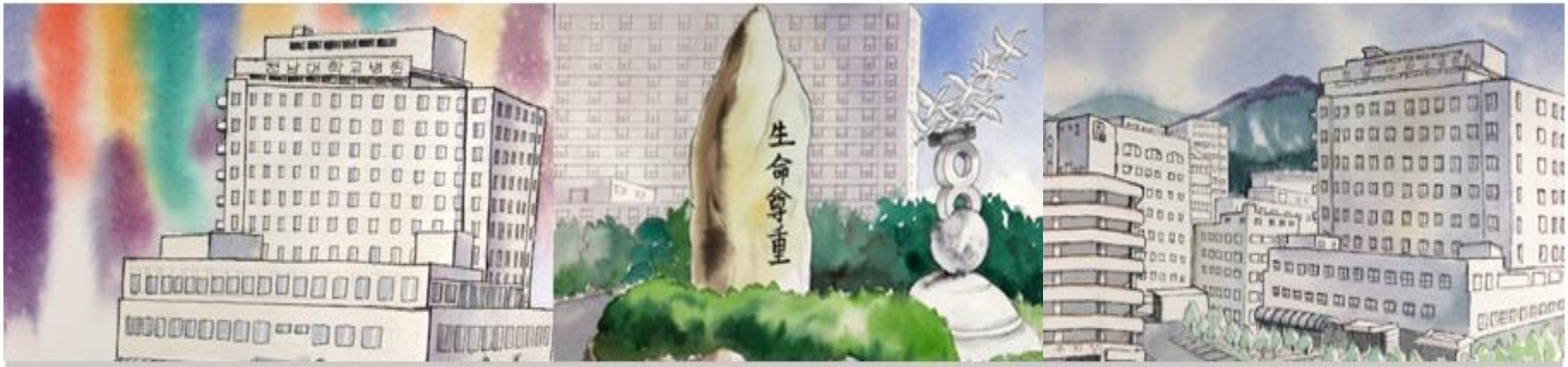
Reverse Remodeling of Heart Failure



Chonnam National University Hospital

Kye Hun Kim, MD, PhD

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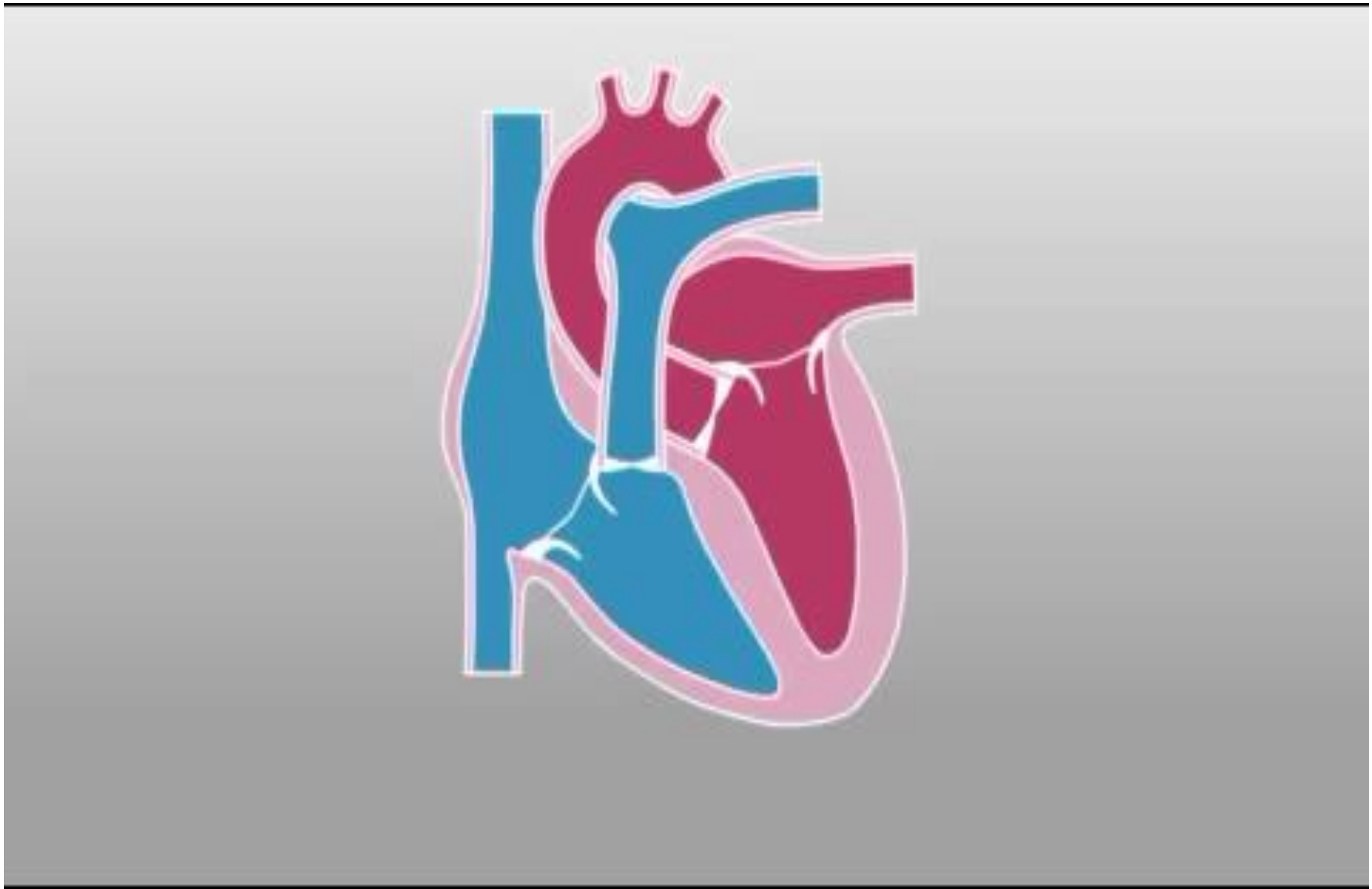
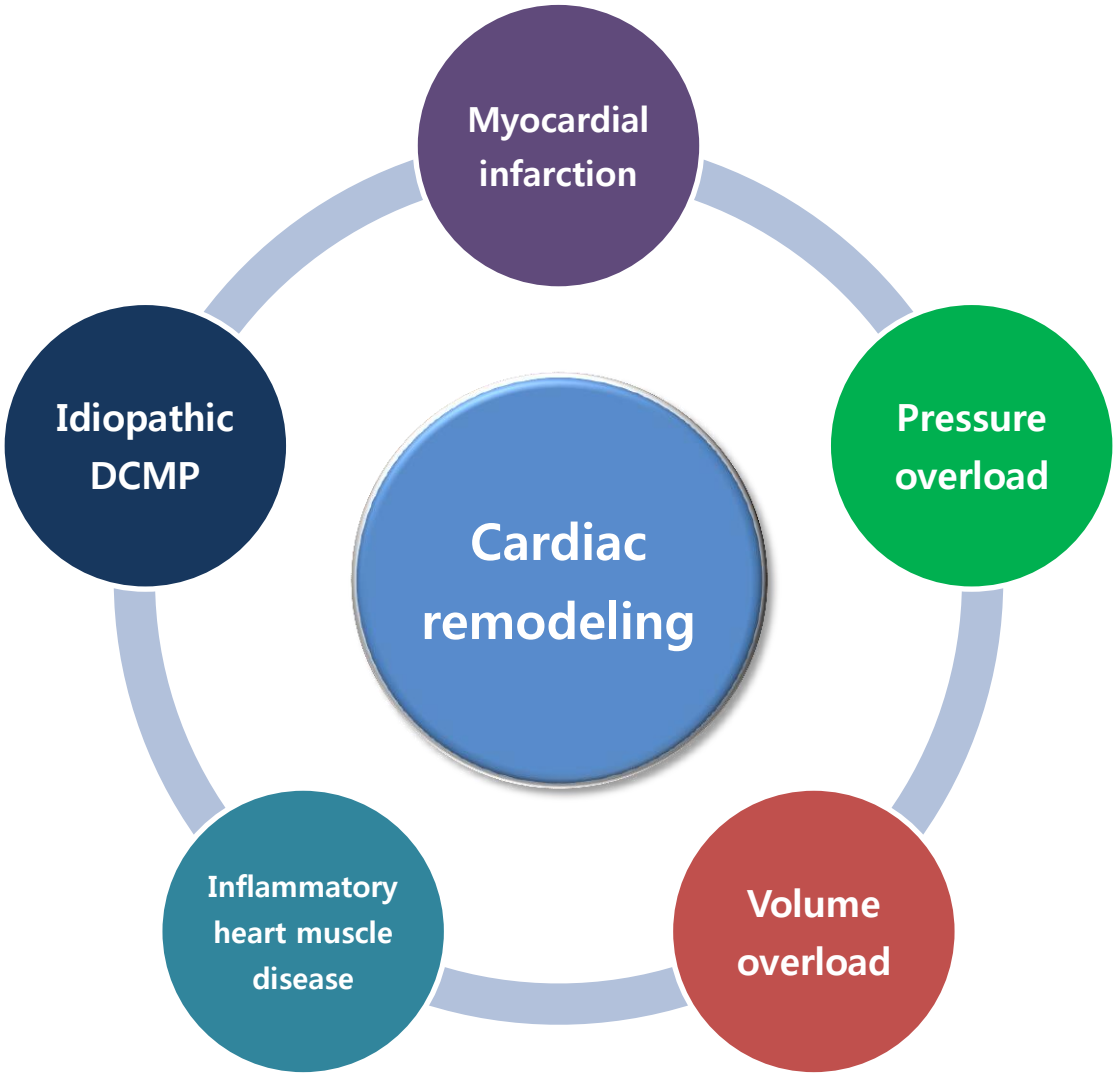
Cardiac remodeling



Conditions that may initiate cardiac remodeling

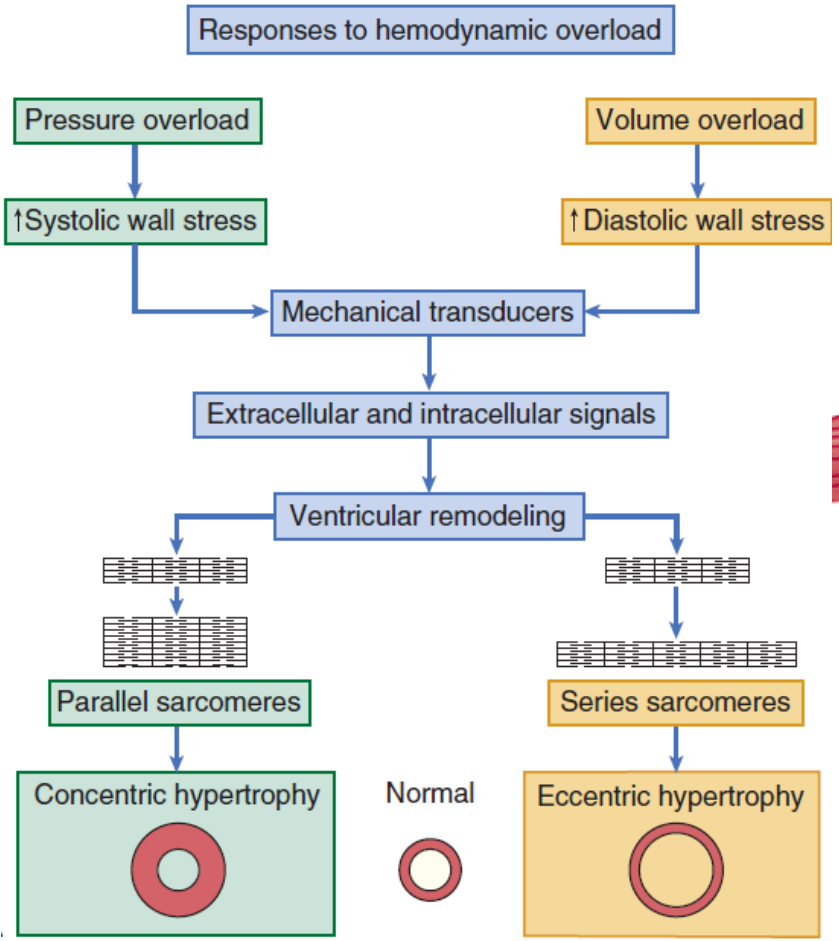


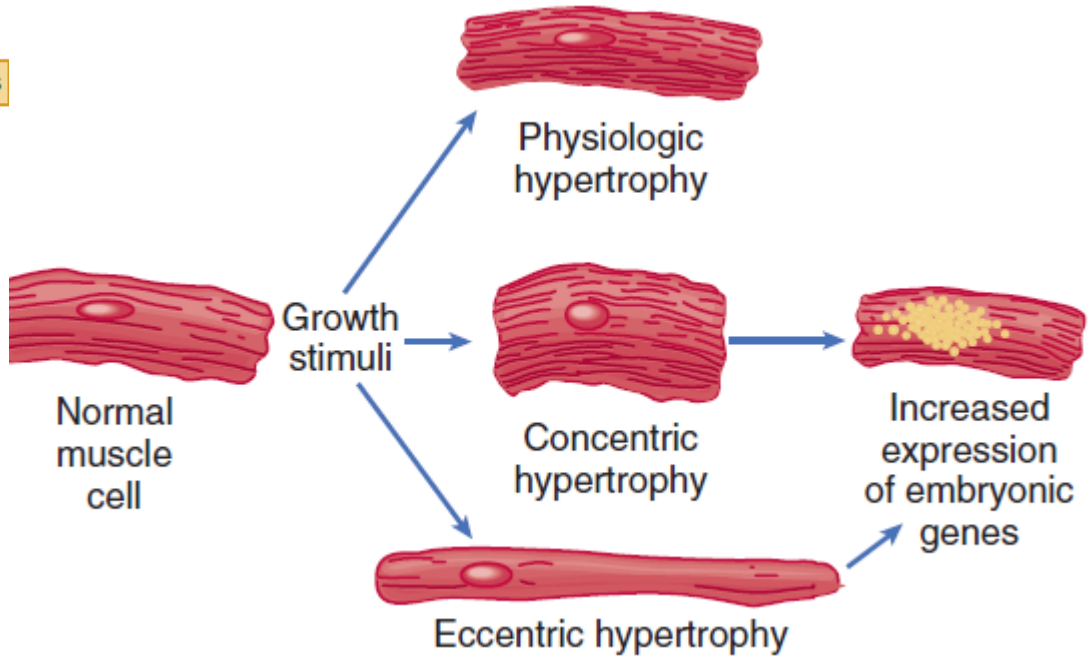
Left ventricular remodeling

Alterations in myocyte biology	Myocardial changes	Alterations in left ventricular chamber geometry
Excitation-contraction coupling	**Myocyte loss**	**LV dilatation**
Myosin heavy chain (fetal) gene expression	Necrosis	**Increased LV sphericity**
β-adrenergic desensitization	Apoptosis	**LV wall thinning**
Hypertrophy	Autophagy	**Mitral valve incompetence**
Myocytolysis	**Alterations in extracellular matrix**	
Cytoskeletal proteins	Matrix degradation	
	Myocardial fibrosis	

