



Mysterious Reverse Left Ventricular Remodeling Despite Suboptimal Medical Therapy: A Case Report

Dr I. AZDAY¹, Dr K. ZRIGUI², Dr L. EL MRINI³, Dr Z. NADHIL⁴, Pr N. FELLAT⁵

^{1,2,3,4,5}Cardiology A Department, Ibn Sina University Hospital Center, Rabat, Morocco.

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ABSTRACT

Left ventricular reverse remodeling is an important feature of recovery in heart failure, usually associated with appropriate medical or device-based therapy. We report an unusual case of marked reverse remodeling despite suboptimal medical treatment. A 72-year-old woman presented with epigastric pain and NYHA class III exertional dyspnea. Electrocardiography showed sinus rhythm with complete left bundle branch block. Echocardiography revealed a dilated left ventricle, regional wall-motion abnormalities, and reduced ejection fraction of 36%. Coronary angiography demonstrated a severe distal left anterior descending artery lesion, while viability assessment showed no viability in the corresponding territory. Because of hyperkalemia and impaired renal function, medical treatment was limited, and the patient was discharged on calcium-channel blocker and single antiplatelet therapy. One year later, she was asymptomatic, and echocardiography demonstrated normalized ventricular dimensions without dykinetic abnormalities and recovery of ejection fraction to 62%. This unexpected improvement highlights the complex and incompletely understood mechanisms underlying reverse cardiac remodeling.

Corresponding Author:
Dr I. AZDAY

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INTRODUCTION

Heart failure (HF) is the incapacity of the heart to provide an adequate blood flow or pressure to the body or a combination of both. HF remains the leading cause of death in the world despite the numerous advances in its treatment as the number of patients suffering from advanced HF is far more important than the number of available hearts for transplantation. (1) The complex and feared consequence of HF is the “cardiac remodeling”, it is defined as maladaptive and progressive changes on the molecular, cellular, tissue and whole human body levels. (2) (3)

In order to suppress it or ideally “reverse remodeling”, it is necessary to target the signaling pathways that are involved in their generation. (4)

This clinical case describes a spectacular reverse remodeling of the heart without an optimal medical treatment.

CASE PRESENTATION

A 72-year-old woman presented to our Cardiology department epigastric pain and exertional dyspnea III NYHA

for the last 10 days. She has multiple Cardiac risk factors such as age, menopause, hypertension and dyslipidemia. Her EKG found a sinus rhythm with a heart rate at 70 beats per minute, a complete left bundle branch block with secondary repolarization disorders (without Sgarbossa criteria: total score: 0).

Her blood count exam was normal; we found a hyperkalemia and an altered renal function (glomerular filtration rate at 49 ml/min/m³). We had trouble treating her hyperkalemia and ended up treating it few days later with the help of our colleagues from the nephrology department.

The patient underwent first a trans-thoracic echocardiography (TTE), that showed a dilated left ventricle with a diastolic diameter at 60 mm, a systolic diameter at 50 mm, associated with segmental wall abnormalities specially akinesia of apex and adjacent segments and hypokinesia of the remaining myocardial segments in the context of a reduced ejection fraction (EF) at 36 %. (Figure 1)

