Remodeling the failing heart: the biology and future treatment options

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Myocardial remodeling: definitions

- phenotypic *plasticity*: remodeling is characterized by changes in myocardial structure that happen in response to either mechanical overload or a loss of substance such as that occurring after myocardial infarction.

- Myocardial remodeling is an essential mechanism that allows for cardiac output to be maintained in the presence of chronically abnormal loading conditions or depressed contractility.
A  Ventricular remodeling after acute infarction

- Initial infarct
- Expansion of infarct (hours to days)
- Global remodeling (days to months)

B  Ventricular remodeling in diastolic and systolic heart failure

Normal heart

Hypertrophied heart (diastolic heart failure)

Dilated heart (systolic heart failure)

Patterns of LV remodeling with cardiac magnetic resonance imaging

Reversal of electrical remodeling with LVAD
Remodeling involves:

Myocyte changes
Extracellular matrix changes
Microvascular changes
Myocardial regeneration
Cell-cell cross-talk
Cardiac myocyte
Patterns of myocyte hypertrophy in myocardial remodeling

- Apoptosis
- Growth stimuli
- Normal muscle cell
- Autophagy
- Physiological hypertrophy
- Concentric hypertrophy
- Increased expression of embryonic genes
- Eccentric hypertrophy
Dilated cardiomyopathy

Beuckelmann D et al *Circulation* 1992
Serca2a

- Gene therapy (AAV1-Serca2a)
- Antagomir (miR-25)
- SUMO-ylation
Human myocyte overexpressing SERCA2a

Direct light

Fluorescent light

Cell shortening and Ca\(^{2+}\) transient

Myocyte from a failing heart

Myocyte from a nonfailing heart

Myocyte overexpressing SERCA2a from a failing heart

Force-frequency relationship

Myocyte from a failing heart

Myocyte from a nonfailing heart

Myocyte overexpressing SERCA2a from a failing heart

Hz
Figure 4. Calcium Up-Regulation by Percutaneous Administration of Gene Therapy in Cardiac Disease phase 2 survival curve for all-cause mortality in high-dose recombinant adeno-associated viral vector (AAV) containing human sarcoplasmic reticulum Ca^{2+} ATPase2a (SERCA2a) gene (AAV1/SERCA2a) group versus placebo. The survival curve for patients in high-dose AAV1/SERCA2a and the survival curve for the patients in the placebo group demonstrate a much higher survival probability over time for the patients receiving high-dose AAV1/SERCA2a compared with those in the placebo group.
Inhibition of miR-25 improves cardiac contractility in the failing heart

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Figure 4: Effect on the left ventricular ejection fraction (A) and survival (B) in mice. Kaplan-Meier survival curves for sham-operated mice, mice with thoracic aortic constriction (TAC) and mice with TAC treated with anti-miR-25 (at 3.5 months). Modified from Wahlquist C, Jeong D, Rojas-Muñoz A, et al.²⁹
SUMO1-dependent modulation of SERCA2a in heart failure

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Myofilaments

- Myosin ATPase: omecantiv mecarbil
Figure 1: Time-dependent changes from baseline in key echocardiogram measures for eight patients treated in cohort 5 with 72-h infusions of omecamtiv mecarbil or placebo. Data are mean; error bars show SEM. Patients received 1·0 mg/kg per h for 1 h, followed by 0·5 mg/kg per h for 1 h, and then 0·1 mg/kg per h for 70 h. SET=systolic ejection time. SV=stroke volume. LVESV=left ventricular end-systolic volume. LVEDV=left ventricular end-diastolic volume.
The Myosin Activator Omecamtiv Mecarbil Increases Myocardial Oxygen Consumption and Impairs Cardiac Efficiency Mediated by Resting Myosin ATPase Activity

Jens Petter Bakkehaug, Anders Benjamin Kildal, Erik Torgersen Engstad, Neoma Boardman, Torvind Næsheim, Leif Rønning, Ellen Aasum, Terje S. Larsen, Truls Myrmel and Ole-Jakob How

