decreased in AB cardiomyocytes with increasing pacing frequency, revealing a negative shortening-frequency relationship that was attenuated by both drug treatments. Length/width ratio was decreased in AB and AB-TAD animals with commensurate decreases in left ventricular (LV) end diastolic and end systolic volumes. Normal cardiomyocyte size and LV volumes were preserved in the AB-SAX group. Interestingly, all AB groups exhibited similar gross hypertrophic remodeling (heart weight:body weight ratio) despite differences in cardiomyocyte morphology. In conclusion, saxaglitin appears superior for preserving normal cardiomyocyte morphology and overall function versus tadafalil, independent of changes in cGMP-PKG activity.

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Direct Cardiotoxic Action of Quercetin, a Plant Flavonoid, through Mechanism Independent of Its Anti-Oxidative Action
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Quercetin (3, 3', 4', 5', 7-pentahydroxyflavone, QCT) is a major flavonoid of plants, known to exhibit anti-oxidative, anti-inflammatory, and anti-cancer effects. QCT has been demonstrated to have a cardioprotective effect through its antioxidant activity. In the present study, we found that QCT markedly enhanced the contractility of a single cardiomyocyte isolated from mouse hearts in a dynamic fashion even under conditions with no apparent oxidative stress. Simultaneous measurement of Ca$^{2+}$ transient in a Fura-2 loaded single cardiomyocyte revealed that QCT markedly increased the cytoplasmic Ca$^{2+}$ level at diastolic and systolic levels in regular electrical stimulation. Echocardiography revealed that intravenous administration of QCT also increased the left ventricular systolic function of the heart evaluated by ejection fraction in mice with reduced cardiac function due to a mutation causing genetic dilated cardiomyopathy (delK210 mutation in cardiac troponin T). QCT did not change the maximum force-generating capability and Ca$^{2+}$ sensitivity of force generation in skinned (membrane-permeabilized) cardiac muscle fibers prepared from mouse hearts, indicating that QCT has no direct effects on the contractile machinery in cardiomyocytes. These findings indicate that QCT has a direct cardiotoxic effect through enhancing the Ca$^{2+}$ transient in cardiomyocytes independently of its anti-oxidative action. Studies on the molecular mechanisms underlying these phenomena are in progress.

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DCM Mutation ACTCE361G Causes Uncoupling of Myofibril Sensitivity from Tnl Phosphorylation that can be Reversed by Epigallocatechin-3-Gallate
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We examined the relationships between troponin I phosphorylation and Ca$^{2+}$-sensitivity of force generation in myofibrils isolated from mouse hearts with and without 2-week treatments with L-NIO and apocynin (NADPH-oxidase inhibitors). We found that troponin I phosphorylation level on myofibril contractility was increased in mice treated with L-NIO and apocynin. Echocardiography revealed that intravenous administration of QCT also increased the left ventricular systolic function of the heart evaluated by ejection fraction in mice with reduced cardiac function due to a mutation causing genetic dilated cardiomyopathy (delK210 mutation in cardiac troponin T). QCT did not change the maximum force-generating capability and Ca$^{2+}$ sensitivity of force generation in skinned (membrane-permeabilized) cardiac muscle fibers prepared from mouse hearts, indicating that QCT has no direct effects on the contractile machinery in cardiomyocytes. These findings indicate that QCT has a direct cardiotoxic effect through enhancing the Ca$^{2+}$ transient in cardiomyocytes independently of its anti-oxidative action. Studies on the molecular mechanisms underlying these phenomena are in progress.

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Differential Involvement of Various Sources of Reactive Oxygen Species in Thyroxin-Induced Hemodynamic Changes and Contractile Dysfunction of the Heart and Diaphragm Muscles
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Thyroid hormones are key regulators of basal metabolic state and oxidative metabolism. Hyperthyroidism has been reported to cause significant alterations in hemodynamics, and cardiac and diaphragm muscle function, all of which have been linked to increased oxidative stress. Previously, we have shown that thyroxin (T4) treatment in mice resulted in hypertension, increased cardiac reactive oxygen species (ROS), cardiac hypertrophy, and cardiac contractile dysfunction. Here, we sought to investigate the functional impact of T4 on diaphragm muscle function as well as to identify the role and the source(s) of ROS in these distinct phenotypes of our model. Whole-body T4 mice with and without 2-week treatments with allopurinol (xanthine oxidase inhibitor), apocynin (NADPH-oxidase inhibitor), L-NIO (nitric oxide synthase inhibitor), or MitoTEMPO (mitochondria-targeted antioxidant) were studied. Blood pressure and echocardiography were non-invasively evaluated, followed by ex-vivo assessments of isolated heart and diaphragm muscle functions. Treatment with L-NIO attenuated the T4-induced hypertension in mice. However, apocynin improved the left ventricular (LV) dysfunction without preventing the cardiac hypertrophy in these mice. Both allopurinol and MitoTEMPO reduced the T4-induced fatty acidosis of the diaphragm muscles. In conclusion, we show here for the first time that T4 exerts differential effects on various sources of ROS to induce distinct cardiovascular and skeletal muscle phenotypes. Additionally, we find that T4-induced LV dysfunction is independent of cardiac hypertrophy, while NADPH-oxidase is a key player in this process. Furthermore, we prove the significance of both xanthine-oxidase and mitochondrial ROS pathways in T4-induced fatty acidosis of diaphragm muscles.