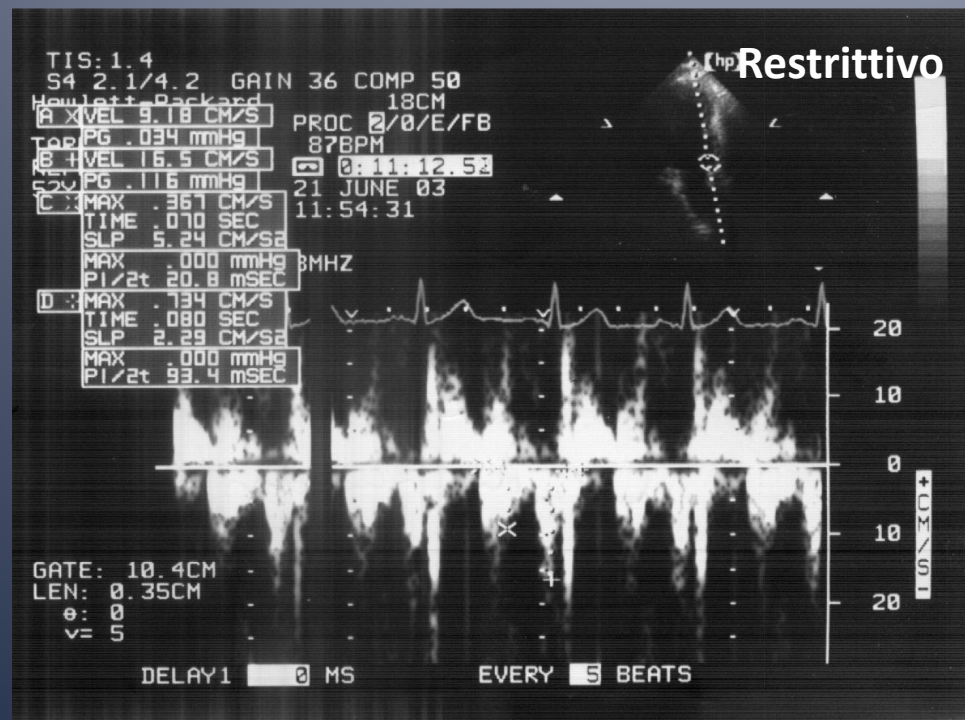
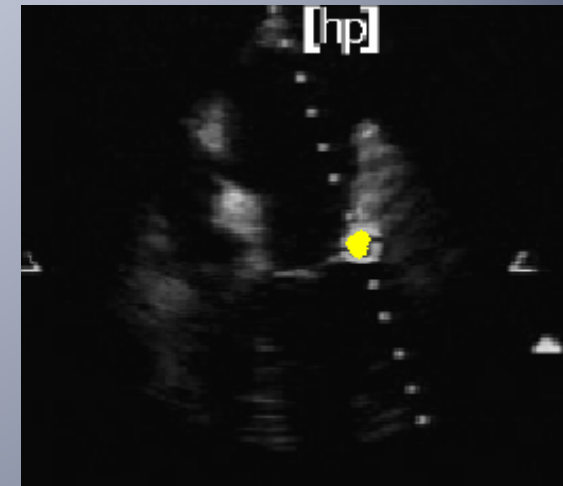
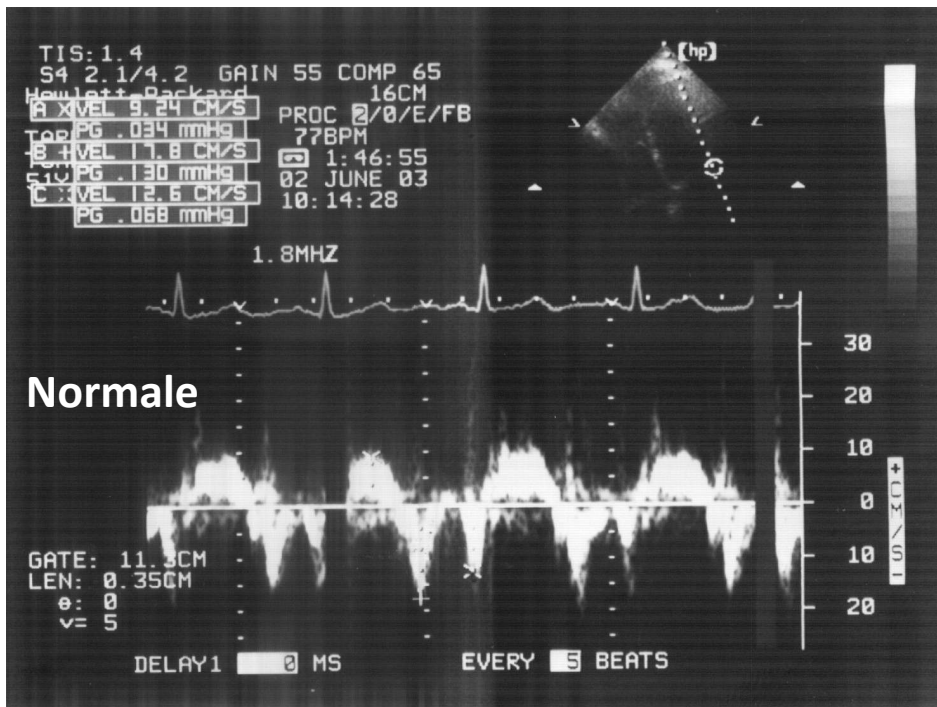


As diastolic function worsens and LV diastolic pressure rises, LV diastolic filling occurs primarily during early diastole, because the LV pressure at end-diastole is so high that atrial contraction contributes less to LV filling than normal.



Valutazione della Funzione Diastolica

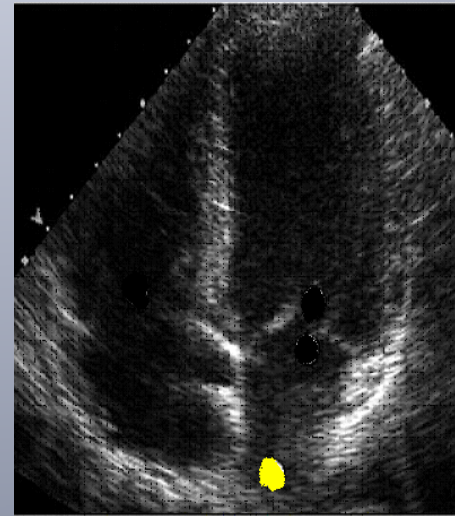
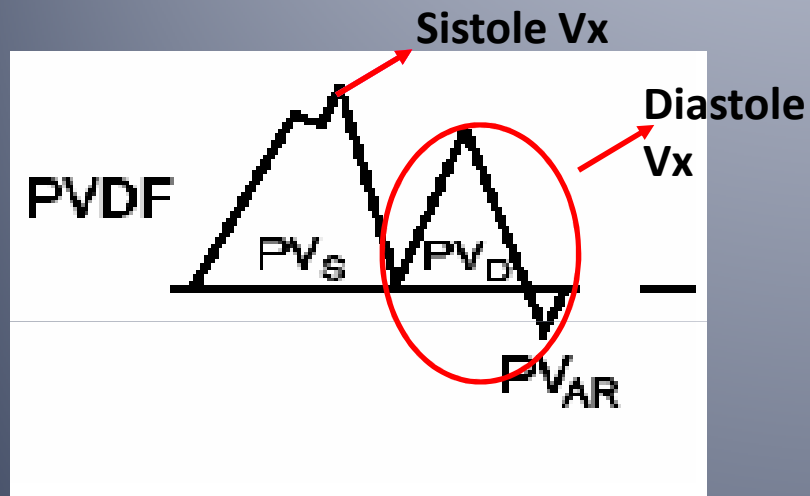
- **Ecocardiografia**
 - Doppler pulsato
 - **Doppler Tessutale TDI**
 - Flusso Venoso Polmonare
 - Color Doppler Mmode transmitralico
 - Speckel Tracking



Valutazione della Funzione Diastolica

- **Ecocardiografia**
 - Doppler pulsato
 - Doppler Tessutale TDI
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 - Speckel Tracking