J Am Coll Cardiol 2012;60:2465-2472
Braunwald's heart disease, 10th edition

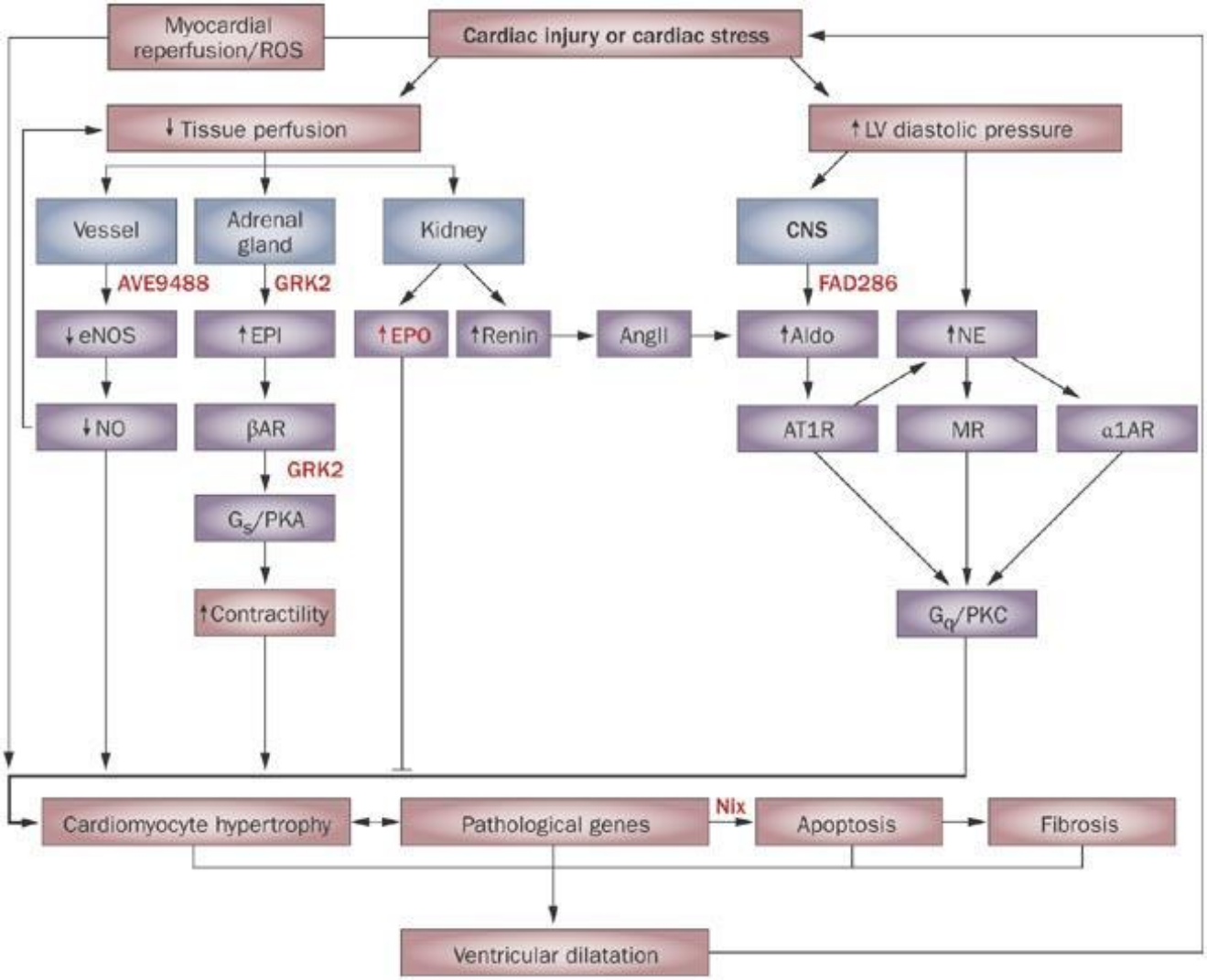
Left ventricular remodeling





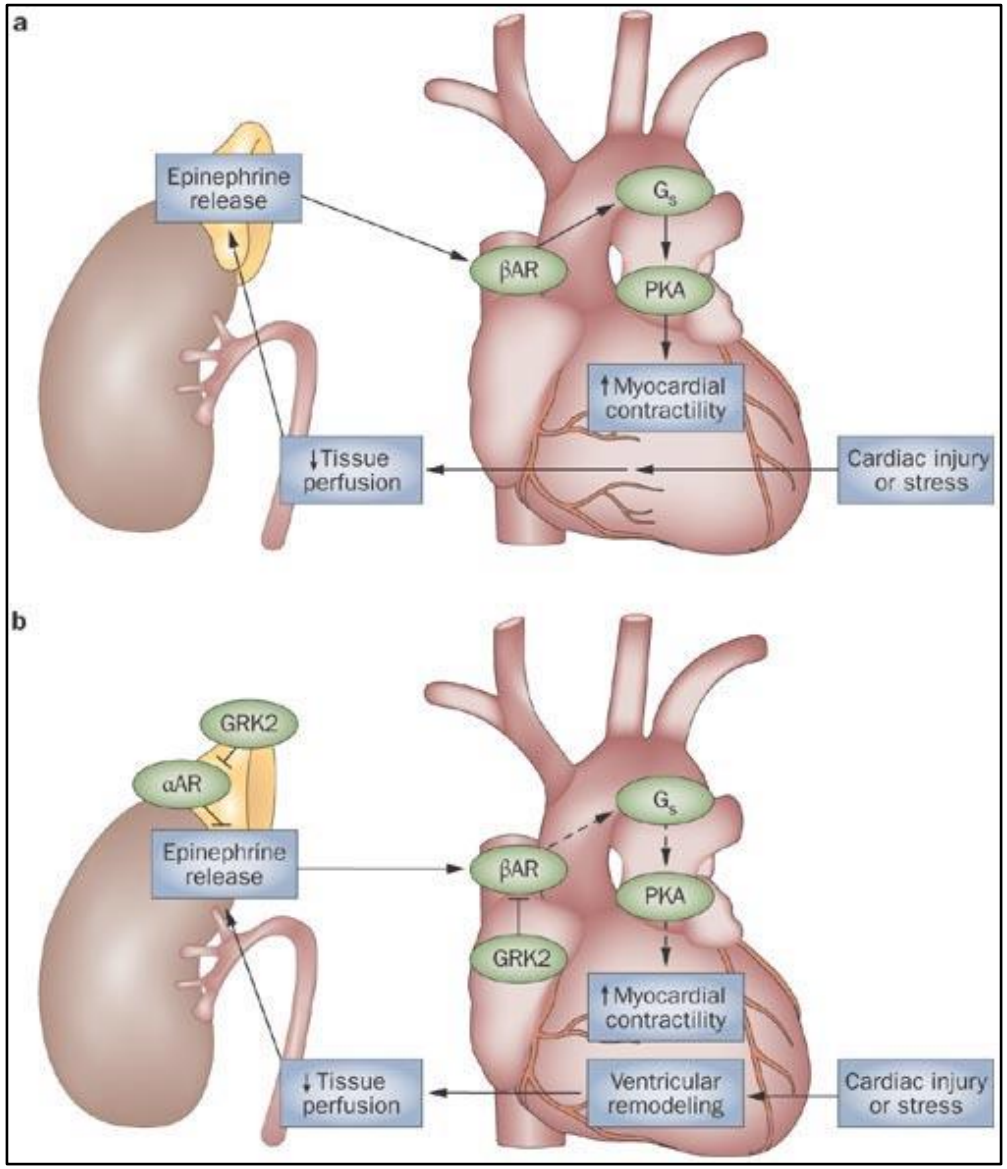
Braunwald's heart disease, 10th edition

Neurohormonal activation



Nature Reviews Cardiology 2009;6:283-291

Neurohormonal activation

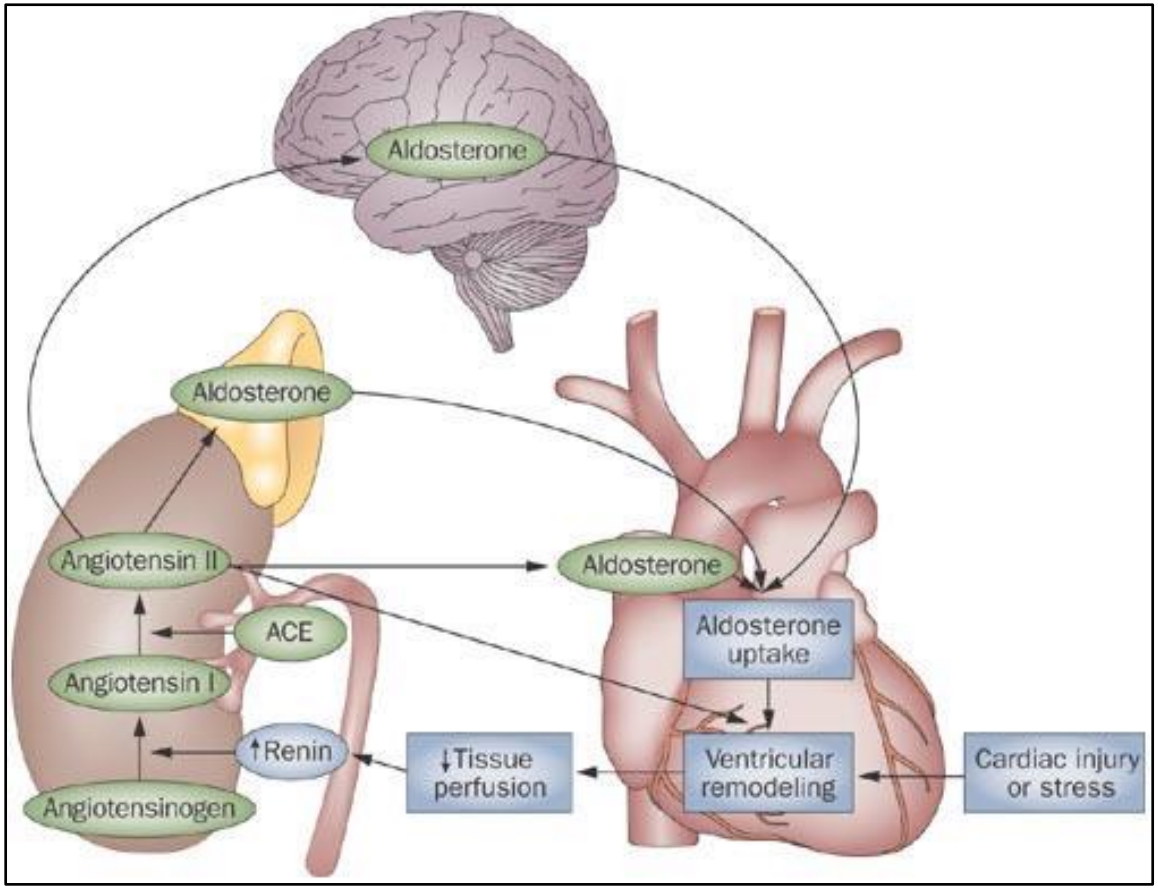


Activation of the sympathetic nervous system

Nature Reviews Cardiology 2009;6:283-291

Neurohormonal activation

Activation of the renin-angiotensin-aldosterone system



Nature Reviews Cardiology 2009;6:283-291

Neurohormonal activation

- Initially, adaptive changes
- Over the long term, contributes to pathologic remodeling (mostly, RAAS)
- The release of BNP from myocytes may be protective against pathologic remodeling

J Am Coll Cardiol 1992;20:248.
Proc Natl Acad Sci U S A 2000;97:4239.

Cellular changes

PROTEIN	CHANGE IN HUMAN HEART FAILURE
Plasma Membrane	
L-type calcium channels	Decreased*†
Sodium/calcium exchanger	Increased*†
Sodium pump	Reexpression of fetal isoforms
$Beta_1$-adrenergic receptor	Decreased*†
$Beta_2$-adrenergic receptor	Increased*
$Alpha_1$-adrenergic receptor	Increased*
Sarcoplasmic Reticulum	
SERCA2A	Decreased*†
Phospholamban	Hypophosphorylated
Ryanodine receptor	Hyperposphorylated†
Calsequestrin	Normal*
Calreticulin	Normal*
Contractile Proteins	
Myosin heavy chain (MYHC)	Reversion to fetal isofom (↓MYHC6:MYHC7)
Myosin light chain (MYLC)	Reversion to fetal isoform
Actin	Normal*
Titin	Isoform switch (↑N2BA:N2B), hypophosphorylated
Troponin I	Normal*, hypo- and hyperphosphorylated‡
Troponin T	Isoform switch, hyperphosphorylated‡
Troponin C	Normal*
Tropomyosin	Normal*

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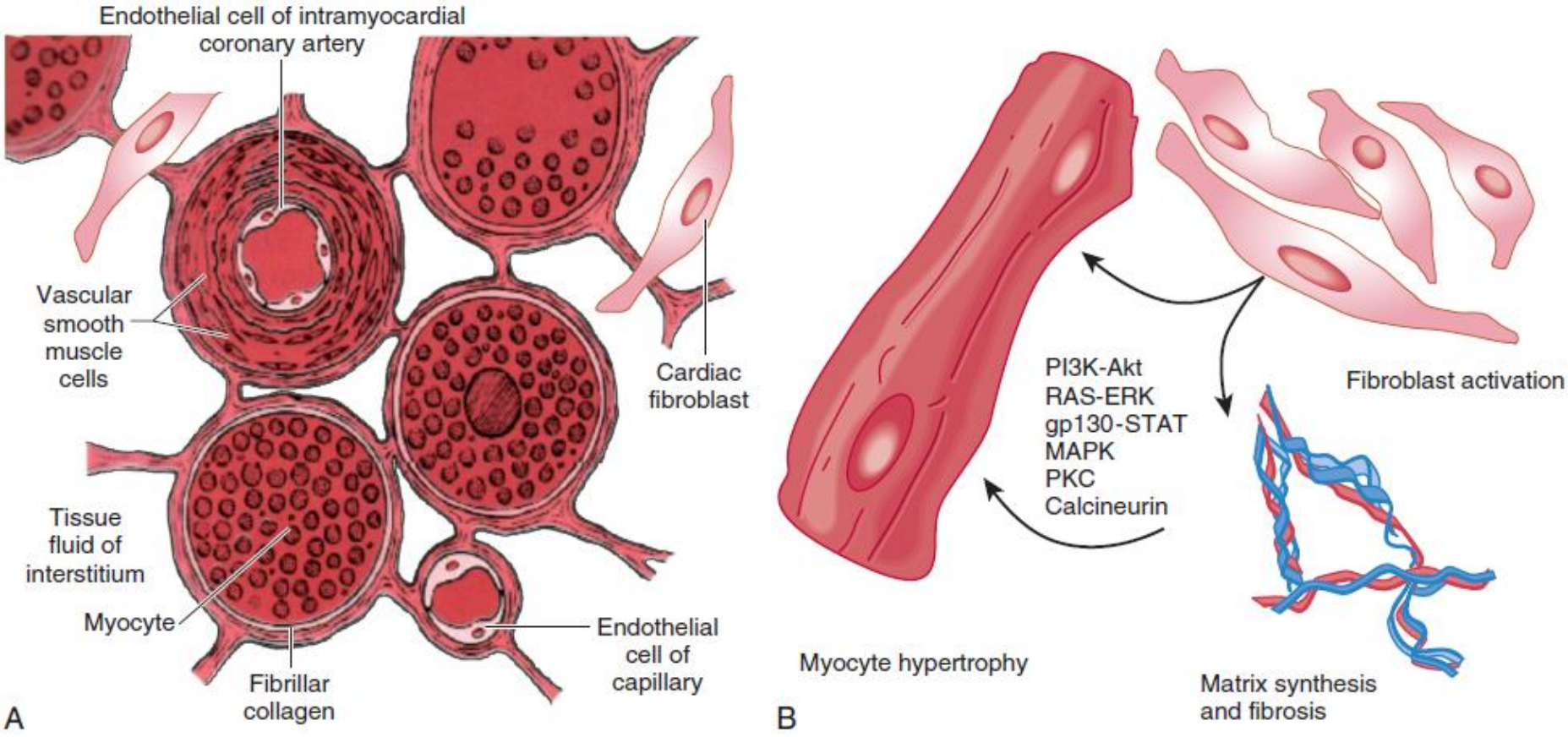
Extracellular matrix changes



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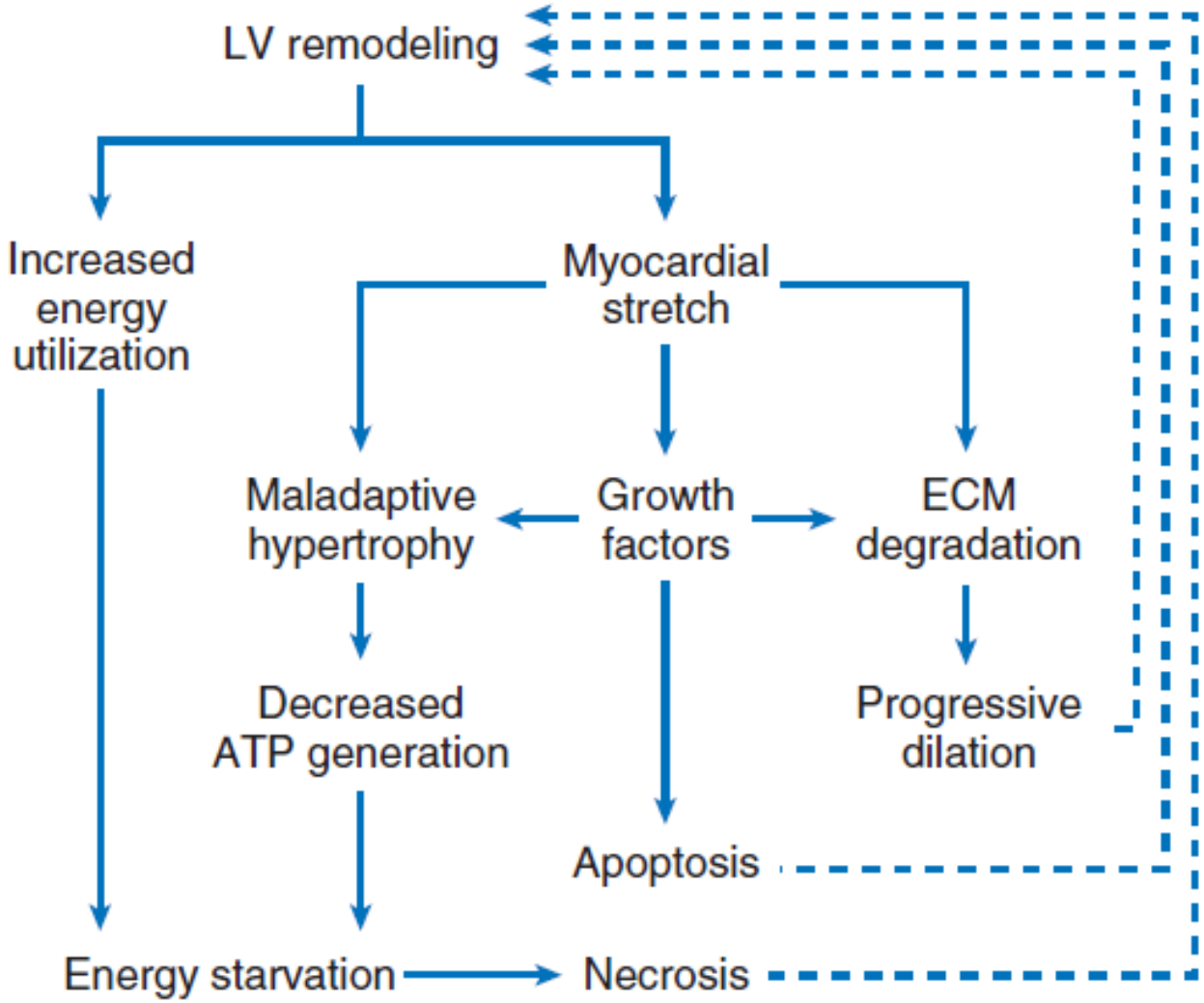
Negative results from LV remodeling

- Increased wall stress
- Afterload mismatch
- Episodic subendocardial hypoperfusion
- Increased oxygen utilization
- Functional mitral regurgitation
- Worsening hemodynamic overload
- Stretch-induced activation of
  - Maladaptive signal transduction pathways
  - Maladaptive gene programs

