

direction: down

```
stressors: {
  label: "Initial myocardial and systemic stressors"
  direction: right

  ischemia: "Ischemia /\ninfarction"
  overload: "Pressure /\nvolume overload"
  cardiomyopathy: "Cardiomyopathy /\nmyocarditis"
  neurohormonal: "Neurohormonal\nactivation"
  metabolic: "Metabolic disease /\nCKD / obesity"
  aging: "Aging / toxins /\ninfiltrative disease"
}
```

```
cardiomyocyte: {
  label: "Failing cardiomyocyte and\nmyocardial microenvironment"

  receptors: {
    beta: "β1,3 AR"
    at1: "AT1-R"
    et: "ETA-R"
    mr: "V1aR"
  }

  intracellular: {
    sr: "Sarcoplasmic\nreticulum"
    nucleus: "Nucleus"
    gene: "Gene expression\nreprogramming"
    mito: "Mitochondria"
  }

  environment: {
    fibroblast: "Fibroblast /\nMyofibroblast"
    endothelium: "Endothelium"
    immune: "Immune cell"
  }
}
```

```
sns: "Chronic sympathetic signaling"
raas: "RAAS / aldosterone /\nendothelin / vasopressin"
mechanical: "Mechanical stress and\nhypertrophic signaling"
inflammation: "Inflammation and\nimmune signaling"
```

```
calcium: {
  label: "Calcium handling and excitation-contraction coupling"

  ltype: "L-type\nCa2+ channel"
  ryr2: "RyR2"
  troponin: "Troponin I\nphosphorylation"
  serca: "SERCA2a-mediated\nreuptake"
}
```

```
abnormalities: {
  label: "Abnormalities in heart failure"
```

```

serca2a: "SERCA2a"
phospholamban: "Phospholamban inhibition"
ryr2leak: "RyR2 leak (diastolic Ca2+ leak)"
delayed: "Reduced relaxation"
systolic: "Reduced systolic Ca2+"
arrhythmias: "Ventricular arrhythmias"
}

mitochondria: "Mitochondrial dysfunction\nand oxidative stress"
fibrosis: "Fibrosis and extracellular\nmatrix remodeling"
cell_death: "Cell death and\nelectrical instability"
nopkg: "NO-cGMP-PKG pathway\n(especially HFpEF)"

hfref: "HFrefEF phenotype"
hfpef: "HFpEF phenotype"

consequences: {
  label: "Integrated myocardial consequences"
  direction: right

  contractility: "Impaired\ncontractility"
  relaxation: "Impaired\nrelaxation"
  energy: "Energetic\nfailure"
  hypertrophy: "Hypertrophy /\ndilatation"
  stiffness: "Stiffness"
  fib: "Fibrosis"
  rhythm: "Arrhythmias"
  reserve: "Reduced\nreserve"
}

network: {
  label: "Self-perpetuating molecular network"

  cycle: "Injury / stress → neurohormonal + inflammatory activation
→ calcium dysregulation → remodeling, congestion and end-organ
dysfunction"
  cycle2: "mitochondrial dysfunction → fibrosis → remodeling,
congestion and end-organ dysfunction → dysfunction"
}

therapy: {
  label: "Major therapeutic interruption points"
  direction: right

  beta: "β-blockers"
  arni: "RAAS / ARNI\ninhibition"
  mra: "Mineralocorticoid\nreceptor antagonists"
  sglt2: "SGLT2\ninhibitors"
  devices: "Devices /\nrevascularization /\nvalve intervention"
}

stressors -> cardiomyocyte

```

sns -> cardiomyocyte
mechanical -> cardiomyocyte
raas -> cardiomyocyte
inflammation -> cardiomyocyte

cardiomyocyte -> calcium
cardiomyocyte -> fibrosis

cardiomyocyte -> abnormalities
nopkg -> abnormalities

cell_death -> mitochondria

calcium -> mitochondria
mitochondria -> fibrosis

consequences -> mitochondria
consequences -> fibrosis

hfref -> consequences
hfpef -> consequences

therapy -> network