NORMALE



Doppler pulsato:

sbocco in Asx della vena polmonare superiore dx

onda S: - compliance e Pr.Asx media

- dislocamento sistolico dell'annulus mitralico
- IM

→ velocità inversamente correlata alla Pr.A

onda D: - influenzata dagli stessi fattori onda E

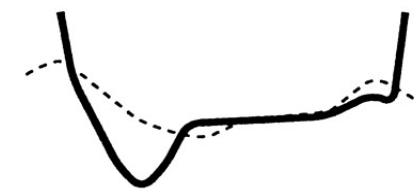
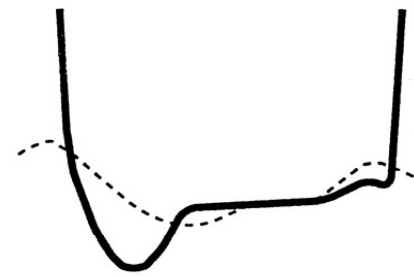
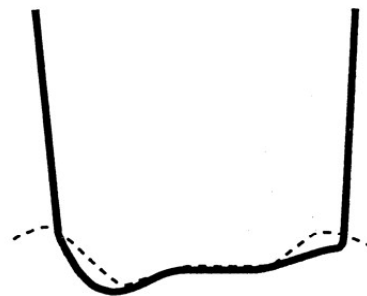
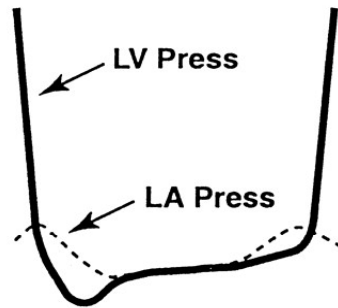
DIASTOLIC HEART FAILURE

Normal

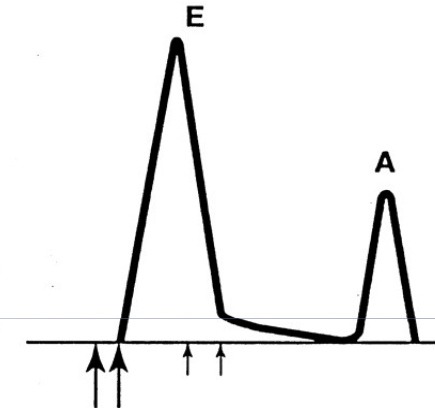
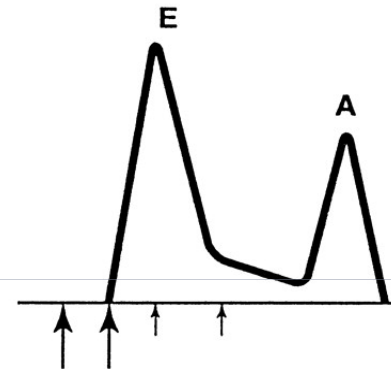
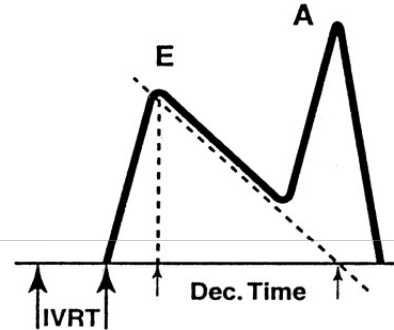
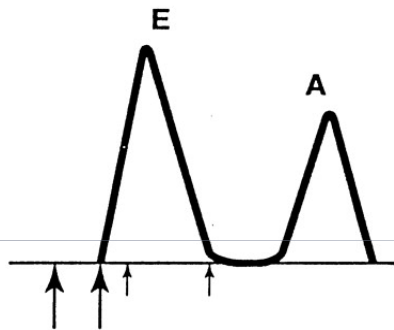
Impaired Relaxation

Pseudonormal

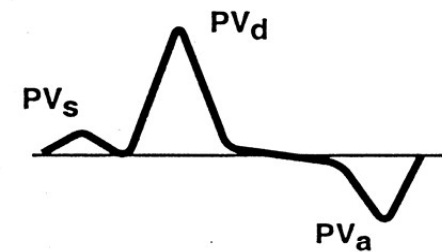
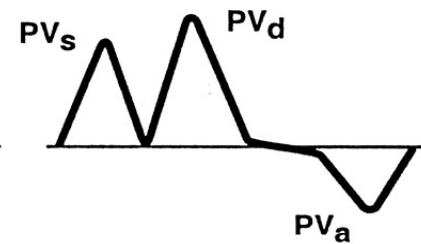
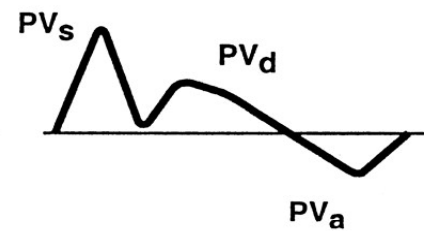
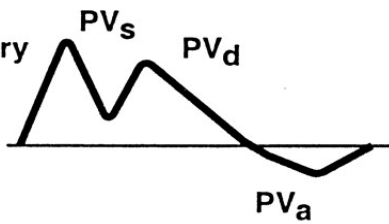
Restrictive



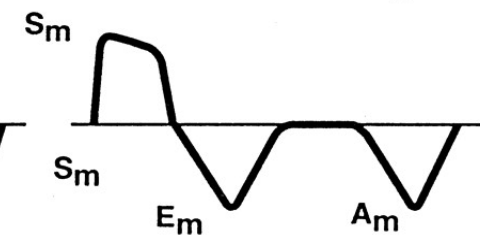
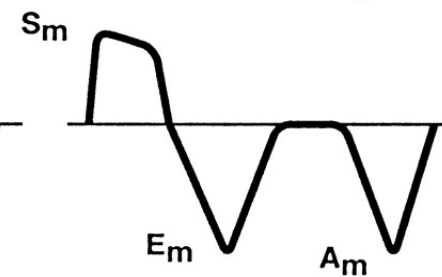
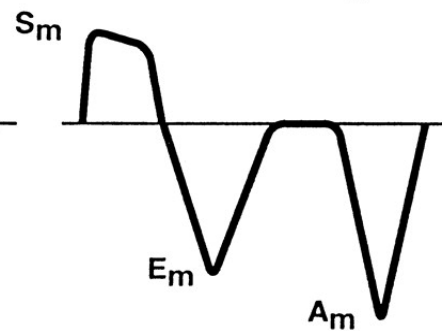
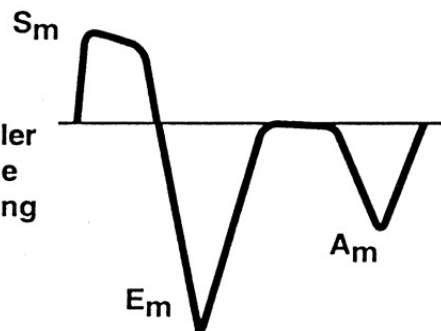
Mitral Doppler Velocity