LV remodeling is self-amplifying



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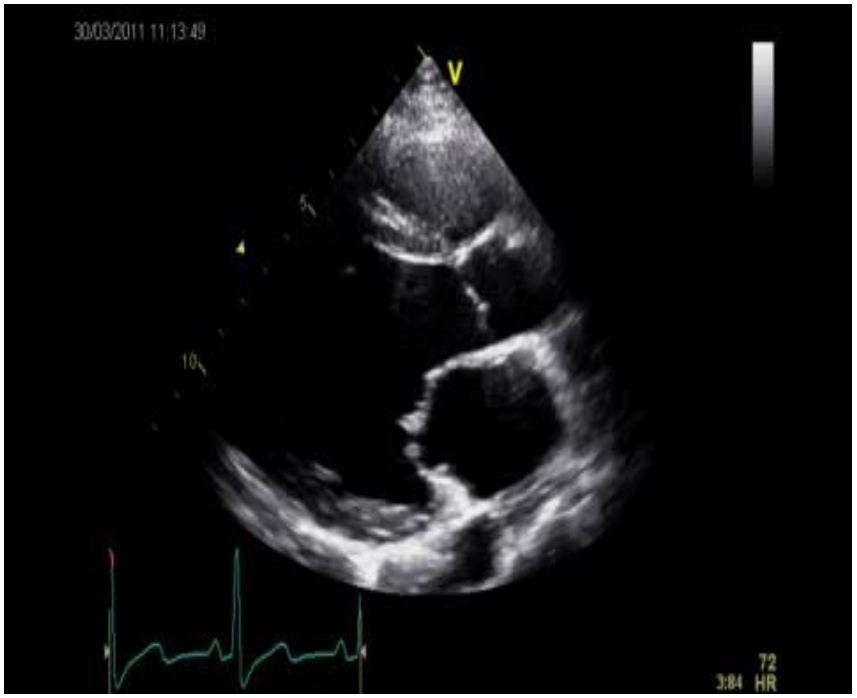
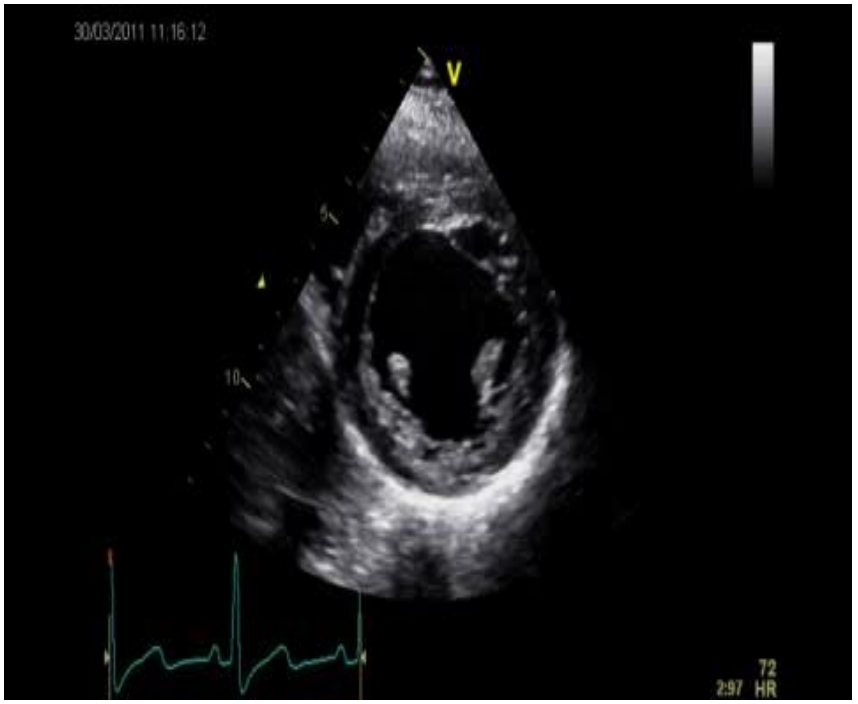
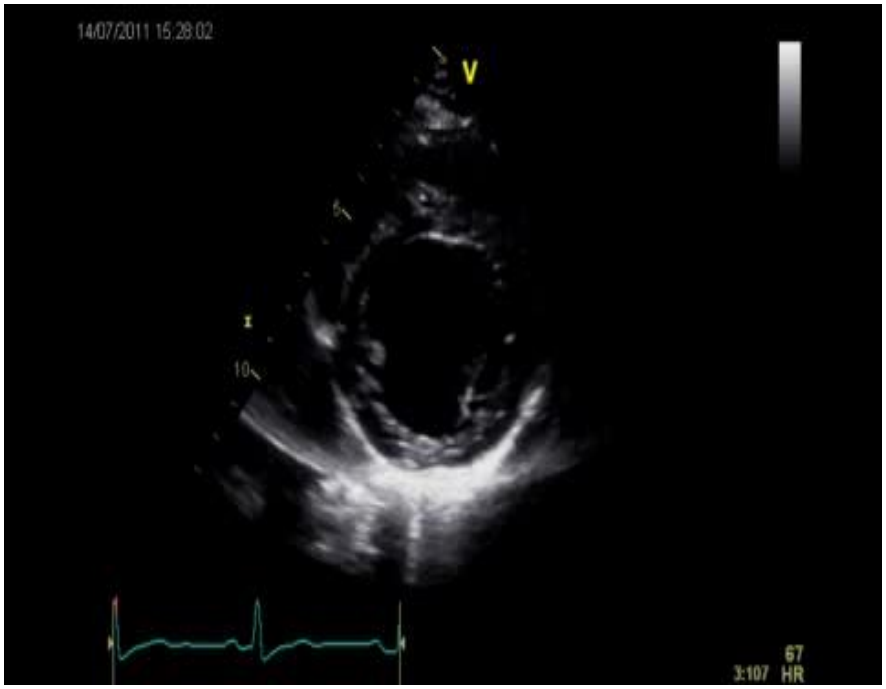
Kong O O (60/M): Dyspnea

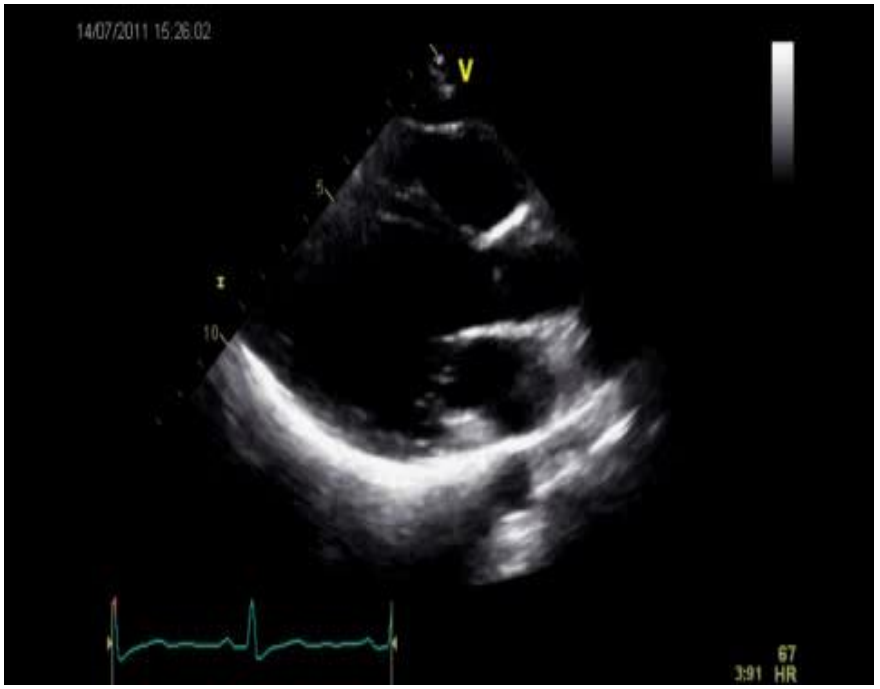




NT-Pro BNP: 7371 pg/ml

Kong O O (60/M): FU Echocardiography





NT-Pro BNP: 420 pg/ml

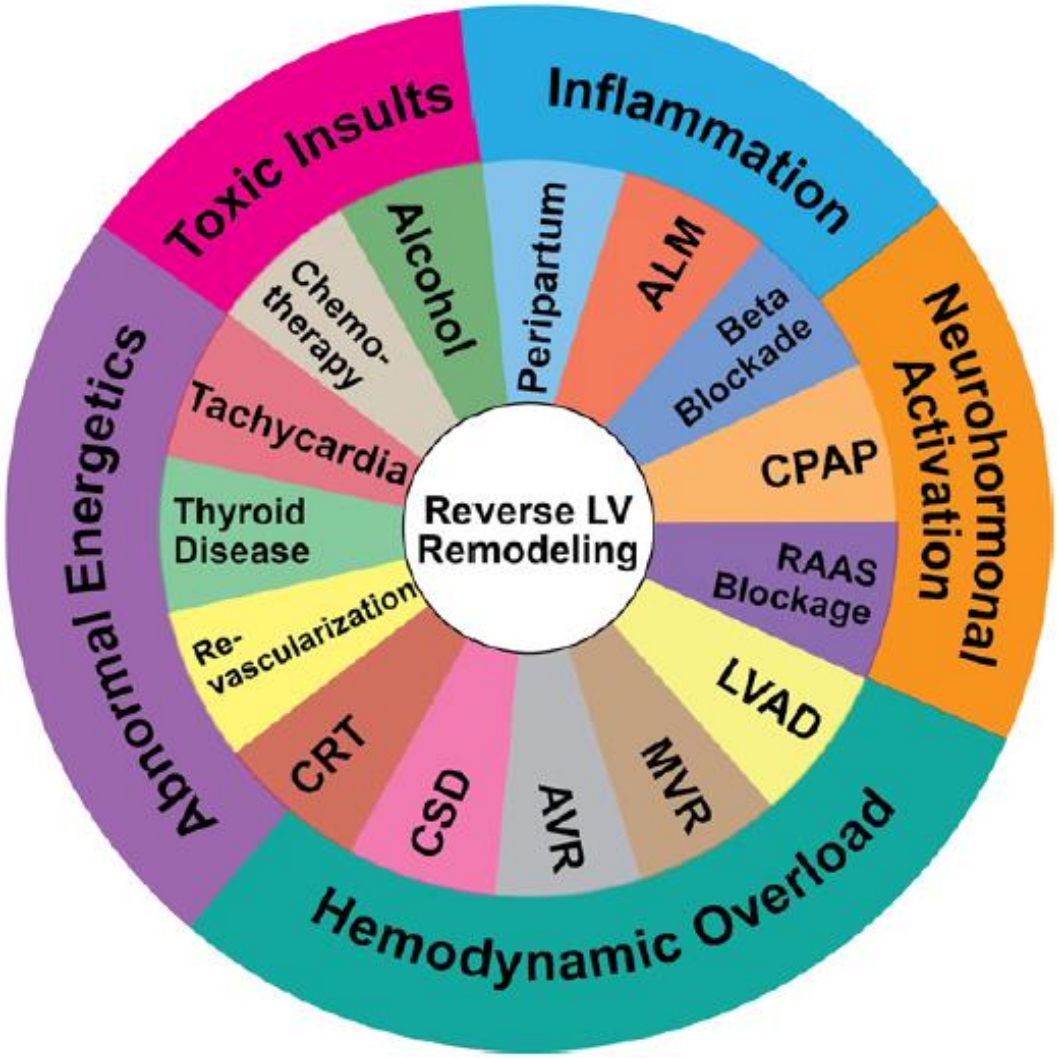
Reverse remodeling

- **Regression** of pathological myocardial hypertrophy, chamber shape distortions, and dysfunction

- First used to describe the leftward shift in the LV end-diastolic pressure-volume curve of the failing heart **after hemodynamic unloading** with a left ventricular assist device (LVAD) or a myocardial wrap with the latissimus dorsi muscle

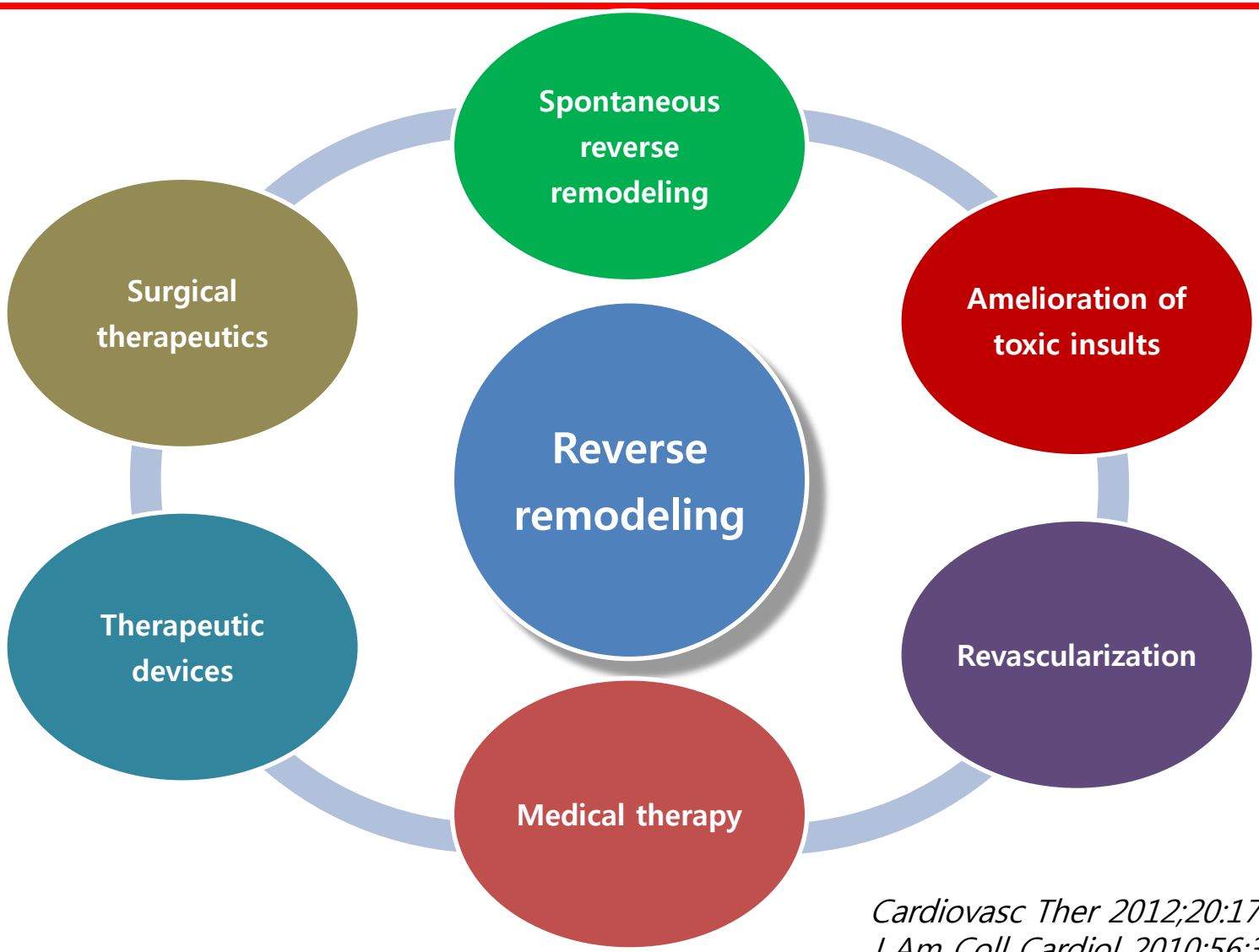
Circulation 1995;91:2314-8
Circulation 1995;91:2717-20

Reverse remodeling in clinical settings



J Am Coll Cardiol 2012;60:2465-2472

Reverse remodeling



Cardiovasc Ther 2012;20:172-81
J Am Coll Cardiol 2010;56:392-406

Contents

Spontaneous reverse remodeling

Peripartum cardiomyopathy (PPCM)

- About 50% of patients with PPCM recover baseline ventricular function within 6 months of delivery

Acute lymphocytic myocarditis

Subtype	*n*	*Early death*	*Early mortality*	*Late death*	*Overall mortality*
Acute					
Common	*9*	*2*	*22%*	*0*	*22%*
Fulminant	*21*	*9*	*43%*	*1*	*48%*
Chronic					
Persistent	*3*	*1*	*33%*	*0*	*33%*
Recurrent	*2*	*1*	*50%*	*0*	*50%*
Latent	*13*	*5*	*38%*	*3*	*62%*

Int J Cardiol 2007;118:295-303.
Jpn Circ J 2001;65:961-4.

Long-term exercise training

Improved LV function after 6 months,

	Exercise Training Group (n=45)		Control Group (n=44)	
	Baseline	6 Months	Baseline	6 Months
EDV, mL/m^2	142±26	135±26*	147±41	156±42*†
ESV, mL/m^2	107±24	97±24*	110±34	118±34*‡
EF, %	25±4	29±4*	25±4	25±5‡

And was associated with improved QOL.

	Exercise Training Group (n=45)		Control Group (n=44)	
	Baseline	6 Months	Baseline	6 Months
Clinical score	7.0±2.7	5.3±2.1*	7.2±2.1	7.2±2.1†
Symptoms perceived during daily physical activity	13.4±1.8	10.9±1.3*	13.8±1.4	13.4±1.8‡

Circulation 2003;108:554-559

Amelioration of toxic insults

Reverse remodeling from tachycardia-induced CMP

Patient	Age (years)	Sex	Arrhythmia	Time* (days)	Presentation				The -rapy	After treatment			Time† (days)	Recu -rrent	Sudden death
					HR (bpm)	NYHA	BNP	EF		HR (bpm)	NYHA	EF			
1	40	F	AF	20	175	2	103	0.25	Rate	78	1	0.53	14	N	N
2	59	F	AF	30	130	3	760	0.28	Rate	60	1	0.54	34	Y	N
3	67	M	AF, WPW	6	170	2	N/A	0.27	Both	86	1	0.56	64	N	N
4	59	M	AFL	20	170	2	322	0.35	Rate	60	1	0.51	56	N	N
5	52	M	AFL	7	150	2	73	0.29	Rate	80	1	0.65	62	Y	N
6	49	F	AFL	30	160	3	305	0.51	Rate	70	1	0.67	35	N	N
7	72	M	AFL	14	160	3	1330	0.25	Rate	76	1	0.52	240	N	Y
8	63	M	AFL	12	150	3	N/A	0.47	RF	74	1	0.65	21	N	N
9	50	M	AFL, WPW	14	100	2	14	0.31	RF	70	1	0.58	21	N	N
10	30	M	AVNRT	28	190	2	788	0.25	RF	70	1	0.50	21	N	N
11	12	F	IVT	120	160	2	857	0.17	RF	60	1	0.54	50	N	N
12	70	M	IVT	-‡	200	2	N/A	0.43	RF	66	1	0.51	24	N	N
Mean	51.9 ± 17.6			26.0 ± 34.3	156.3 ± 28.7	2.3 ± 0.5	505.7 ± 449.1	31.9 ± 10.2		70.8 ± 8.4	1.0 ± 1.0	54.3 ± 10.4	53.5 ± 61.3		

* Time from the occurrence of symptoms due to tachyarrhythmia to hospitalization due to congestive heart failure. † Time from hospitalization to normalization of left ventricular dysfunction. ‡ a patient did not have any prior symptoms suggesting tachyarrhythmia. Arrhythmia indicates arrhythmia believed to be the cause of tachycardia-induced cardiomyopathy; HR, heart rate; NYHA, New York Heart Association functional class; BNP, brain natriuretic peptide; EF, ejection fraction; AF, atrial fibrillation; WPW, Wolff-Parkinson-White syndrome; AFL, atrial flutter; AVNRT, atrioventricular nodal reentrant tachycardia; IVT, idiopathic ventricular tachycardia from the right ventricular outflow tract; and RF, radiofrequency catheter ablation.

