CLINICAL INVESTIGATION

Pharmacological treatment of left ventricular remodeling: recent trial results

Ventricular remodeling, recently characterized as an inhomogeneous entity, has quickly become a therapeutic target. It is assumed that prevention of ventricle remodeling would stop the progression of heart failure. In this review we discuss briefly the issue of ventricular remodeling along with underlying mechanisms leading to cardiac hypertrophy and/or dilatation. Furthermore, we discuss the pharmacologic approaches to prevent left ventricle remodeling, either in animal studies or human trials.

Keywords: • animal studies• heart failure • human trials • ventricular remodeling

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Left ventricular dilatation, described as an early [1] and delayed postinfarction phenomenon [2], was named as remodeling later on [3], and eventually defined as cardiac remodeling during the International Forum on Cardiac Remodeling in Apr 1998 [4]. It is defined as genome expression, molecular, cellular and interstitial changes that are manifested clinically as changes in size, shape and function of the heart after cardiac injury [4]. In addition to myocardial infarction (MI) as the cause of ventricular remodeling, the following precipitating factors are recognized: physical exercise [5], pregnancy [6], volume overload (as in aortic valve or mitral valve regurgitation), pressure overload (as in hypertension), myocarditis, idiopathic dilated cardiomyopathy, some chemotherapeutic agents [7,8], diabetes [9–11] and right ventricle pacing [12–15].

The macroscopic alterations of increased left ventricle volume and more spherical configuration are related to variety of histological modifications at the level of myocyte (hypertrophy, apoptosis) and extracellular matrix (fibroblast proliferation, fibrosis). The heart and cardiomyocytes enlarge in response to injury or increased workload as a mean to reduce ventricular wall and septal stresses. From this point of view cardiac hypertrophy might be considered as adaptive and physiologic process, but when the inciting injury exists unabated, the positive remodeling might transform into pathologic remodeling with eccentric hypertrophy, decreased contractility and eventually an overt heart failure. Hypertrophy of noninfarcted segments of myocardium, in postinfarction period, is the mean to maintain stroke volume and cardiac output [16].

Physiological hypertrophy

Several patterns of cardiac remodeling can be distinguished macroscopically (Figure 1). Physiological hypertrophy, as seen in athletes or during pregnancy, is characterized by left ventricle enlargement, proportional thickening and elongation of individual cardiomyocytes and absent interstitial fibrosis. It does not carry a risk of fetal program reactivation, reduction in cardiac function, induction of arrhythmia or transition to heart failure [17,18]. This type of hypertrophy is mediated by signaling through insulin-like growth factor-1 and growth hormone that is transduced downstream by phosphoinositide 3-kinase/Akt signaling [19–23].

Pressure overload induced concentric hypertrophy appears to be related to activation of one of the MAPKs branches, the pathway of ERK1/2 [24]. The MAPKs are a