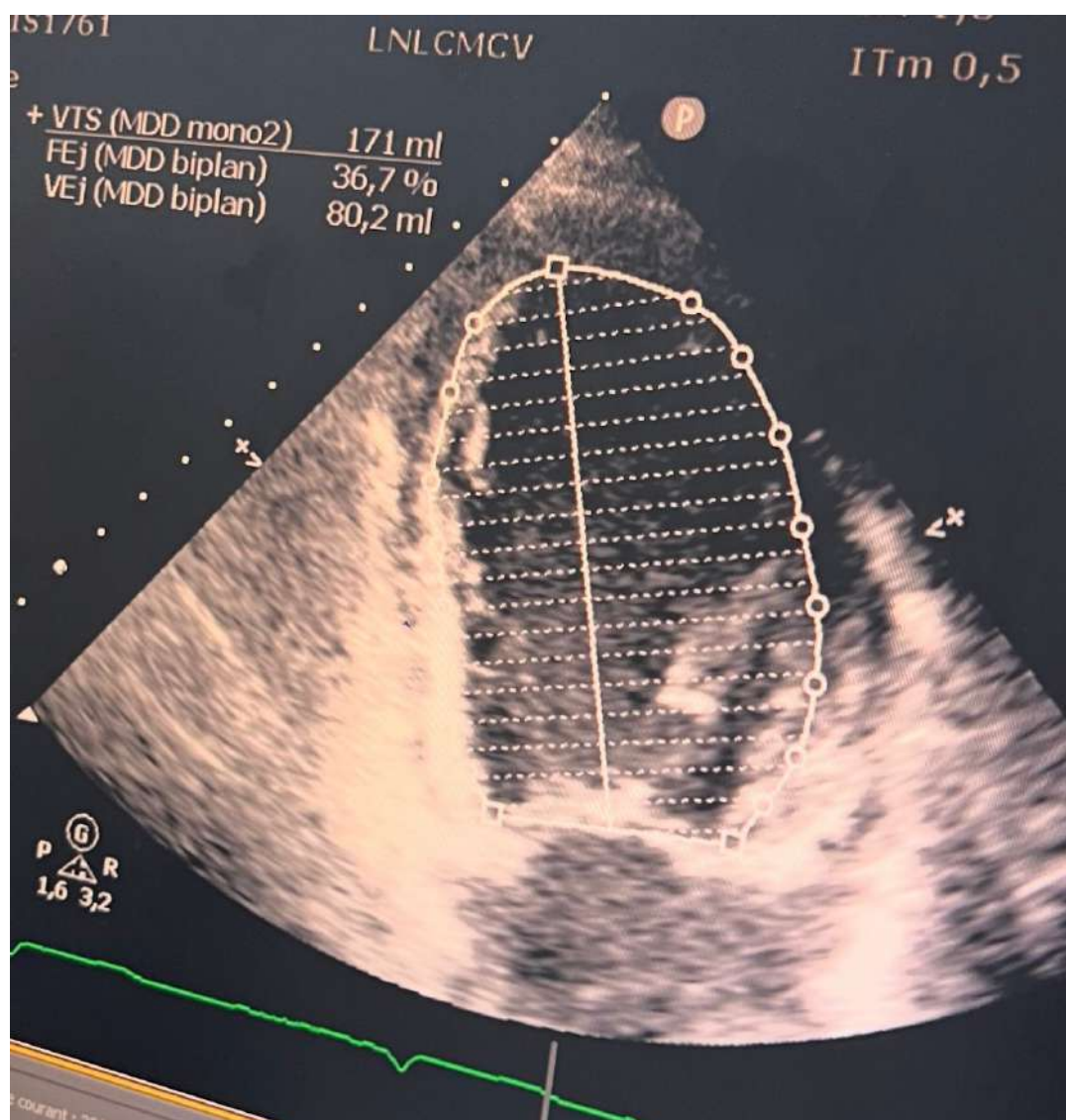


Figure 1 : TTE showing a reduced LV EF at 36%.

The next step after treating her hyperkalemia and prepping her was to do a coronary angiogram that concluded to a severe

lesion of the left anterior descending artery (LAD) at its distal portion. (Figure 2)

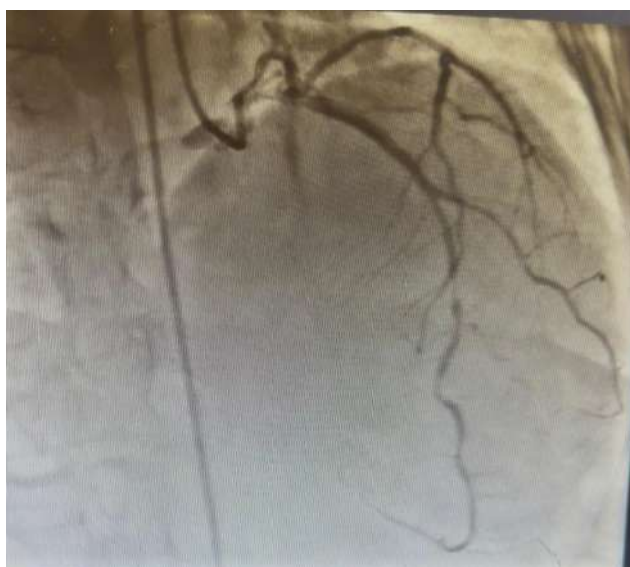


Figure 2 : A coronary angiography showing a severe lesion of the distal LAD.

