

flowchart TB

%% =====

%% INITIAL MYOCARDIAL AND SYSTEMIC STRESSORS

%% =====

```
subgraph ST["Initial myocardial and systemic stressors"]
direction LR
S1["Ischemia / infarction"]
S2["Pressure / volume overload"]
S3["Cardiomyopathy / myocarditis"]
S4["Neurohormonal activation"]
S5["Metabolic disease / CKD / obesity"]
S6["Aging / toxins / infiltrative disease"]
end
```

%% =====

%% INPUT SIGNALS

%% =====

```
SNS["Chronic sympathetic signaling"]
MECH["Mechanical stress and hypertrophic signaling"]
RAAS["RAAS / aldosterone / endothelin / vasopressin"]
IMMUNE["Inflammation and immune signaling"]
```

%% =====

%% CENTRAL CELL

%% =====

```
subgraph CELL["Failing cardiomyocyte and myocardial
microenvironment"]
direction TB
```

```
subgraph RECEPTORS
direction LR
β1["β1,3 AR"]
AT["AT1R"]
ET["ETaR"]
V1["V1aR"]
end
```

end

```
subgraph INTRACELLULAR
direction LR
SR["Sarcoplasmic reticulum"]
NUC["Nucleus"]
GENE["Gene expression reprogramming"]
MITO["Mitochondria"]
end
```

```
subgraph ENVIRONMENT
direction LR
FIB["Fibroblast / Myofibroblast"]
ENDO["Endothelium"]
IMM["Immune cell"]
```

end

end

```
%% =====  
%% CALCIUM HANDLING  
%% =====
```

```
subgraph CA["Calcium handling and excitation-contraction coupling"]  
direction LR  
LTYPE["L-type Ca2+ channel"]  
RYR["RYR2"]  
TROP["Troponin I phosphorylation"]  
SERCA["SERCA2a-mediated reuptake"]  
end
```

```
%% =====  
%% ABNORMALITIES  
%% =====
```

```
ABN["Abnormalities in heart failure  
• SERCA2a  
• Phospholamban inhibition  
• RyR2 leak (diastolic Ca2+ leak)  
• Reduced relaxation  
• Reduced systolic Ca2+  
• Ventricular arrhythmias"]
```

```
NO["NO-cGMP-PKG pathway  
(especially HFpEF)"]
```

```
CELLDEATH["Cell death and electrical instability"]
```

```
%% =====  
%% DOWNSTREAM  
%% =====
```

```
MITODYS["Mitochondrial dysfunction and oxidative stress"]
```

```
FIBROSIS["Fibrosis and extracellular matrix remodeling"]
```

```
subgraph CONS["Integrated myocardial consequences"]  
direction LR  
C1["Impaired contractility"]  
C2["Impaired relaxation"]  
C3["Energetic failure"]  
C4["Hypertrophy / dilation"]  
C5["Stiffness"]  
C6["Fibrosis"]  
C7["Arrhythmias"]  
C8["Reduced reserve"]  
end
```

```
HFrEF["HFrEF phenotype"]
```

```
HFPEF["HFpEF phenotype"]
```

```
NETWORK["Self-perpetuating molecular network
```

```
Injury / stress
```

```
→ neurohormonal activation
```

```
→ inflammatory fibrosis
```

```
→ calcium dysregulation
```

```
→ remodeling, congestion and end-organ dysfunction
```

```
→ mitochondrial dysfunction"]
```

```
%% =====
```

```
%% THERAPY
```

```
%% =====
```

```
subgraph THERAPY["Major therapeutic interruption points"]
```

```
direction LR
```

```
T1["β-blockers"]
```

```
T2["RAAS / ARNI inhibition"]
```

```
T3["Mineralocorticoid receptor antagonists"]
```

```
T4["SGLT2 inhibitors"]
```

```
T5["Devices / revascularization / valve intervention"]
```

```
end
```

```
%% =====
```

```
%% CONNECTIONS
```

```
%% =====
```

```
ST --> CELL
```

```
SNS --> CELL
```

```
MECH --> CELL
```

```
RAAS --> CELL
```

```
IMMUNE --> CELL
```

```
CELL --> CA
```

```
CELL --> ABN
```

```
CA --> ABN
```

```
NO --> ABN
```

```
CA --> MITODYS
```

```
CA --> FIBROSIS
```

```
CELLDEATH --> MITODYS
```

```
MITODYS --> FIBROSIS
```

```
CONS --> MITODYS
```

```
FIBROSIS --> CONS
```

```
ABN --> CONS
```

```
CONS --> HFREF
```

```
CONS --> HFPEF
```

CONS --> NETWORK

T1 -. -> NETWORK

T4 -. -> NETWORK

T5 -. -> NETWORK