Pulmonary Vein Velocity

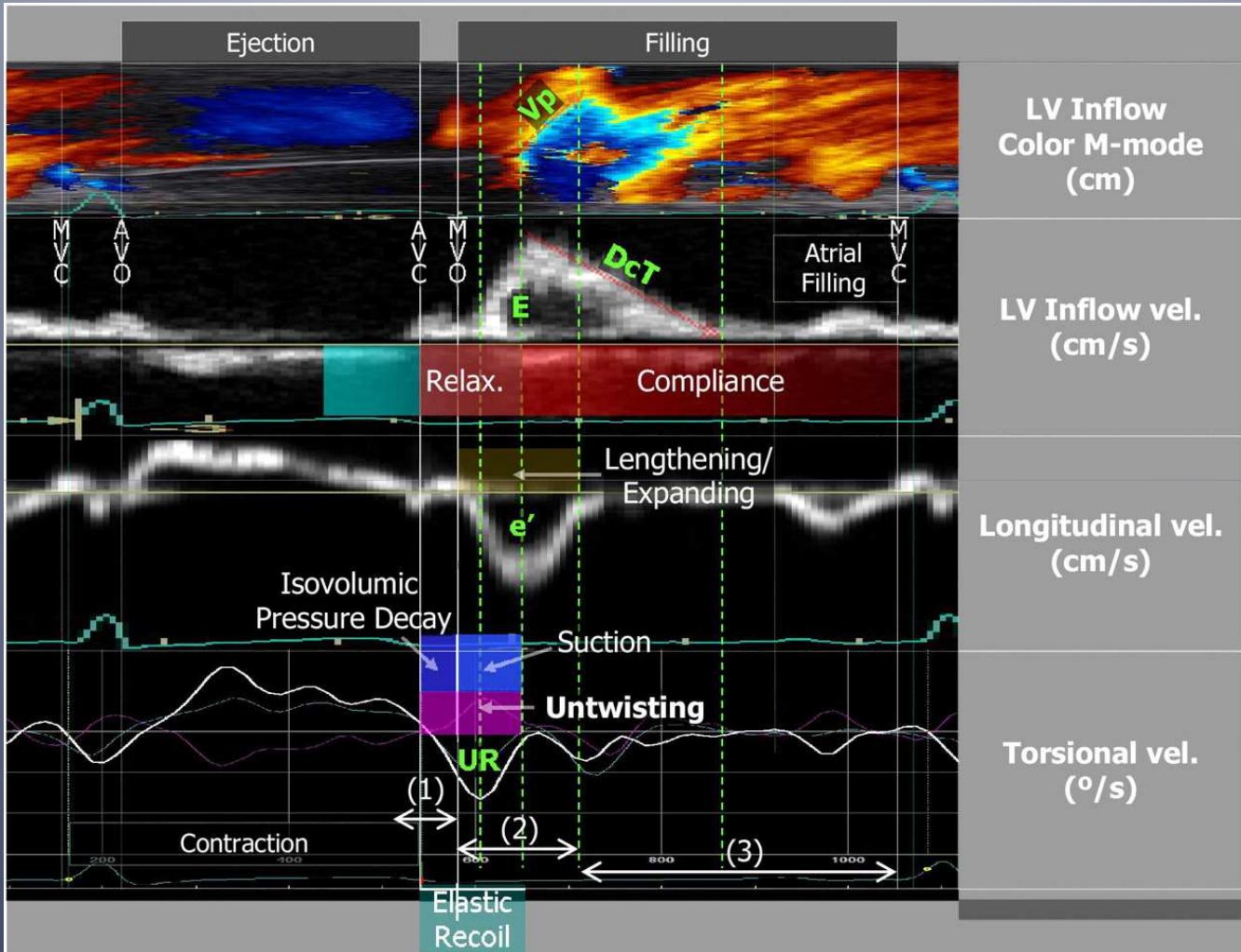


Doppler Tissue Imaging



Valutazione della Funzione Diastolica

- **Ecocardiografia**
 - Doppler pulsato
 - Doppler Tessutale TDI
 - Flusso Venoso Polmonare
 - **Color Doppler Mmode transmitralico**
 - Speckel Tracking

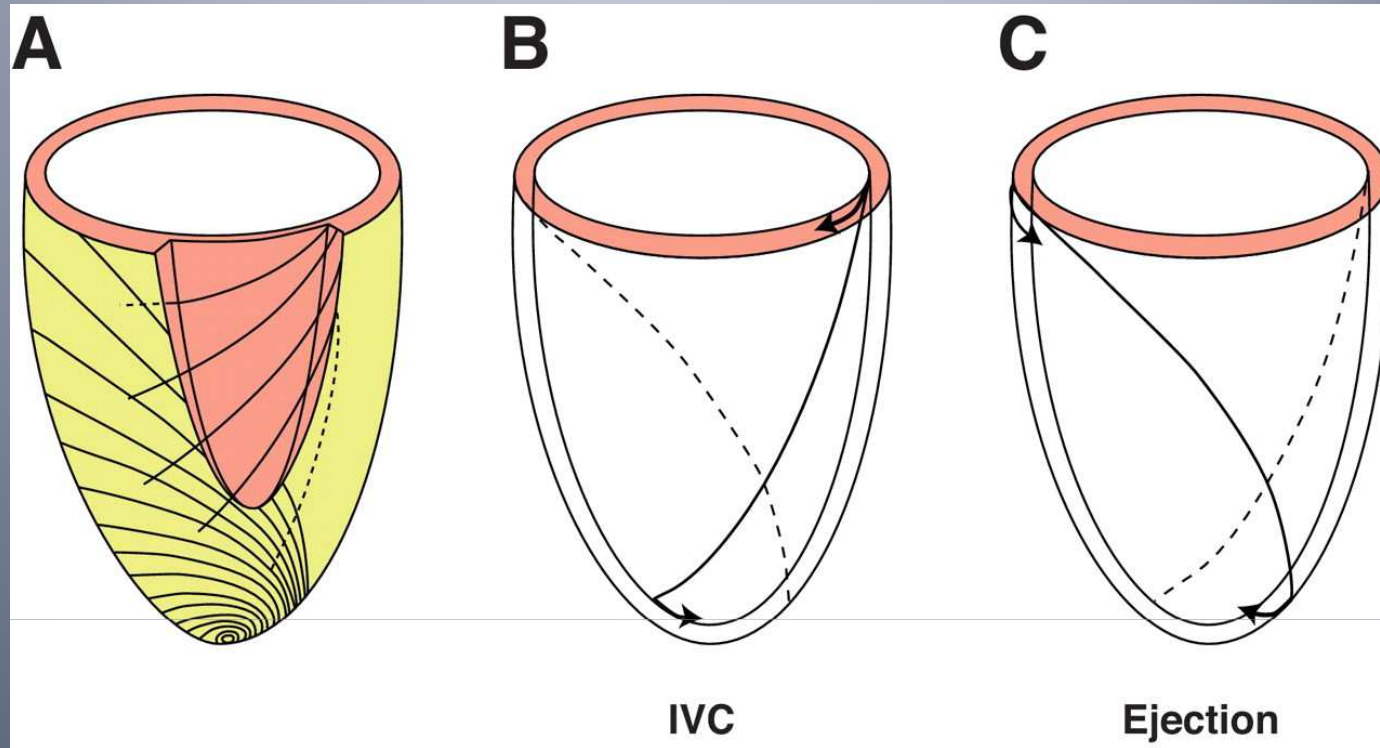


Notomi, Y. et al. J Am Coll Cardiol Img 2009;2:717-719

Valutazione della Funzione Diastolica

- **Ecocardiografia**
 - Doppler pulsato
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 - Color Doppler Mmode transmitralico
 - **Speckel Tracking**