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As we had akinetic territories in the TTE, we completed with a cardiac viability ultrasound that didn't find viability on the LAD territory.

We put the patient under medical treatment as we were limited with hyperkalemia: the patient left our department under calcium Channel blockers (CCB) and a single anti platelet therapy.

We lost contact with the patient before receiving her in our cardiology consult one year later.

She had no cardio-vascular symptoms, her clinical examination was normal.

We did a TTE that showed a non-dilated LV with a diastolic diameter at 40 mm, a systolic diameter at 29 mm without any dyskinetic disorders and a preserved EF (62 %). (Figure 3)

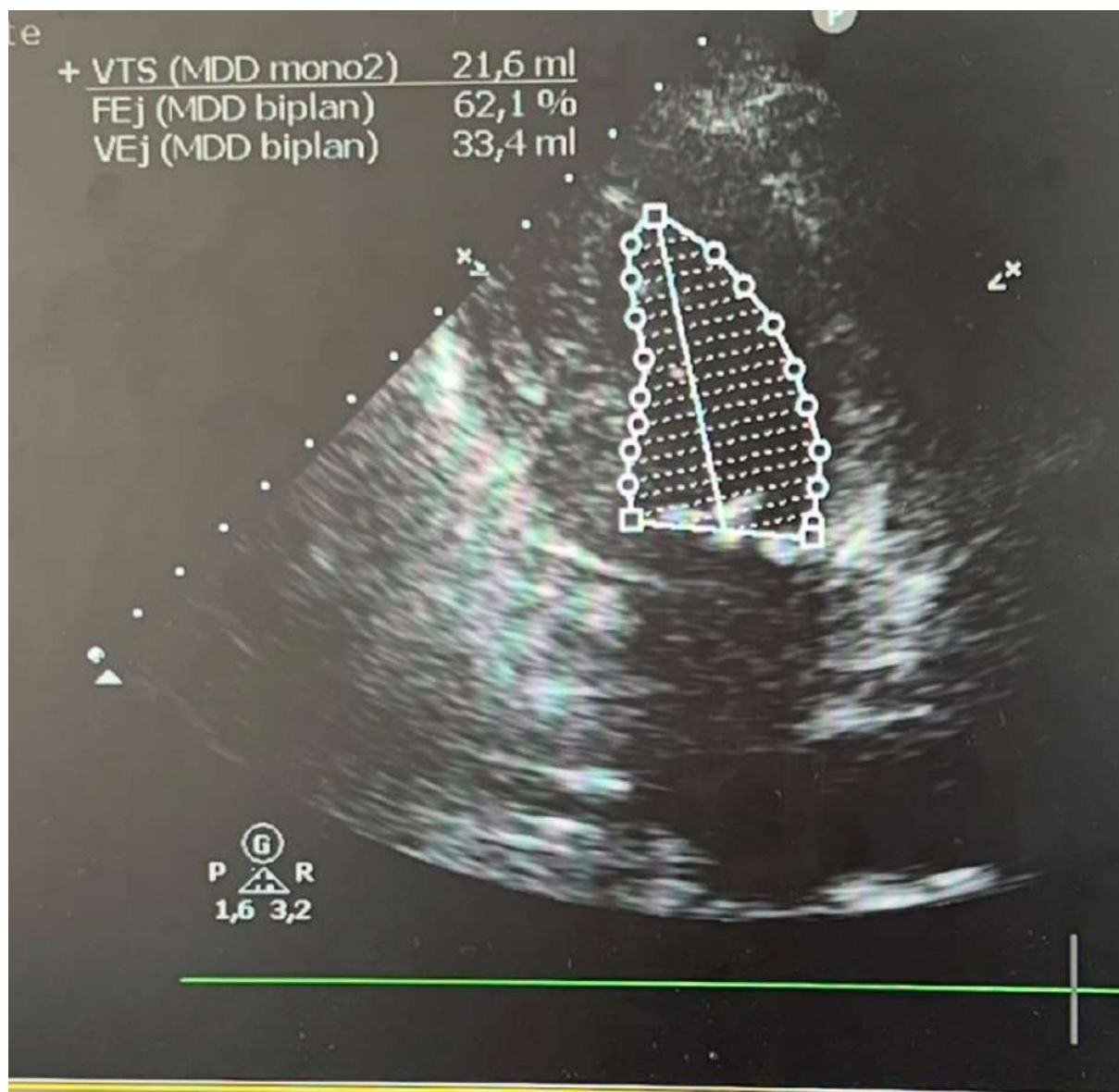


Figure 3: TTE after non optimal medical treatment showing a preserved EF of 62%.

DISCUSSION

LV remodeling became popular in the mid 1980, when the landmark study documented a progressive LV dilatation and reduced function after a coronary occlusion.(5)

At first the term was used to define the anatomical changes, then it was used to define any alteration due to HF or any other cardiac disease that involves LV hypertrophy, LV dilatation or both. The cellular remodeling is caused by molecular modifications that result in fetal gene expression and compromise the excitation-contraction coupling,

myofilament function, cell-survival signaling, bioenergetics and the cellular metabolic state. (2)

Besides the cardiomyocytes remodeling, remodeling of the extracellular matrix (ECM) is important in the deforming of the cardiac chamber and the alteration of fibrous and vascular elements of the myocardium. Chamber dilatation is usually associated to a more spherical shape of the ventricle reducing the efficiency of ejection as the cardiomyocytes need to shorten in order to achieve the same ejected net volume. Cardiac hypertrophy was traditionally considered as an adaptive mechanism but this idea is now increasingly queried

.the idea that if the stimulus for hypertrophy is pathologic, the remodeling response is pathological and its suppression is beneficial. It has been supported by clinical and experimental data.(6)