Int Heart J 2008;49:39-47.

Revascularization

Primary treatment of an STEMI induced a >10% Increased in LVEF in 39% of patients

Table 2 Baseline clinical, angiographic, and echocardiographic parameters in the reverse left ventricular remodelling (r-LVR) group when compared with the no reverse left ventricular remodelling (no r-LVR) group

	r-LVR (43 pts)	No r-LVR (67 pts)	p
Mean age (years)	57 ± 9	60 ± 11	0.24
Male, *n* (%)	38 (88)	54 (81)	0.861
Hypertension, *n* (%)	33 (77)	39 (60)	0.454
Diabetes, *n* (%)	4 (9)	19 (19)	0.082
Smokers, *n* (%)	30 (70)	39 (58)	0.671
Hypercholesterolaemia, *n* (%)	19 (44)	25 (37)	0.775
Family history of CAD, *n* (%)	12 (30)	17 (25)	0.991
ST-segment reduction (%)	65 ± 33	42 ± 51	**0.02**
Killip Class>1, *n* (%)	10 (24)	17 (26)	0.981

Eur Heart J 2009;30:566-575

Revascularization

… and it brought better survival rate.

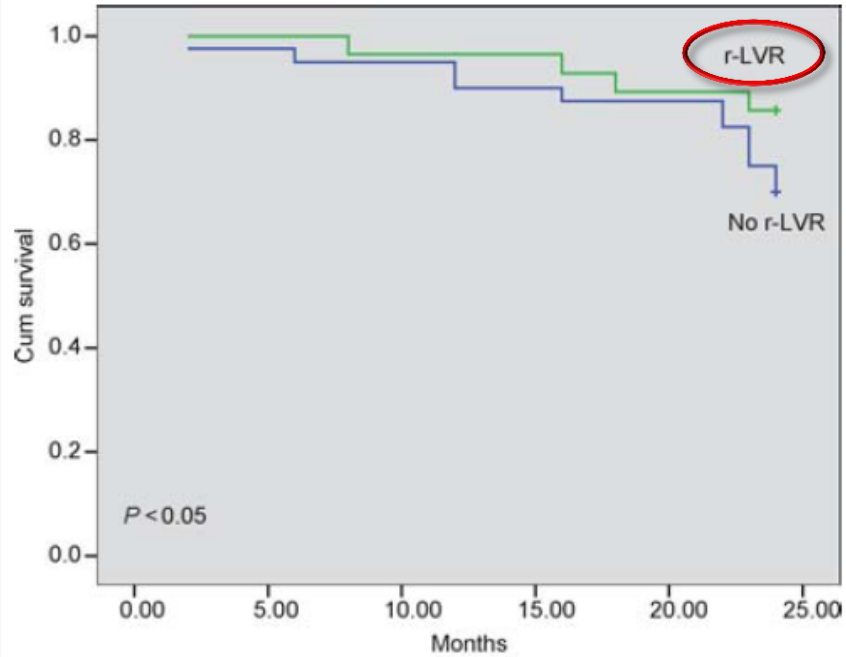
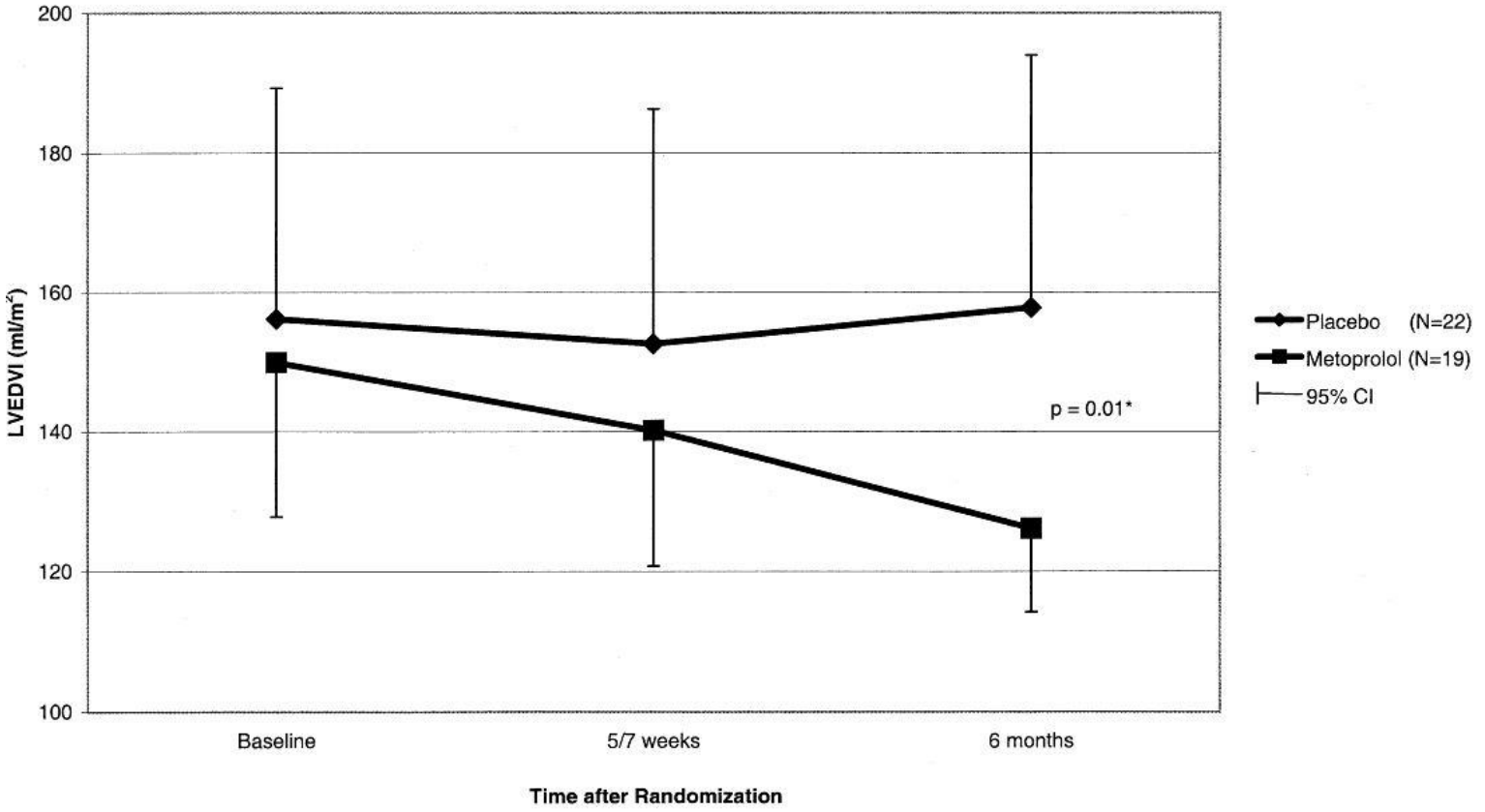


Figure 1 Kaplan–Meier curves showing patients with r-LVR had a significantly higher 2-year event-free survival rate (log-rank test $P < 0.05$) than those without r-LVR.

Eur Heart J 2009;30:566-575

β-blockers

Long-term metoprolol therapy showed evidence of reverse remodeling in chronic heart failure.



J Am Coll Cardiol 2000;36:2072-80.

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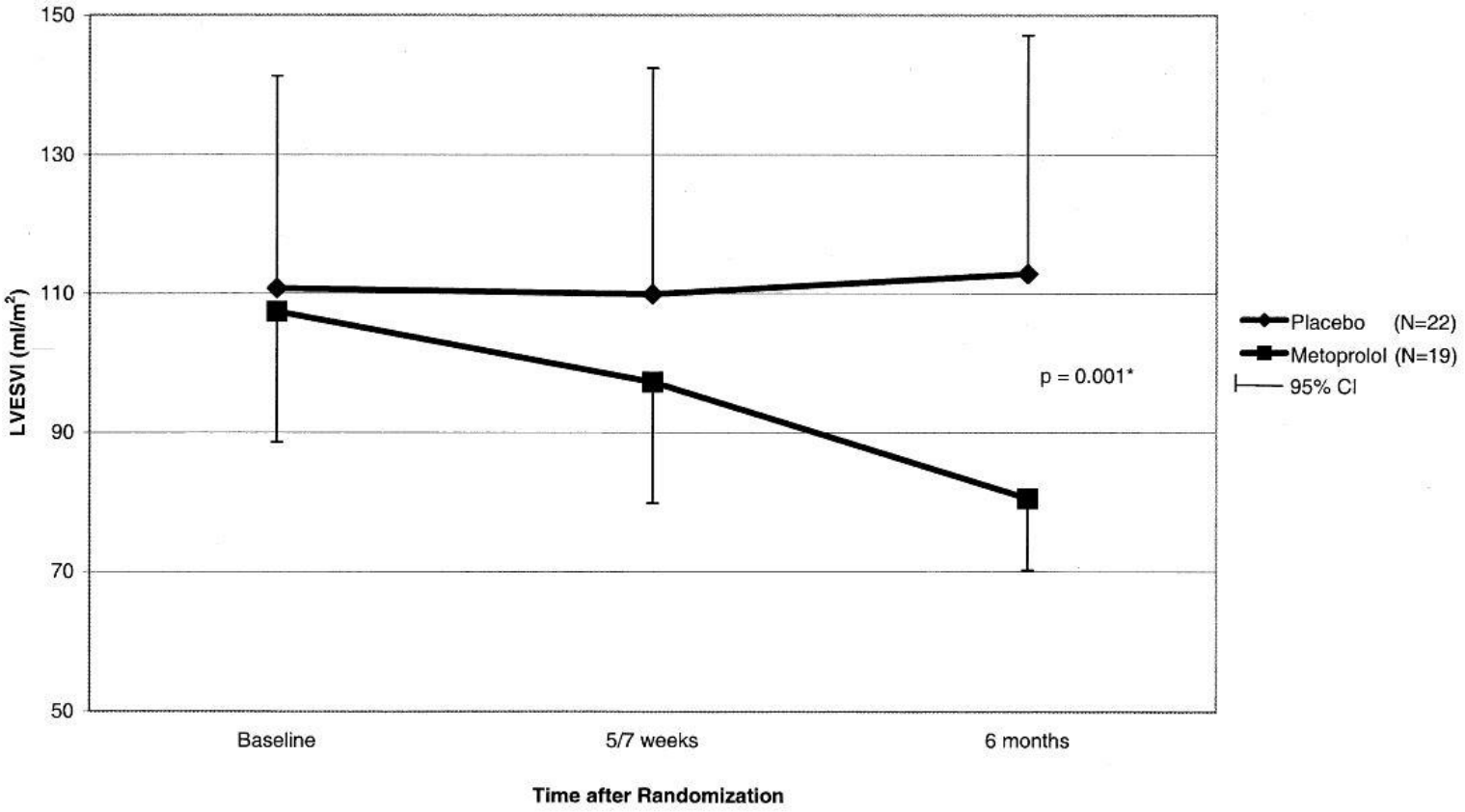

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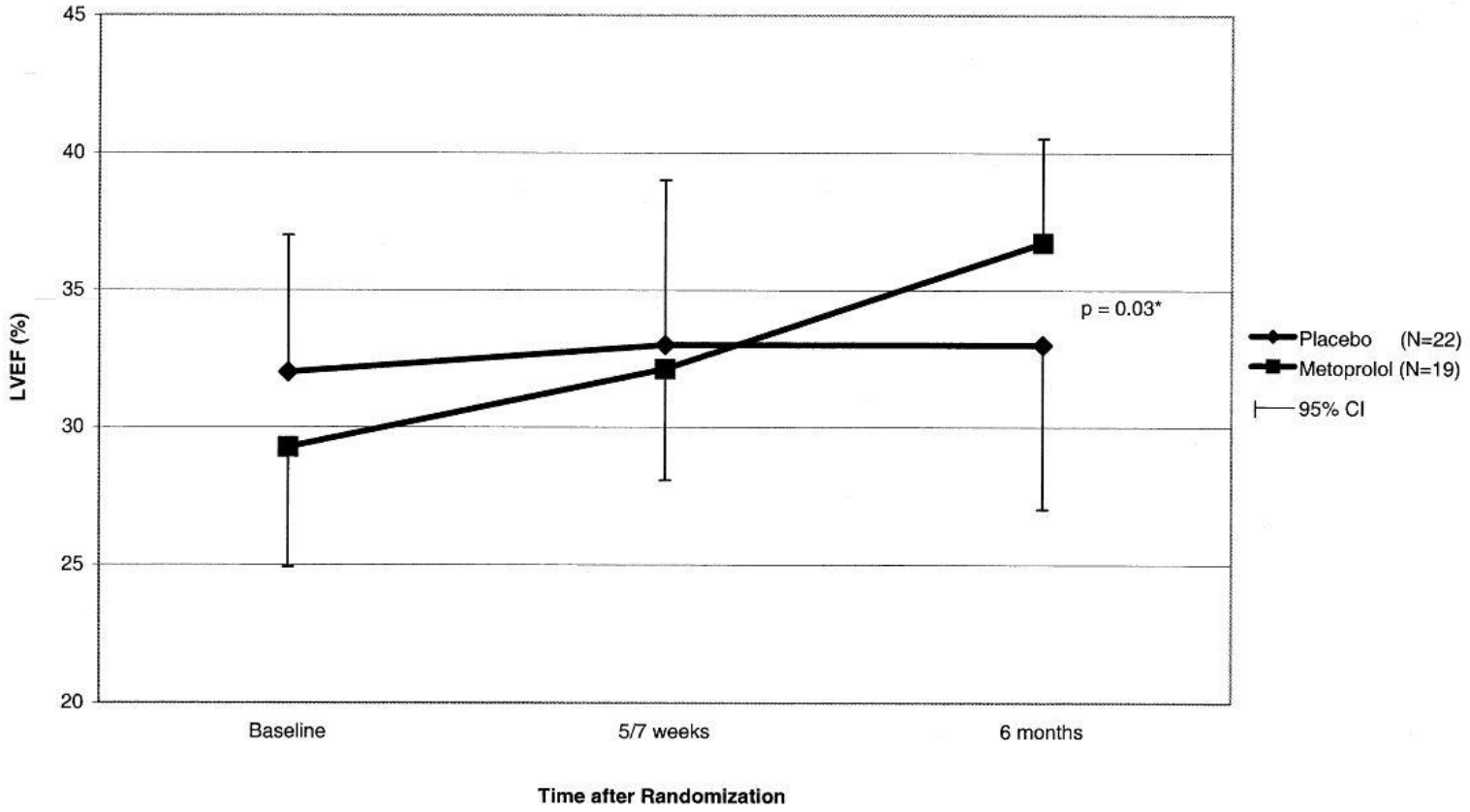

