Traditional inotropic agents used in treating acute decompensated heart failure increase cardiac contractility by increasing the calcium transient. β-adrenergic agents activate (β-adrenergic) receptors resulting in an increase in cAMP and activation of the PKA signaling cascade. Numerous proteins are phosphorylated including phosphodiesters that result in the increase of the calcium transient and thus contractility. Phosphodiesterase (PDE) inhibitors increase the cAMP concentrations by slowing cAMP degradation also resulting in a calcium transient increase. PDE inhibiting compounds result in increased mortality in clinical trials likely due to altering the calcium transient (Packer et al., 1991; Cohn et al., 1998).

Myosin activators, via a distinct and novel mechanism, directly stimulate activity of the myosin ATPase in the cardiac sarcomere. In vitro enzymatic assays demonstrate that myosin activators accelerate the rate limiting step of the myosin enzymatic cycle, reported by phosphate release, almost 2-fold (bottom panel). This portion of the cycle constitutes transition from the weakly to the strongly bound state of myosin. Thus, by reducing the time spent in the weakly bound state, myosin activators shift the myosin enzymatic cycle in favor of the strongly bound, force producing state. See abstract 147 for biochemical details.

**REFERENCES**