DIASTOLE- Mechanism of LV Twist

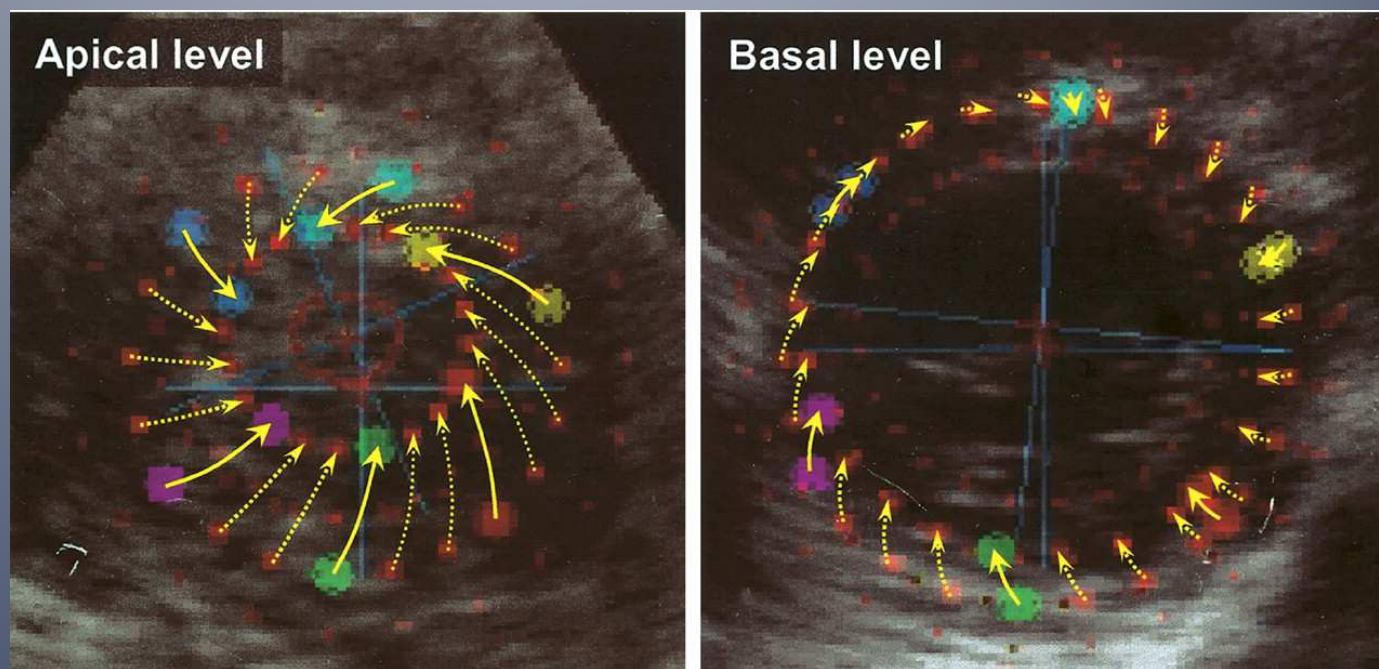


Bertini, M. et al. J Am Coll Cardiol Img 2009;2:1425-1435

- Is much more complicated than just filling
- New imaging techniques have revealed more complex anatomy than previously realized
- Now recognized that diastole consists of twisting motion

DIASTOLE- Mechanism of LV Twist

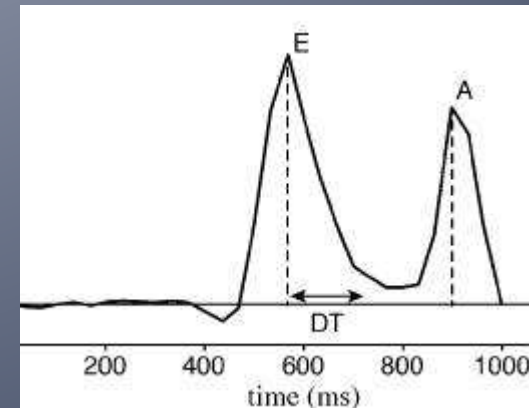
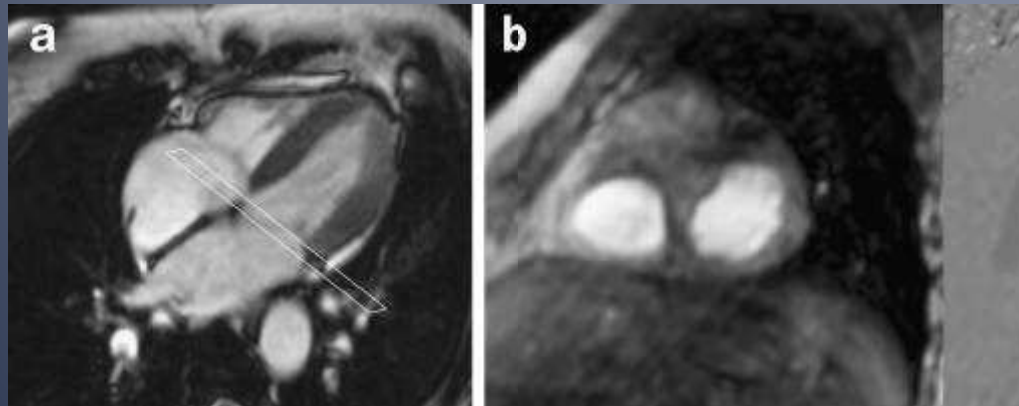
- This LV torsion generates stored energy (like a coil or spring) which is released in early diastole to produce ventricular recoil that leads to upward annular motion and suction



Notomi, Y. et al. J Am Coll Cardiol 2005;45:2034-2041

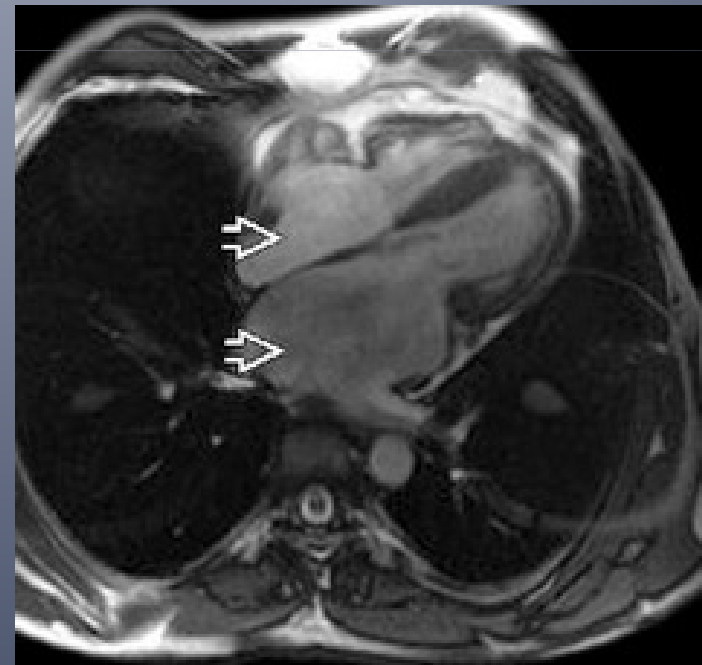
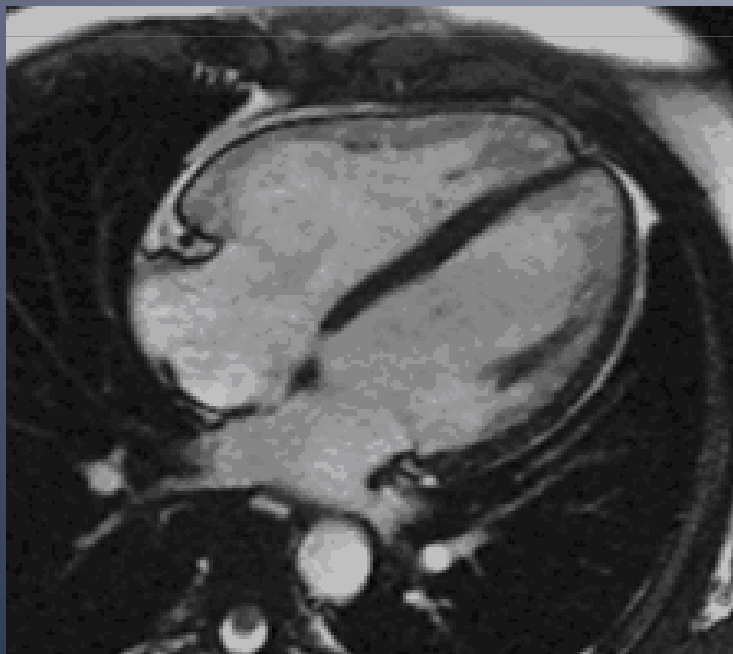
Valutazione della Funzione Diastolica

- **Risonanza Magnetica Cardiaca (CMR)** (volumi, cinesi, spessori, funzione ventricolare, cavita' atriali, apparati valvolari, flussimetria, pericardio)



...inoltre

- **CMR** permette migliore valutazione ventricolo destro



High Prevalence of Right Ventricular Systolic Dysfunction in Early Systemic Sclerosis

CHRISTOPHE MEUNE, YANNICK ALLANORE, JEAN-YVES DEVAUX, ODILE DESSAULT, DENIS DUBOC, SIMON WEBER, and ANDRÉ KAHAN

ABSTRACT. Objective. To assess right ventricular (RV) function in patients with early systemic sclerosis (SSc) and the acute effects of calcium channel blockers on RV ejection fraction (RVEF).

Methods. Forty-two consecutive patients with SSc with less than 5 years' disease duration and normal pulmonary arterial pressure (35 women, 7 men; mean age 54.3 ± 9.7 years; 16 with diffuse and 26 with limited cutaneous forms, systolic pulmonary arterial pressure 30.3 ± 5.4 mmHg) were prospectively evaluated. All underwent pulmonary function testing, echocardiography, and radionuclide ventriculography at rest and 2 hours after receiving 40 mg oral nicardipine, and were compared at baseline with 20 gender and age matched controls.