Circ Heart Fail. 2015 May 29. pii: CIRCHEARTFAILURE.114.002152. [Epub ahead of print]
Mitochondria

• Cardiolipin protection by SS peptides
SS peptides protect mitochondria from oxidative damage
200 Evaluable pts with Anterior STEMI
Anticipated sx to PCI < 4 hrs, TIMI 0/1 flow in prox or mid LAD

Blinded

Bendavia IV at 0.05 mg/kg/hr
15 but no more than 60 minutes prior to the anticipated time of the PCI and continued for 1 hour after

Volume-matched IV Placebo
15 but no more than 60 minutes prior to the anticipated time of the PCI and continued for 1 hour after

Primary Endpoint: Area under the curve for creatine kinase-MB (CK-MB) enzyme obtained over the initial 72 hours following the initial PCI procedure

EMBRACE-STEMI study design.
Membrane receptors

- The beta3-adrenergic receptor
β-adrenergic stimulation of NO Synthase attenuates the inotropic effect

Which β-adrenergic receptor?

β1+2-adrenergic receptor blockade unveils a negative inotropic effect of isoproterenol, a non-specific β-adrenergic agonist

By what mechanism?


β3 AR coupling in mammalian heart

Effect on remodeling?
1. hypertrophy
2. coronary vasodilatation
3. fibrosis
4. metabolism?

Dessy et al. *Circulation*, 2004; 110(8): 948
β3AR protects against cardiac hypertrophy

**In vitro**

![AdV:GFP](image1)

![AdV:hβ3AR](image2)


**In vivo**

Targets downstream NOS/cGMP

- β$_3$AR
- G$_{ai}$
- NOS
- NO
- sGC
- cGMP
- PKG
- Troponin-I-P
- Titin-P
- Myofilament Ca++ sensitivity
- Hypertrophy
- Myocyte/tissue elasticity
The cardiac fibroblast and myocyte-fibroblast cross-talk
β3AR protects against myocardial fibrosis

Myocardial fibrosis after TAC 9 weeks

Myocardial fibrosis after Angiotensin II infusion by minipump (14 days)

POTENTIAL PARACRINE FACTORS INVOLVED IN THE ANTIFIBROTIC EFFECT FROM $\beta_3$-AR CARDIAC MYOCYTES TO CARDIAC FIBROBLASTS

Secretome from cardiac myocytes

M. Mayr (King's College London, Cardiovascular Division)

Gel-free proteomic analysis

Principal Components Analysis

Standardised Expression Profiles

Results in vitro
This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement N° 634559
Membrane receptors

• Combined AT1-R antagonist and neprilysin inhibitor: LCZ 696
Figure 2. Kaplan-Meier Curves for Key Study Outcomes, According to Study Group.
Shown are estimates of the probability of the primary composite end point (death from cardiovascular causes or first hospitalization for heart failure) (Panel A), death from cardiovascular causes (Panel B), first hospitalization for heart failure (Panel C), and death from any cause (Panel D).
The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial

Figure 2: NT-proBNP at 4, 12, and 36 weeks in the LCZ696 and valsartan groups
The endothelial cell and endothelial-myocyte cross-talk
Close apposition of cardiac myocytes and capillary endothelial cells
Targeting Endothelial Signalling Pathways

- Relaxin-2
- Laminar shear forces
- Serelaxin

Pro-NRG-1

NRG-1 like substances: GGF-2 & EGF binding domain

NOS-3

NO donors

NEP inhibitors: LCZ696

NEP breakdown products

Natriuretic peptides: Neseritide Ularitide

NRG-1

ErbB2

ErbB4

Kinase

Kinase

AKT

ERK

NOS-3

sGC stimulators

sGC activators

cGMP

PDE5

5’GMP

PGC

PKG

PDE5 inhibitors

Cardiomyocyte/smooth muscle cell
Activation of Human Brown Adipose Tissue by a \( \beta_3 \)-Adrenergic Receptor Agonist

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That’s all

• Questions