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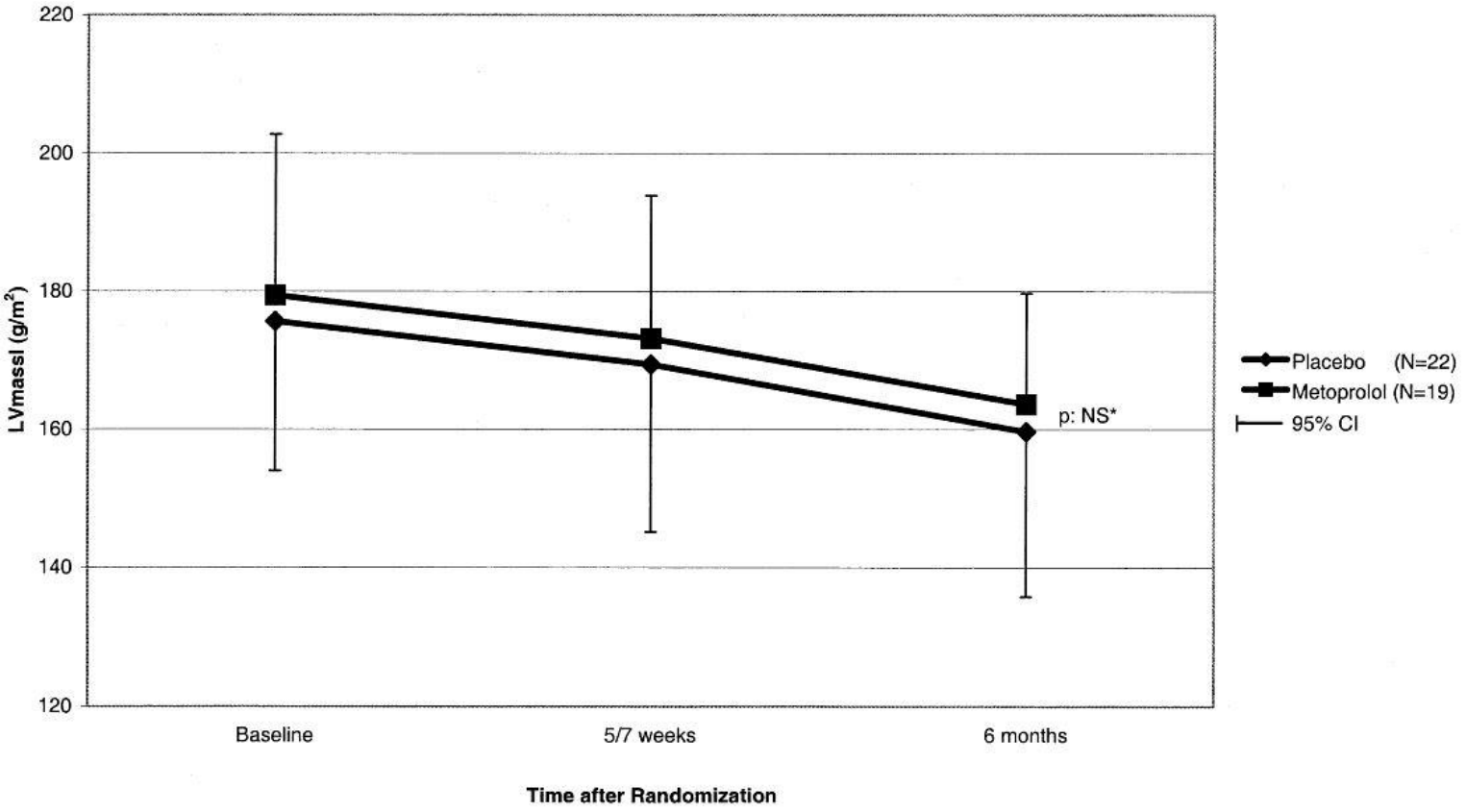
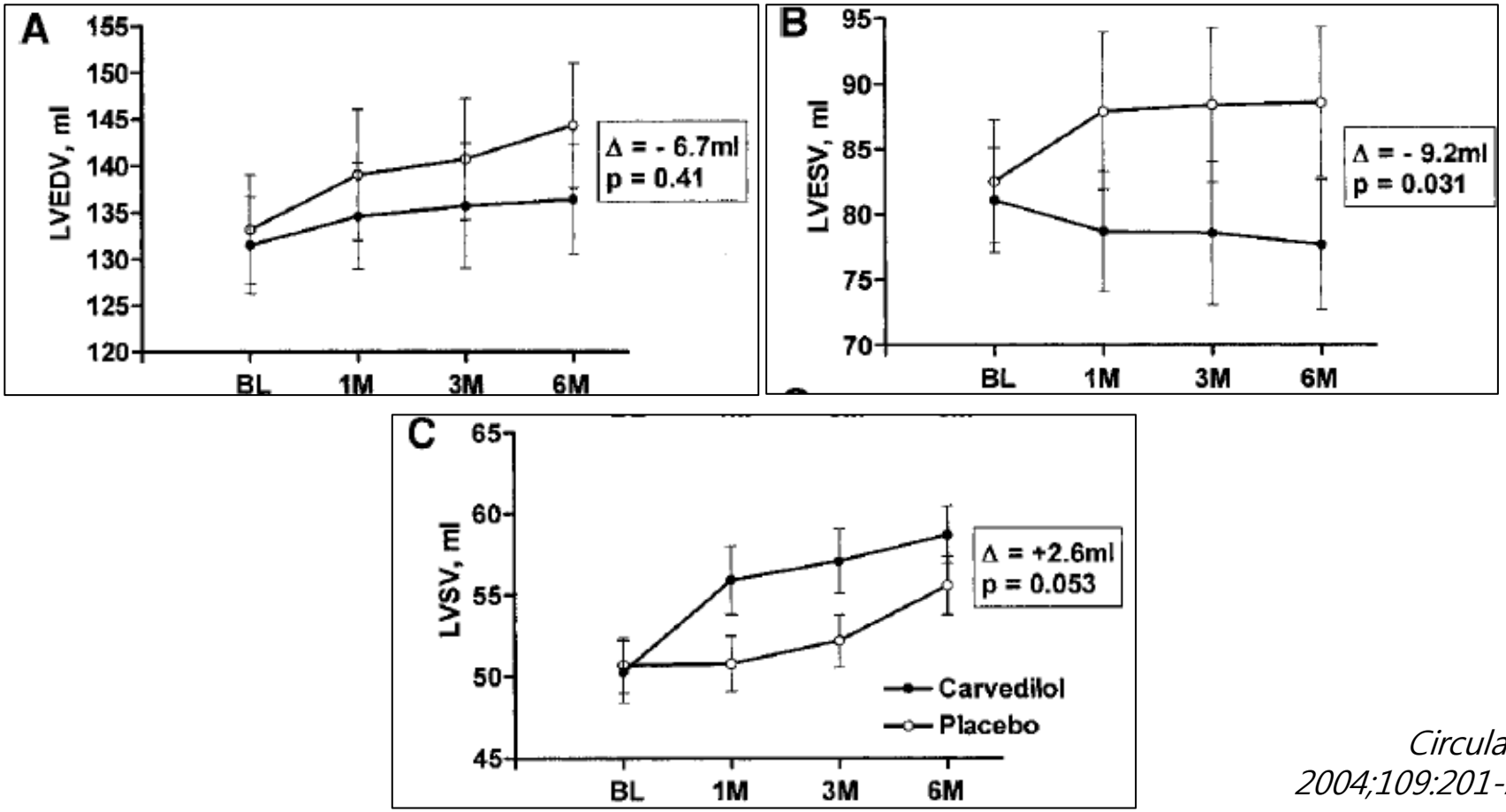


J Am Coll Cardiol 2000;36:2072-80.

β-blockers

Carvedilol also attenuated cardiac remodeling after myocardial infarction.



Circulation 2004;109:201-206.

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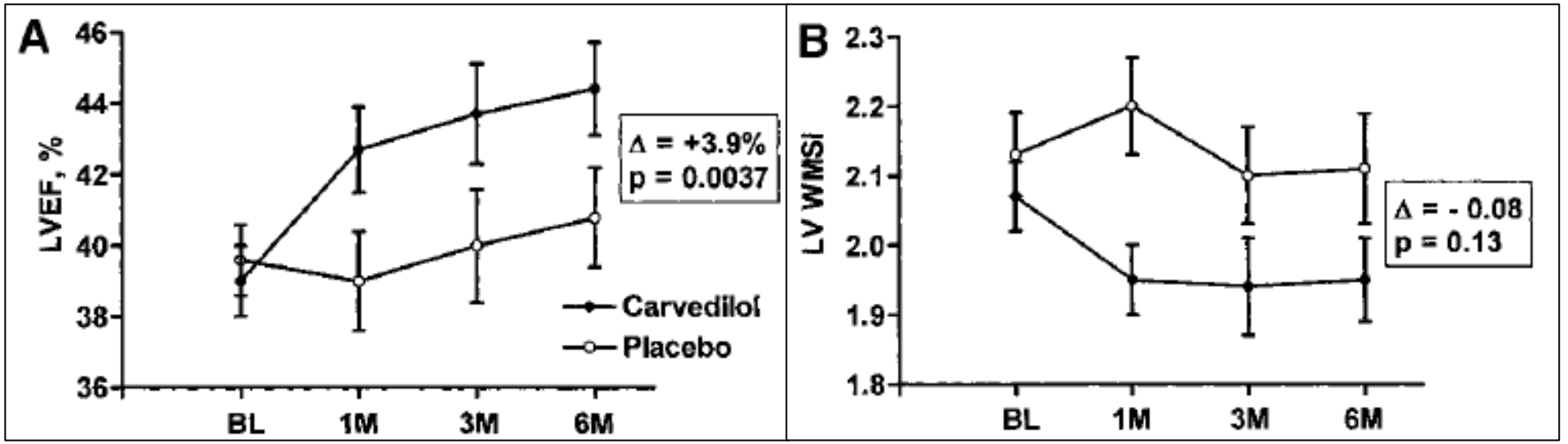
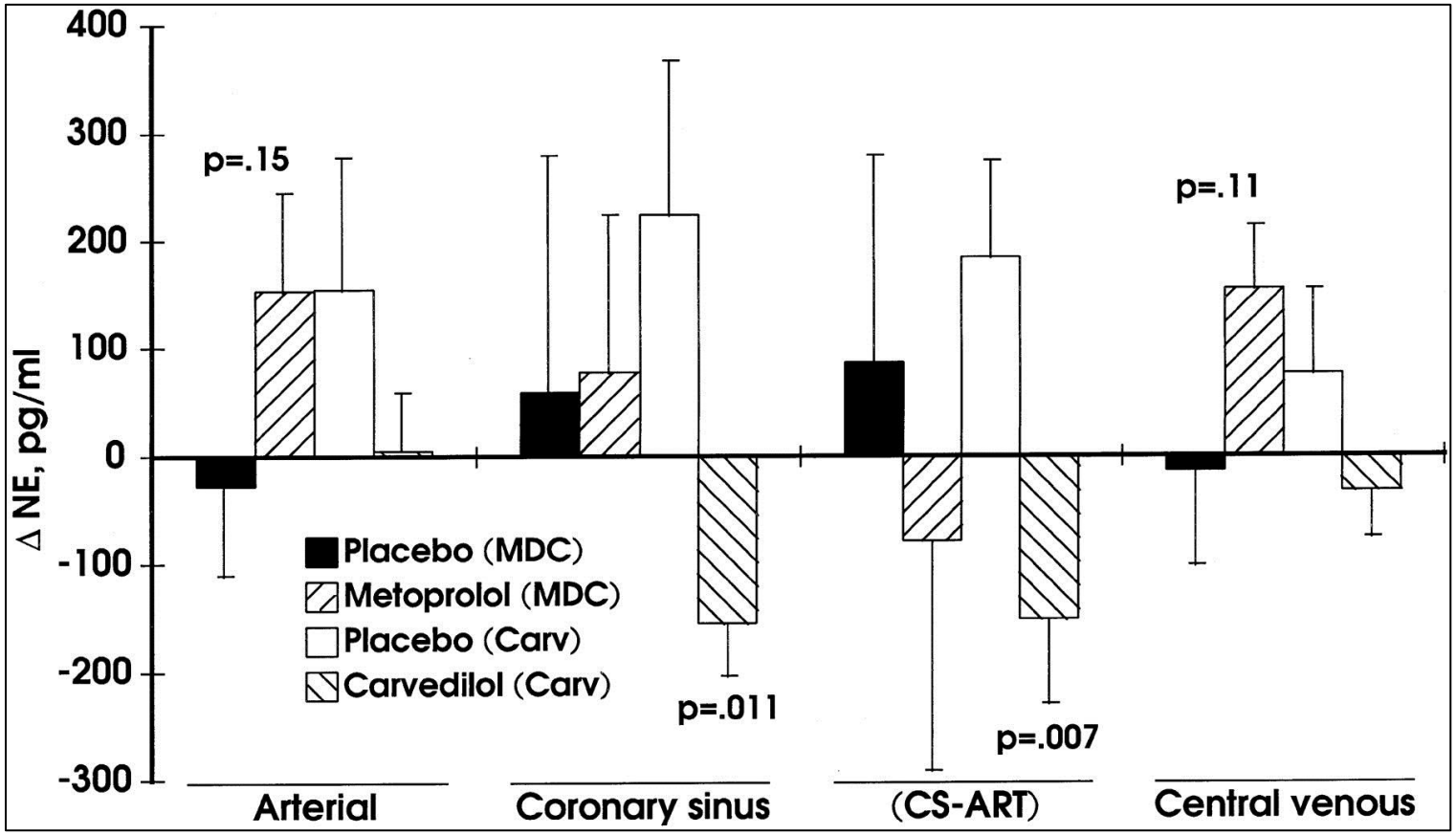


Circulation 2004;109:201-206.

β-blockers

Carvedilol significantly decreased level of norepinephrine,



Circulation 1996;94:2817-25.

Renin-angiotensin-aldosterone system (RAAS) antagonism

Antagonism of the RAAS prevents forward remodeling in patients with systolic dysfunction.

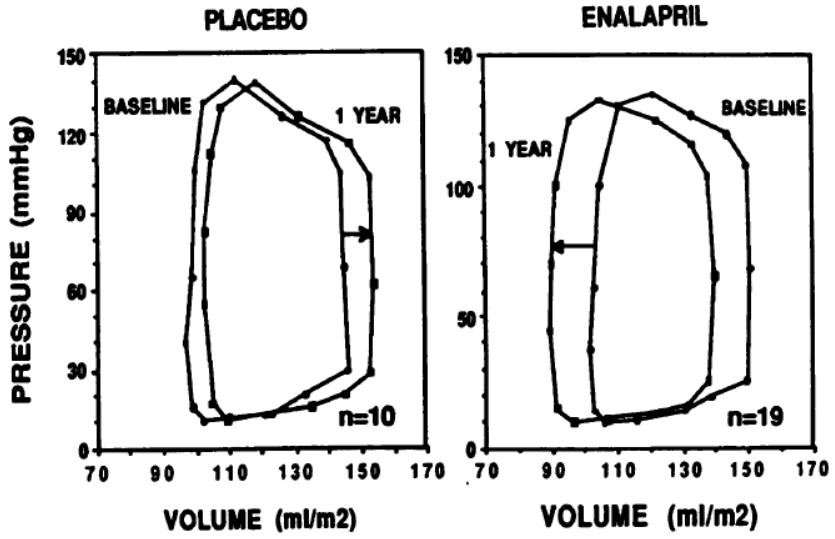
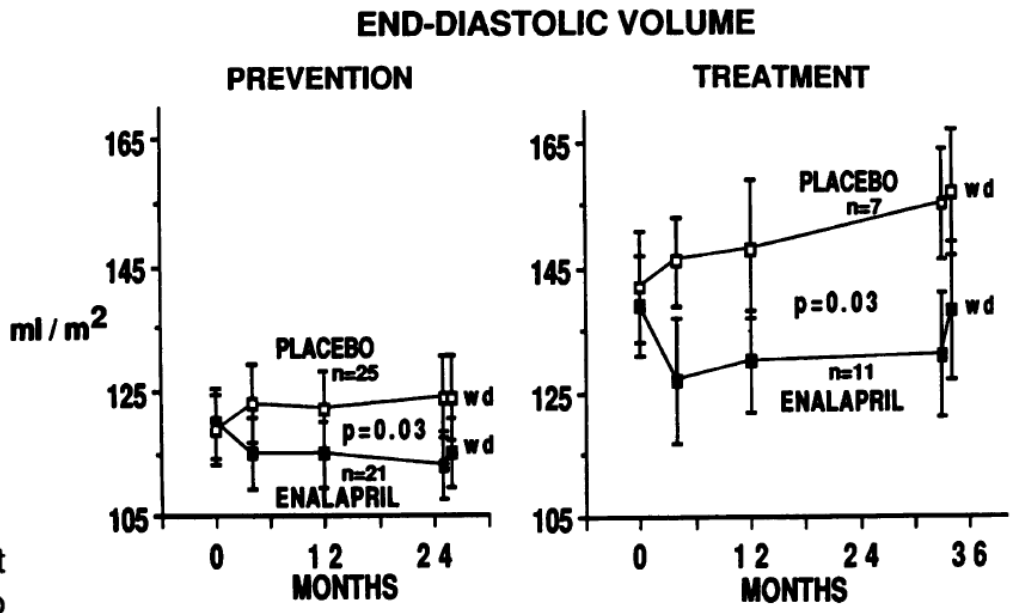


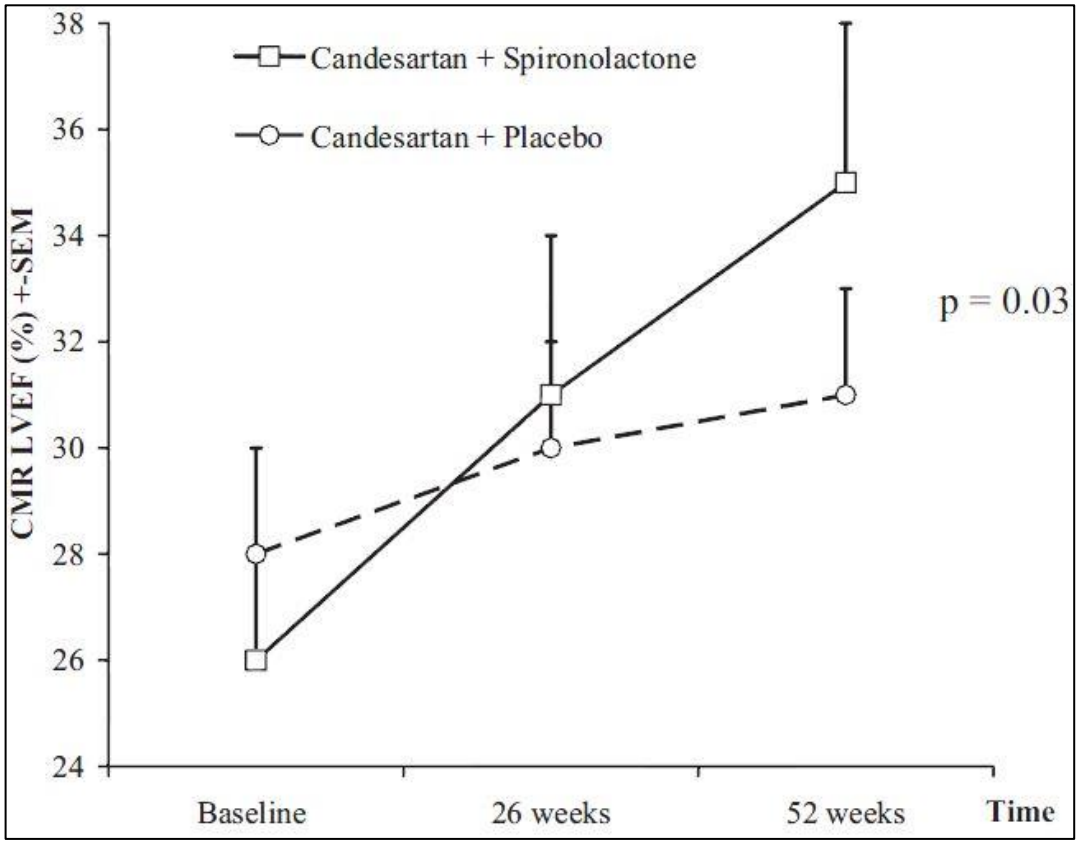
FIG 1. Mean left ventricular pressure-volume loops at baseline and 1 year in patients randomized to placebo and to enalapril. At 1 year, the entire curve was shifted to the right for the placebo group and to the left for the enalapril group.



Circulation 1993;88:2277-83.

Renin-angiotensin-aldosterone system (RAAS) antagonism

More intensive RAAS antagonism brought definite reverse remodeling.



J Am Coll Cardiol 2007;50:591-596.