Results. None of the patients with SSc had clinical evidence of heart failure. At baseline, SSc patients had significantly lower LVEF ($68.5\% \pm 7.9$ vs $72.4\% \pm 5.0$, $p = 0.049$) and RVEF ($36.5\% \pm 7.0$ vs $45.8\% \pm 5.7$, $p < 0.0001$). Sixteen patients had reduced RVEF ($< 35\%$), 3 had reduced LVEF ($< 55\%$), and 10 had reduced peak filling rate (PFR). RVEF correlated to both LVEF and PFR ($r = 0.64$, $p < 0.0001$, and $r = 0.36$, $p = 0.0037$, respectively), whereas no correlation was found with pulmonary function impairment or pulmonary arterial pressure. Nicardipine resulted in a significant increase in RVEF (from $36.5\% \pm 7.0$ to $42.3\% \pm 8.4$, $p < 0.001$) whereas afterload indicated by mean arterial pressure did not differ significantly.

Conclusion. Reduced RVEF appears to be a common feature in early SSc; it may be due to intrinsic myocardial involvement and is acutely improved by nicardipine. (J Rheumatol 2004;31:1941-5)

Coinvolgimento
Ventricolo destro

Cardiac Magnetic Resonance Imaging Detects Subclinical Right Ventricular Impairment in Systemic Sclerosis

GIAN PAOLO BEZANTE, DANIELA ROLLANDO, MARTA SESSAREGO, NICOLETTA PANICO, MAURIZIO SETTI, GILBERTO FILACI, GIUSEPPE MOLINARI, MANRICO BALBI, MAURIZIO CUTOLO, ANTONIO BARSOTTI, FRANCESCO INDIVERI, and MASSIMO GHIO

ABSTRACT. Objective. To assess myocardial involvement in patients with systemic sclerosis (SSc) with no signs or symptoms of cardiac impairment (New York Heart Association functional class I).

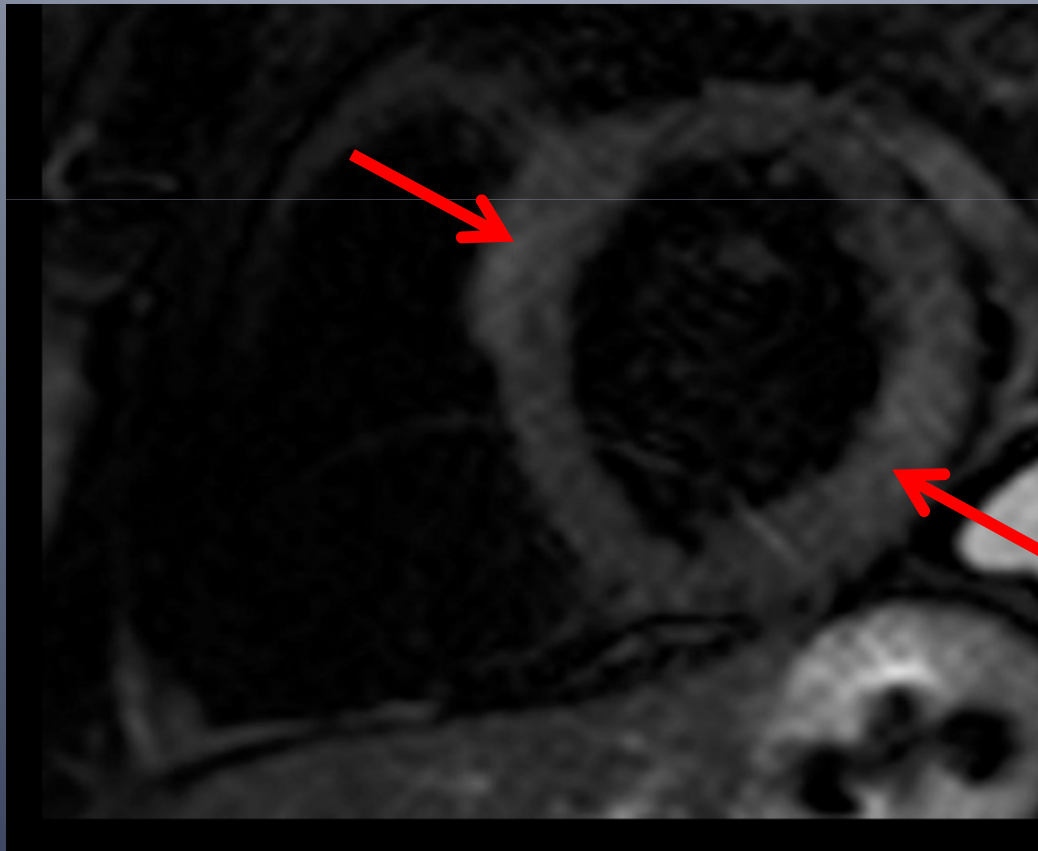
Methods. Fifty patients (45 women, 5 men, age 53.3 ± 12.9 yrs) who did not complain of serious diseases other than SSc were recruited out of 119 consecutive patients with SSc. Thirty-three were found to have limited cutaneous SSc (lSSc) and 17 diffuse SSc (dSSc). All underwent cardiovascular magnetic resonance imaging (MRI) to determine right and left systolic and diastolic volumes and ventricular ejection fractions (RVEF and LVEF). Thirty-one healthy subjects matched for sex, age, and body surface area (BSA) were studied as controls. Diffusion lung capacity test (DLCO) and high resolution computed tomography were performed to evaluate lung involvement.

