Pathophysiology of Heart Failure and Targets for Pharmacological Therapy

SGK Zürich 11.06. 2015

PD Dr. med. Otmar Pfister
Director of the Heart Failure Program
Division of Cardiology
University Hospital Basel
Disclosures:

I received consultant and / or speaker fees from:

Novartis, Roche, Servier, Vifor, Orion Pharma,
Heart Failure: Clinical Definition

Clinical syndrome caused by the inability of the heart to fill with (diastolic failure) and/or to eject (systolic failure) sufficient blood under normal cardiac filling pressures to maintain a systemic perfusion that is adequate to meet the metabolic demands of the organism.
Determinants of Cardiac Function

Heart Rate
Myocardial Function (systolic /diastolic)

Preload
Cardiac Filling

Afterload
Resistance

Ω
Triggers of Neurohormonal Activation

- Left Ventricular Dysfunction
  - Cardiac Filling Pressure ↑
  - Cardiac Output ↓

- Neurohormonal Activation
Treatment Target: Neurohormonal Activation

- Adrenergic System
- Renin-Angiotensin-Aldosterone System
- Direct Cardiotoxicity
- Vasoconstriction
- Fluid-Retention
- Heart Rate↑
- Contractility↑
- Myocyte Damage
- Myocardial Dysfunction↑
- Hypertrophy↑

Beta-Adrenergic Blockers
Angiotensin Converting Enzyme Inhibitors
Angiotensin II-Receptor Blockers
Mineralocorticoid Receptor Antagonists

Otmar.Pfister@usb.ch
Myocardial Remodeling

Remodeling stimuli
- Cytokines
- Neurohormones
- ROS

Increased wall stress

Molecular / Cellular
- Myocyte hypertrophy
- Altered interstitial matrix
- Fetal gene expression
- Altered Ca-handling
- Myocyte death

Morphologic / Functional
- Ventricular enlargement
- Systolic/diastolic dysfunction

Adapted from: Atlas of Heart Failure, 4th Ed., W.S. Colucci
Myocardial Remodeling: Therapeutic Concepts

Cell Replacement Therapies

Pharmacological Therapies

ACEI, ARB, MRA
Beta blockers, GLP-1?

ICD and CRT

Cardiomyocyte Loss

Cardiomyocyte Hypertrophy

Fibrosis

Insulin Resistance

Electrophysiological Changes

Necrosis
Apoptosis
Autophagy

Biomechanical Stress
Neurohumoral Activation

RAAS Activation
TGFβ
Inflammation

Metabolic derangement
Lipotoxicity

Structural Alterations
Ion Channel Remodeling

Burchfield JS et al., Circulation 2013
Treatment Target: Afterload Reduction

Cardiac Output

Afterload

Afterload Reduction

Normal

Ventricular Dysfunction

Otmar.Pfister@usb.ch
Pivotal Role of Cyclic Guanosine-Monophosphat (cGMP) for Cardiac Function

Endothelial NO Synthase

Nitric Oxide (NO)

Soluble Guanylate Cyclase

GTP

cGMP

Guanylate Cyclase

Myocardial Function
- Relaxation
- Energy Utilization
- Apoptosis
- Remodeling

Vascular Function
- Vasodilation

Otmar.Pfister@usb.ch
Strategies to increase cGMP

- **Endothelin Receptor B**
  - Endothelial NO Synthase

- **Relaxin 2** (Serelaxin)

- **Natriuretic Peptides** (NEP-Inhibitor, LCZ696)

- **Nitric Oxide (NO)**
  - Soluble Guanylate Cyclase
  - Guanylate Cyclase

- **sGC Stimulators** (Riociguat, Vericiguat)

- **PD5 Inhibitors** (Sildenafil)

- **Degradation**
The Optimal Drug for Heart Failure should…

- Unload the Heart
- Preserve Myocardial Homeostasis and Structure
- Protect Systemic Organ Function
- Reduce Mortality and Morbidity
Vielen Dank

Otmar Pfister
Klinik für Kardiologie
Universitätsspital Basel
Otmar.pfister@usb.ch