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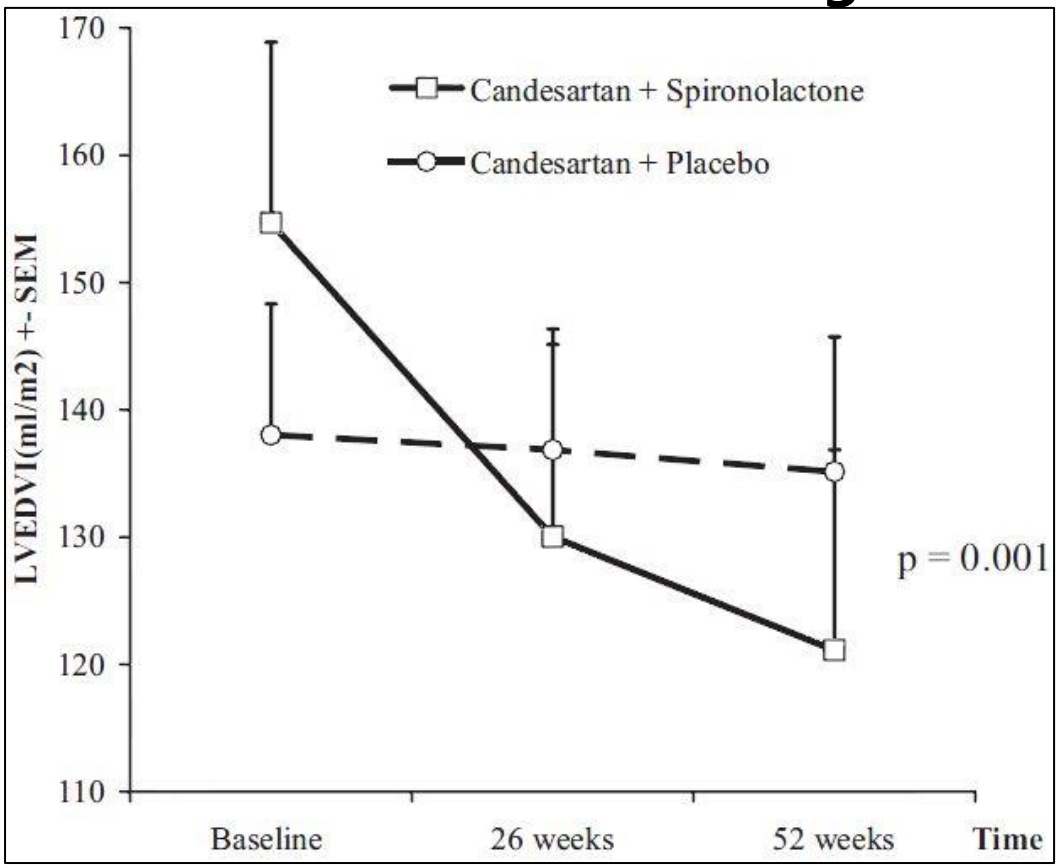

J Am Coll Cardiol 2007;50:591-596.

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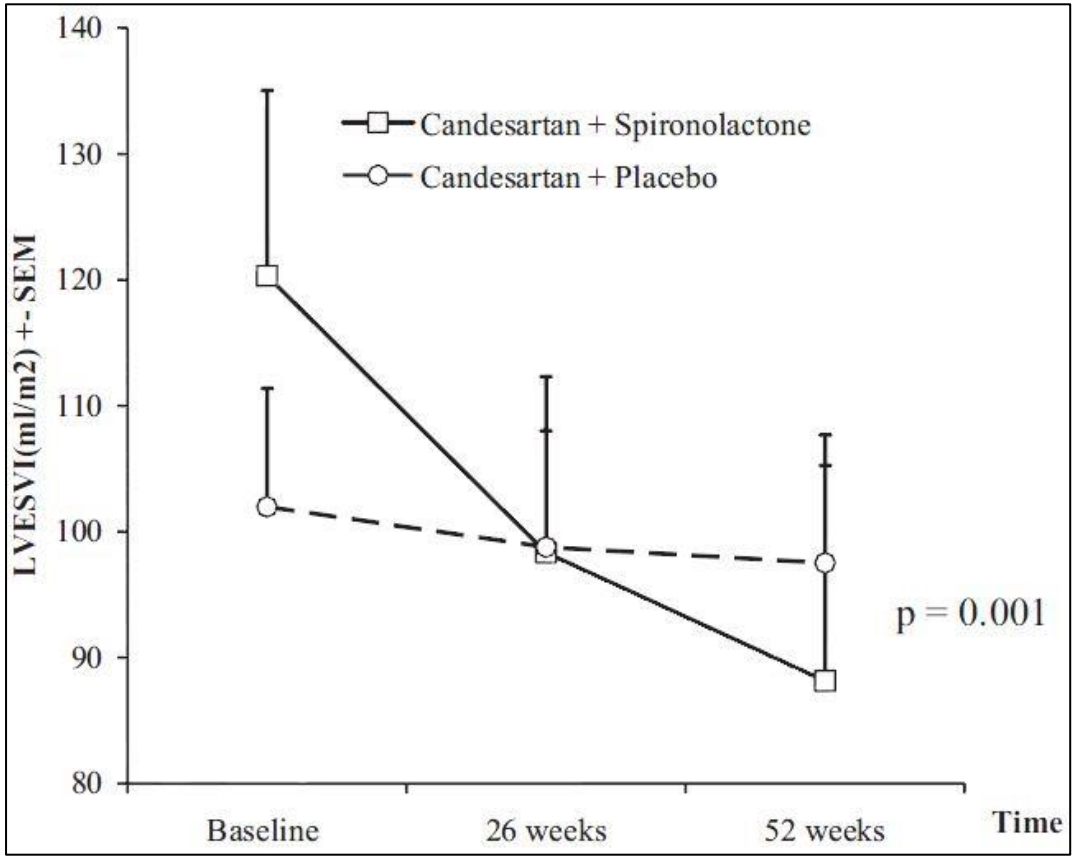


J Am Coll Cardiol 2007;50:591-596.

Vasodilator therapy

Combination of hydralazine and isosorbide dinitrate improves left ventricular systolic function.

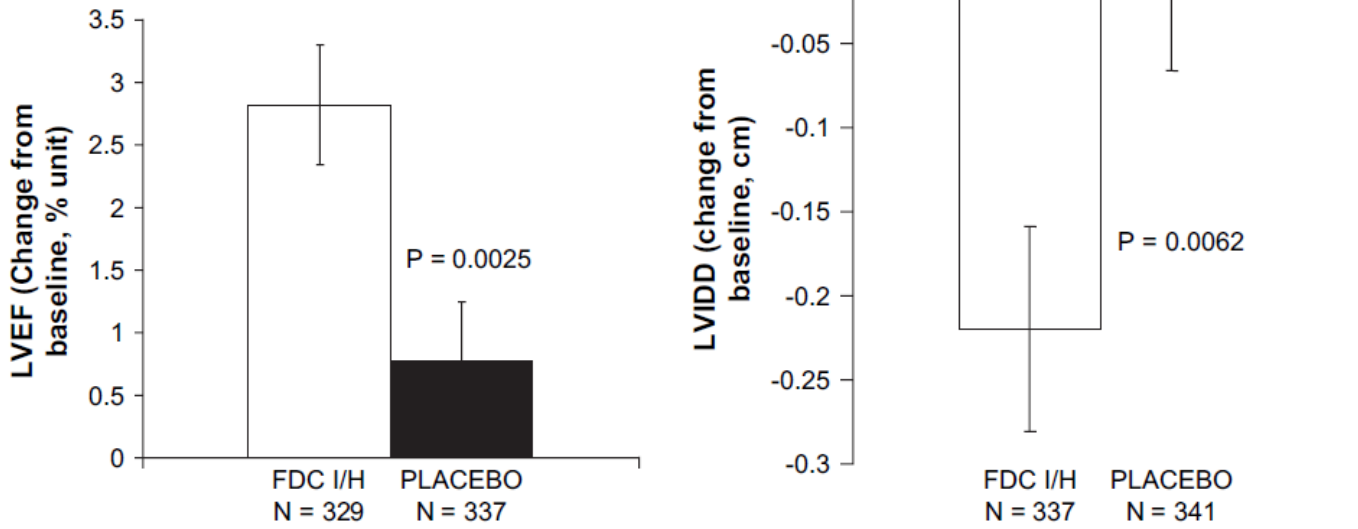


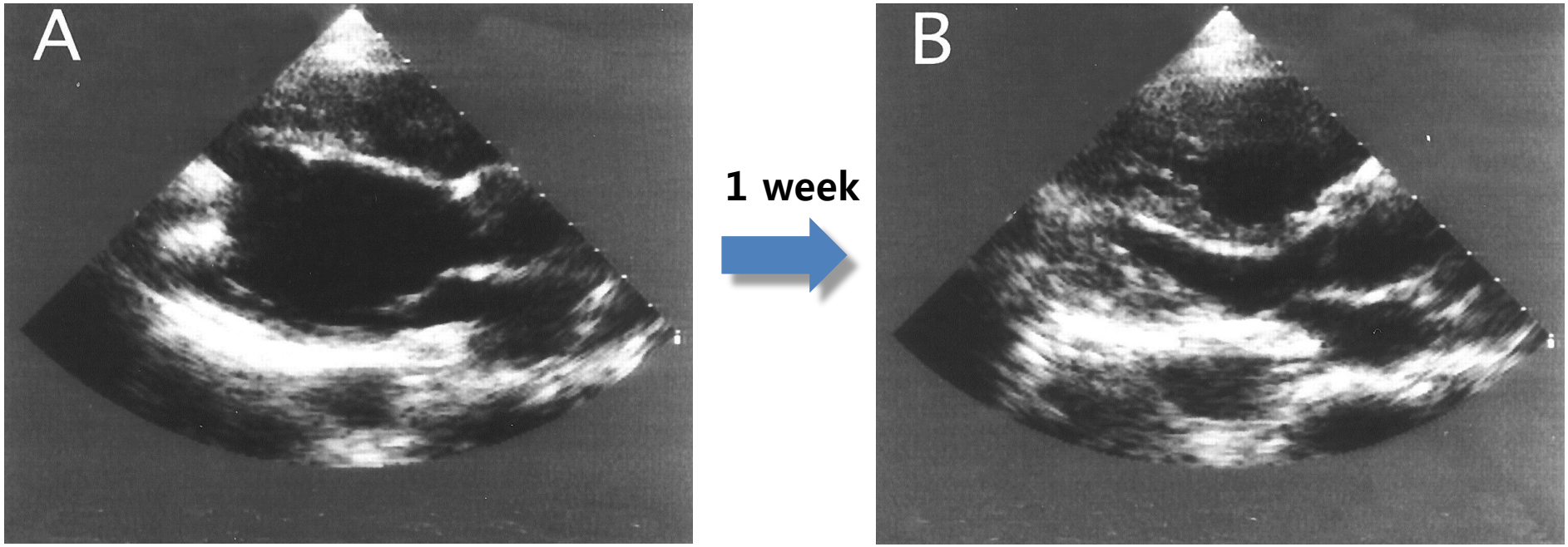
Fig. 3. Changes of left ventricular ejection fraction and internal dimension at end-diastole from baseline at 6 months. Results represent mean ± SEM.

J Card Fail 2007;13:331-9.

Contents

Left ventricular assist devices (LVAD)

LVAD provides substantial volume unloading of the heart



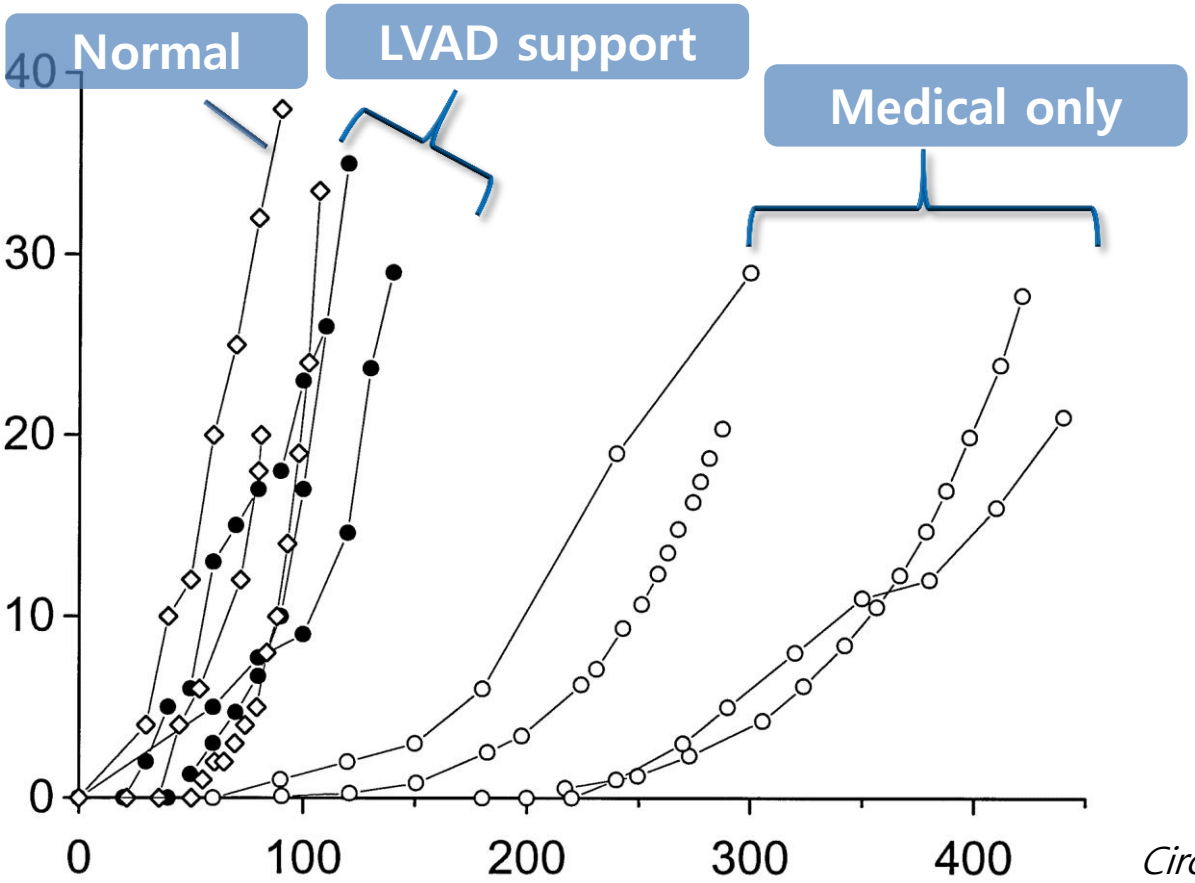
LVEDd > 60 mm

LVEDd ≒ 30 mm
Thickened LV wall

Circulation 1995;91:2717-2720

Left ventricular assist devices (LVAD)

LVAD provides better EDPVR in patients with end-stage heart failure, than medical therapy only



Circulation 1995;91:2717-2720

Left ventricular assist devices (LVAD)

LVAD induces
Regression of cellular hypertrophy

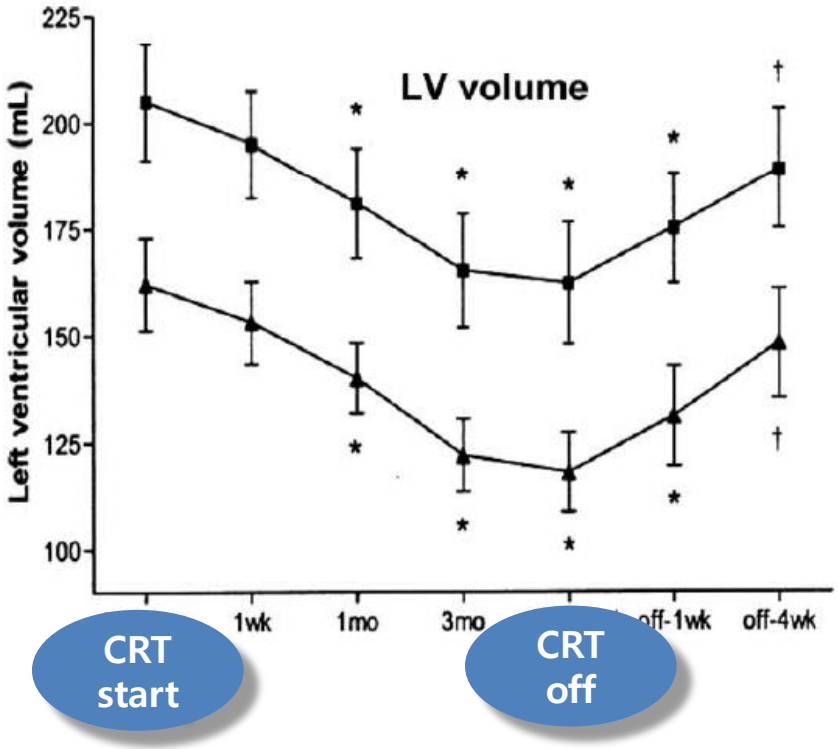
Human Cardiac Myocyte Morphometric Data

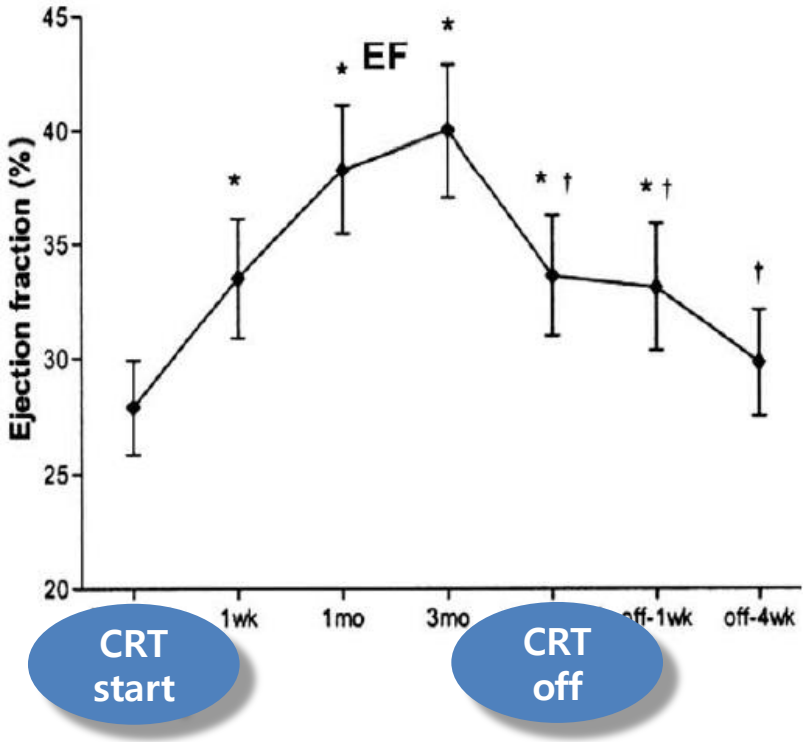
Variable	HF	HF/LVAD	Nonfailing
Rods, %	30±3	24±5	27±8
Volume, μm^3	51 888±2067	37 443 ±3307[1]	27 947±1980[1]
Length, μm	201±6	161 ±7[1]	136±4[1]
Width, μm	31.5±0.9	25.1 ±1.5[1]	26.2±1.3[1]
Thickness, μm	10.9±0.7	11.8 ±0.7	10.1±1.0
Length–to–thickness ratio	21.0±1.7	14.2 ±1.3[1]	14.0±1.3
Mononucleated cells, %	48±3	50 ±2	75±2
Binucleated cells, %	51±3	50±2	25 ±2

Circulation 1998;98:656-662.

