

# La cardiopatia acromegalica

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# La cardiopatia acromegalica

Bari,
7-10 novembre 2013

## Complicanze cardiovascolari in pazienti con acromegalia

- **Ipertensione**
- **Disfunzione endoteliale/aterosclerosi**
- **Coronaropatia**
- **Cardiomiopatia acromegalica**
- **Valvulopatie**
- **Aritmie**

# La cardiopatia acromegalica

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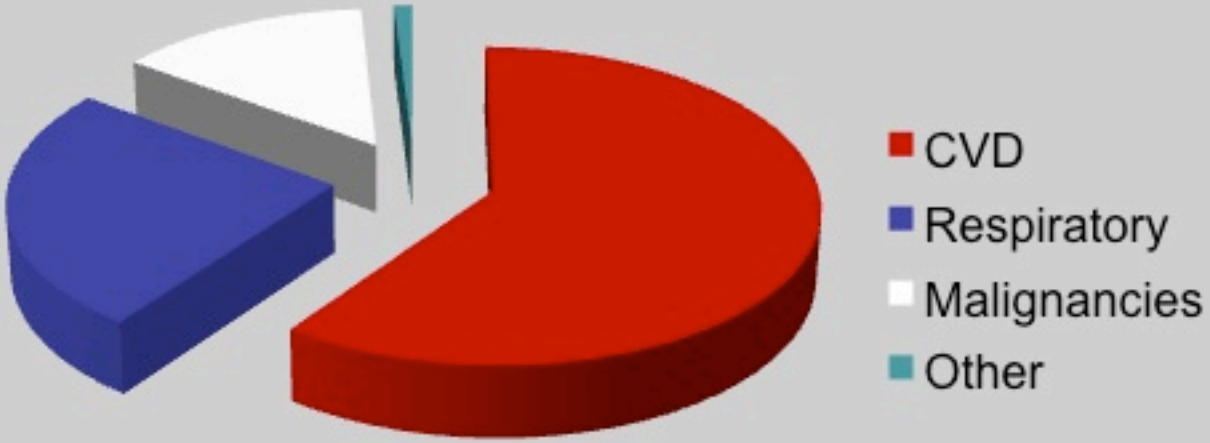
## Cause di morte in pazienti con acromegalia




Wright Q J Med 1970; Bates Q J Med 1993; Extabe J Endocrinol Invest 1993 ; Rajasoorya Clin Endocrinol 1994; Albosch J Clin Endocrin Metab 1998; Swearingen J Clin Endocrin Metab1998; Orme J Clin Endocrin Metab 1998

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## Determinanti di mortalità pazienti con acromegalia

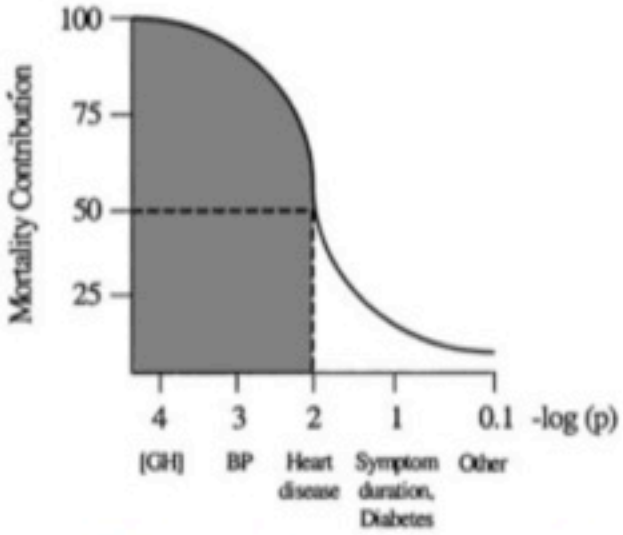


FIG. 1. Depiction of mortality determinants in patients with acromegaly. The x-axis reflects the *P* value (log) as calculated from published retrospective reports. [From S. Melmed: *J Clin Endocrinol Metab* 86:2929–2934, 2001 (19). Permission granted by The Endocrine Society.]

# La cardiopatia acromegalica

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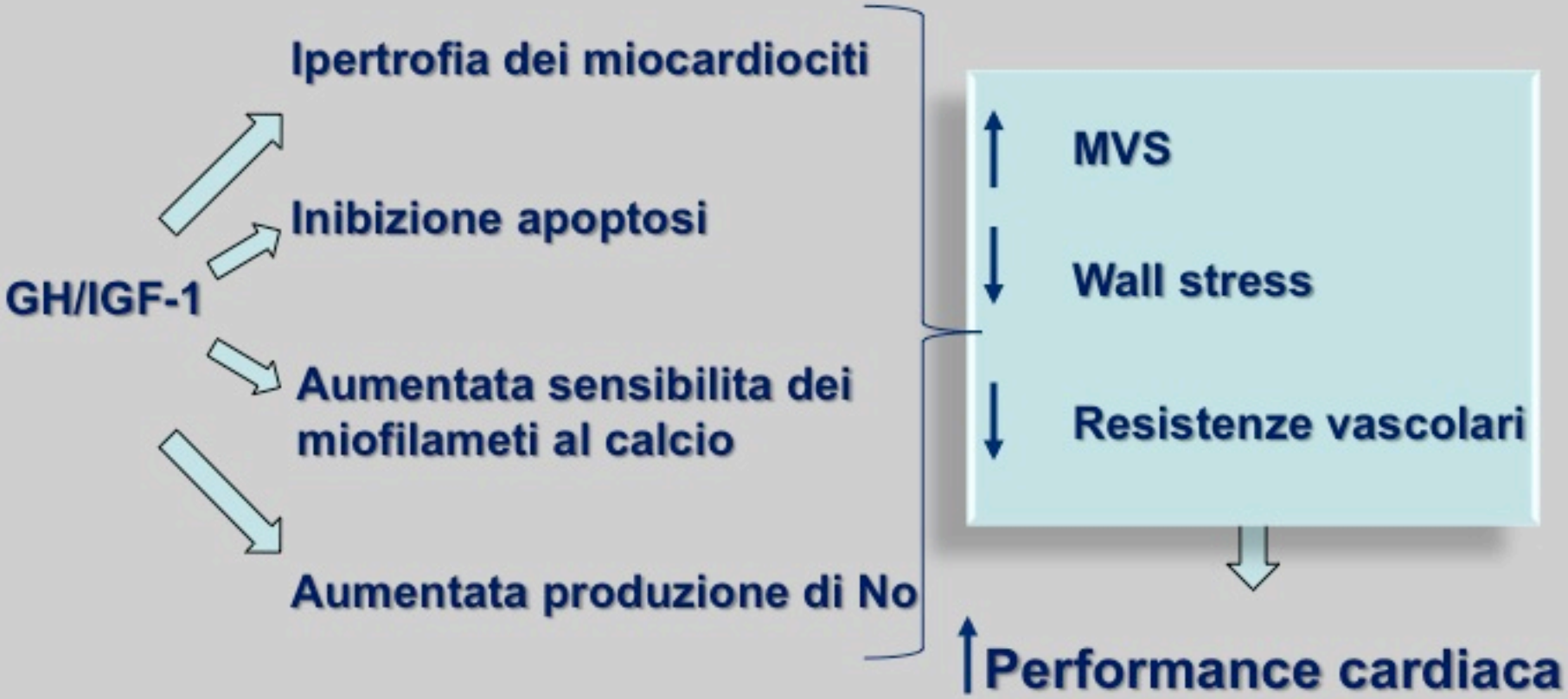
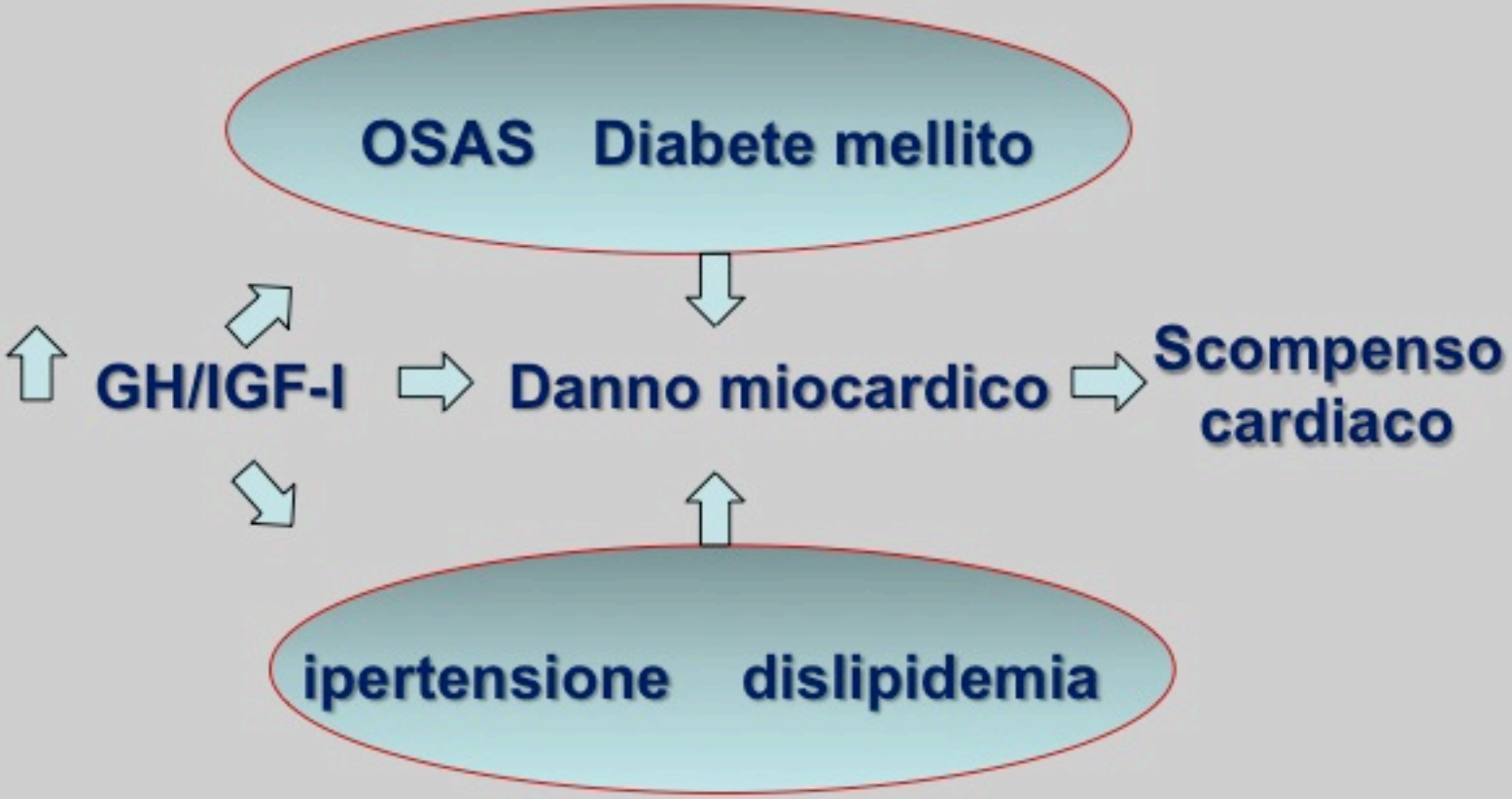
## Effetti del GH sull'apparato cardiovascolare