Animal studies involving the subject proved that pathological stress induces different molecular changes than a matched duration of physical exercise. Therefore the response to pathological stress is never truly adaptative. (7)

This notion was supported by trials in humans where it was proven that the antihypertensive agents responsible of reducing the LV mass, lower the mortality.(8)

There is a growing sentiment and accumulating evidence that many of the maladaptive responses caused by HF can and should be targeted. (9)

“Reverse remodeling “ was first presented in study about cardiac myoplasty.(10)

In this study the latissimus dorsi muscle (back muscle) was used to envelop the heart and paced synchronously with the ventricular systole in order to evaluate the systolic function. Pressure and volume data at various times after surgery showed that the heart had shrunk towards the normal size. As a result the term “ reverse remodeling” became associated with any alteration in HF that was chronically reversed by therapy.(11) (12)

In addition to hemodynamic stress, sustained angiotensin releases due to an activation of the renin-angiotensin-aldosterone system can worsen cardiac fibrosis, cellular necrosis and cause cardiomyocyte hypertrophy.(13)

Many therapies can participate in the mechanism of “reverse remodeling.

The first treatment shown to reverse cardiac remodeling by targeting this pathway were angiotensin-converting enzyme (ACE). (14)

Same effects were observed with angiotensin-receptor -blockers (ARBs) with two subtypes (AT1R and AT2R) with a controversial role of AT2R in the myocardium and the benefit of using dual angiotensin-receptor -blockers remains unclear. (15) (16) (17) (18) (19) (20)

Both ACE and ARBs increase NO production and reduce LV mass. (21) (22)

In failing human hearts, the aldosterone receptor is upregulated. (23)

So its blockade by using aldosterone antagonist (like eplerenone or spironolactone), reduce fibrosis, improves cardiac function and increase the impact of ACE on LV remodeling.(24)

A randomized trial of eplerenone in patients with mild to moderate HF didn’t show reverse remodeling 9 months after treatment when another randomized trial in patients with LV dysfunction after myocardial infarction, eplerenone did improve patients outcomes. Thus, further investigation are needed.(25) (26) (27)