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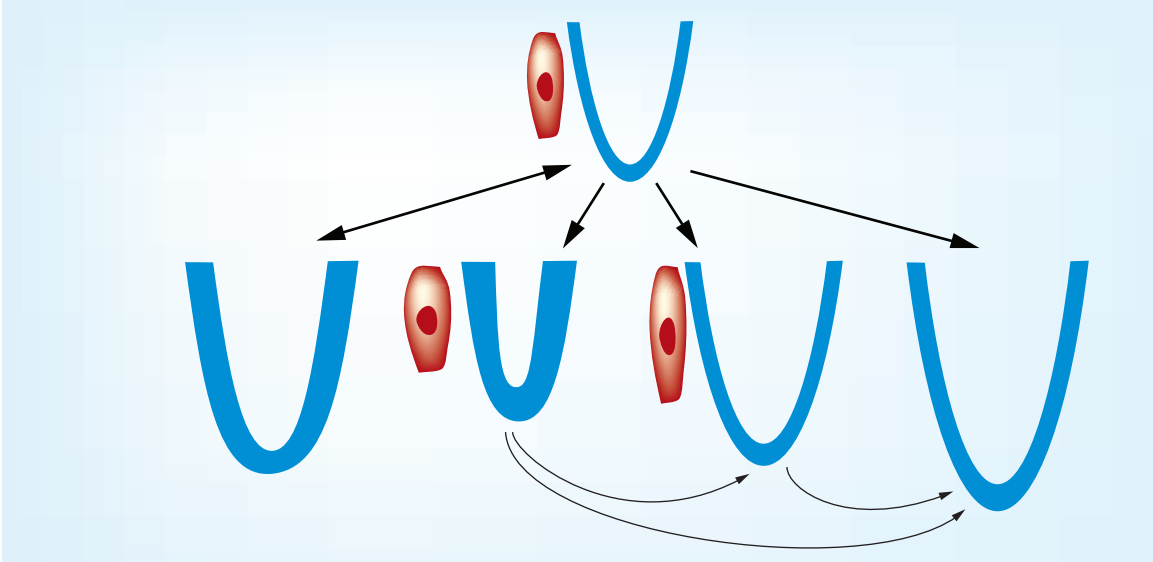

	Physiologic hypertrophy	Concentric hypertrophy	Eccentric hypertrophy	Overt heart failure
Fetal program		↑	↑	↑
Fibrosis	–	↑↑	–/↑	↑↑
Cellular dysfunction	–	–/↑	–/↑	↑↑

Figure 1. Macro-, micro- and subcellular changes observed in different types of heart remodeling and their interrelationship.

downstream pathways of multiple steps of phosphorylation-based amplification cascades [25,26]. Mutant mice overexpressing MEK1, under transcriptional control of α-myosin promoter, exhibited ERK1/2 activation, massive cardiac hypertrophy, increased width of cardiomyocytes. At the same time, there was no evidence of fibrosis or increased lethality up to 12 months of observation [27].

Another phenotype of hypertrophy, the eccentric one, occurring in response to volume overload, is mediated by preferential expression of MEK5-ERK5 branch of MAPK pathway [28,29]. Transgenic mice overexpressing activated ERK5, exhibited progressive right and left ventricular dilation by 6 weeks of age. From the microscopic perspective, the cardiomyocytes were elongated with decreased transverse cross-section area and sarcomeres were assembled in a serial manner. There was no evidence of extracellular collagen deposition and no signs of apoptosis [29].

Transition to heart failure & pathological remodeling

From the physiologic point of view, the three above-mentioned phenotypes of hypertrophy and the respective pathways responsible for, should be considered as adaptive and beneficial. However, heart with adaptive hypertrophy as well as normal heart, under specific conditions and signaling, may transit to an insufficient muscle with overt heart failure. The transition from compensated hypertrophy to failing heart includes: re-expression of fetal genes, altered expression of genes for proteins involved in excitation–contraction coupling, changes in the energetic and metabolic state of myocyte, mismatch between vascular and cardiomyocyte growth, myocyte necrosis and apoptosis and changes in extracellular matrix [30]. There are two more clinical possibilities available. The first one is, that under specific overload conditions, the heart can progress directly to frank dilation with an overt heart failure. Calcineurin and its downstream effector, nuclear factor of activated T cells (NFAT), when activated by excessive intracellular calcium, lead to increase in heart size and excessive deposition of collagen [31–33]. The other situation is in pressure overload, when overexpression of Ca2+/calmodulin-dependent kinase II leads to cardiac dilation, its reduced function and interstitial fibrosis [34,35]. Table 1 summarizes cardiac remodeling and signaling pathways with more supplementary data.

Animal studies

Apelin is the endogenous ligand for the G-protein-coupled APJ receptor that is expressed at the surface of cells in various organs such as the heart, lung, kidney, liver, adipose tissue, gastrointestinal tract, brain, adrenal glands, endothelium and human plasma.

