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Ventricular Hypertrophy/CHF: Existence of the Frank-Starling Mechanism in the Failing Human Heart: Investigations on the Organ, Tissue, and Sarcomere Levels

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Background: The Frank-Starling mechanism is one of the most important physiological principles for regulation of contractile performance. We therefore studied the question of whether this mechanism may be absent or attenuated in end-stage failing human left ventricular myocardium.

Methods and Results: Different methodological approaches were used to analyze the effects of this mechanism on the organ, tissue, and sarcomere levels: (1) In excised human whole left ventricles (2 donor hearts, 5 failing hearts), diastolic and systolic pressure-volume relationships were obtained. (2) In isolated muscle strip preparations from the left ventricular wall of donor hearts (n = 14) and failing hearts from patients with idiopathic dilated cardiomyopathy (n = 21) and ischemic cardiomyopathy (n = 11), peak developed force was measured at different muscle lengths of the preparation. (3) Skinned fiber preparations were obtained from failing right and left ventricules (n = 12). In all three studies, we clearly observed the existence of the Frank-Starling mechanism: (1) In isolated failing human left ventricles, peak developed isometric pressure is increased when the preload is elevated. (2) Peak developed tension is increased by [nearly equal] 50% to 70% (P < .01) in left ventricular preparations of failing and nonfailing ventricles when the muscles are stretched from 90% to 100% optimum length. (3) An increase in sarcomere length leads to a sensitization of contractile proteins of ventricular skinned fiber preparations from failing human hearts. At 1.9-micro meter sarcomere length, the EC₅₀ value was 5.56 +/- 0.06, and at 2.3 micro meter it was 5.70 +/- 0.05 (P < .01; n = 7).

Conclusions: The Frank-Starling mechanism is maintained in end-stage failing human hearts, whereas significant alterations of diastolic myocardial distensibility are evident in chronic heart failure. (Circulation. 1996;94:683-689.)

Key Words: heart failure, contractility, ventricles.

Three basic mechanisms regulate the contractile strength of the heart in the acute setting. First, muscle force and stroke volume vary directly with sarcomere length and preload, respectively, phenomena broadly referred to as the Frank-Starling law of the heart. [1-3] Second, myocardial force development is heart rate dependent; peak isometric force increases with heart rate in normal mammalian myocardium, [4] including human cardiac muscle. [5-7] Third, cardiac muscle is under neurohumoral control, including the sympathetic and vagal nervous systems [8] and some polypeptides such as angiotensin [9] and endothelin. [10].

In end-stage heart failure, there is clear evidence that the effectiveness of the two latter mechanisms to increase myocardial contractile performance is attenuated. Catecholamine responsiveness is blunted because of downregulation of beta-adrenoceptors and alteration in G₁-proteins, [11-13] and the force-frequency relationship is inverse. [5-7] Recent studies [14,15] also have suggested that the ability of preload to modulate contractile strength is absent in human myocardium in end-stage heart failure. The potential loss of preload-dependent regulation of contractile performance would have major clinical implications and would demand evaluation of the molecular mechanisms underlying such a defect. Therefore, it was the purpose of the present study to further clarify the differences in preload responsiveness of normal and failing human myocardium. Three different types of experiments were performed. First, the impact of preload volume on isovolumic pressure development was determined in explanted, blood-perfused normal and failing human hearts. Second, the distolic and systolic length-tension relationships of isolated intact muscle from normal and failing hearts were obtained. Third, since length dependence of contractile force can be attributed at least in part to an

apparent length dependence of calcium sensitivity of the myofilaments, [16-19] contractile force also was studied in skinned fiber preparations at different sarcomere lengths and calcium concentrations. The data obtained at the organ level, the myocardial tissue level, and the myofilament level all indicate that as in the normal heart, contractile strength of failing myocardium varies directly and strongly with preload; the Frank-Starling mechanism is present in end-stage heart failure.

Methods

Whole Heart Preparations

Five hearts were obtained at the time of transplant from patients with end-stage DCM. All patients were treated with digitalis, diuretics, and ACE inhibitor therapy. The average ejection fraction was 17 + -5% by echocardiography, with an end-diastolic dimension of 6.8 + -0.9 cm. In addition, two normal hearts were obtained from organ donors that were technically not suitable for transplantation. This study was approved by the Institutional Review Boards of Columbia-Presbyterian Center. Family members of normal heart donors gave consent for the specific use of the hearts for research purposes.

