Myofilament mutations alter calcium channel and mitochondrial functional communication

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Hypertrophic cardiomyopathy (HCM) affects 1: 200 of the general population. It is associated with myocyte remodeling, disorganization of cytoskeletal proteins and altered energy metabolism. Some patients are responsive to L-type calcium channel (LTCC) antagonists as therapy. However the role of LTCC in development of the cardiomyopathy is unknown. Since mitochondrial function can be regulated by alterations in LTCC activity, we investigated the role of LTCC in regulating mitochondrial function in mice overexpressing the human HCM causing mutation Arg403Gln ($\alpha MHC^{403/+}$). We examined LTCC kinetics in cardiomyocytes from pre- and post-cardiomyopathic $\alpha MHC^{403/+}$ mice using whole cell patch-clamp technique, and the effect of LTCC activation on mitochondrial membrane potential (Ψ_m, JC-1 fluorescence) and mitochondrial oxygen consumption (flavoprotein autofluorescence). Cardiomyocytes isolated from cardiomyopathic $\alpha MHC^{403/+}$ mice demonstrated similar LTCC current density compared to age-matched *wt* cardiomyocytes. However the inactivation rate of the current was faster in $\alpha MHC^{403/+}$ cardiomyocytes (32.8 ± 2.0, n=14 *versus* 40.7 ± 2.5, n=8; mean ± SEM; $P<0.05$). Application of BayK(-) caused a significantly greater increase in Ψ_m in $\alpha MHC^{403/+}$ *versus wt* cardiomyocytes (28.7±3.5%, n=9 *versus* 14.7±2.0%, n=10; $P<0.05$), that could be attenuated by LTCC antagonists nisoldipine or diltiazem. BayK(-) also caused a greater increase in flavoprotein oxidation in $MHC^{403/+}$ *versus wt* cardiomyocytes (24.6±3.8%, n=7 *versus* 8.8±1.0%, n=15; $P<0.05$). Similar results were recorded in cardiomyocytes isolated from pre-cardiomyopathic $\alpha MHC^{403/+}$ mice. Our data indicate that $\alpha MHC^{403/+}$ mice exhibit altered cardiac LTCC kinetics and a hypermetabolic mitochondrial state following LTCC activation. This may contribute to the development of the cardiomyopathy because the responses occur in pre-cardiomyopathic mice. LTCC antagonists may be effective in reducing the cardiomyopathy by "normalizing" mitochondrial function.