Cardiac resynchronization therapy (CRT)

CRT decreased LV volume and increased LVEF, all of which were reversed when CRT was turned off.

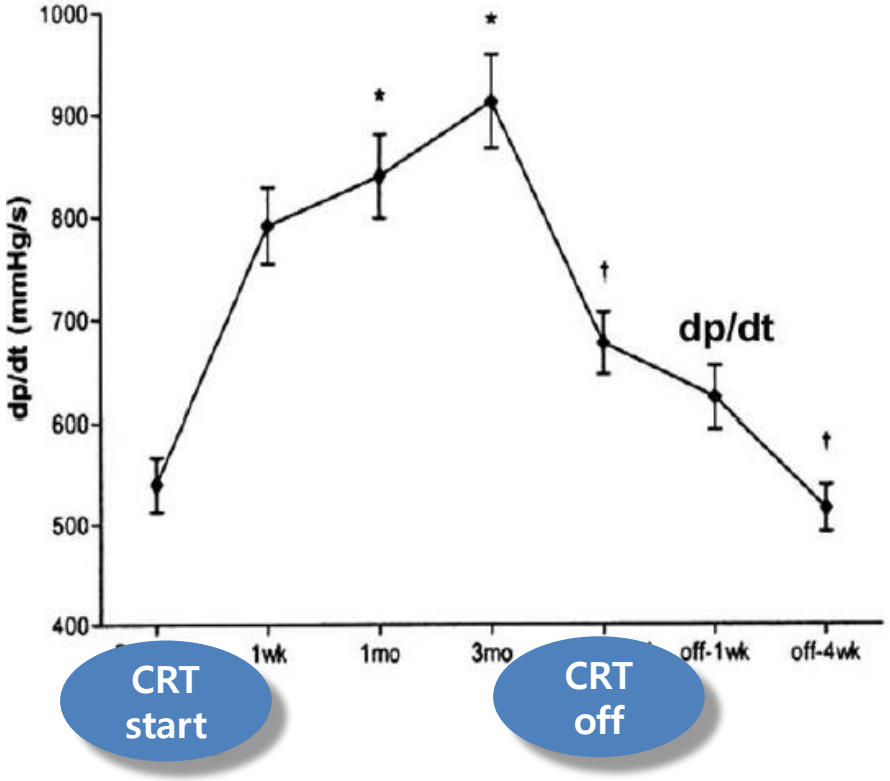


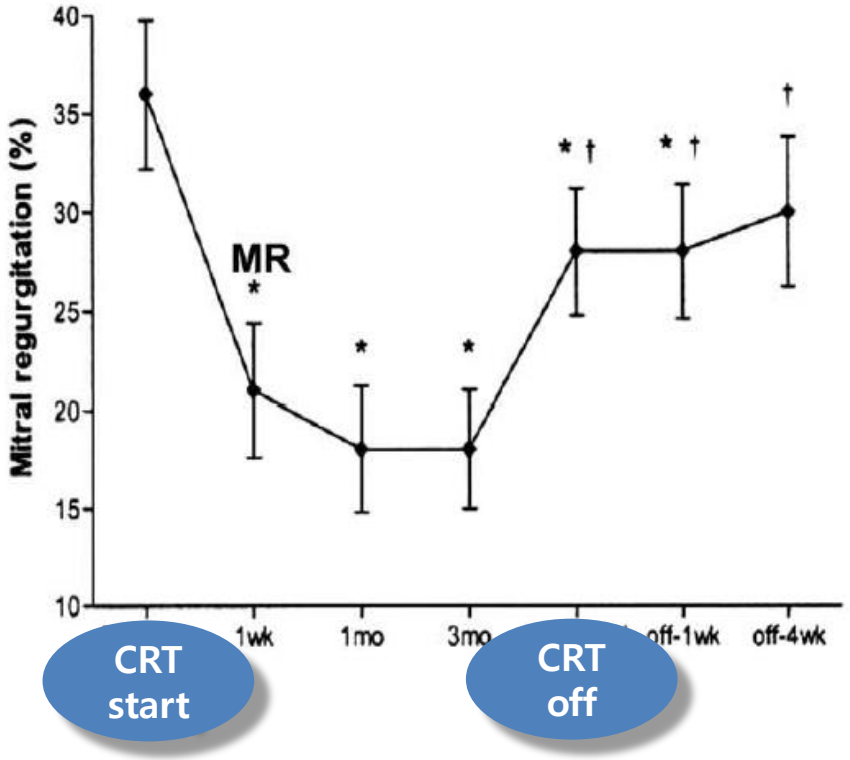


Circulation 2002;105:438-445.

Cardiac resynchronization therapy (CRT)

CRT improved dP/dt and mitral regurgitation, all of which were reversed when CRT was turned off.

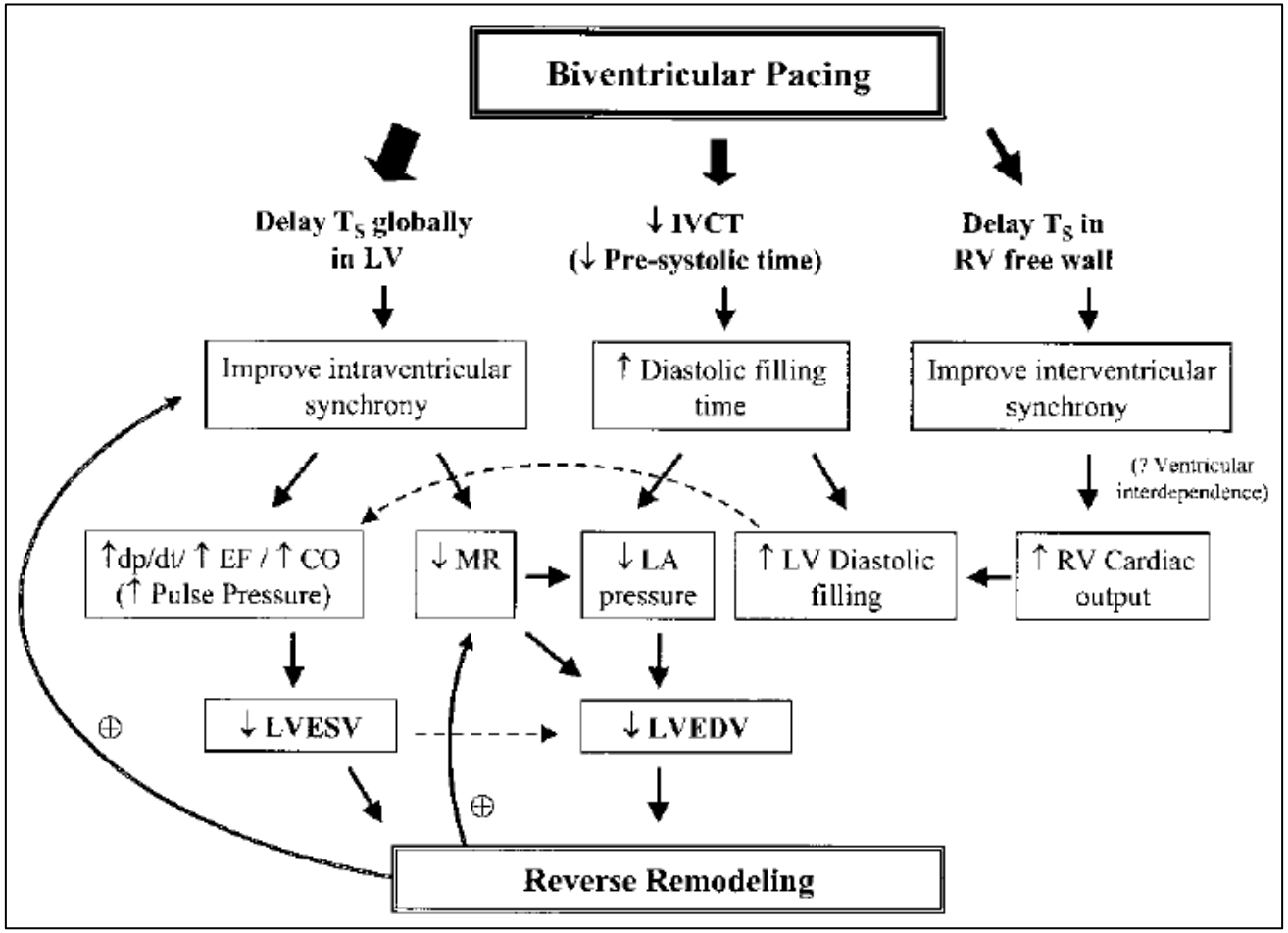




Circulation 2002;105:438-445.

Cardiac resynchronization therapy (CRT)

Proposed mechanisms of benefit of CRT



Circulation 2002;105:438-445.

Cardiac resynchronization therapy (CRT)

Amelioration of dyssynchronous myocardial contraction with CRT has been associated with substantial regression of myocardial dilatation and hypertrophy, presumably by reducing LV wall stress.

Table 2 Reverse remodeling in CRT trials

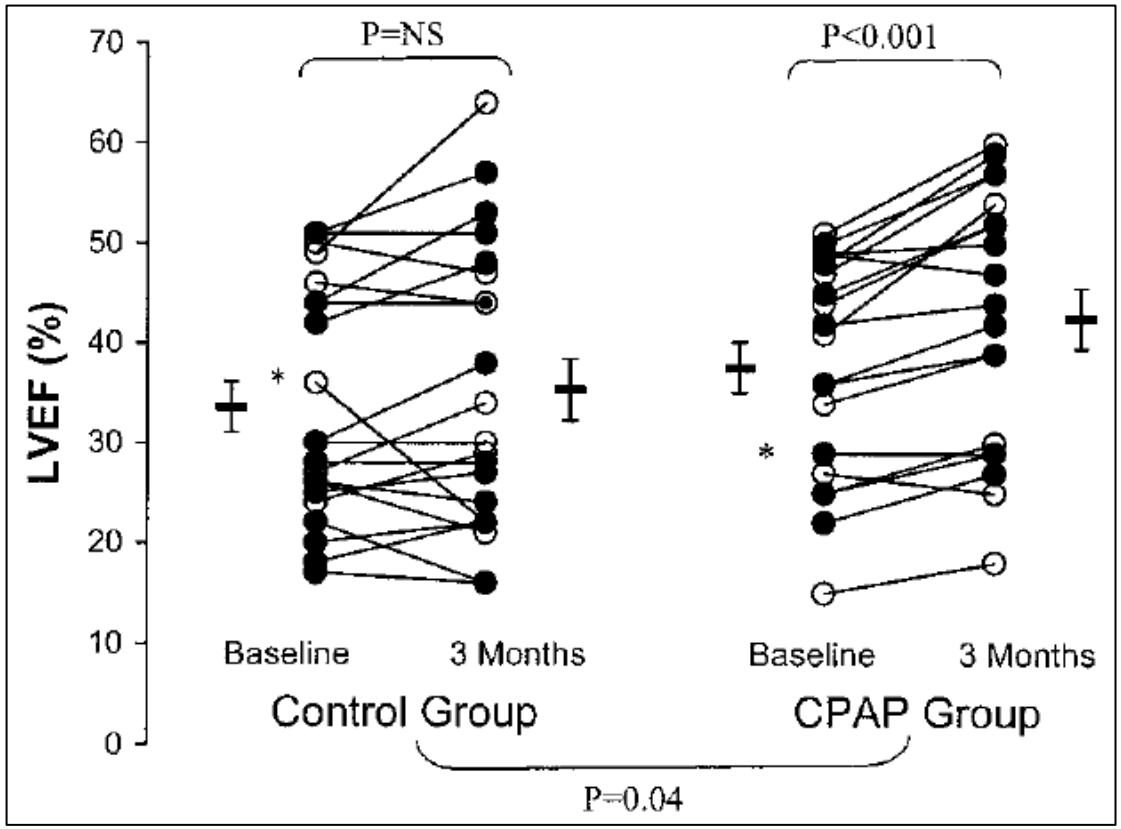
Trial	No. of patients	NYHA	Rx Duration	ΔLVEDD/V	ΔLVESD/V	ΔLVEF	ΔMR
MUSTIC [82]	34	III	12 mo.	↓−14% (D)	↓−18% (D)	–	↓−27%
MIRACLE-ICD [83]	369	III–IV	6 mo.	↓−6.2% (V)	–	↑+2.1%	↓−7.3%
CARE-HF [83]	813	III–IV	18 mo.	–	↓−21% (V)	↑+6.9%	↓−20%
REVERSE [84,85]	287	I–II	24 mo.	↓−30% (V)	↓−15% (V)	↑+3.8%	–
MADIT-CRT [86]	1820	I–II	2.4 yr.	↓−21% (V)	↓−35% (V)	↑+11%	–

MUSTIC, Multisite Stimulation in Cardiomyopathies; MIRACLE-ICD, Multicenter InSync ICD Randomized Clinical Evaluation; CARE-HF, Cardiac Resynchronization in HF; REVERSE, Resynchronization Reverses Remodeling in Systolic LV Dysfunction; MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy; ΔLVEDD/V, change in left ventricular end-diastolic diameter (D) or volume (V); ΔLVESD/V, change in left ventricular end-systolic diameter (D) or volume (V); ΔLVEF, change in left ventricular ejection fraction; ΔMR, change in mitral regurgitation grade.

Circulation 2003;107:28-31.
Cardiovasc Ther 2012;30:172-181.

Continuous positive airway pressure (CPAP)

CPAP for 3 months improved ventricular function and reduced sympathetic activity in patients with OSA and HF.



Am J Respir Crit Care Med 2004;169:361-6.

Surgical therapy

Batista procedure (partial left ventriculectomy)

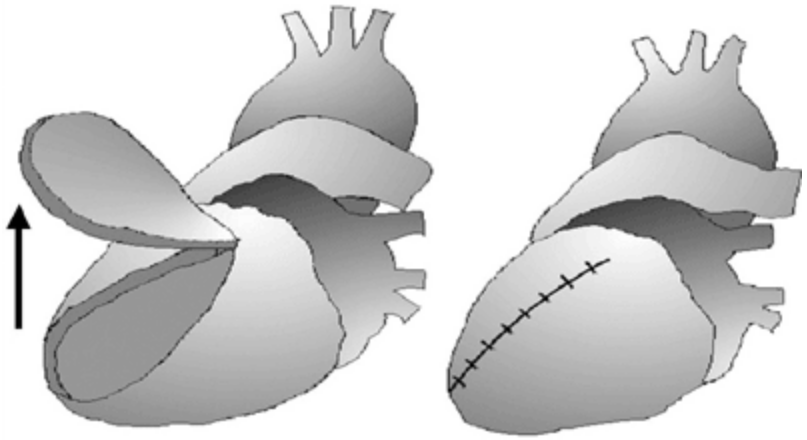


Fig. 1 – Partial left ventriculectomy

- Restoration of a normal ratio between wall thickness and the radius of the LV, to normalize systolic wall stress
- High perioperative mortality
- Outcome in terms of clinical improvement is impredictable

J Card Surg 1996;11:96-7.

Surgical therapy

Mitral annuloplasty at the time of CABG brought greater decreases in LV dimensions and increases in LVEF.

	Before surgery	End of CPB	1 week	3±0.5 months	13±7 months[a]	*P*-value
Total pts, *n*	38	38	38	38	34	-
Total deaths, *n*	-	-	1	3	5	-
Survival, %	-	100	97	92	85	-
NYHA	3.3±0.6	-	-	1.8±0.6	1.5±0.6	<0.001
MR, grade	3.6±0.5	0.4±0.4	0.5±0.5	0.6±0.6	0.6±0.8	<0.001
LVEDD, mm	60±7	-	57±8	57±8	57±8	<0.001
LVESD, mm	47±9	-	44±10	43±10	42±9	<0.001
FS, %	23±9	-	24±8	26±8	28±10	<0.001
LA, mm	51±5	-	48±5	46±4	45±4	<0.001
LVEDV, ml	188±33	-	173±36	172±35	171±30	<0.001
LVESD, ml	129±35	-	117±34	112±37	105±33	<0.001
EF, %	31±8	-	33±8	36±10	39±10	<0.001
LCH, mm	-	8±1	8±1	8±2	8±2	ns
MVA, cm^2		2.6±0.5	26±0.5	-	-	ns

CPB, cardiopulmonary bypass; NYHA, New York Heart Association; MR, mitral regurgitation; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; FS, fractional shortening; LA, left atrium; LCH, leaflet coaptation height; MVA, mitral valve area

[a] Still missing: $n=4$ patients [11%].

Eur J Cardiothoracic Surg 2005;27:1011-1016.

