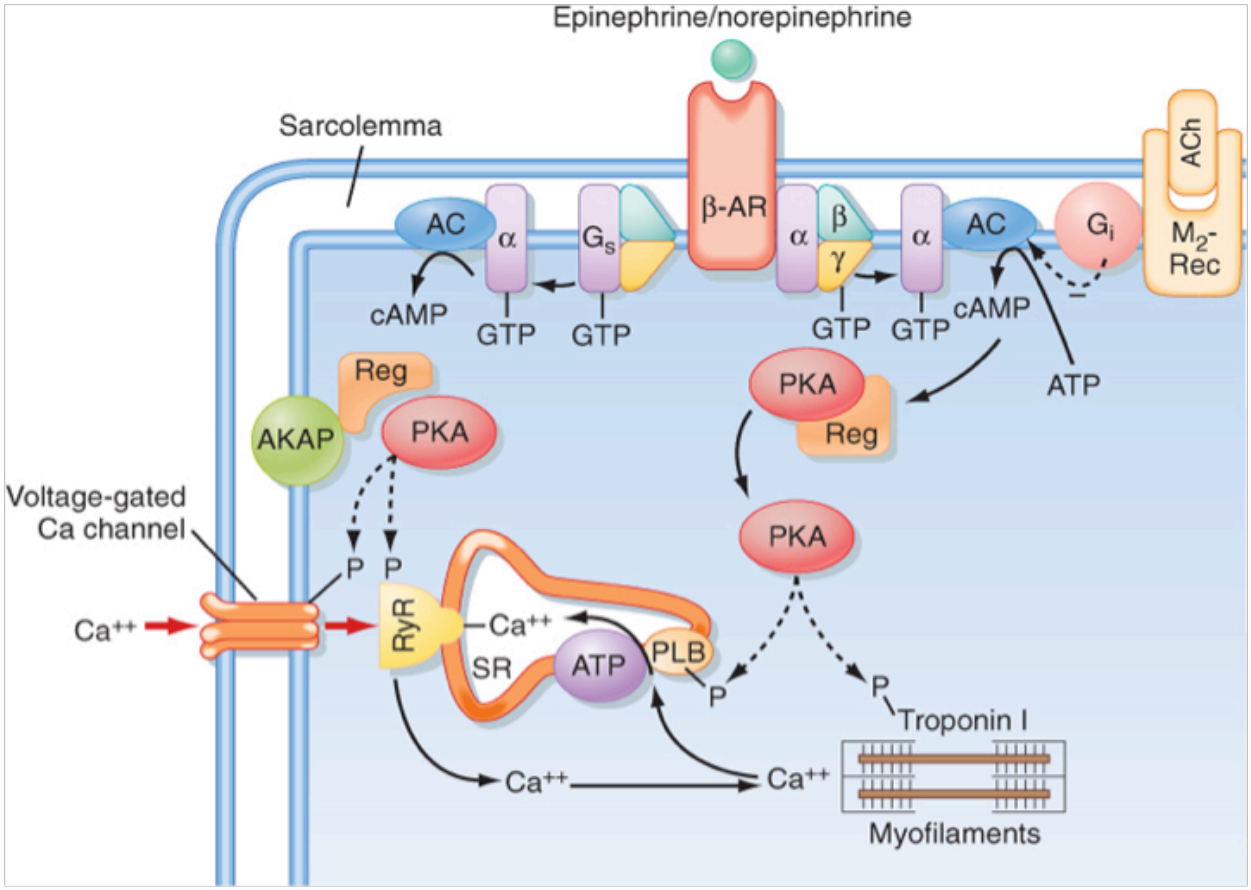
Module 5 Discussion Question - Instructor's Response

Imagine a cardiac muscle in which sympathetic stimulation does NOT result in phosphorylation of Troponin-I (everything else that normally results from sympathetic stimulation would happen; only the phosphorylation of Troponin-I would not happen). If the muscle is subjected to sympathetic stimulation what do you expect would happen to the amplitude and time course of twitch force (as compared to a "normal" cardiac muscle under sympathetic stimulation)? Briefly explain. Please **post your response to the discussion board by 9:00 PM on Day 4 of this Module.**

First, a reminder of the effects of sympathetic stimulation on the normal heart (video 2, slide 5):



The following information is taken from Bers[1]; refer to the paper for additional details.

Sympathetic stimulation of the heart increases both developed force and heart rate. The sympathetic presynaptic nerve terminals release epinephrine, a β-adrenergic agonist, that binds to its receptor on the cardiac cell sarcolemma; this binding initiates a

[1] Bers DM, Cardiac excitation-contraction coupling, Nature 2002 415:198-205.

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2nd messenger cascade that begins with the activation of a stimulatory G-protein, which causes adenylate cyclase to stimulate production of cyclic AMP, which then activates protein kinase A (PKA). PKA then phosphorylates several proteins; it is this protein phosphorylation that is responsible for the effects of sympathetic stimulation on the heart.

An increased heart rate requires a faster relaxation (of twitch force); this is made possible by phosphorylation of phospholamban associated with SR SERCA, which increases the rate of re-uptake of Ca^{2+} into the SR, and by phosphorylation of troponin I (TnI), which increases the rate of dissociation of Ca^{2+} from the myofilaments. Note that phosphorylation of TnI effectively reduces the calcium sensitivity of the myofilaments, which would reduce twitch force if $[Ca^{2+}]_i$ did not change. However, according to Bers (see footnote 1), the reduced sensitivity of the myofilaments for Ca^{2+} is more than made up for by the increased Ca^{2+} content of the SR[2], which results in a larger (than normal) release bolous of Ca^{2+} into the myofilament space. PKA also phosphorylates the SL voltage-gated calcium channel and the SR RyR Ca^{2+} relese channel, both of which contribute to the increase in SR calcium release and thus an increase in twitch force.

So – failure of sympathetic stimulation to result in TnI phosphorylation, with no other effects (compared to the normal heart) would result in an increased force of contraction (removal of the desensitization of the myofilaments for Ca^{2+} secondary to TnI phosphorylation). Failure of TnI phosphorylation would also result in a slowing of the rate of Ca^{2+} removal from troponin-C and, thus, a prolonged relaxation (of twitch force).

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[2] Due to the increased uptake of Ca^{2+} into SR secondary to the effect of phosphorylation of phospholamban associated with the SR SERCA.

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