# La cardiopatia acromegalica



## Fisiopatologia della cardiopatia acomegalica



# La cardiopatia acromegalica

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## ACROMEGALY AND THE HEART: A CLINICAL AND PATHOLOGIC STUDY *

By Milton R. Hejtmancik, M.D., James Y. Bradfield, Jr., M.D., and George R. Herrmann, M.D., F.A.C.P., Galveston, Texas

Heart disease has long been known as a frequent complicating factor and a common cause of exitus in acromegaly. Only nine years after the recognition of the features of acromegaly by Marie [1] in 1886, Hallopeau [2] reported cardiac enlargement in the clinical and autopsy findings of three patients with the disease. Fournier [3] drew particular attention to the features of cardiac failure in a series of 25 patients, pointing out the frequent association of cardiomegaly with hypertrophy of all the viscera. Similar reports, consisting usually of one or two cases, have appeared from time to time in the French and German literature, and have been excellently summarized by Courville and Mason.[4] No conclusive evidence has been brought forth for the etiology and mechanism of such cardiac hypertrophy and myocardial changes.

The size of the heart at times has been enormous, the largest recorded weight being 1,295 gm. by Humphry and Dixon.[5] Other reported large hearts include weights of 1,275 gm. in Osborne's case quoted by Hinsdale,[6] 1,200 and 1,340 gm. by Courville and Mason,[4] and 1,050 gm. by Cushing and Davidoff.[7] Cardiomegaly is a common but not invariable finding, and the heart weights in acromegaly are usually well below such extreme levels.

In a study of the anamnesis of 100 cases of acromegaly, Davidoff [7] recorded none of the pathognomonic symptoms of heart failure, although asthenia was noted in 33 per cent. Blood pressures under 120 mm. systolic were noted in 30 per cent of his cases, but appearance of hypertension was not mentioned. Courville and Mason [4] observed 24 patients with acromegaly; of this group, 18 presented evidence of heart failure, an incidence of 75 per cent. In only three of these cases were elevated systolic or diastolic blood pressures recorded. No specific electrocardiographic changes were described. However, there were noted first notching and widening of the QRS complexes, and later various arrhythmias and T wave changes.

Barrellmeyer [8] has recently studied the circulatory system in a series of 21 cases of acromegaly, of which eight showed the typical full-blown picture and 13 showed evidence of peripheral growth considered illustrative of the *formes frustes* type. Of the 21 cases, 14 had abnormal electrocardiograms, nine with ST depressions in more than one lead and five with intraventricular

* Received for publication December 28, 1949.
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Supported in part by a grant-in-aid from the H. H. Wolcott Fund for Cardiovascular Research.



Hejtmancik Ann Intern Med 1951; 34:1445-56

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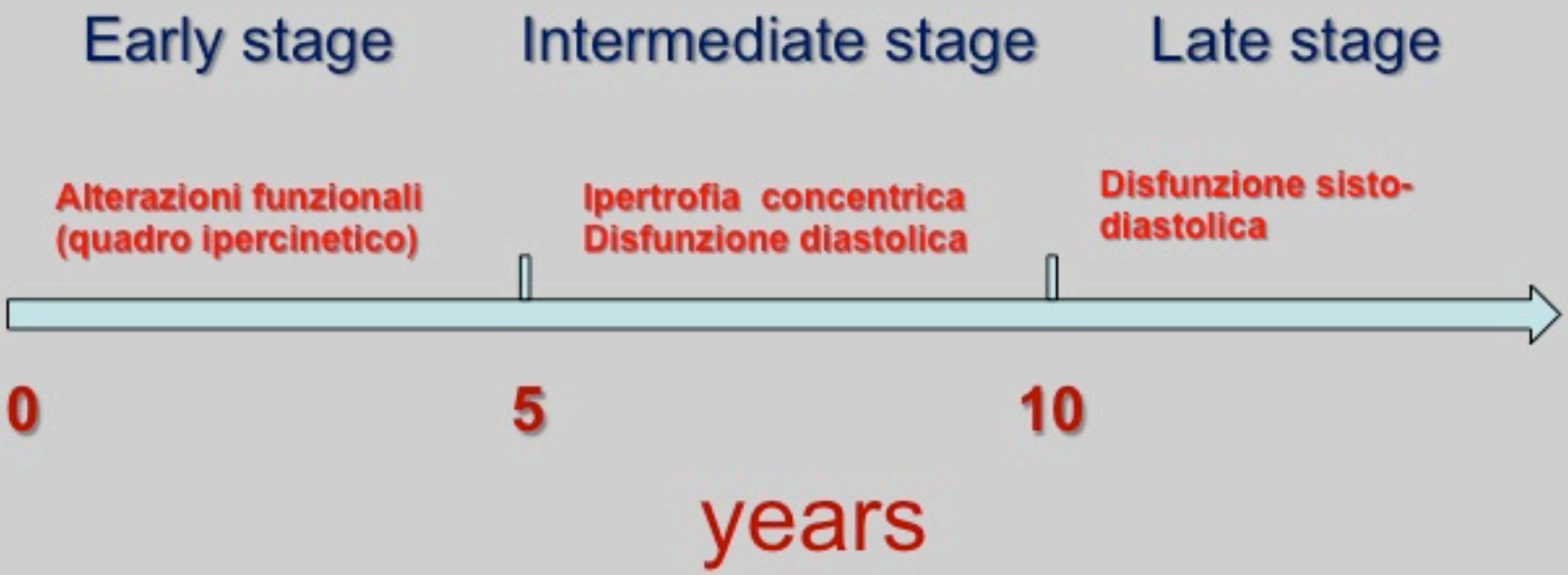
## Fasi della cardiomiopatia acromegalica



# La cardiopatia acromegalica

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## Fasi della cardiomiopatia acromegalica

**"Early stage"**

- ***Aumento della contratilità cardiaca***
- ***Riduzione delle resistenze vascolari periferiche***
- ***Aumentata gittata cardiaca***

# La cardiopatia acromegalica

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## Fasi della cardiomiopatia acromegalica

**TABLE 2.** Echocardiographic data of the LV in patients and controls

| | Controls (n = 10) | Patients (n = 10) |
|---|---|---|
| IVST (mm) | 9.0 ± 1.2 | 11.0 ± 1.5[a] |
| Diastolic PWT (mm) | 9.0 ± 1.0 | 10.7 ± 0.8[b] |
| LVEDVi (mL/m$^2$) | 55 ± 6 | 64 ± 10[c] |
| LVESVi (mL/m$^2$) | 23 ± 4 | 25 ± 6 |
| Relative wall thickness | 0.40 ± 0.04 | 0.41 ± 0.06 |
| LVMi (g/m$^2$) | 81 ± 16 | 110 ± 20[a] |

[a] $P < 0.005$ *vs.* controls.
[b] $P < 0.001$ *vs.* controls.
[c] $P < 0.05$ *vs.* controls.

Fazio J Clin Endocrinol Metab 85:179-182. 2000

# La cardiopatia acromegalica

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## Fasi della cardiomiopatia acromegalica

**TABLE 3.** Doppler-echocardiographic data of LV in acromegalic patients and controls

| | Controls (n = 10) | Patients (n = 10) |
|---|---|---|
| Systolic function | | |
| SI ($ml/m^2$) | 33 ± 2 | 39 ± 6[a] |
| CI ($L/min \cdot m^2$) | 2.30 ± 0.34 | 2.85 ± 0.57[b] |
| SVR ($dyn \cdot sec \cdot cm^{-5}$) | 1731 ± 225 | 1428 ± 248[b] |
| Diastolic function | | |
| E (cm/sec) | 77 ± 11 | 76 ± 15 |
| A (cm/sec) | 46 ± 7 | 49 ± 8 |
| E/A ratio | 1.70 ± 0.22 | 1.58 ± 0.32 |
| MDT (msec) | 156 ± 27 | 151 ± 24 |
| IRT (msec) | 82 ± 7 | 80 ± 14 |

[a] $P < 0.01$.
[b] $P < 0.001$ *vs.* controls.