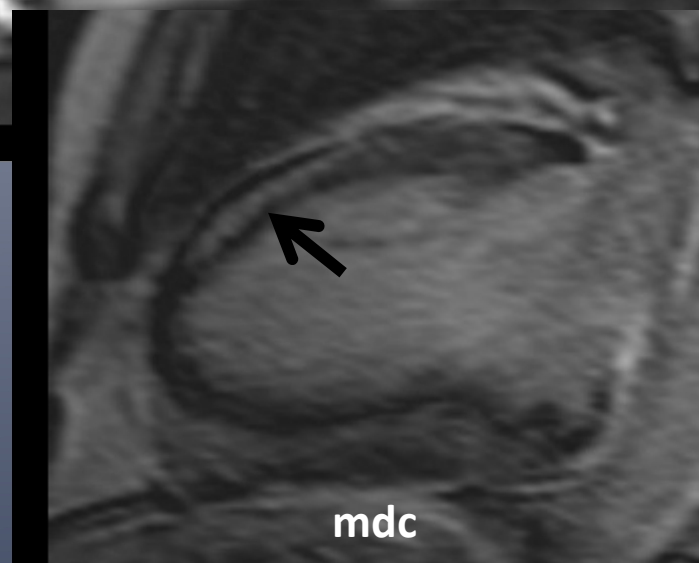
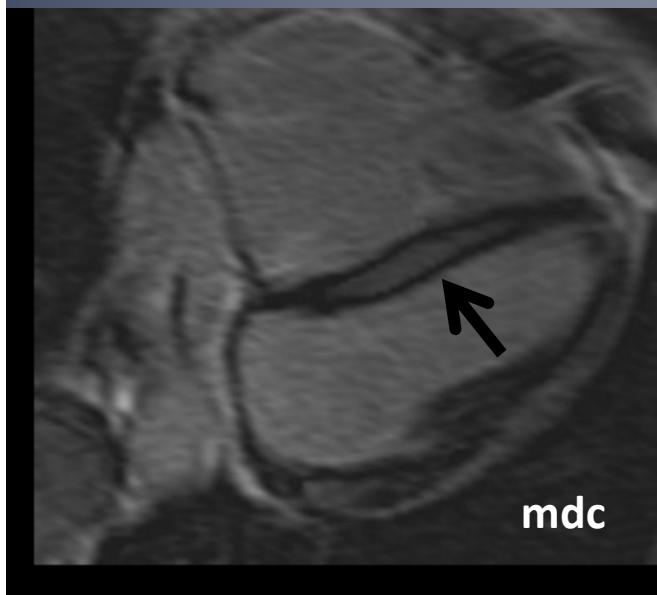
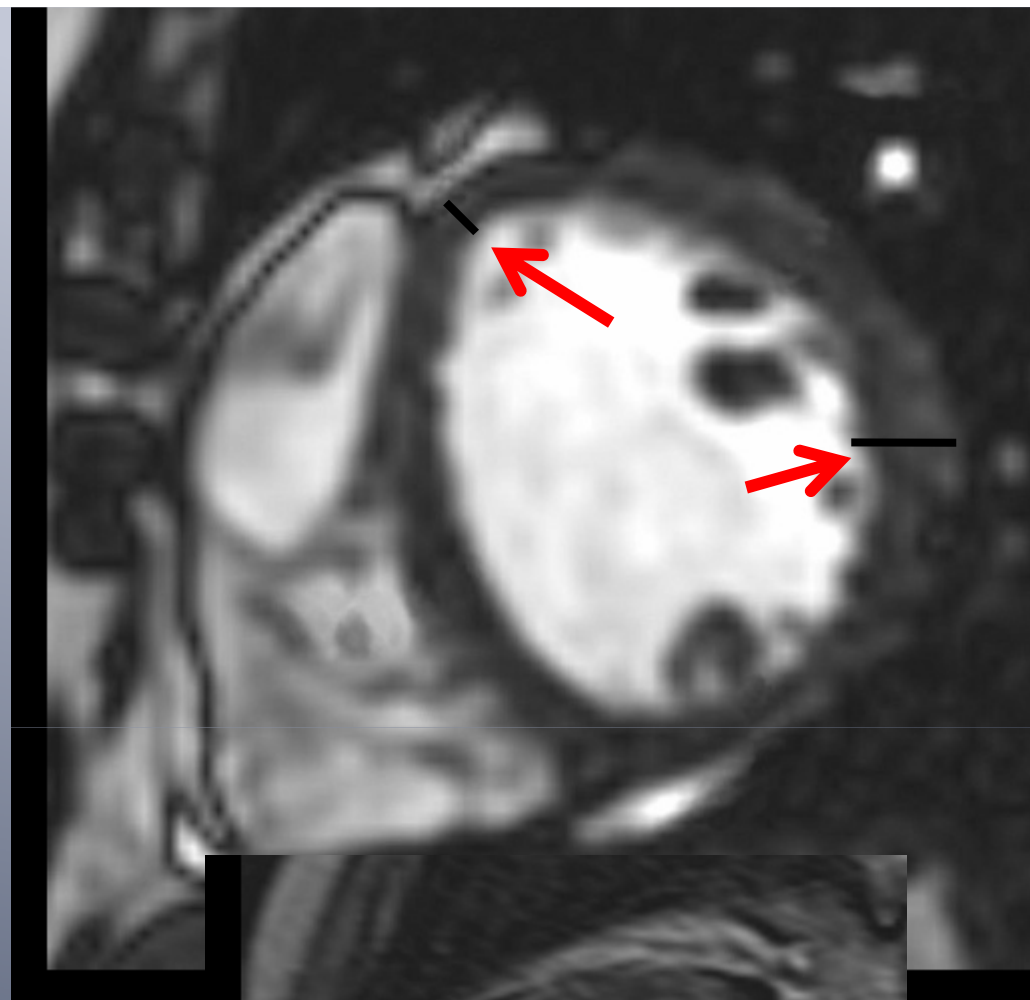
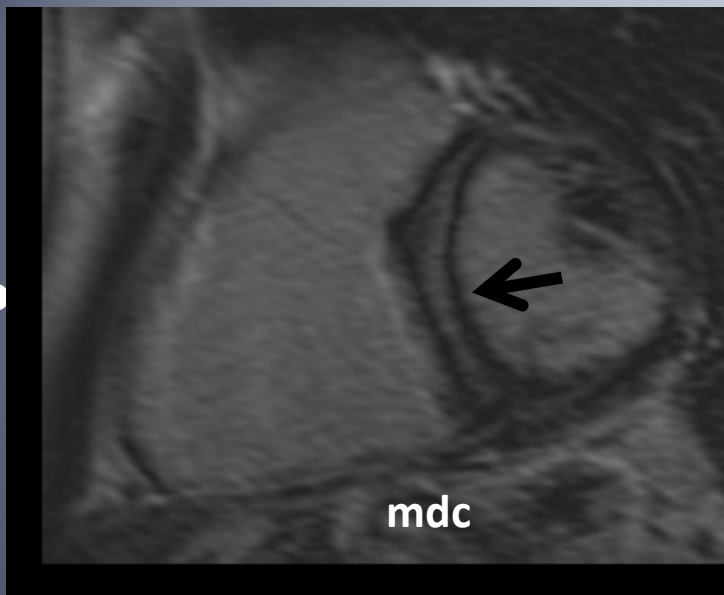
Results. Disease duration between patients with lSSc (14.1 ± 11.4 yrs) and those with dSSc (6.9 ± 4.4 yrs) was found to be significantly different ($p < 0.003$). lSSc patients were older than those with dSSc (54.8 ± 13.7 yrs vs 50.4 ± 9.9 yrs, respectively; $p < 0.04$). Anticentromere antibodies and Scl-70 were positive in 23 (46%) and 17 patients (34%). Except for the left and right systolic volumes, all unadjusted cardiac MRI measures were significantly reduced in SSc compared to the controls ($p < 0.001$ and $p < 0.009$). These differences persisted after adjustment for subjects' height and BSA. Raw RVEF data and RVEF data matched for height and BSA were significantly reduced in dSSc patients in comparison to lSSc ($p < 0.03$).

Conclusion. Compromised RVF was found in patients with asymptomatic SSc. Unlike standard diagnostic techniques, cardiac MRI appears to be a rapid and noninvasive means of determining subclinical right myocardial involvement that is otherwise undetected in patients with SSc. (First Release Nov 1 2007; J Rheumatol 2007;34:2431-7)

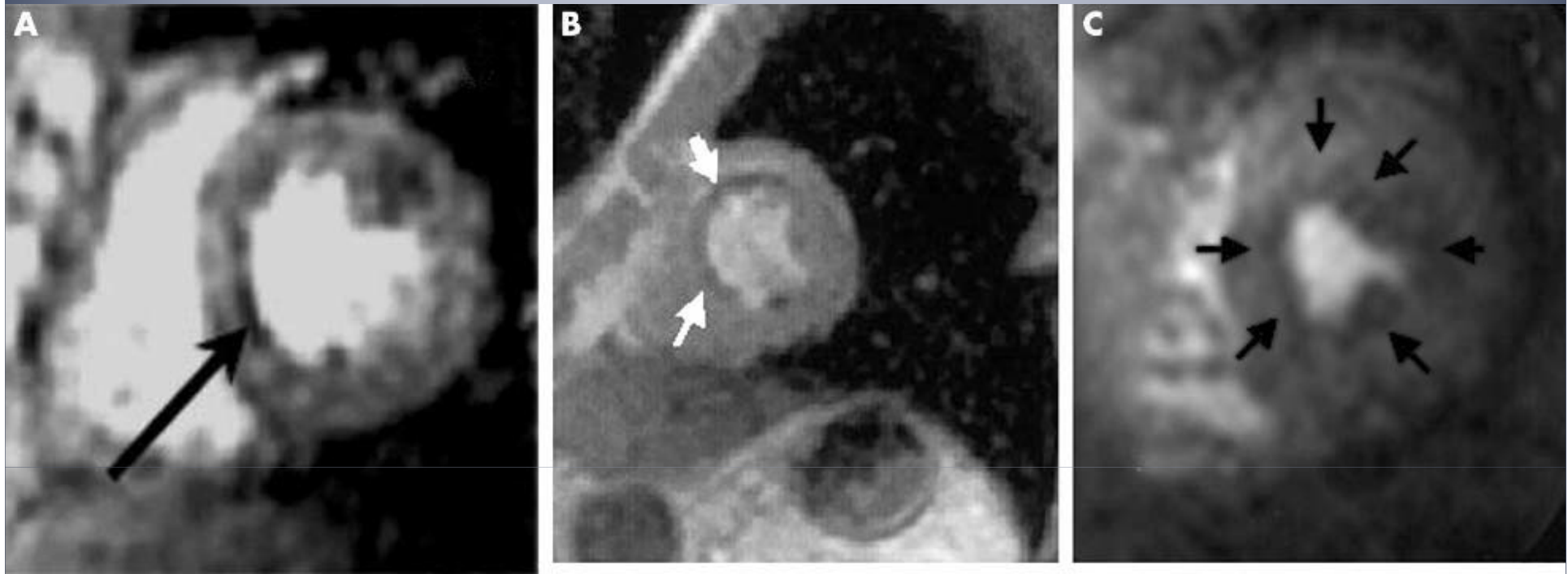
Risonanza Magnetica Cardiaca

CMR consente una caratterizzazione
tessutale





Perfusion



Our main finding was that 14 days of treatment with **nifedipine** improved both myocardial perfusion and function, as evaluated by two modern, highly sensitive and quantitative methods, MRI and TDE.