Pchejetski *et al.* [36] in a murine model have proven that apelin inhibits transforming growth factor (TGF-β)-stimulated activation of cardiac fibroblasts through

Table 1. Summary of physiologic, pathologic and antihypertrophic signalling pathways with short description of their effects.

	Macroscopic/clinical	Signaling pathway	Nuclear compartment (literature)	Effect/experimental model (literature) [REF.]
Physiologic	Physiologic hypertrophy	IGF-1/GH > PI3-K/Akt	Histone acetyltransferase p300, CREB-binding protein	Ventricle enlargement, proportional cardiomyocyte thickening and elongation/rat, mice [17–23]
	Concentric hypertrophy	MAPKKK > MEK-1/ERK 1/2	Histone deacetylases: class I, class II and class III (sirtuins) [68–72]	Increased width of cardiomyocyte, massive cardiac hypertrophy/mice [24–27]
	Eccentric hypertrophy	MAPKKK > MEK5/ERK5		Right and left ventricle dilation, elongation of cardiomyocytes, decreased cross-section area of myocytes/mice [28,29]
Pathologic	Transition to overt heart failure	PKCα > SERCA2		Expression of Prkca induces dilated cardiomyopathy/mice [73–75]
	Transition to overt heart failure	S100A1 > RyR2		Downregulation of S100A1 protein leads to acute heart failure/mice [76–78]
	Transition to overt heart failure	P53 > Hif-1α		Accumulation of p53 stimulates transition from hypertrophy to heart failure/mice [79–81]
	Transition to overt heart failure	Stretch receptors > ERK2/JNK		Expression of matrix metalloproteinases, collagen depletion/mice [14,82–84]
	Transition to overt heart failure	ASK-1 and Bcl-2, Nix, Bnip3, Puma proteins		Cardiomyocyte apoptosis/mice [85–87]
	Heart failure	Calcineurin > NFAT		Increased heart size, excessive deposition of collagen/mice [31–33]
	Heart failure	CaMKII		Increased heart size, its reduced function, interstitial fibrosis/mice [34,35,88]
Antihypertrophic		Natriuretic peptides		[89,90]
		Nitric oxide		[91,92]
		NOTCH pathway		Reduced proliferation of myofibroblasts, expansion of Nkx2.5-positive cardiac precursor cells/mice [93]

CaMKII: Ca2+/calmodulin-dependent kinase II; NFAT: Nuclear factor of activated T cells.

a SphK1-dependent mechanism. They have reported that the administration of apelin during the phase of reactive fibrosis prevents structural remodeling of the myocardium and ventricular dysfunction. Ashley *et al.* [37] have studied apelin in a murine model and have reported that it reduces left ventricular preload and afterload, and increases contractile reserve without evidence of hypertrophy. These results associate apelin with a positive hemodynamic profile and suggest that it may be an attractive target for pharmacotherapy

in the management of patients with progressive heart failure.

Fasudil hydrochloride, Rho-kinase inhibitor, drug registered for human use in Japan has been tested in animal models of cardiac remodeling and heart failure. Hattori *et al.* [38] have tested fasudil orally in a murine model of MI. At 4 weeks, left ventricle cavity dilatation and dysfunction evaluated by echocardiography were significantly suppressed in the fasudil group. The beneficial effects of fasudil were accompanied by suppression of cardiomyocyte hypertrophy, interstitial fibrosis and suppression of TGF-beta2, TGF-beta3 and macrophage migration inhibitory factor. Rho-kinase activity as evaluated by the extent of phosphorylation of the ERM family, a substrate of Rho-kinase, was significantly increased in the noninfarcted left ventricle (LV) in the control group and was significantly suppressed in the fasudil group. The authors have concluded that the results suggest a therapeutic importance of the molecule for the prevention of post-MI heart failure.