Fazio J Clin Endocrinol Metab 85:179-182. 2000

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## Fasi della cardiomiopatia acromegalica

**"Intermediate stage"**

- ***Ipertrofia concentrica (biventricolare)***
- ***Disfunzione diastolica***
- ***Calcificazioni valvolari***
- ***Ridotta performance cardiaca da sforzo***

# La cardiopatia acromegalica

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## Fasi della cardiomiopatia acromegalica

***Prevalenza di ipertrofia ventricolare***

***•40-70%***

Rogriguez 1989; Lim 1992; Fazio 1993; Terzolo 1995

# La cardiopatia acromegalica

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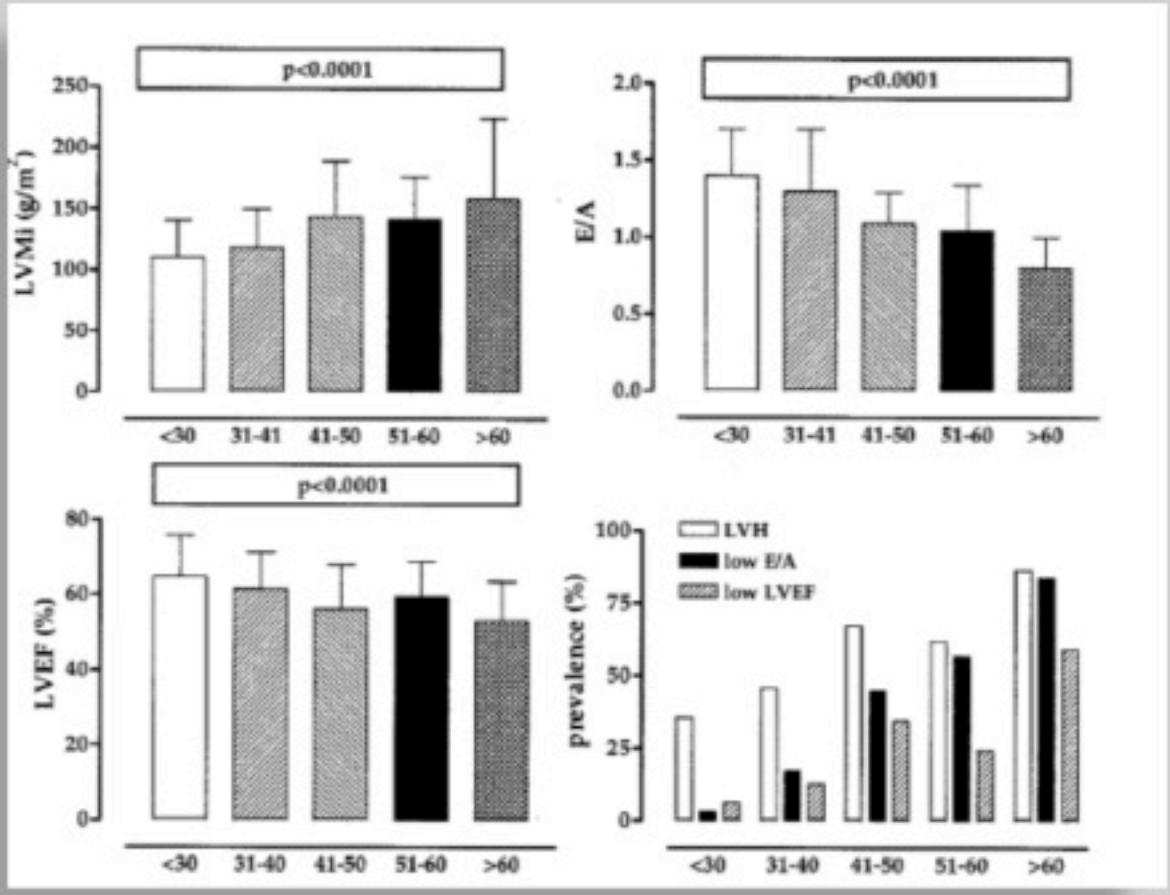
## Fasi della cardiomiopatia acromegalica

**"Late stage"**

- ***Disfunzione sisto-diastolica***
- ***Aumento massa miocardica***
- ***Dilatazione ventricolare***
- ***Disfunzione valvolare (insufficienza)***
- ***Aumento delle resistenze periferiche***
- ***Scompenso cardiaco refrattario***

# La cardiopatia acromegalica




Colao Endocrine Reviews 2004; 25:102-220

# La cardiopatia acromegalica



## Alterazioni anatomopatologiche

- ***Fibrosi interstiziale***
- ***Aumento collagene extracellulare***
- ***Rimodellamento matrice extracellulare***
- ***Derangement miofibrillare***
- ***Aree di necrosi miocitaria***
- ***Infiltrazione di linfomonociti***

Ipertrofia compensata

Cardiomiopatia dilatativa

# La cardiopatia acromegalica

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## Istologia prima e dopo trattamento

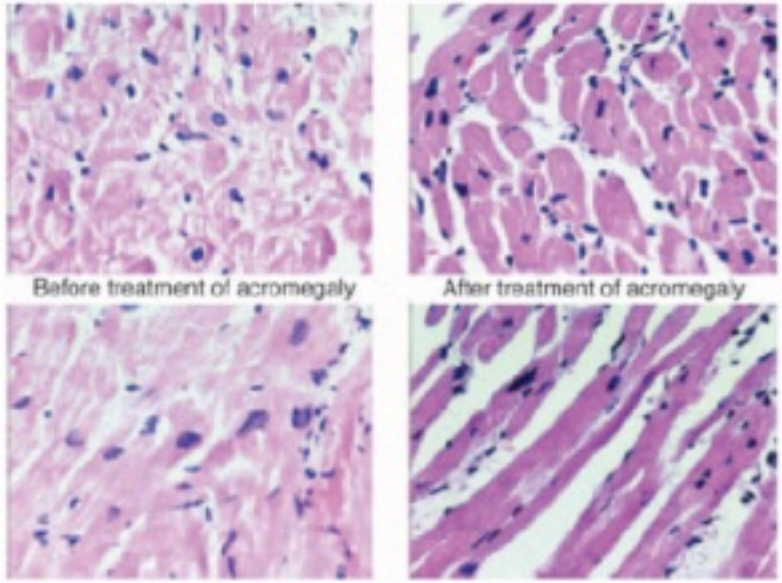


FIG. 3. Histological view of the heart obtained at myocardial biopsy in a patient with CHF before treatment and after cure of acromegaly. Before treatment (*left*) an extensive intracellular myofibrillolysis with areas of myocytolysis and cellular infiltrate is observed. After the effective treatment of acromegaly (*right*), biopsy shows major regression of the disorders. [Courtesy of Albert Beckers, CD-ROM, Pituitary adenomas, 2003, Albert Beckers and GraphMed, Liège, Belgium.]

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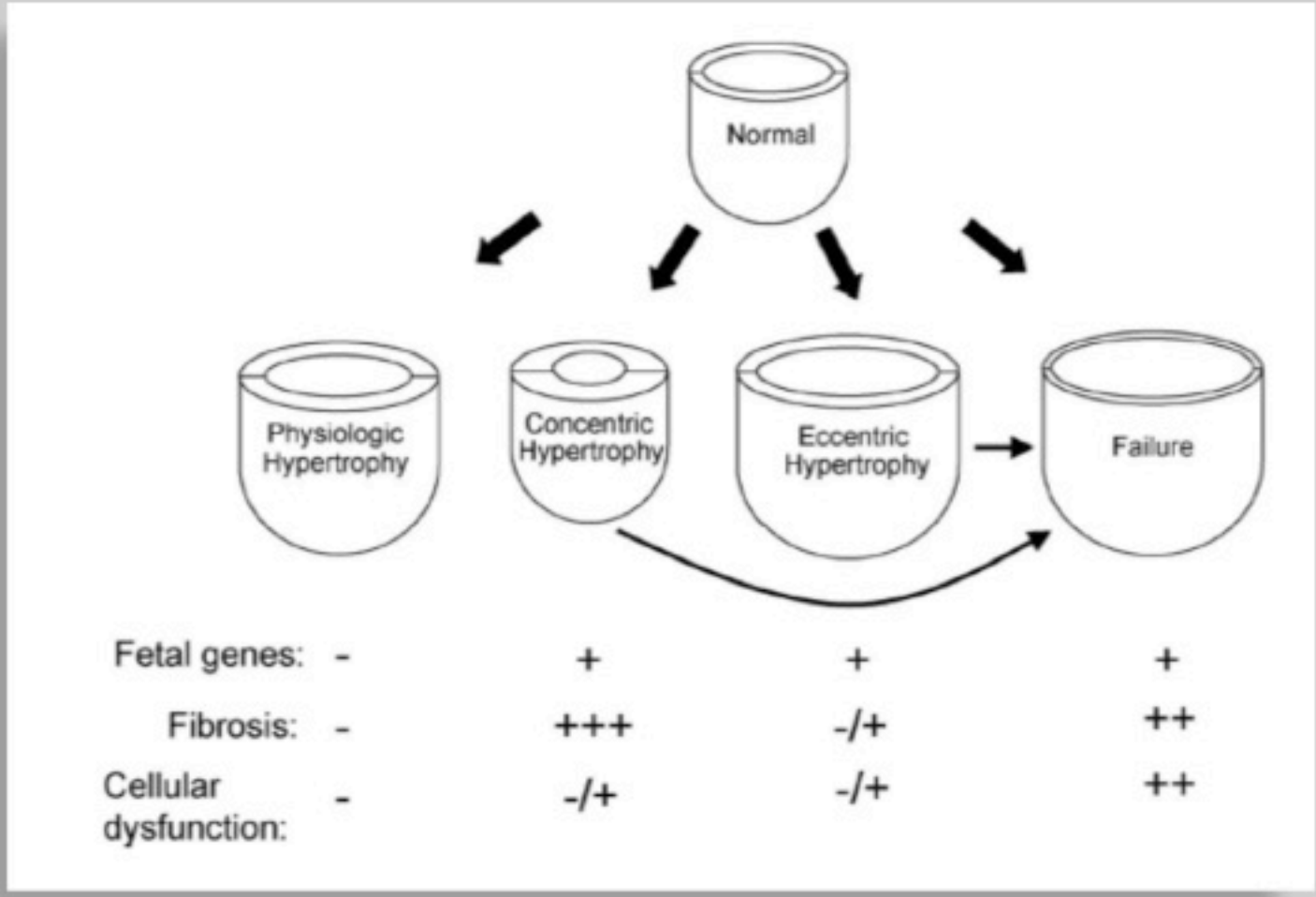
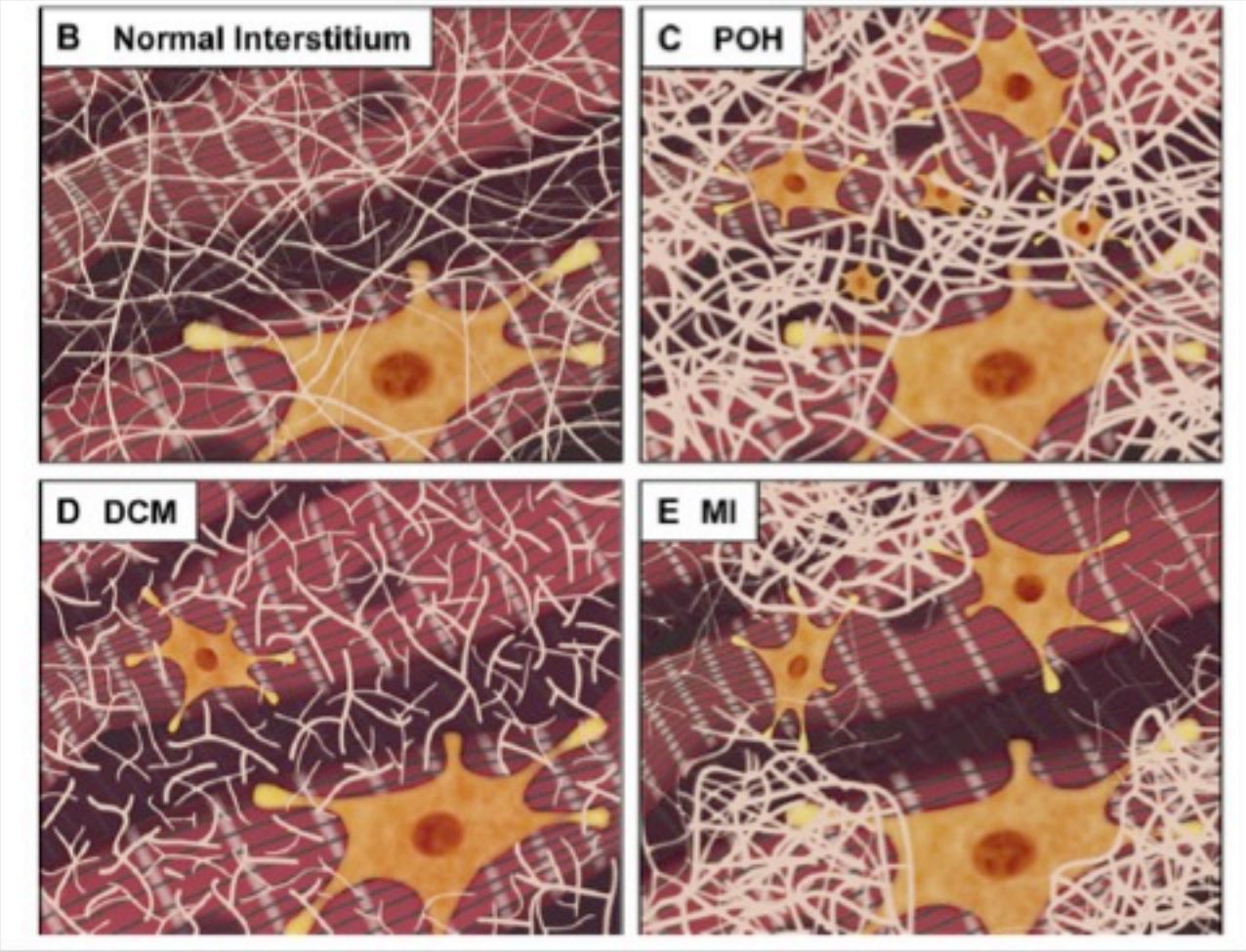