Ann Rheum Dis 2005;64:1268–1273.

Short-term treatment with **bosentan** simultaneously improves myocardial perfusion and function, as evaluated by highly sensitive and quantitative methods, in patients with SSc. Whether additional remodeling effect may be observed after longterm treatment with bosentan remains to be determined.

J Rheumatol 2006;33;2464-2469

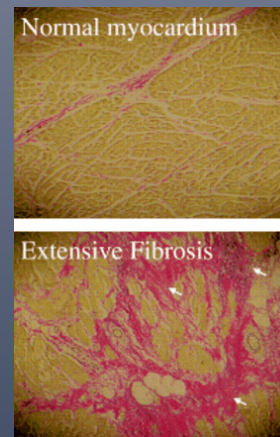
Work-up

- Echocardiography
- MRI?
- Plasma BNP
- ECG Holter
- Exercise test
- Myocardial biopsy?



Screening for biological markers of possible cardiac dysfunction can be beneficial. One increasingly common example of these surrogate measures is B-type natriuretic peptide (BNP), which is secreted from cardiomyocytes in response to atrial or ventricular wall stretch. Plasma concentrations of BNP correlate with the risk of death and cardiovascular events [15] and N-terminal portion of pro-BNP (NT-pro-BNP) can be measured in clinical practice

Rheumatology 2009;48:iii45–iii48



Disfunzione Diastolica vs Scompenso Diastolico

- **Diastole:** Fase della rivoluzione cardiaca caratterizzata dal rilassamento della muscolatura degli atri e dei ventricoli con conseguente dilatazione delle loro cavità
- La **disfunzione diastolica** avviene quando processo è rallentato o incompleto
- Lo **scompenso cardiaco** è una complessa **sindrome clinica** che risulta da alterazioni strutturali o funzionali che rendono il ventricolo incapace di riempirsi o di produrre gettata cardiaca sufficiente

In particolare

- Lo **Scompenso Diastolico** è una sindrome clinica caratterizzata dai sintomi e segni dello scompenso con **funzione sistolica (EF) conservata e anormale funzione diastolica**
- Questo avviene quando il ventricolo è incapace di riempirsi con un volume di sangue adeguato a un normale valore di pressione diastolica tale da mantenere un appropriata gettata sistolica

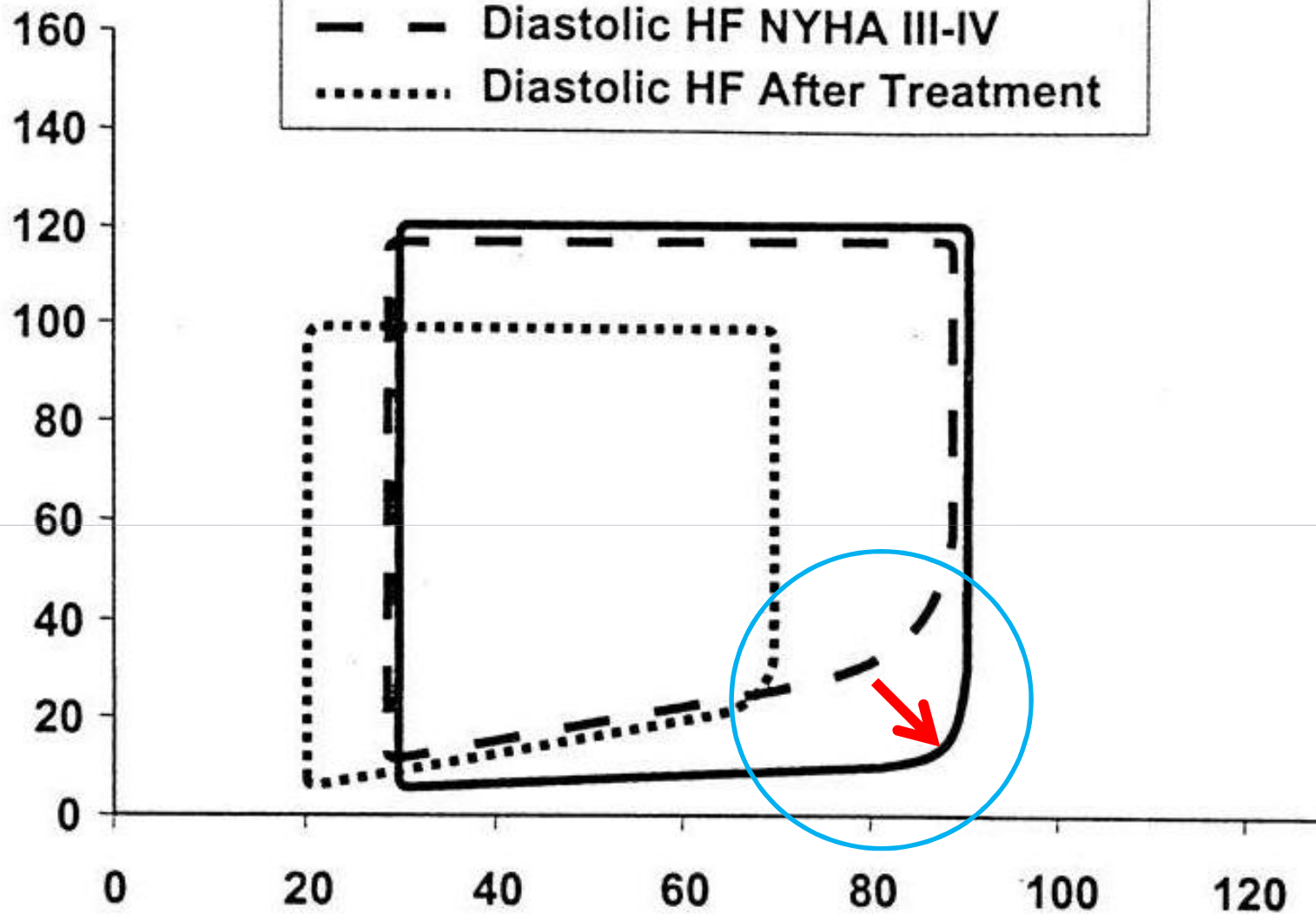
Prevalence of Specific Signs and Symptoms in Patients with Systolic or Diastolic Heart Failure

<i>Signs and symptoms</i>	<i>Prevalence (%)</i>	
	<i>Diastolic heart failure: EF >50%</i>	<i>Systolic heart failure: EF <50%</i>
History		
Dyspnea on exertion	85	96
Paroxysmal nocturnal dyspnea	55	50
Orthopnea	60	73
Physical examination		
Jugular venous distention	35	46
Rales	72	70
Displaced apical impulse	50	60
S3	45	65
S4	45	66
Hepatomegaly	15	16
Edema	30	40
Chest radiograph		
Cardiomegaly	90	96
Pulmonary venous hypertension	75	80

Trattamento: quale?