The fact that the prolonged stimulation of B- adrenergic receptors (B-Ars) induce myocellular toxicity, dilatation and

systolic dysfunction when the B1-AR is overexpressed, plus the fact that high levels of catecholamine are not only a marker of HF but rather a direct contributor. All of this has led to investigate the benefit of B-AR blockade in HF patients that is now considered to be the second class of therapy involved in “reverse remodeling”. (28) (29) (30) (31)

The exact mechanism of B-AR blockade that lead to a beneficial effect on reverse remodeling is still unknown but it seems like it involved B-AR function, myocardial energy utilization and calcium handling. (32) (33) (34)

Patients with HF often have a delay in electrical conduction leading to a dyssynchrony of the heart. Whether this delay is defined by QRS duration or echocardiography dyssynchrony, it is an independent predictor of increased mortality in patients with HF.(36)

Some animal studies revealed that LV dyssynchrony involve regional variations in myocyte hypertrophy, blood flow and oxygen consumption. (37)

Cardiac resynchronization therapy (CRT) in which biventricular stimulations is applied was developed to counter this pathophysiology. It improves net systolic function without affecting diastolic volume.(38)

Studies of benefit of CRT in HF showed that it triggers potent changes in cell-survival signaling (involving the kinase Akt) , upregulates B-adrenergic responses and normalizes ion-channel function. (41) (42)

Another alternative that is quite successful is LV assist devices (LVADs) usually used as a bridge before cardiac-transplantation but in cases of responsive patients LVADs can be used as a destination therapy. Studies showed that the size of myocytes decreases in the LV but not in the right ventricle (RV) proving that this change is a result of the mechanical unloading of the LV and not a neurohormonal modulation. (43) (44) (45)

Although LVADs have also an impact on the neurohormonal system as they restore the heart rate, contractile reserve, increases B-AR density on cardio-myocytes and improve calcium response to catecholamine stimulation.(11) (12)

LVADs implantation according to one histological analysis increase cardiac microvascular density and fibrosis. (46)

Some nuclear changes were noticed in the “reverse remodeling “ implying that cardiac regeneration is a part of the remodeling mechanism after LVADs implantation.(47)

Lately focus in term of reverse cardiac remodeling has shifted into cell based therapies .This cells offer to replace the damaged or lost myocytes .For example intracoronary administration of bone-marrow derived cells improves cardiac ejection fraction .They have proven their efficacy in reducing LV end-systolic volume but not end-diastolic volume .The mechanism by which stem cells improve Systolic function of the LV remains uncertain but the role of paracrine signaling is highly suspected .(48) (49) (50) (51)

It has been reported by the vasodilator heart failure Trial (V-HeFT) investigators that, combination of vasodilatory

medication (hydralazine +isosorbide dinitrate) leads to an increase in ejection fraction and survival rate. The HeFT II showed better result with only enalapril. (52) (53) (54) (55) Since reverse remodeling include a stable decline in chamber volumes, the surgical removal of LV muscle (ventriculectomy) with a reconstruction was proposed in 1990s but with an important rate of failures and recurrence of HF .(56)(57)

Some therapies didn't improve LV remodeling and made in some cases the clinical outcome even worse: Calcium-antagonists, Statins, TNF inhibitors, Renin-Inhibitors and endothelin-inhibitors. (58) (59) (60)

As one can confirm the last decades have been dedicated to targeting cells via extracellular ligand-receptor interactions in matter of HF medical therapy but the focus in future will move toward manipulating intracellular signaling pathways with a large list of potential targets.

CONCLUSION

As years pass by new proteins, protein-protein interactions or signaling pathways are revealed to have a major role in “reverse remodeling”.Some therapies targeting these changes prove their efficacy others don't.But the progress most go on and this complex topic won't be closed anytime soon.Many experts are dedicated to finding an explanation of the “reverse remodeling” but a gray area persists and there are cases that remains mysterious like the one that we report.