Kehat Circulation 2010; 122:2727-2735

# La cardiopatia acromegalica




Eckhouse Heart Failure Clin 2012;8:7-20

# La cardiopatia acromegalica

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## Alterazioni anatomopatologiche

**TABLE 2. Anatomic and Functional Characteristics of Acromegalic Patients**

| Patient | LV Mass/BSA, g/m² | E/A | LVEDD, mm | LVEDP, mm Hg | EF, % |
|---|---|---|---|---|---|
| 1 | 162 | 0.65 | 51.6 | 15 | 56 |
| 2 | 338 | 0.66 | 81.3 | 25 | 22 |
| 3 | 114 | 0.73 | 54.0 | 13 | 50 |
| 4 | 170 | 0.66 | 48.4 | 13 | 40 |
| 5 | 140 | 0.49 | 50.3 | 15 | 39 |
| 6 | 170 | 0.47 | 51.6 | 14 | 51 |
| 7 | 165 | 0.69 | 48.9 | 13 | 44 |
| 8 | 199 | 0.75 | 52.0 | 15 | 54 |
| 9 | 159 | 0.69 | 46.1 | 14 | 56 |
| 10 | 152 | 0.65 | 54.4 | 14 | 68 |

LV indicates left ventricle; BSA, body surface area; E/A, ratio between early and late diastolic ventricular filling; LVEDD, left ventricular end-diastolic diameter; LVEDP, left ventricular end-diastolic pressure; and EF, ejection fraction.

Frustaci A et al. Circulation 1999;99:1426-1434

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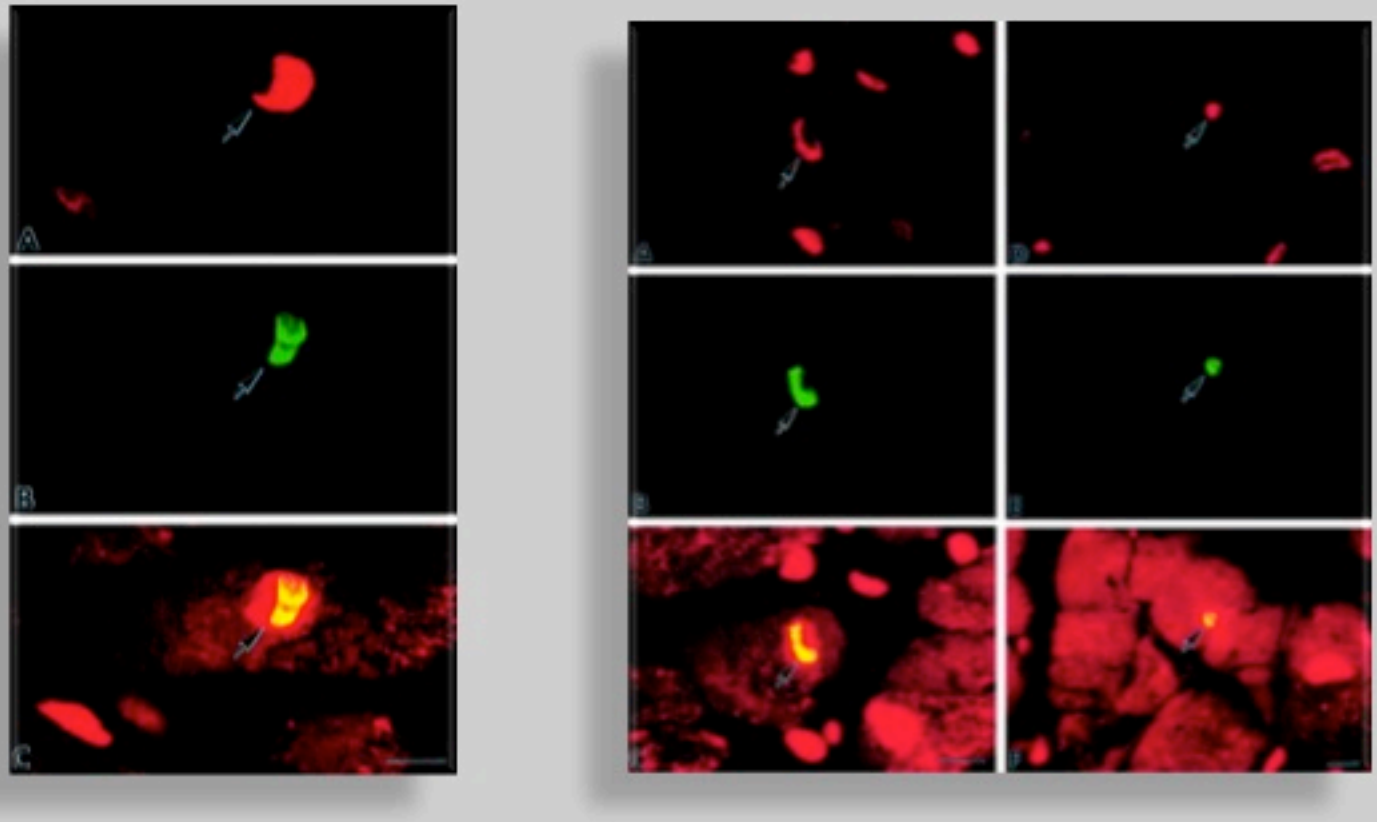
Acromegaly: TdT assay and confocal microscopy of the left ventricle.



Frustaci A et al. Circulation 1999;99:1426-1434

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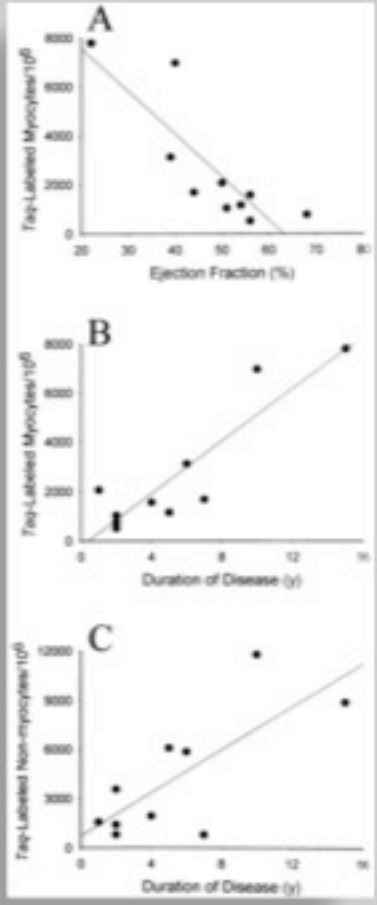
**Correlation between myocyte apoptosis measured by Taq in situ ligation and EF (A) and myocyte apoptosis and duration of disease (B).**




Frustaci A et al. Circulation 1999;99:1426-1434

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- Miociti con DNA danneggiato non rientrano nel ciclo cellulare
- IGF-1 riduce solo in parte la stimolazione dell'apotosi nel cuore scompensato
- Livelli cronicamente elevati di IGF-1 possono causare una downregulation dei recettori sulle miocellule