Fasudil is also effective in prevention of isoproterenol-induced heart failure in rats [39]. Wang *et al.* have reported that fasudil significantly decreased JNK activation, ERK translocation to the nucleus and subsequent c-fos, c-jun expression and upregulated c-FLIP(L) expression. They have concluded that fasudil can effectively prevent isoproterenol-induced heart failure. Ho *et al.* [40] reported on beneficial effect of fasudil to suppress exercise-induced hypertrophy and functional impairment. Rats, exercising for 12 weeks and fed fasudil, have suppressed myocardial hypertrophy, myocyte cross-sectional area, hypertrophy-related pathways (IL6/STAT3-MEK5-ERK5, calcineurin-NFATc3, p38 and JNK MAPK), hypertrophic markers (ANP/BNP), proapoptotic molecules (cytochrome C, cleaved caspase-3 and PARP) and fibrosis-related pathways (FGF-2-ERK1/2) and fibrosis markers (uPA, MMP-9 and -2) in comparison with rats exercising without fasudil supplementation.

1-trifluoromethoxyphenyl-3-(1-propionylpiperidine-4-yl)urea, a soluble epoxide hydrolase inhibitor was proven effective in suppression of cardiac fibrosis in murine model of MI [41]. Sirish *et al.* have reported that treatment with 1-trifluoromethoxyphenyl-3-(1-propionylpiperidine-4-yl)urea resulted in a decrease in cardiac fibrosis, diminished proliferative capacity of different populations of cardiac fibroblasts as well as a reduction in the migration of fibroblasts into the heart from the bone marrow.

Dos Santos *et al.* [42] have studied the activity of circulating dipeptidyl peptidase IV and found a negative correlation with left ventricle ejection fraction in heart failure patients. Moreover, rats with heart failure displayed higher peptidase activity in the plasma and heart tissue compared with sham-operated rats. Positive correlations were observed between the plasma peptidase activity and LV end-diastolic pressure and lung congestion. A heart failure subgroup of rats, started treatment with the peptidase inhibitor, sitagliptin – oral hypoglycemic medicine for 6 weeks, whereas the remaining rats were administered water. Hemodynamic measurements demonstrated that radiofrequency LV-ablated rats treated with sitagliptin exhibited a significant attenuation of heart failure (HF)-related cardiac dysfunction, including LV end-diastolic pressure, systolic performance and chamber stiffness. Sitagliptin treatment also attenuated cardiac remodeling and cardiomyocyte apoptosis and minimized pulmonary congestion. However, sitagliptin use in patients with Type 2 diabetes and pre-existing heart failure was associated with an increased risk of HF-related hospitalizations among patients [43].

There are several reports on bioengineering or RNA interference methodology described in animal models targeting some of the pathways involved in cardiac remodeling. Tank *et al.* [44] have developed RNA interference (miR) to silence connective tissue growth factor (CTGF or CCN2) and found it to block multiple proinflammatory and profibrotic pathways in activated primary cardiac fibroblasts. The RNAi-strategy was developed in murine fibroblasts and then investigated in human fibroblasts grown from human endomyocardial biopsies. In murine model, CCN2 silencing resulted in strongly reduced expression of stretch-induced chemokines, matrix metalloproteinases, extracellular matrix (Col3a1) and a cell-to-cell contact protein (Cx43), suggesting multiple signal pathways to be linked to CCN2. The authors have demonstrated that this RNA interference strategy is technically applicable to human fibroblasts, but they might express different responses to CCN2 depletion.

Fiedler *et al.* [45] have blocked endothelial miR-24 in murine model, leading to lower infarct size via prevention of endothelial apoptosis and enhancement of vascularity, which led to preserved cardiac function and survival.

Szabo *et al.* [46] have reported on alternative way to inhibit connective tissue growth factor. They have used monoclonal antibody to connective tissue growth factor in two models of murine heart hypertrophy induced by thoracic aorta constriction or angiotensin II infusion. They have found different efficacy of monoclonal antibody treatment – the antibody protects from adverse LV remodeling and LV dysfunction in hearts subjected to pressure overload by thoracic aorta constriction.

