Contraction frequency dependence of twitch and diastolic tension in human dilated cardiomyopathy (Tension-frequency relation in cardiomyopathy)

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Summary: We studied isometric twitch tension and diastolic tension at 37 °C as a function of stimulation frequency (12–240 min⁻¹) in very thin (.07-.5mm²), parallel fibered strips of left-ventricular myocardium. Non-failing control tissue (C) was obtained from epicardial biopsies taken during myocardial revascularization surgery on patients with normal ventricular function. End-stage failing tissue was obtained from endocardial and epicardial biopsies from explanted hearts with idiopathic dilated cardiomyopathy (DCM). The methods and apparatus for biopsy and dissection of myocardium are described. Maximal peak twitch tension at optimal stimulation frequency of 163 ± 5 min⁻¹ was 41.8 ± 10 mN/mm² in non-failing myocardium and it was reduced by 70 % (p < .02) to 12.9 ± 1.6 mN/mm² at an optimal frequency of 72 ± 17 min⁻¹ in DCM. The peaks of the tension-frequency curves occurred at frequencies between 12 and 60 min⁻¹ in most DCM strips (5/9), while in C most of the peaks (8/9) fell between 156 and 180 min⁻¹. The peaks from four DCM hearts fell in an intermediate range of frequencies (96–144 min⁻¹) which also included one non-failing peak at 132 min⁻¹. Diastolic tension declined in both groups as stimulation frequency increased above 12 min⁻¹ and it began increasing when stimulation frequency rose above optimal frequency by 19 ± 5 % and 110 ± 50 % in C and DCM, respectively. Total duration of the isometric twitch diminished with tachycardia remaining shorter than stimulation intervals up to 140 ± 16 min⁻¹ (3.1 ± 1 times optimal frequency) in DCM and up to 161 ± 14 min⁻¹ (not different than optimal frequency) in C. Decline in peak twitch tension above optimal stimulation frequency was 4 to 6 times larger than the accompanying rise in diastolic tension in both groups. The premature decline in tension at lower than normal degrees of tachycardia in DCM does not arise from incomplete relaxation of the twitch response. The 70 % deficit in tension generating ability of DCM may be a major contributor to heart failure. Moderate shift in the peak of the tension-frequency curves to lower frequencies (130 min⁻¹) in C does not appear to predispose end-stage failure, but it may make the ventricle more susceptible to dilation.

Key words: Idiopathic dilated cardiomyopathy; cardiac failure; twitch tension-frequency relation; diastolic tension-frequency relation; biopsy and dissection techniques

Introduction

In primary congestive heart failure, ventricular performance is depressed. In addition to low cardiac output at rest the necessary increase in cardiac output with exercise is

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greatly diminished or absent in cardiomyopathy, possibly as a result of absence of the normal decrease in end-systolic ventricular volume and a smaller than normal increase in stroke volume (14, 24). Measurements obtained by cardiac catheterization in cardiomyopathic as compared with normal patients show increased end-diastolic pressure, reduced rates of left-ventricular pressure generation and relaxation and a lowering of the positive slope of the pressure-rate vs. contraction frequency relation (5). The elevated end-diastolic pressures may also be attributed to reduced diastolic compliance of the ventricle, as well as to the reduced systolic emptying resulting from the diminished rates of pressure build-up and relaxation (7).

Evidence that these defects in cardiac performance may be related to alterations in myocardial contractility and its inotropic response to tachycardia has been accumulating (8, 9, 10, 19, 21). Measurements of twitch tension in isolated left-ventricular strips from explanted cardiomyopathic hearts compared with non-failing hearts show reductions in peak rates of generation and relaxation of twitch tension and a decrease in slope of the tension-rate vs contraction frequency relation which parallel the cath-lab measurements (19, 21).

Measurements of aequorin light emission during the twitch of isolated trabeculae from cardiomyopathic hearts are consistent with a decrease in rate of calcium uptake during relaxation and show an increase in end-diastolic calcium concentration is present in the failing myocardium (8, 9, 10). These changes may be related to a reduction in Ca$^{2+}$ ATPase of the sarcoplasmic reticulum in the failing hearts (3).

We studied the stimulation frequency dependence of contraction and relaxation in isolated myocardial strips to further understand the role of the tension-frequency relation in heart failure and to determine if the onset of incomplete relaxation of the twitch above a critical contraction frequency might be the mechanism of reduction in twitch tension in myocardium from failing hearts. In order to compare the performance of endstage failing myocardium from heart transplant recipients with myocardium from non-failing hearts, a method was developed to safely obtain viable left-ventricular biopsies from patients with normal left-ventricular function who were undergoing myocardial revascularization surgery.

The results show reduced contractility and reduced inotropic response to tachycardia in failing myocardium and do not support the hypothesis that incomplete relaxation is the basis for the reduced contractility in DCM.

Methods

Severely failing myocardium (NYHA IV). Left-ventricular tissue was obtained from the explanted hearts of five patients (46 ± 3 years old; three males, two females) undergoing cardiac transplantation surgery following a protocol approved by the Committee for the Protection of Human Subjects at Brigham and Women’s Hospital, Boston, MA. These patients were diagnosed as having end-stage (NYHA IV) heart failure due to idiopathic dilated cardiomyopathy (Ejection Fraction = 0.12 ± 0.01 SEM). Excised hearts were washed of blood with chilled saline solution. Left-ventricular myocardium was dissected into 2-4 g sheets from the inner or outer walls of the left ventricle within 15 min of explantation.

Non-failing myocardium. With full approval from the University of Vermont Committee on Human Research and signed, informed consent, left-ventricular biopsies were