Causes of reduced myocardial efficiency in experimental pulmonary hypertension

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Myocardial efficiency of pulmonary hypertensive (PH) patients and isolated right ventricular papillary muscles from PH rats can be severely reduced. We aimed to determine the causes of the efficiency reduction in isolated papillary muscles of monocrotaline-injected PH rats (MCT, 60mg/kg; 8 control and 16 MCT male Wistar rats). After 3 weeks PH was confirmed by echocardiography and right ventricular papillary muscles were isolated. Work and suprabasal oxygen consumption were determined using the work loop technique: 4 min 5 Hz sinusoidal length changes at 92.5% of optimum length (L0), amplitude 0.15 L0 in 1.5 mM Ca2+ Tyrode solution at 37°C. Morphological and enzymehistochemical characteristics of the muscle and free wall were also quantified. Cardiolipin content was determined by HPLC-MS. Passive tension (overall m±SD: 23.9±9.3 mN/mm²) and active tension at 0.5Hz (75±28 mN/mm² myocyte) were similar in control and MCT muscles at L0. Net efficiency of control muscles was 15.5±4.9% and correlated with cross-sectional area of myocytes (273±88 μm²) in the muscle (r=0.84, P=0.017), indicating that larger myocytes are more efficient. However, net efficiency of MCT muscles was lower (9.4±7.4%, P=0.027) and did not correlate with myocyte cross-sectional area (448±88μm²). The stimulus phase for maximum work was 40±12° in control and differed (P=0.019) from 27±9° in MCT muscles, indicating slower force development in MCT muscles. Power output per loop tended to be lower in MCT muscles (1.24±0.56 versus 0.83±0.75 μJ/mm² myocyte, P=0.16). Work loops after crossbridge inhibition by blebbistatin (10μM) were -0.38±0.22 μJ/mm², indicating similar viscoelastic properties of control and MCT muscles. The stimulus phase for maximum work correlated with work (r=0.72, P=0.002) and efficiency (r=0.65, P=0.006) in MCT muscles, but not with myofibrillar CaATPase activity. Oxygen consumption during stimulation after blebbistatin correlated negatively with efficiency (r=-0.60, P=0.006), indicating increased oxygen consumption for non-contractile reactions in MCT muscles. Oligomycin-resistant MgATPase activity increased (P=0.004) whereas cardiolipin 72:8 decreased (P=0.023) in right-sided myocardium of MCT, indicating changes of the mitochondrial inner membrane. Monoamine oxidase A activity (P=0.004) and glucose-6-phosphate dehydrogenase activity (P=0.0004) in myocytes increased, indicating oxidative stress and increased oxygen consumption other than oxidative phosphorylation. These results demonstrate that metabolic rather than sarcomeric changes cause reduced myocardial efficiency in experimental pulmonary hypertension.