Kumarswamy *et al.* [47] have administered intravenously adeno-associated vector type 9/ sarcoplasmic

reticulum Ca^{2+}-ATPase (AAV9/SERCA2a) to rats with chronic post-MI heart failure. The treatment has led to normalization of miR-1 expression and normalization of expression of enhanced sodium–calcium exchanger 1 (NCX-1), along with improved cardiac function.

Wang *et al.* [48] have tested hepatocyte growth factor mesenchymal stem cells in the treatment of MI in rat. Using echocardiography they have confirmed that transplantation with HGF-MSCs significantly improved left ventricular function. Implanted stem cells were detected 4 weeks after implantation. Decreased infarcted scar area and increased angiogenesis formation could be found in group with hepatocyte growth factor mesenchymal stem cells.

Human trials

Neuregulin NRG1 activates the extracellular signal-regulated kinase 1/2 (ERK1/2) and PI3K→Akt pathways in cardiomyocytes two potently cardioprotective systems [49]. Recombinant neuregulin improves cardiac function, reduces pathological changes and extends survival in rodent models of cardiomyopathy. It also improves contractility/relaxation in pacing-induced HF in dogs. Two studies in humans with chronic HF indicate that neuregulin is safe, and may improve cardiac dimensions and function. Phase II and III trials of subcutaneous administration of neuregulin 1 in chronic HF are ongoing (NCT01251406). A Phase I trial of the neuregulin isoform in patients with LV dysfunction and symptomatic HF is due to report (NCT01258387). The safety issue of neuregulin in chronic treatment is potential tumorigenic effects [50,51].

Omecamtiv mecarbil, formerly CK-1827452, is a direct myosin activator resulting in improved number of strongly bound actin–myosin bridges [52]. Higher plasma concentrations were also associated with reductions in end-systolic and end-diastolic volumes. Omecamtiv mecarbil improved cardiac function in patients with heart failure caused by left ventricular dysfunction and could be the first in class of a new therapeutic agent [53]. Currently, a study on the intravenous use of omecamtiv mecarbil in acute heart failure (ATOMIC-AHF, www.ClinicalTrials.gov Identifier: NCT01300013) is finished. Another study on oral formulation of omecamtiv mecarbil in chronic heart failure is still recruiting patients (COSMIC-HF, www.ClinicalTrials.gov Identifier: NCT01786512).

Relaxin and serelaxin are targeting the relaxin receptor. Serelaxin is a recombinant form of human relaxin, a hormone produced during pregnancy. Relaxin mediates the haemodynamic changes that occur during pregnancy: vasodilation by increasing the production of nitric oxide (NO), and an inhibition of angiotensin II and endothelin. In addition to vasodilation, the effects of serelaxin are also seen in the kidneys and in heart. Serelaxin can increase stroke volume without increasing the energy demand on the already strained heart of acute heart failure patients [54]. The RELAX-AHF trial (www.ClinicalTrials.gov identifier NCT00520806) tested the hypothesis that serelaxin-treated patients would have greater dyspnoea relief compared with patients treated with standard care and placebo [55]. One-thousand one hundred and sixty-one patients were randomly assigned to serelaxin or placebo. Active treatment improved the primary dyspnea endpoint. No significant effects were recorded for the secondary endpoints of cardiovascular death or readmission to hospital for heart failure or renal failure. Serelaxin treatment was associated with significant reduced mortality at day 180 (placebo, 65 deaths; serelaxin, 42; HR 0·63, 95% CI: 0·42–0·93; p = 0·019).