BEYOND REVERSE CARDIAC REMODELING

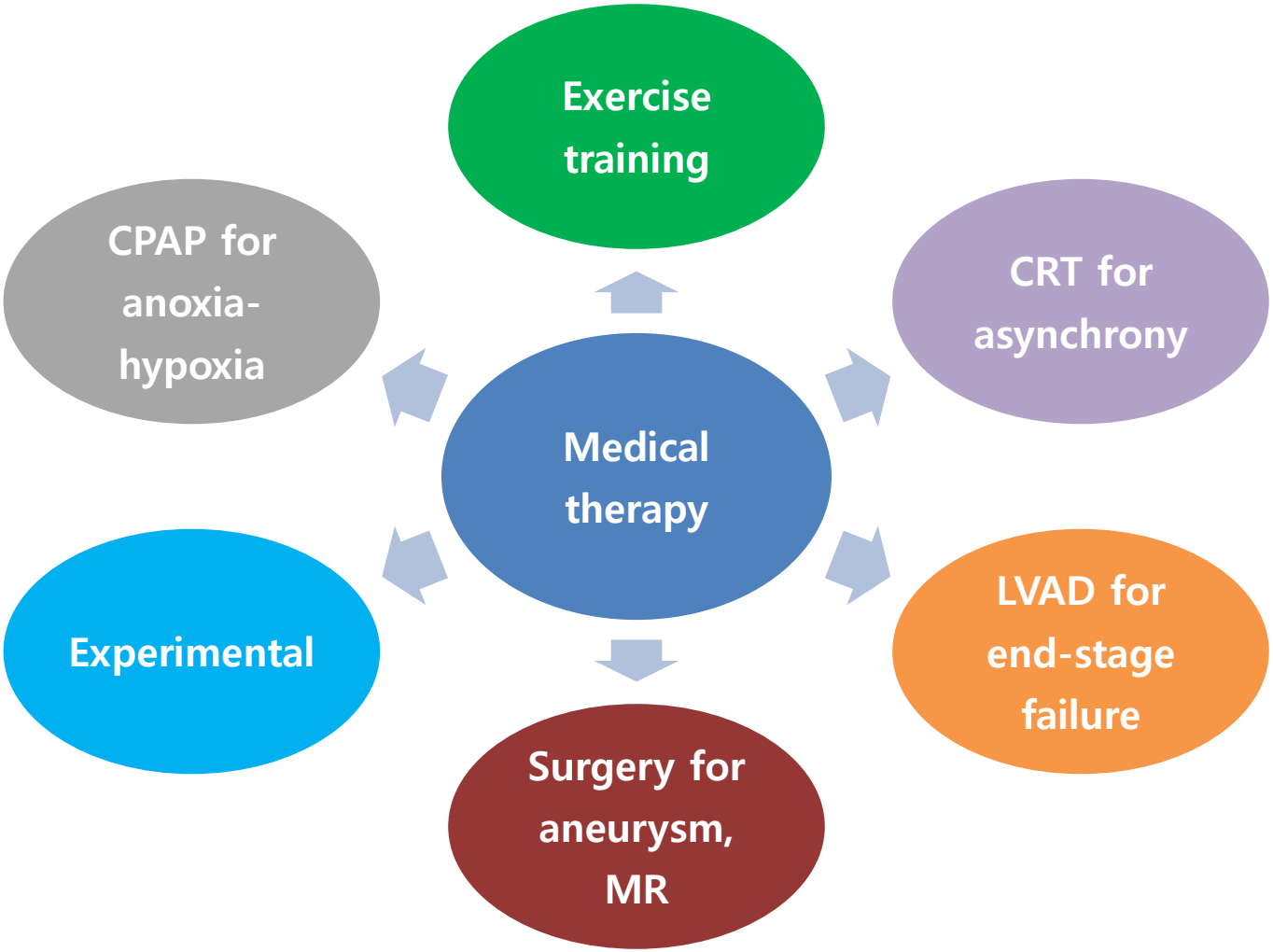
Determinants of reverse remodeling

COMPONENT	ACE INHIBITOR	BETA BLOCKING AGENT	LVAD	CSD
Myocyte Defects				
Hypertrophy	Decreased	Decreased	Decreased	Decreased
Myocytolysis	ND	Decreased	Decreased	ND
Excitation-contraction coupling	Increased	Increased	Increased	Increased
Fetal gene expression	Decreased	Decreased	Decreased	Decreased
Beta-adrenergic desensitization	Decreased	Decreased	Decreased	Decreased
Cytoskeletal proteins	ND	ND	Increased	ND
Myocyte contractility	ND	Increased	Increased	Increased
Myocardial Defects				
Myocyte necrosis	Decreased	Decreased	Decreased	ND
Myocyte apoptosis	Decreased	Decreased	Decreased	Decreased
MMP activation	Decreased	Increased	Decreased	Decreased
Fibrosis	Decreased	Decreased	Increased	Decreased
Other				
LV volume	Stabilized	Decreased	Decreased	Decreased

CSD = cardiac support device; LVAD = left ventricular assist device; ND = not done.

Braunwald's heart disease, 10th edition

Multimodal therapeutical possibilities



Eur Heart J 2004;6:D66-D78.

Reverse remodeling
➔ myocardial recovery?

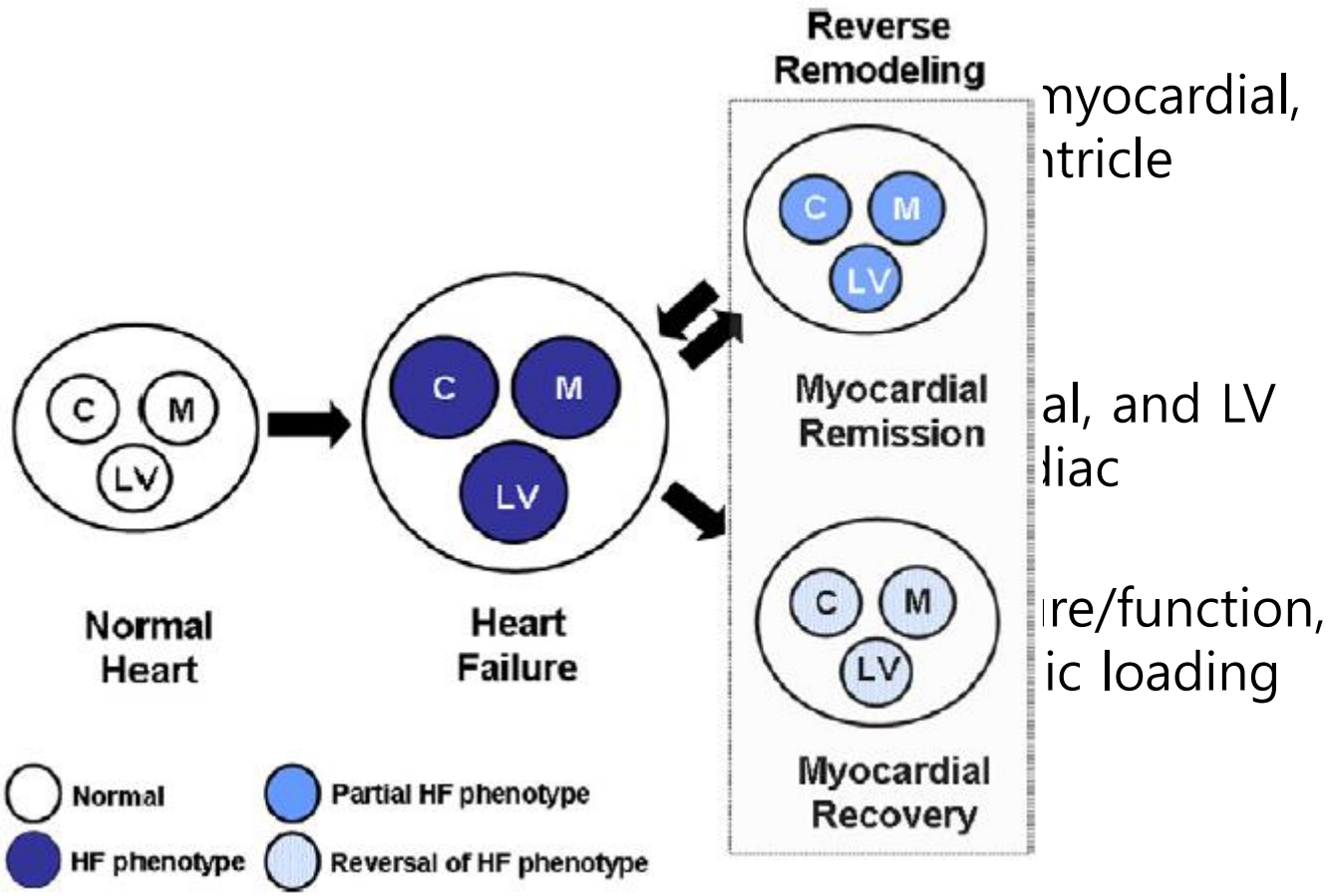
Hemodynamic unloading and reverse remodeling only **rarely** result in myocardial recovery.

Study, Year(s)	Design	N	Adjuvant Antiremodeling Drug Protocol	Protocol for Monitoring Cardiac Function	Unloading Duration, Months	Recovery, n (%)		HF Recurrence/Follow-Up
						Overall	Nonischemic	
U.S multicenter, 2007	P	67	Not standardized	Yes	4.5	6 (9)	5 (13.5)	Freedom from death or Tx 100%/6 months
Berlin group, 2008, 2010–2012, 2010	R	188	Not standardized	Yes	4.3	35 (18.6)	35 (18.6)	Freedom from recurrent HF 74% and 66%/3 and 5 yrs, respectively
Harefield group, 2006	P	15	Yes	Yes	10.6	11 (73)	11 (73)	Freedom from recurrent HF 100% and 89%/1 and 4 yrs, respectively
Harefield group, 2011	P	20	Yes	Yes	9.5	12 (60)	12 (60)	Freedom from recurrent HF 83.3%/3 yrs
University of Athens-Harefield group, 2007	P	8	Yes	Yes	6–10	4* (50)	4* (50)	Freedom from recurrent HF 100%/2 yrs
Gothenburg group, 2006	P	18	Not standardized	Yes	6.7	3 (17)	3 (20)	Freedom from recurrent HF or Tx 33%/8 yrs
Pittsburgh group, 2003	R	18	Not standardized	Yes	7.8	6 (33)	5 (38)	Freedom from recurrent HF 67%/1 yr
Osaka group, 2005	R	11	Not standardized	N/A	15.1	5 (45)	5 (45)	Freedom from recurrent HR 100%/8–29 months
Pittsburgh group, 2010	R	102	N/A	N/A	4.9	14 (13.7)	14 (13.7)	Freedom from recurrent HF or death 71.4%/5 yrs
Multicenter, 2001	R	271	N/A	N/A	1.9	22 (8.1)	22 (8.1)	Freedom from recurrent HF or death 77%/3.2 yrs
Columbia group, 1998	R	111	N/A	N/A	6.2	5 (4.5)	4 (8)	Freedom from recurrent HF or death 20%/15 months

J Am Coll Cardiol 2010;56:392-406

Reverse remodeling & recovery

- **Reverse**
  - The bi… myocardial, and ar… ntricle
- **Myocar…**
  - Norma… al, and LV geome… diac remod…
  - Allows … re/function, in the … ic loading condit…



J Am Coll Cardiol 2010;56:392-406

Reverse remodeling **does not** lead to a normal heart

- **Gene expression profiling studies**
  - Only ~5% of dysregulated genes revert appreciably to normal after LVAD support, despite typical morphological and functional responses to LVAD support

- **Force generation**
  - Still less than nonfailing heart, although maximal Ca^{2+}-saturated force generation is improved after LVAD support

Circ Heart Fail 2011;4:224-33
Circulation 2001;104:I229-32
N Engl J Med 2006;355:1873-84

Reverse remodeling **does not** lead to a normal heart

- **Extracellular matrix (ECM)**
  - 3D organization and interactions of ECM with other cardiac structures are not essentially normalized
  - Chamber radius to wall thick ratio remains elevated (nearly twice normal)

- **Normalization after LVAD**
  - EDPVRs are shifted leftward after LVAD support
  - However, LV wall thickness/LV wall radius ratio does not return to normal

    ➔ myocardium is still exposed to physiological stress

Eur Heart J 2007;28:613-27.

Reverse remodeling **does not** lead to a normal heart

The regression of the heart failure phenotype and the accompanying return toward a more normal cardiac phenotype during reverse remodeling

DOES NOT

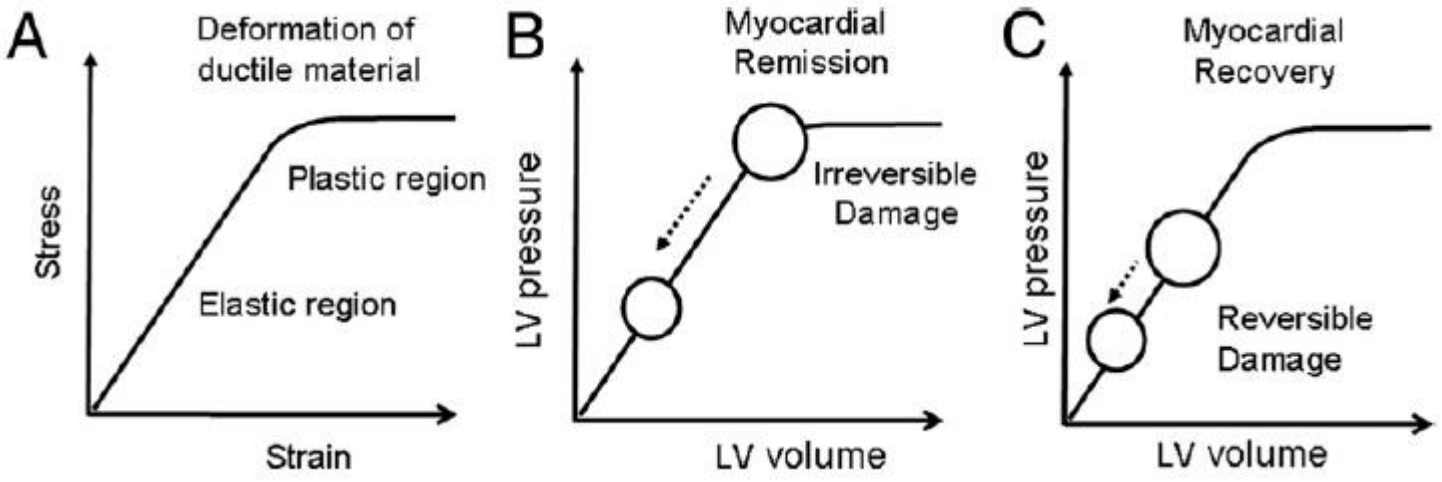
Signify that the cellular/molecular biology and physiology of these hearts is normal.

J Am Coll Cardiol 2012;60:2465-72.

Stress vs. strain diagram

Reversal of the heart failure phenotype in hearts that have…

Sustained irreversible damage	• Long-standing injury (infarction, gene abnormalities…) • Irreversible changes at the DNA level and 3D-organization of the ECM	**Remission (B)**
Reversible damage	• Transient injury (viral infection, inflammation, toxic injury…)	**Recovery (C)**



J Am Coll Cardiol 2010;56:392-406

We still do not understand…

Reverse cardiac remodeling : A hard way to go

Lack of understanding of the biology

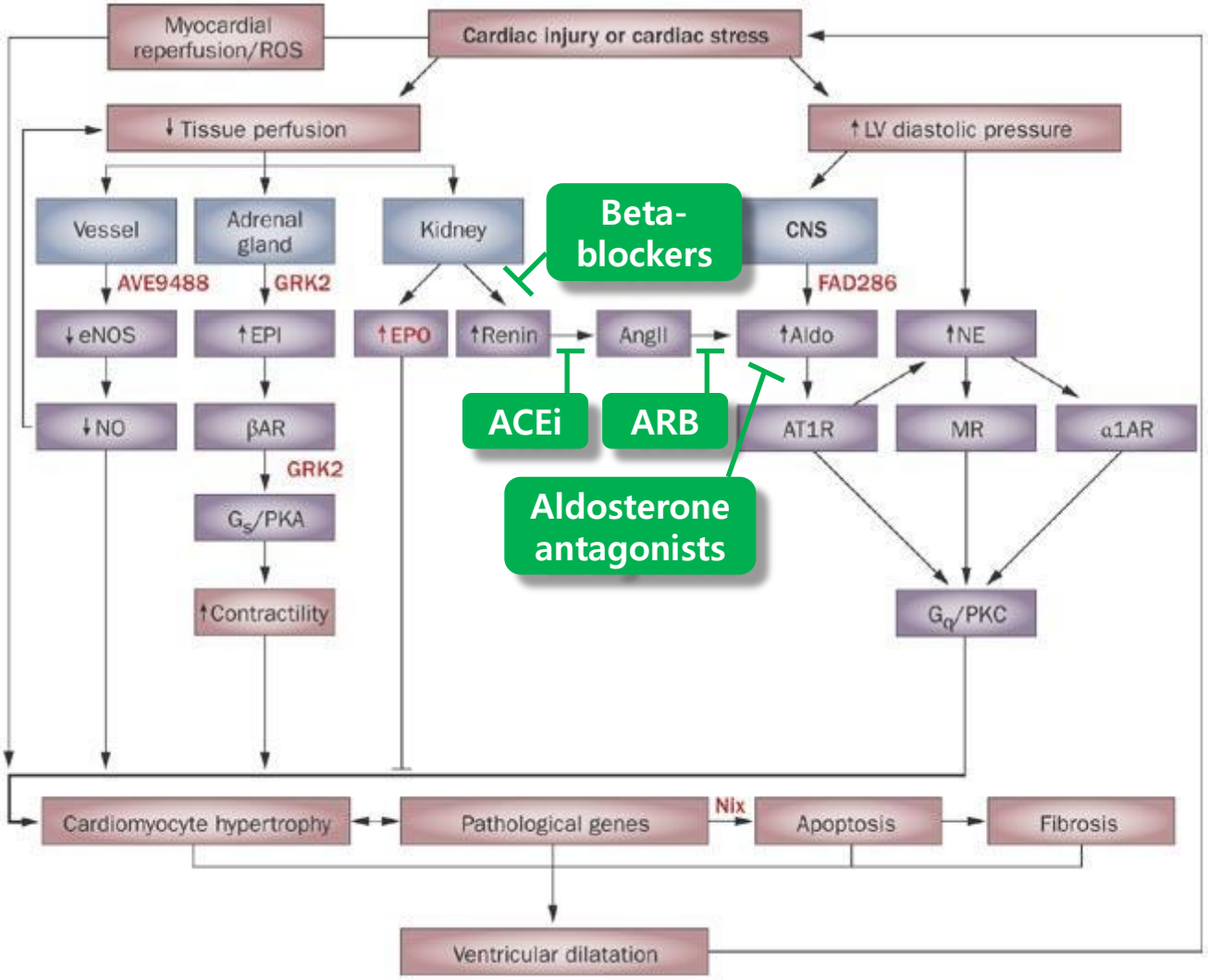
Disparate outcomes of remodeling

Need for multidisciplinary study

Multiple underlying etiology

Thanks for your attention !!

Molecular targets



Nature Reviews Cardiology 2009;6:283-291