REFERENCES

1. Lloyd-Jones, D. *et al.* Heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation* 121, e46–e215 (2010).
2. Kehat, I. & Molkentin, J. D. Molecular pathways underlying cardiac remodeling during pathophysiological stimulation. *Circulation* 122, 2727–2735 (2010).
3. Cohn, J. N., Ferrari, R. & Sharpe, N. Cardiac remodeling—concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. *J. Am. Coll. Cardiol.* 35, 569–582 (2000).
4. Mudd, J. O. & Kass, D. A. Reversing chronic remodeling in heart failure. *Expert Rev. Cardiovasc. Ther.* 5, 585–598 (2007).
5. Pfeffer, J. M., Pfeffer, M. A. & Braunwald, E. Influence of chronic captopril therapy on the infarcted left ventricle of the rat. *Circ. Res.* 57, 84–95 (1985).
6. Esposito, G. *et al.* Genetic alterations that inhibit *in vivo* pressure-overload hypertrophy prevent cardiac dysfunction despite increased wall stress. *Circulation* 105, 85–92 (2002).
7. Perrino, C. *et al.* Intermittent pressure overload triggers hypertrophy-independent cardiac dysfunction and vascular rarefaction. *J. Clin. Invest.* 116, 1547–1560 (2006).
8. Devereux, R. B. *et al.* Regression of hypertensive left ventricular hypertrophy by losartan compared with atenolol: the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial. *Circulation* 110, 1456–1462 (2004).
9. Mudd, J. O. & Kass, D. A. Tackling heart failure in the twenty-first century. *Nature* 451, 919–928 (2008).
10. Kass, D. A. *et al.* Reverse remodeling from cardiomyoplasty in human heart failure. External constraint versus active assist. *Circulation* 91, 2314–2318 (1995).
11. Klotz, S. *et al.* Left ventricular assist device support normalizes left and right ventricular beta-adrenergic pathway properties. *J. Am. Coll. Cardiol.* 45, 668–676 (2005).
12. DiPlato, K., Mattiello, J. A., Jeevanandam, V., Houser, S. R. & Margulies, K. B. Myocyte recovery after mechanical circulatory support in humans with end-stage heart failure. *Circulation* 97, 2316–2322 (1998).
13. Gray, M. O., Long, C. S., Kalinyak, J. E., Li, H. T. & Karliner, J. S. Angiotensin II stimulates cardiac myocyte hypertrophy via paracrine release of TGF- β 1 and endothelin-1 from fibroblasts. *Cardiovasc. Res.* 40, 352–363 (1998).
14. Sharpe, N. *et al.* Early prevention of left ventricular dysfunction after myocardial infarction with angiotensin-converting-enzyme inhibition. *Lancet* 337, 872–876 (1991).
15. Sharpe, N. *et al.* Early prevention of left ventricular dysfunction after myocardial infarction with angiotensin-converting-enzyme inhibition. *Lancet* 337, 872–876 (1991).
16. Granger, C. B. *et al.* Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 362, 772–776 (2003).
17. Sadoshima, J., Qiu, Z., Morgan, J. P. & Izumo, S. Angiotensin II and other hypertrophic stimuli mediated by G protein-coupled receptors activate tyrosine kinase, mitogen-activated protein kinase, and 90-kD S6 kinase in cardiac myocytes. The critical role of Ca²⁺-dependent signaling. *Circ. Res.* 76, 1–15 (1995).
18. Habashi, J. P. *et al.* Angiotensin II type 2 receptor signaling attenuates aortic aneurysm in mice through ERK antagonism. *Science* 332, 361–365 (2011).