- Non esistono trials multicentrici, randomizzati, in doppio cieco, controllati vs placebo nei pazienti con scompenso diastolico
- Le Linee-guida si basano su studi di piccoli gruppi di pazienti o su esperienza clinica o su concetti basati sulla fisiopatologia

LV Pressure (mm Hg)



LV Volume (mL / m²)

Diastolic Heart Failure: Treatment

Symptom-targeted treatment

Decrease pulmonary venous pressure

Reduce LV volume

Maintain atrial contraction

Prevent tachycardia

Improve exercise tolerance

Use positive inotropic agents with caution

Nonpharmacological treatment

Restrict sodium to prevent volume overload

Restrict fluid to prevent volume overload

Perform moderate aerobic exercise to improve cardiovascular conditioning, decrease heart rate, and maintain skeletal muscle function

Pharmacological treatment

Diuretics, including loop diuretics, thiazides, spironolactone

Long-acting nitrates

β -Adrenergic blockers

Calcium channel blockers

Renin-angiotensin-aldosterone antagonists, including ACE inhibitors, angiotensin II receptor blockers, and aldosterone antagonists

Disease-targeted treatment

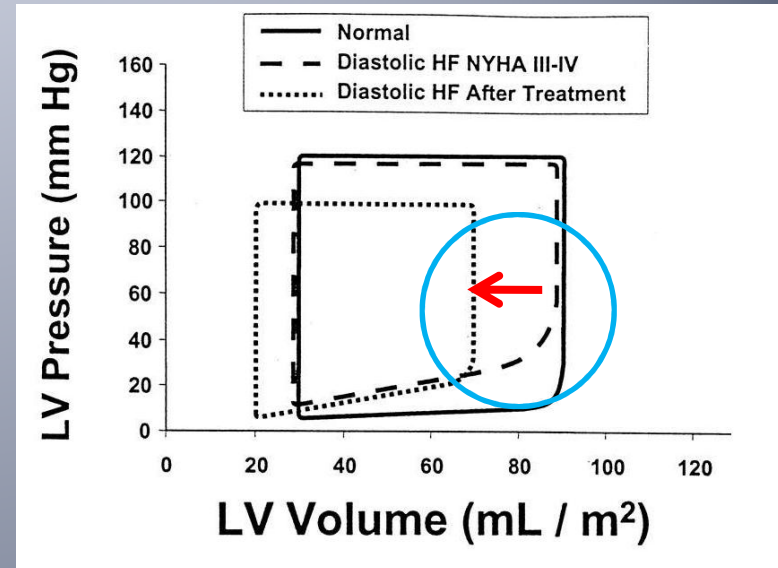
Prevent/treat myocardial ischemia

Prevent/regress ventricular hypertrophy

Mechanism-targeted treatment

Modify myocardial and extramyocardial mechanisms

Modify intracellular and extracellular mechanisms



Fondamentale!!!
Trattare la malattia di base
Quando?

Early and widespread subclinical cardiac dysfunction is understood to occur in many SSc patients. Several in vivo studies, using SPECT, echocardiography and MRI, have shown **a higher incidence of abnormalities compared with post-mortem findings** [3, 4, 7, 13, 14]. These results suggest the existence of reversible functional and vasospastic abnormalities (demonstrated by SPECT, echocardiography and MRI) as well as fixed abnormalities due to fibrosis or organic abnormalities of small coronary vessels (demonstrated by post-mortem studies and the methods used in vivo)

Symptom-Targeted Treatment:

Decrease LV Diastolic Pressure

The initial step in treating patients presenting with diastolic heart failure is to reduce pulmonary congestion by decreasing LV volume, maintaining synchronous atrial contraction, and increasing the duration of diastole by reducing heart rate.

By decreasing LV diastolic volumes, LV pressures “slide” down the curvilinear diastolic pressure-volume relationship toward a lower, less steep portion of this curve.

LV diastolic pressures can be decreased by reducing total blood volume, decreasing central blood volume (nitrates), and blunting neurohumoral activation.

Treatment with diuretics and nitrates should be initiated at low doses to avoid hypotension and fatigue.

Hypotension can be a significant problem.

Tachycardia is poorly tolerated in patients with diastolic HF for several reasons.

β -Blockers and some calcium channel blockers can thus be used to prevent excessive tachycardia and produce a relative bradycardia (60-70 bpm).

Improve Exercise Tolerance:

Patients with diastolic HF have a marked limitation in exercise tolerance. This could be due to:

- The inability to use the Frank-Starling mechanism.
- The abnormal relaxation velocity-versus-heart rate relationship.
- The presence of an exaggerated rise in blood pressure in response to exercise.

β -Blockers, calcium channel blockers, and AT_1 antagonists may have a salutary effect on symptoms and exercise capacity in many patients with diastolic HF.

However, the beneficial effect of these agents on exercise tolerance is not always paralleled by improved LV diastolic function or increased relaxation rate.

Use Positive Inotropic Drugs With Caution:

They are generally not used in the treatment of patients with isolated diastolic HF (little potential benefit, potential to worsen the pathophysiological)

May be beneficial in the short-term treatment of pulmonary edema associated with diastolic heart failure because they enhance SR function, promote more rapid and complete relaxation, increase splanchnic blood flow, increase venous capacitance, and facilitate diuresis.

Treatment of Systolic Versus Diastolic HF

With a number of notable exceptions, many of the drugs used to treat diastolic heart failure are in fact the same as those used to treat systolic heart failure.

However, the rationale for their use, the pathophysiological process that is being altered by the drug, and the dosing regimen may be entirely different depending on whether the patient has systolic or diastolic heart failure.

For example, β -blockers. In diastolic heart failure, however, β -blockers are used to decrease heart rate, increase the duration of diastole, and modify the hemodynamic response to exercise.

In systolic HF, β -blockers are used chronically to increase inotropic state and modify LV remodeling. In systolic heart failure, β -blockers must be titrated slowly and carefully over an extended time period.

This is generally not necessary in diastolic HF.

Diuretics, the doses of diuretics used to treat diastolic HF are generally smaller than the doses used in systolic HF.

Some drugs are used only to treat either systolic or diastolic HF but not both. For example, calcium channel blockers such as diltiazem, nifedipine, and verapamil have no place in the treatment of systolic HF.

Mechanism-Targeted Treatment (Future Directions):

An ideal therapeutic agent should target the underlying mechanisms that cause diastolic HF.

A therapeutic agent might improve Ca^{++} homeostasis and energetics, blunt neurohumoral activation, or prevent and regress fibrosis.

Fortunately, some pharmaceutical agents that fit these design characteristics are already in existence, and many more are under development.

Unfortunately, randomized, double-blind, placebo-controlled, multicenter trials that examine the efficacy of these agents used either singly or in combination have been slow to develop.

Difficulties for these kinds of studies:

- Lack of recognition of the importance of diastolic HF.
- Inability to define a homogeneous study population.
- Lack of agreement on the definition and diagnostic criteria for diastolic HF.

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Evaluation of cardiac abnormalities by Doppler echocardiography in a large nationwide multicentric cohort of patients with systemic sclerosis

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Cardiac Magnetic Resonance Imaging Detects Subclinical Right Ventricular Impairment in Systemic Sclerosis

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ABSTRACT. *Objective.* To assess myocardial involvement in patients with systemic sclerosis (SSc) with no signs or symptoms of cardiac impairment (New York Heart Association functional class I).

Methods. Fifty patients (45 women, 5 men, age 53.3 ± 12.9 yrs) who did not complain of serious diseases other than SSc were recruited out of 119 consecutive patients with SSc. Thirty-three were found to have limited cutaneous SSc (lSSc) and 17 diffuse SSc (dSSc). All underwent cardiovascular magnetic resonance imaging (MRI) to determine right and left systolic and diastolic volumes and ventricular ejection fractions (RVEF and LVEF). Thirty-one healthy subjects matched for sex, age, and body surface area (BSA) were studied as controls. Diffusion lung capacity test (DLCO) and high resolution computed tomography were performed to evaluate lung involvement.

Results. Disease duration between patients with lSSc (14.1 ± 11.4 yrs) and those with dSSc (6.9 ± 4.4 yrs) was found to be significantly different ($p < 0.003$). lSSc patients were older than those with dSSc (54.8 ± 13.7 yrs vs 50.4 ± 9.9 yrs, respectively; $p < 0.04$). Anticentromere antibodies and Scl-70 were positive in 23 (46%) and 17 patients (34%). Except for the left and right systolic volumes, all unadjusted cardiac MRI measures were significantly reduced in SSc compared to the controls ($p < 0.001$ and $p < 0.009$). These differences persisted after adjustment for subjects' height and BSA. Raw RVEF data and RVEF data matched for height and BSA were significantly reduced in dSSc patients in comparison to lSSc ($p < 0.03$).

Conclusion. Compromised RVF was found in patients with asymptomatic SSc. Unlike standard diagnostic techniques, cardiac MRI appears to be a rapid and noninvasive means of determining subclinical right myocardial involvement that is otherwise undetected in patients with SSc. (First Release Nov 1 2007; J Rheumatol 2007;34:2431-7)