Frustaci A et al. Circulation 1999;99:1426-1434

# La cardiopatia acromegalica

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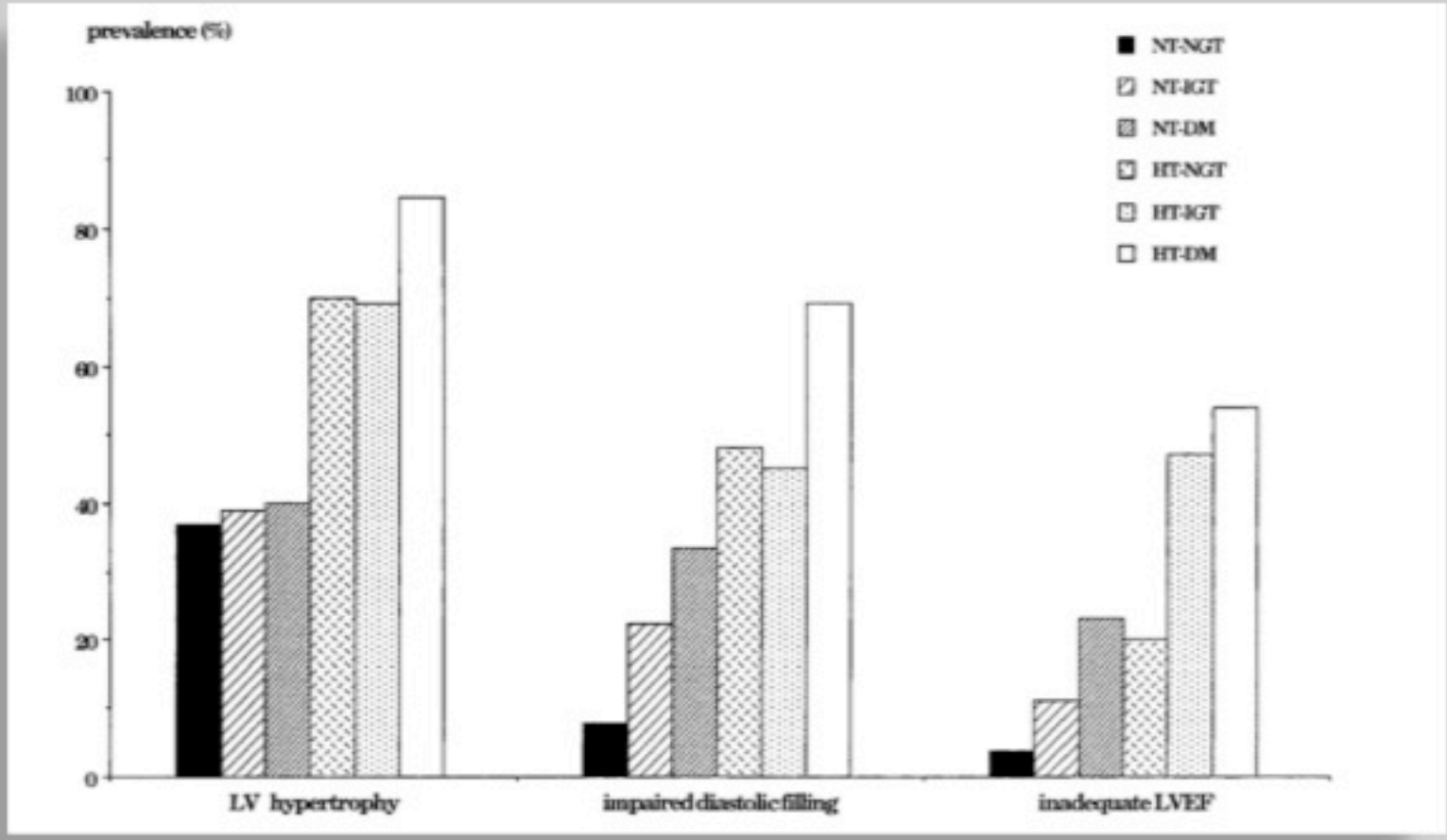
**Cardiac Involvement in Acromegaly: Specific Myocardiopathy or Consequence of Systemic Hypertension?***

# La cardiopatia acromegalica




Colao J Clinic Endocrinol Metab 2000; 85:193-199

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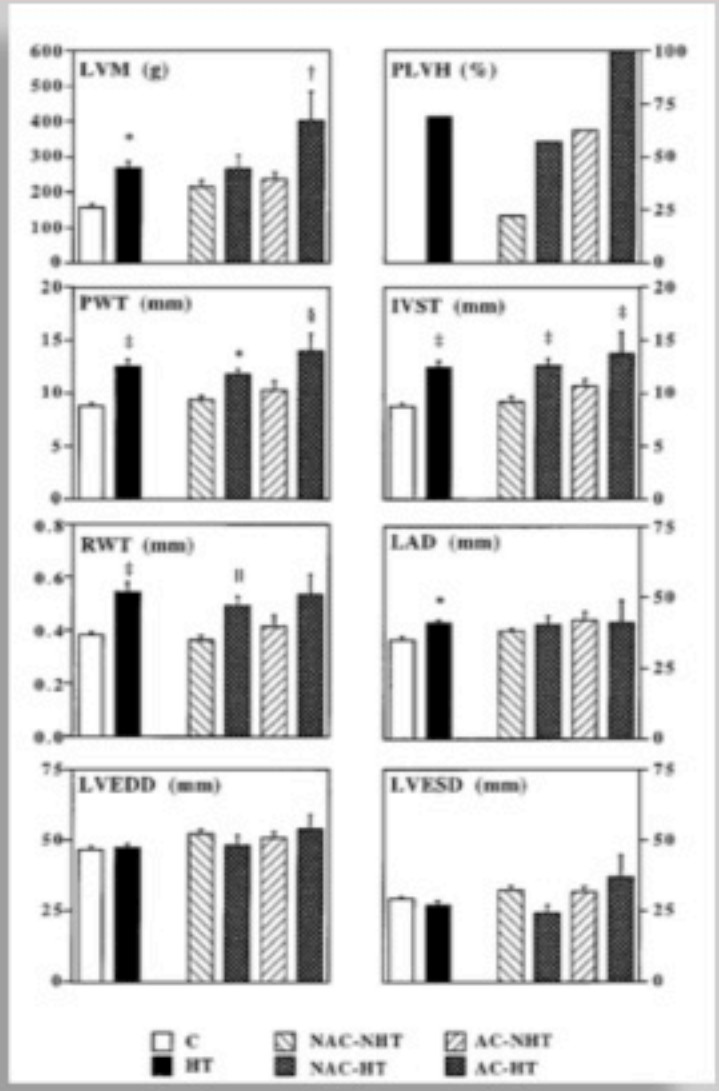


Lopez –Velasco J Clin Endocrinol Metab 1997:1047-1053

# La cardiopatia acromegalica

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## Determinanti della cardiopatia acromegalica

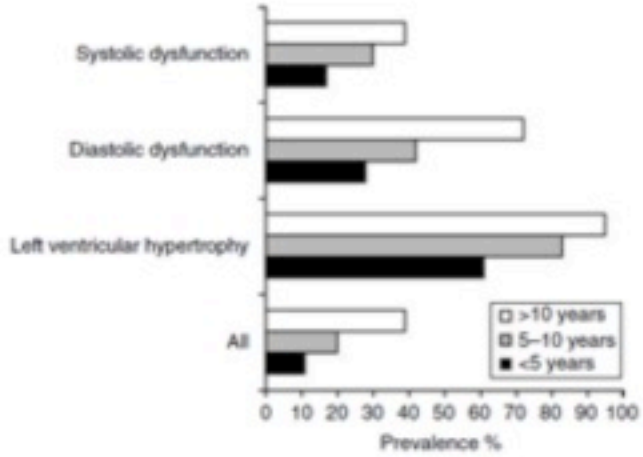


**Figure 2** Calculation of the odds ratio for the presence of left ventricular hypertrophy, diastolic and systolic dysfunction and a combination of these complications in patients with estimated duration of acromegaly ≥10 years compared with those with estimated disease duration <10 years.

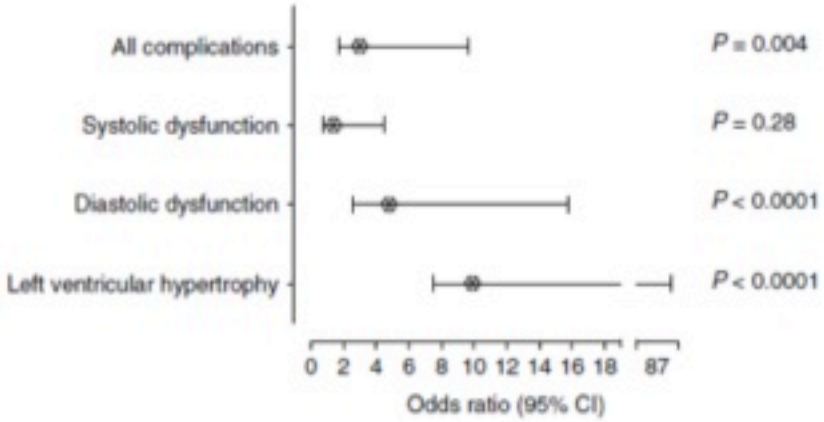


**Figure 1** Prevalence of left ventricular hypertrophy, diastolic and systolic dysfunction and of a combination of these complications at diagnosis of acromegaly in relation to estimated disease duration.

Colao Eur J End 2011; 165; 713-721

# La cardiopatia acromegalica

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**Table 2** Cardiac parameters in young acromega

| Parameter | P |
|---|---|
| Systolic blood pressure (mmHg) | NS |
| Diastolic blood pressure (mmHg) | NS |
| Heart rate (beats/min) | NS |
| Left ventricular End-diastolic diameter (mm) | = 0·04 |
| Left ventricular End-systolic diameter (mm) | NS |
| Interventricular septum diastolic thickness (mm) | = 0·002 |
| Posterior wall diastolic thickness (mm) | NS |
| Left ventricular mass (g) | = 0·0002 |
| Left ventricular mass index (g/m$^2$) | = 0·0008 |
| Fractional shortening (%) | NS |
| Ejection fraction (%) | NS |
| Isovolumic relaxation time (ms) | = 0·01 |
| Peak early diastolic mitral velocity (cm/s) | = 0·004 |
| Peak late diastolic mitral velocity (cm/s) | NS |
| Peak early/late diastolic mitral velocity ratio | = 0·002 |
| Mitral deceleration times (ms) | NS |
| Peak early diastolic tricuspid velocity (cm/s) | NS |
| Peak late diastolic tricuspid velocity (cm/s) | = 0·01 |
| Peak early/late diastolic tricuspid velocity ratio | NS |