19. Avila, M. D., Morgan, J. P. & Yan, X. Genetically modified mouse models used for studying the role of the AT2 receptor in cardiac hypertrophy and heart failure. *J. Biomed. Biotechnol.* 2011, 141039 (2011).
20. Solomon, S. D. *et al.* Changes in ventricular size and function in patients treated with valsartan, captopril, or both after myocardial infarction. *Circulation* 111, 3411–3419 (2005).
21. Lonn, E. *et al.* Effects of ramipril on left ventricular mass and function in cardiovascular patients with controlled blood pressure and with preserved left ventricular ejection fraction: a substudy of the Heart Outcomes Prevention Evaluation (HOPE) Trial. *J. Am. Coll. Cardiol.* 43, 2200–2206 (2004).
22. Ciulla, M. M. *et al.* Different effects of antihypertensive therapies based on losartan or atenolol on ultrasound and biochemical markers of myocardial fibrosis: results of a randomized trial. *Circulation* 110, 552–557 (2004).
23. Yoshida, M. *et al.* Mineralocorticoid receptor is overexpressed in cardiomyocytes of patients with congestive heart failure. *Congest. Heart Fail.* 11, 12–16 (2005).
24. Brilla, C. G., Zhou, G., Matsubara, L. & Weber, K. T. Collagen metabolism in cultured adult rat cardiac fibroblasts: response to angiotensin II and aldosterone. *J. Mol. Cell Cardiol.* 26, 809–820 (1994).
25. Hayashi, M. *et al.* Immediate administration of mineralocorticoid receptor antagonist spironolactone prevents post-infarct left ventricular remodeling associated with suppression of a marker of myocardial collagen synthesis in patients with first anterior acute myocardial infarction. *Circulation* 107, 2559–2565 (2003).
26. Udelson, J. E. *et al.* Randomized, double-blind, multicenter, placebo-controlled study evaluating the effect of aldosterone antagonism with eplerenone on ventricular remodeling in patients with mild-to-moderate heart failure and left ventricular systolic dysfunction. *Circ. Heart Fail.* 3, 347–353 (2010).
27. Pitt, B. *et al.* Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N. Engl. J. Med.* 348, 1309–1321 (2003).
28. Mann, D. L., Kent, R. L., Parsons, B. & Cooper, G. 4th. Adrenergic effects on the biology of the adult mammalian cardiocyte. *Circulation* 85, 790–804 (1992).
29. Engelhardt, S., Hein, L., Wiesmann, F. & Lohse, M. J. Progressive hypertrophy and heart failure in β_1 -adrenergic receptor transgenic mice. *Proc. Natl Acad. Sci. USA* 96, 7059–7064 (1999).
30. Lowes, B. D. *et al.* Myocardial gene expression in dilated cardiomyopathy treated with beta- blocking agents. *N. Engl. J. Med.* 346, 1357–1365 (2002).
31. Reiken, S. *et al.* Beta-blockers restore calcium release channel function and improve cardiac muscle performance in human heart failure. *Circulation* 107, 2459–2466 (2003).
32. Reiken, S. *et al.* Beta-blockers restore calcium release channel function and improve cardiac muscle performance in human heart failure. *Circulation* 107, 2459–2466 (2003).
33. Bohm, M., Deutsch, H. J., Hartmann, D., Rosee, K. L. & Stablein, A. Improvement of postreceptor events by metoprolol treatment in patients with chronic heart failure. *J. Am. Coll. Cardiol.* 30, 992–996 (1997).
34. Beanlands, R. S. *et al.* The effects of β_1 -blockade on oxidative metabolism and the metabolic cost of ventricular work in patients with left ventricular dysfunction: a double-blind, placebo-controlled, positron-emission tomography study. *Circulation* 102, 2070–2075 (2000).
35. Baldasseroni, S. *et al.* Left bundle-branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: a report from the Italian network on congestive heart failure. *Am. Heart J.* 143, 398–405 (2002).
36. van Oosterhout, M. F., Arts, T., Basingthwaight, J. B., Reneman, R. S. & Prinzen, F. W. Relation between local myocardial growth and blood flow during chronic ventricular pacing. *Cardiovasc. Res.* 53, 831–840 (2002).
37. Nelson, G. S. *et al.* Left ventricular or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left bundle-branch block. *Circulation* 102, 3053–3059 (2000).
38. Chakir, K. *et al.* G_{α_s} -biased β_2 -adrenergic receptor signaling from restoring synchronous contraction in the failing heart. *Sci. Transl. Med.* 3, 100ra88 (2011).
39. Aiba, T. *et al.* Electrophysiological consequences of dyssynchronous heart failure and its restoration by resynchronization therapy. *Circulation* 119, 1220–1230 (2009).
40. Chakir, K. *et al.* G_{α_s} -biased β_2 -adrenergic receptor signaling from restoring synchronous contraction in the failing heart. *Sci. Transl. Med.* 3, 100ra88 (2011).
41. Aiba, T. *et al.* Electrophysiological consequences of dyssynchronous heart failure and its restoration by resynchronization therapy. *Circulation* 119, 1220–1230 (2009).