Another study (www.ClinicalTrials.gov identifier NCT01543854) [56] was aimed to evaluate the haemodynamic effects of serelaxin in patients with acute heart failure. This double-blind, multicenter study randomized 71 acute heart failure patients with increased pulmonary capillary wedge pressure to serelaxin or placebo within 48 h of hospitalization. Major endpoints were peak change from baseline in pulmonary capillary wedge pressure (PCWP) and cardiac index. Among patients eligible for hemodynamic analysis, those treated with serelaxin had a significantly higher decrease in peak PCWP. Among secondary hemodynamic endpoints, a highly significant reduction in pulmonary artery pressure was observed throughout the serelaxin infusion. Right atrial pressure, systemic/pulmonary vascular resistance and systolic/diastolic BP decreased from baseline with serelaxin versus placebo and treatment differences reached statistical significance at some time points. Serelaxin administration improved renal function and decreased N-terminal probrain natriuretic peptide levels versus placebo. Treatment with serelaxin was well tolerated with no apparent safety issues.

There are several papers on different types of cells transplanted into ischemic or postinfarction myocardium [57–61]. Traverse *et al.* [61] did not find any improved recovery of global and regional LV function at 1 year, irrespective of cell delivery at 3 or 7 days post-percutaneous coronary intervention (PCI). Conversely, Karantalis *et al.* [58] have concluded their experiment that intramyocardial injection of autologous mesenchymal stem cells into akinetic yet non-revascularized segments produces comprehensive regional and global left ventricle function improve-

ment. Although, of note this study has no control group. Heldman *et al.* [60] have tested mesenchymal and bone marrow derived stem cells, administered transendocardially. Mesenchymal stem cells administered transendocardially have led to reduced infarct size, but there were not any differences observed in left ventricle volume and function in 6 months long follow-up.

The Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease Phase II study [62–64] has tested intracoronary administration of adeno-associated virus type 1/sarcoplasmic reticulum Ca^{2+}-ATPase in patients with advanced heart failure. The study, over a 12 months long clinical, laboratory and echocardiographic follow-up demonstrated safety and suggested benefit of this treatment in advanced heart failure.

PARADIGM-HF study (www.ClinicalTrials.gov identifier NCT01035255) conducted in a group of 8442 patients in NYHA class II–IV and reduced left ventricle ejection fraction of 40% or less, compared a combination of valsartan with neprilysin inhibitor as active treatment and enalapril as comparator [65]. Neprilysin is neutral endopeptidase that degrades natriuretic peptides, bradykinin and adrenomedullin. Study endpoint was a composite of death for cardiovascular reasons and heart failure hospitalization. The study was terminated early because of significant difference in primary outcome in favor of a valsartan/neprilysin inhibitor.

The papers by van Berlo *et al.* [66] and Tarone *et al.* [67] provide supplementary data to this review.

Conclusion & future perspective

In this review, we have highlighted animal and human studies addressing the therapies used to modify signaling pathways in order to prevent heart remodeling and halt progression of heart failure. Most of the therapies, which were promising in animal models, failed in human studies. Use of adeno-associated vector/SERCA2a is one of the treatments that successfully transferred from animal to human level. Cell therapy and RNA interfering are of great interest and bear huge interventional capability. Combination therapies, such as angiotensin receptor/neprilysin inhibitor, are also of great promise. Drug combinations addressing two compartments, such as cardiomyocyte and extracellular matrix, are warranted in this issue. Otherwise, progress in miR/antagomir research might offer a very narrow, specific therapeutic target. In our opinion the near future will bring an outbreak in gene delivery/miR/antagomir therapeutic options that will be successful in coping with the increasing epidemic of heart failure.

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For uniformity of nomenclature we tried to check every signaling pathway reported with the Kyoto Encyclopedia of Genes and Genomes at www.genome.jp/kegg

Executive summary

- Cardiac remodeling is an inhomogenous entity that might lead to overt heart failure.
- Animal studies provide the evidence for underlying mechanisms and signaling pathways leading to remodeling.
- Animal models of cardiac remodeling are perfect targets to test different therapeutic options.
- Only a limited number of therapeutic strategies proved effective in human trials.
- Of the latter, gene delivery/miR/antagomir technology is of great promise and a combination therapy of angiotensin receptor/neprilysin inhibitor has already been proved effective.

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