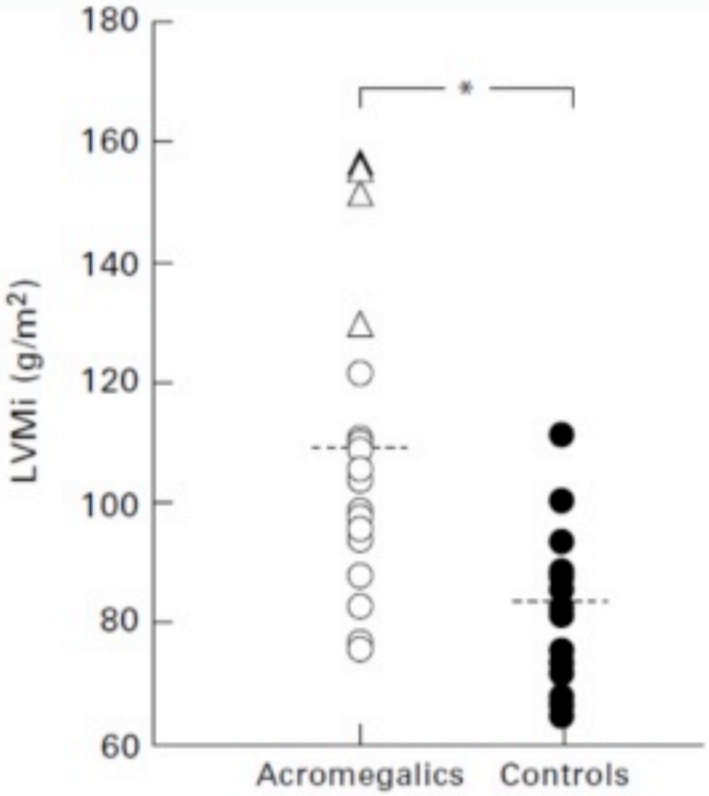


**Fig. 1** Left ventricular mass index (LVMi) in acromegalic patients with and without left ventricular hypertrophy (LVH) and controls. △ Acromegalics with LVH ($n = 4$); ○ Acromegalics without LVH ($n = 16$); ● Controls ($n = 20$). * $P = 0·0008$ between both groups of acromegalics and controls.

Minniti Clinical Endocrinol 1998; 49, 101-106



# E’ reversibile la cardiopatia acromegalica?

# La cardiopatia acromegalica

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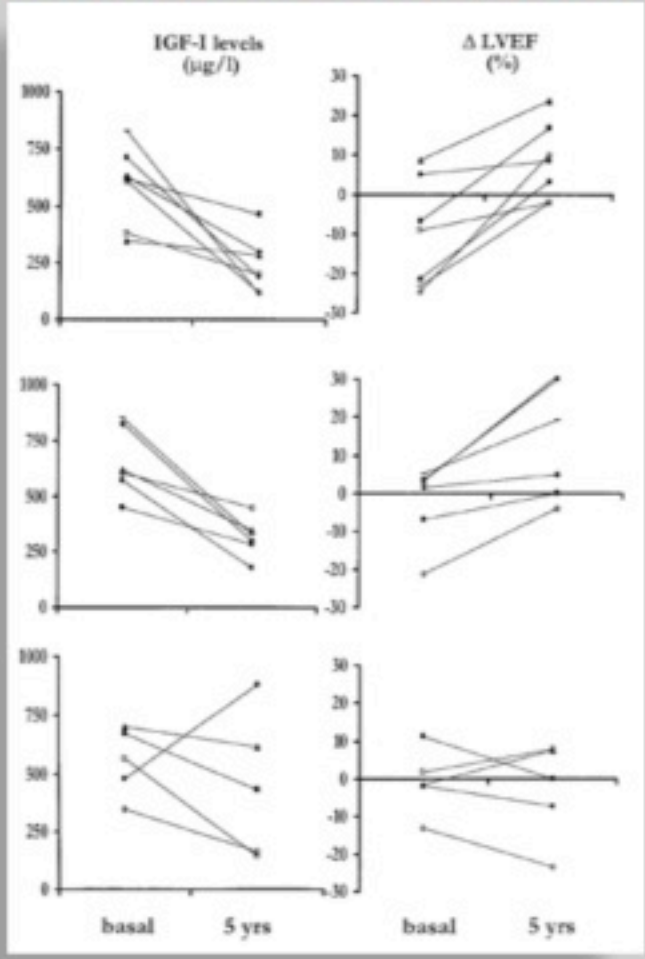
## Reversibilità della cardiopatia acromegalica

**Surgery**

**Surgery**
**Plus octr.**

**Persisting elevated**
**GH and IGF-1 level**




Colao J Clin endocrinol Metabol 2001; 86; 1551-1557

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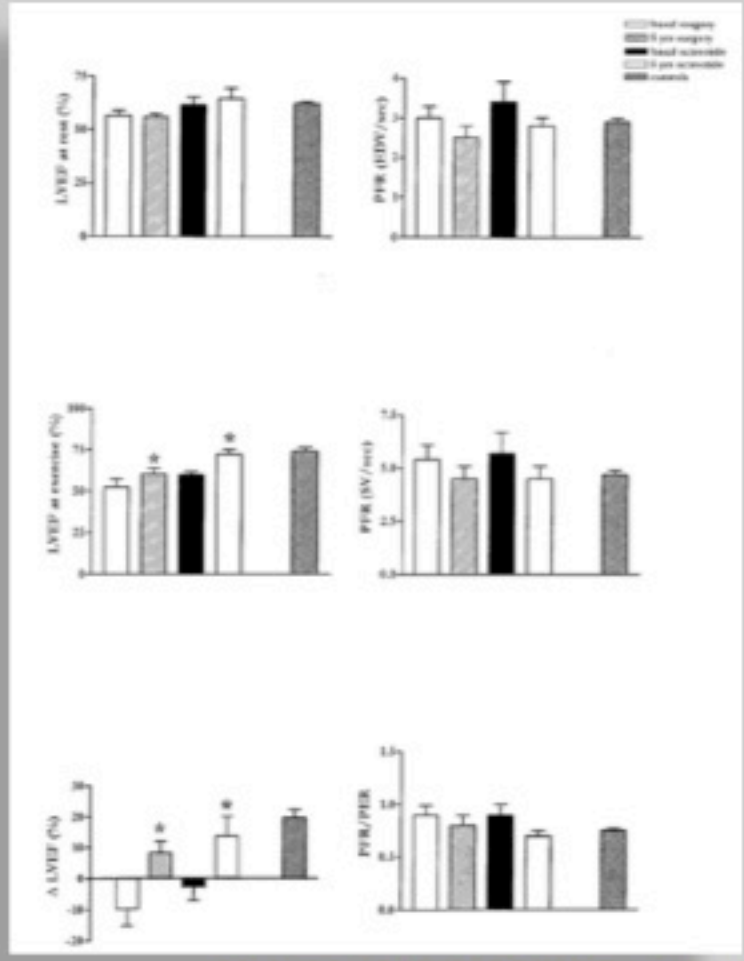
## Reversibilità della cardiopatia acromegalica



Colao J Clin endocrinol Metabol 2001; 86; 1551-1557

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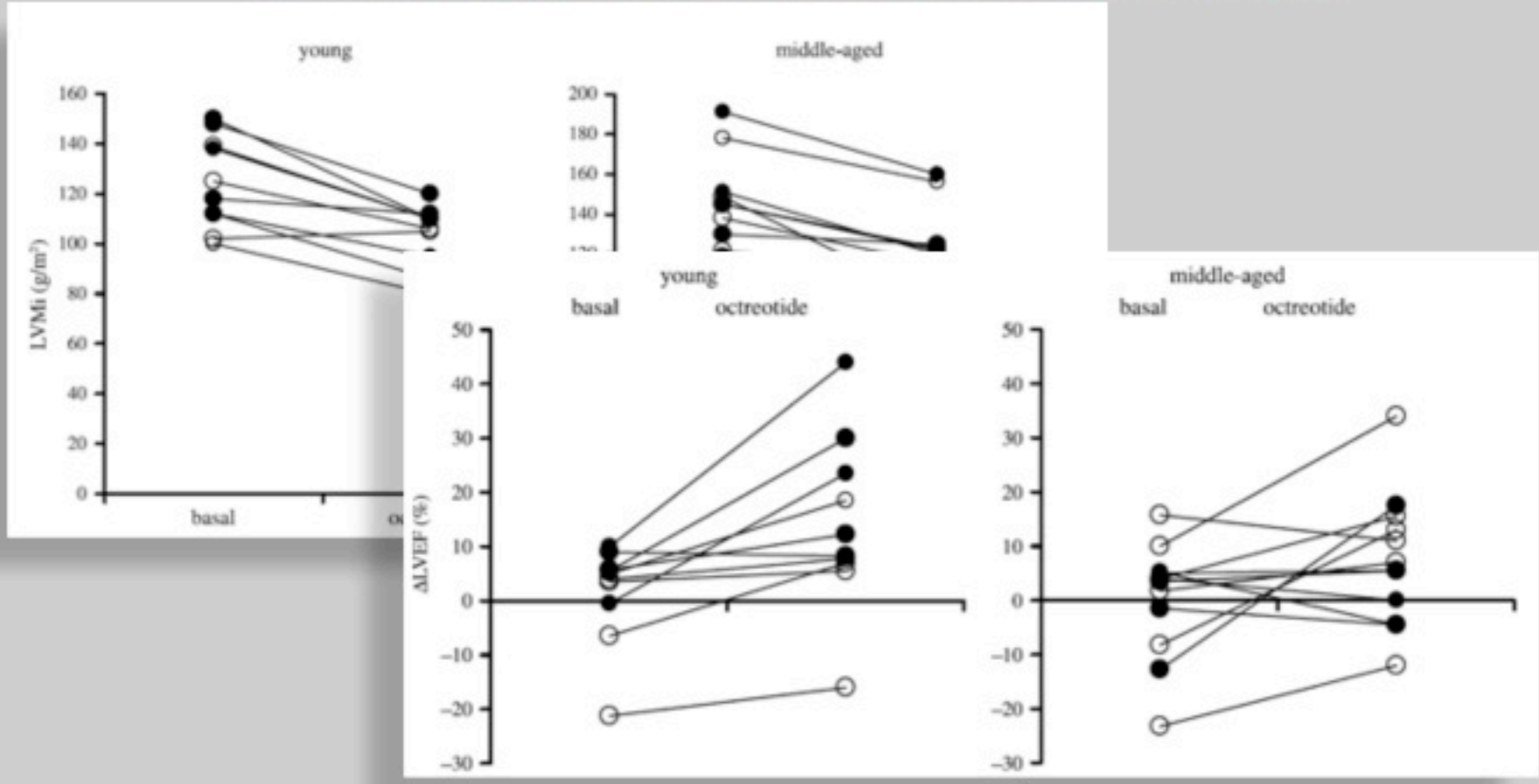
## Reversibilità della cardiopatia acromegalica