42. Zafeiridis, A., Jeevanandam, V., Houser, S. R. & Margulies, K. B. Regression of cellular hypertrophy after left ventricular assist device support. *Circulation* 98, 656–662 (1998).
43. Delgado, R. 3rd, Radovancevic, B., Massin, E. K., Frazier, O. H. & Benedict, C. Neurohormonal changes after implantation of a left ventricular assist system. *ASAIO J.* 44, 299–302 (1998).
44. Barbone, A. *et al.* Comparison of right and left ventricular responses to left ventricular assist device support in patients with severe heart failure: a primary role of mechanical unloading
45. Drakos, S. G. *et al.* Impact of mechanical unloading on microvasculature and associated central remodeling features of the failing human heart. *J. Am. Coll. Cardiol.* 56, 382–391 (2010).
46. Wohlschlaeger, J. *et al.* Hemodynamic support by left ventricular assist devices reduces cardiomyocyte DNA content in the failing human heart. *Circulation* 121, 989–996 (2010).
47. Williams, A. R. *et al.* Intramyocardial stem cell injection in patients with ischemic cardiomyopathy: functional recovery and reverse remodeling. *Circ. Res.* 108, 792–796 (2011).
48. Lee, S. T. *et al.* Intramyocardial injection of autologous cardiospheres or cardiosphere-derived cells preserves function and minimizes adverse ventricular remodeling in pigs with heart failure post-myocardial infarction. *J. Am. Coll. Cardiol.* 57, 455–465 (2011).
49. Abdel-Latif, A. *et al.* Adult bone marrow-derived cells for cardiac repair: a systematic review and meta-analysis. *Arch. Intern. Med.* 167, 989–997 (2007).
50. Mirotsov, M., Jayawardena, T. M., Schneckpeper, J., Gnechchi, M. & Dzau, V. J. Paracrine mechanisms of stem cell reparative and regenerative actions in the heart. *J. Mol. Cell Cardiol.* 50, 280–289 (2011).
51. Münzel, T. *et al.* Hydralazine prevents nitroglycerin tolerance by inhibiting activation of a membrane-bound NADH oxidase. A new action for an old drug. *J. Clin. Invest.* 98, 1465–1470 (1996).
52. Cohn, J. N. *et al.* Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. *N. Engl. J. Med.* 314, 1547–1552 (1986).
53. Cohn, J. N. *et al.* A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N. Engl. J. Med.* 325, 303–310 (1991).
54. Taylor, A. L. *et al.* Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N. Engl. J. Med.* 351, 2049–2057 (2004).
55. Athanasuleas, C. L. *et al.* Surgical ventricular restoration in the treatment of congestive heart failure due to post-infarction ventricular dilation. *J. Am. Coll. Cardiol.* 44, 1439–1445 (2004).
56. Jones, R. H. *et al.* Coronary bypass surgery with or without surgical ventricular reconstruction. *N. Engl. J. Med.* 360, 1705–1717 (2009).
57. Krum, H. *et al.* Double-blind, randomized, placebo-controlled study of high-dose HMG CoA reductase inhibitor therapy on ventricular remodeling, pro-inflammatory cytokines and neurohormonal parameters in patients with chronic systolic heart failure. *J. Card. Fail.* 13, 1–7 (2007).
58. Udelson, J. E. *et al.* Effects of amlodipine on exercise tolerance, quality of life, and left ventricular function in patients with heart failure from left ventricular systolic dysfunction. *Am. Heart J.* 139, 503–510 (2000).
59. Kjekshus, J. *et al.* Rosuvastatin in older patients with systolic heart failure. *N. Engl. J. Med.* 357, 2248–2261 (2007)