Colao Clinical Endocrinol 2003; 58:169-176

# La cardiopatia acromegalica

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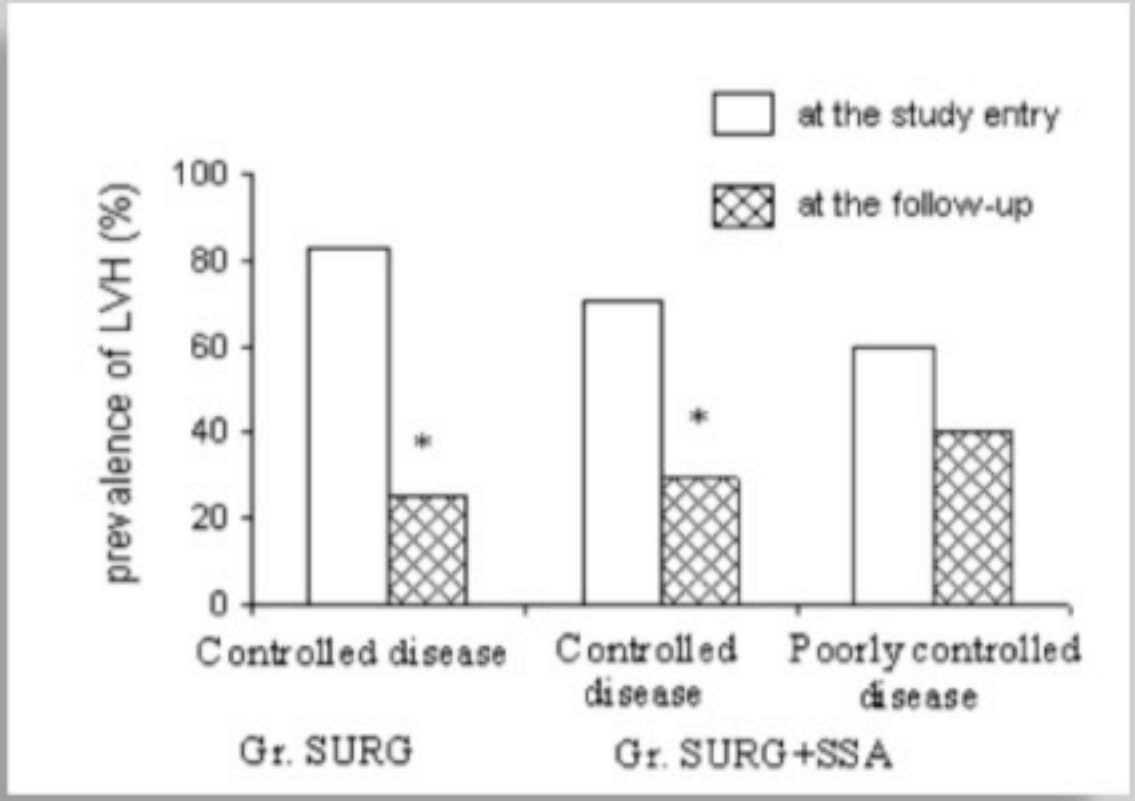
## Reversibilità della cardiopatia acromegalica




De Marinis Pituitary 2008; 11:13-20

# La cardiopatia acromegalica

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## Reversibilità della cardiopatia acromegalica

TABLE 3. Recovery from cardiac disease after treatment of acromegaly

| Year | Ref. | No. of patients | Treatment | Follow-up | Methods | Results | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | LVH | Diastolic function | Systolic function | Others |
| 1985 | 185 | 11 | RT | 3–17 yr | ECG, ECHO | n.a. | n.a. | n.a. | ↑ Cardiovascular events |
| 1989 | 192 | 9 | OCT | 12 months | ECHO | ↓ | n.a. | ↔ | ↓ HR and BP |
| 1991 | 193 | 5 | OCT | 6 months | ECHO | ↓ | ↑ | ↔ | No change in contractility |
| 1992 | 188 | 16 | OCT | 2 months | ECHO | ↓ | n.a. | ↓ | Only in patients with hypertrophy |
| 1993 | 194 | 11 | OCT | 6 months | ECG, ECHO | ↓ | ↑ | ↔ | ↔ BP |
| 1994 | 187 | 6 | OCT | 6 months | ECG, ECHO | ↓ | ↑ | ↔ | ↑ Treadmill exercise, ↔ BP |
| 1999 | 196 | 30 | OCT | 12 months | ERA | n.a. | ↔ | ↑ | ↓ HR only in controlled patients |
| 1999 | 189 | 13 | LAN | 12 months | ECHO | ↓ | ↑ | ↔ | ↔ BP |
| 1999 | 195 | 13 | LAN | 12 months | ECHO | ↓ | ↑ | ↔ | ↔ BP |
| 2000 | 191 | 15 | OCT-LAR | 6 months | ECHO, ERA | ↓ | ↑ | ↔ | Only in controlled patients, ↓ HR |
| 2001 | 193 | 30 | Surgery | 6 months | ECHO | ↓ | ↑ | ↔ | ↓ BP only in controlled patients |
| 2001 | 184 | 18 | Surgery/OCT | 5 yr | ERA | n.a. | ↔ | ↑ | Only in controlled patients |
| 2002 | 97 | 25 | OCT-LAR | 6 months | ECHO, ERA | ↓ | ↑ | ↓ | ↓ HR, when disease duration <5 yr |
| 2002 | 146 | 19 | LAN | 6 months | ECHO | ↓ | ↑ | ↔ | ↓ Arrhythmias from 33.3 to 16.5% |
| 2003 | 199 | 22 | OCT-LAR | 12 months | ECHO, ERA | ↓ | ↑ | ↑ | Mostly in young patients |

n.a., Not assessed; RT, radiotherapy; OCT, octreotide; LAN, lanreotide; ECHO, echocardiogram; ERA, equilibrium radionuclide angiography; LVH, left ventricular hypertrophy; BP, blood pressure; HR, heart rate; ↓, decreased; ↑, increased; ↔, unchanged.

Colao Endocrine Review 2004; 25:102-1152

# La cardiopatia acromegalica

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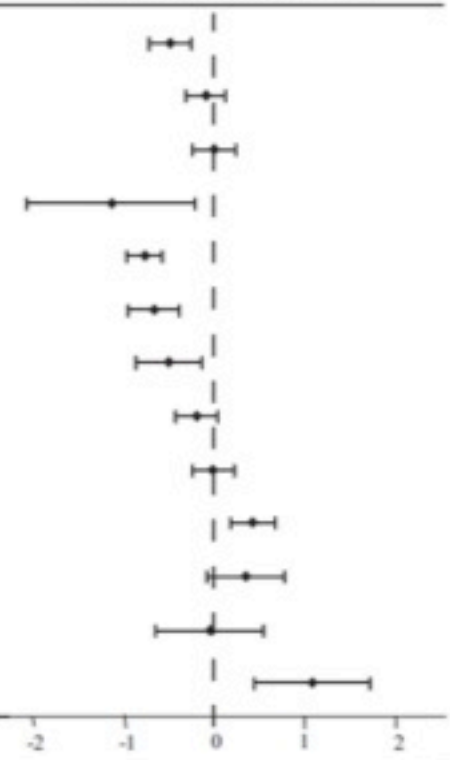
## Reversibilità della cardiopatia acromegalica

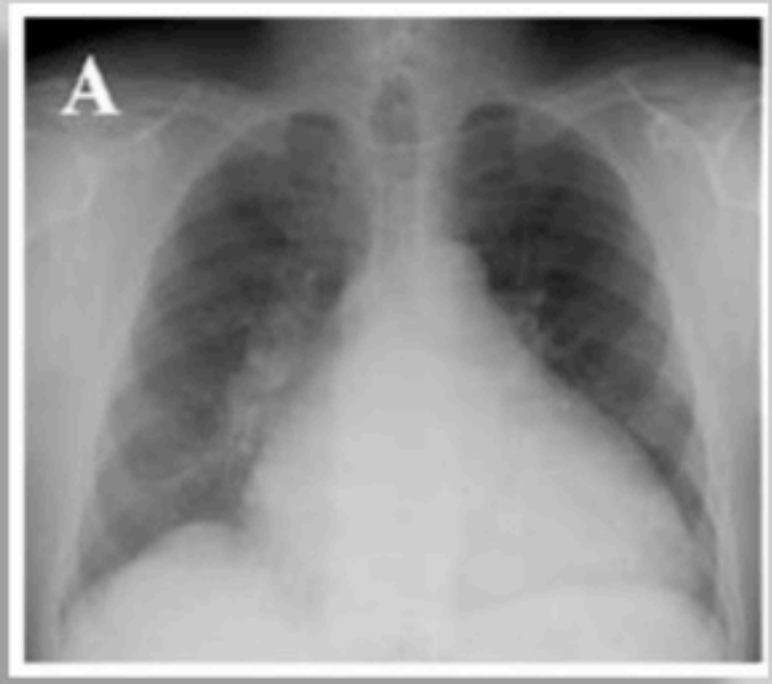
| Factors | Number of trials | Number of Patients | Q test | Weighted mean (SD) change (before - after) |
|---|---|---|---|---|
| HR | 16 | 199 | <0.001 | -5.8 (2.1) beats/min |
| SBP | 16 | 199 | <0.01 | -2.5 (2.9) mmHg |
| DBP | 15 | 180 | <0.05 | -1.7 (1.9) mmHg |
| LVM | 7 | 51 | <0.01 | -50.3 (13.3) g |
| LVMi | 14 | 143 | ns | -22.3 (6.7) g/m$^2$ |
| IVS | 10 | 110 | <0.05 | -0.3 (0.2) mm |
| LVPW | 9 | 91 | <0.01 | -0.8 (0.4) mm |
| LVEDD | 8 | 71 | ns | -1.5 (2.2) mm |
| LVESD | 8 | 75 | ns | 0.4 (2.0) mm |
| E/A | 5 | 61 | ns | 0.2 (0.1) |
| EF | 15 | 188 | <0.001 | 3.3 (1.7) % |
| FS | 6 | 56 | <0.01 | -0.7 (2.0) % |
| Ex Dur | 7 | 75 | <0.01 | 1.6 (0.4) min |



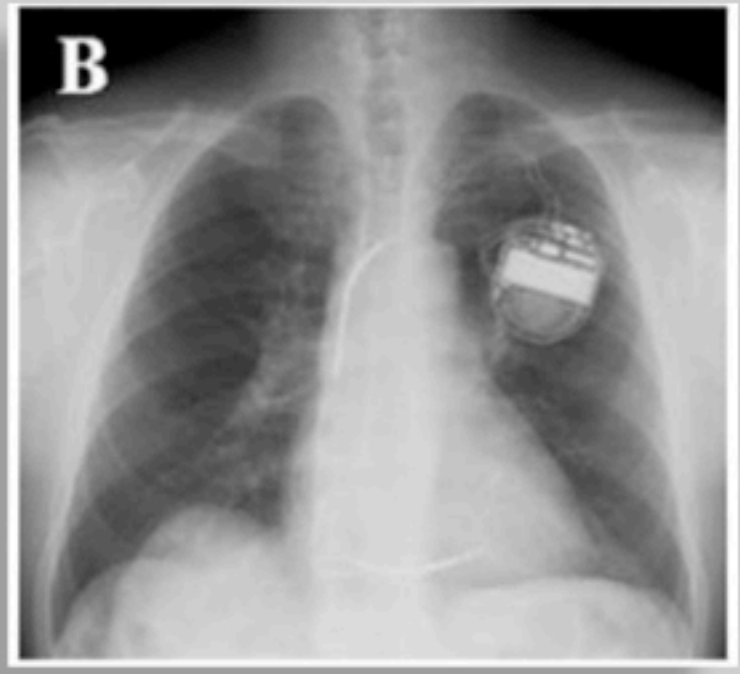

Maison J Clin Endocrinol Metab 2007; 92:1743

# La cardiopatia acromegalica






Prima del trattamento

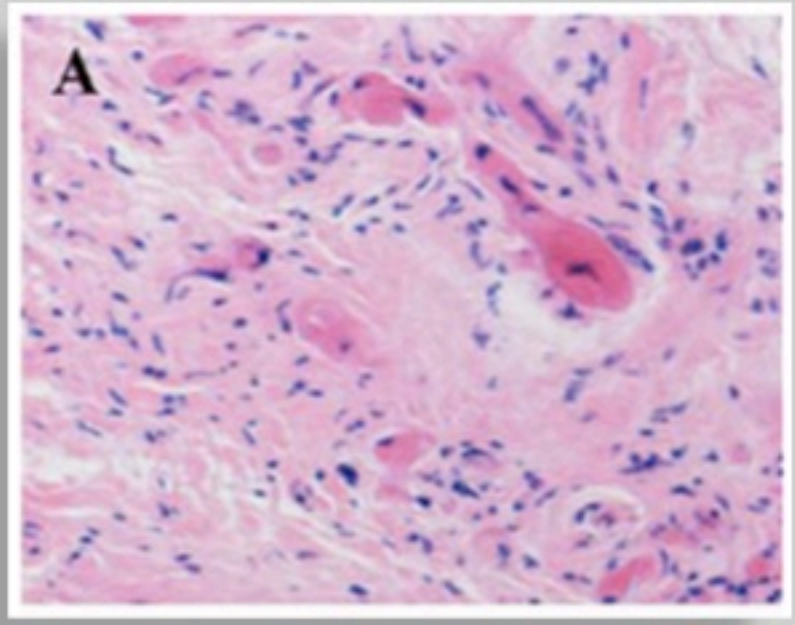


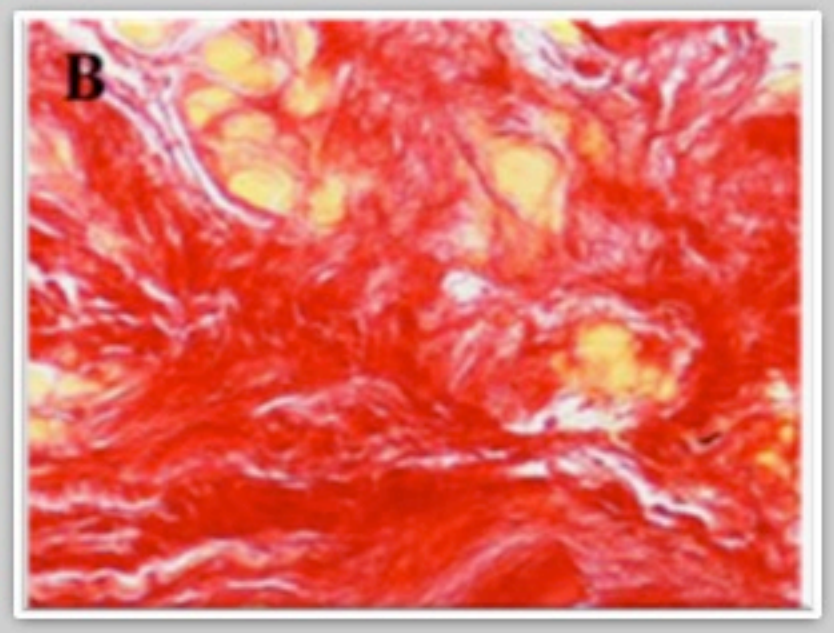

Dopo del trattamento

Yokota, BMJ Case Repors 2010

# La cardiopatia acromegalica

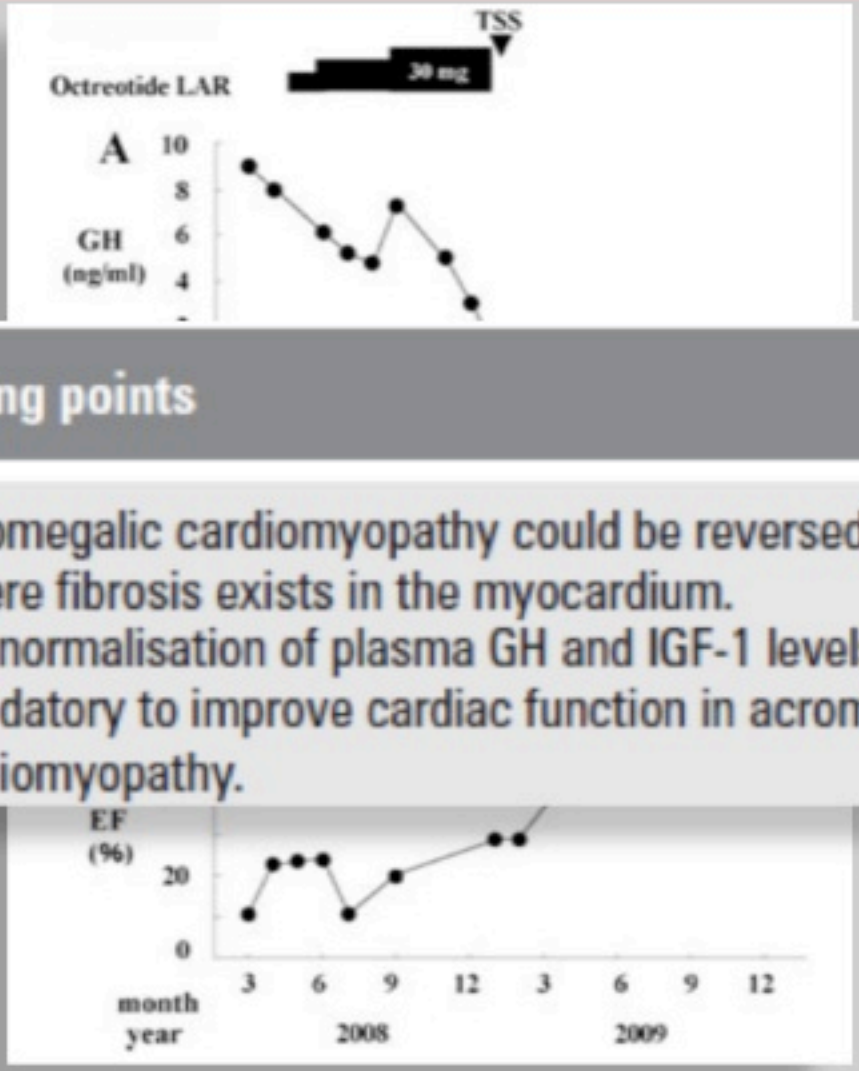





Yokota, BMJ Case Repors 2010

# La cardiopatia acromegalica




## Learning points

- Acromegalic cardiomyopathy could be reversed even if severe fibrosis exists in the myocardium.
- The normalisation of plasma GH and IGF-1 levels was mandatory to improve cardiac function in acromegalic cardiomyopathy.

Yokota, BMJ Case Repors 2010

# La cardiopatia acromegalica

Bari,
7-10 novembre 2013

Pituitary (2013) 16:294–302
DOI 10.1007/s11102-012-0420-x

**A consensus on the dia**
**complications**

S. Melmed · F. F. Casanueva · A. Kl
M. D. Bronstein · P. Chanson · S. W
C. J. Strasburger · J. A. H. Wass ·

**Table 1** Assessment of acromegaly complications at diagnosis and during long-term monitoring

| Diagnosis | During long-term follow-up |
|---|---|
| Blood pressure measurement | Every 6 months or when change of treatment (if hypertensive) |
| Echocardiography | Annually |
| ECG | Annually |
| Epworth scale or sleep study | Annually |
| Echo Doppler of peripheral arterial and venous system | Annually particularly in gigantism |
| OGTT | Fasting blood glucose every 6 months (particularly in uncontrolled disease and during SRL therapy); $HbA_{1c}$ every 6 months if diabetes present |

Melmed 2013; 16:294-302

# La cardiopatia acromegalica

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## Conclusioni

- Eccessiva esposizione a GH/IGF-I causa una specifica cardiomiopatia, aggravata dalla coesistenza di ipertensione arteriosa e diabete
- L'ipertrofia concentrica associata a disfunzione diastolica è la sua più comune manifestazione
- La cardiomiopatia può evolvere in disfunzione sistolica e scompenso cardiaco
- Un adeguato controllo dell'acromegalia può indurre reversibilità della cardiomiopatia sopratutto in soggetti giovani con durata di malattia più breve