Techniques used to revive and preserve heart function were similar to those described previously. [20] In brief, hearts were arrested with cold (4 degrees C) cardioplegic solution, explanted, and transported from the operating room to the laboratory in the same solution. The time from the initiation of cardioplegic arrest to the start of coronary perfusion in the laboratory was less than 2 hours.

The chordae tendineae were severed from the mitral valve, and a metal adapter, used to hold the heart to a volume servo-system (described below), was sutured to the mitral annulus. The right and left coronary arteries were individually cannulated with stiff, 7F polyethylene tubing held in place by suturing to the aortic root. These cannulas then were connected to the arterial port of the perfusion system that was composed of a bubble oxygenator and heater (Harvey, model H200), a blood filter (Shiley), and a peristaltic pump (Harvey Apparatus, model 1215). Coronary venous blood was collected in a large funnel that drained back to the oxygenator. Arterial flow rate was controlled by the finger pump, which provided a coronary perfusion pressure between 100 and 120 mm Hg. The temperature of the perfusate was maintained at 37 degrees C. The hearts were paced at a rate between 50 and 60 bpm by means of bipolar epicardial leads placed near the left ventricular apex. The perfusate was a mixture of recently outdated human packed red blood cells and a physiological Ringer's solution. [20].

A volume servo-system (described in detail previously [20]) was used to control ventricular volume. A linear motor controlled the position of a piston inside a cylinder. A large, compliant, latex balloon was secured to a rigid tube that was connected to the outflow port of the cylinder. The unstretched volume of the balloons was about 300 mL, which was larger than the volumes tested in the hearts. A linear displacement transducer sensed the piston position, thus producing a signal proportional to ventricular volume. Ventricular pressure was measured by a semiconductor pressure sensor (Millar) positioned inside the balloon.

Isolated Heart Protocol and Data Analysis

The ventricles were constrained to contract isovolumically. End-diastolic and end-systolic pressures were measured as ventricular volume was varied slowly over a range that produced end-diastolic pressures between 0 and 20 mm Hg. The resulting pressures were plotted as functions of volume, which resulted in construction of ESPVR and EDPVR. In addition, LVDP, defined as the difference between end-systolic and end-diastolic pressure, was plotted as a function of ventricular volume to quantify the influence of preload on pressure-generating capacity.

Left Ventricular Strip Preparations

For studies of isolated cardiac muscle, explanted hearts were received from the Cardiac Transplantation Center, Bad Oeynhausen, Germany. Preparations were taken from 14 donor hearts that could not be used for transplantation for technical reasons. Donor hearts that were not used for transplantation showed normal ejection fractions (> 50%) by echocardiography and no clinical signs of myocardial infarction or coronary artery disease. Preparations also were available from 11 explanted hearts of patients with end-stage chronic heart failure due to ischemic cardiomyopathy (New York Heart Association class III-IV) and from 21 explanted hearts of patients with heart failure due to DCM (NYHA class IV). Patients were between 13 and 73 years old. Mean left ventricular ejection fraction in the heart failure group was 18 +/- 6%. All of the patients were treated with therapeutic levels of digitalis (digoxin or digitoxin), diuretics (furosemide, xipamide, piretanide), and ACE inhibitors (captopril, enalapril, and lisinopril). One third of the patients received intravenous low-dose dopamine. All patients undergoing heart transplantation had given written informed consent for the myocardial tissue to be used for scientific purposes.

Immediately after explantation, papillary muscles and parts of the free left ventricular wall were dissected and submerged into Krebs-Ringer solution that contained 30 mmol/L BDM (butanedione monoxime [21,22]) and

10-IU/L insulin. The composition of the solution used is given elsewhere. [9] Transportation time, during which the solution was constantly bubbled with 95% $O_2/5\%$ CO₂, was [nearly equal] 7 hours for all hearts. Preparations were performed in a special dissection chamber with the use of a stereomicroscope (VMT Olympus). The cutting procedure for myocardium with the use of special dissection chambers and microdissection scissors is described elsewhere. [9,21,22] Dimensions of the preparations are given in Table 1.

	Donor	DCM	ICM
No. of hearts	14	21	11
No. of preparations	16	22	11
I _{max} , mm	4.2±0.2	4.8±0.2	6.1±0.35
Cross-sectional areas, mm ²	0.35 ± 0.03	0.44 ± 0.02	0.36 ± 0.02
Peak developed tension, mN/mm ²			
At I _{max}	21.7±2.6*	19.4±1.8*	19.3±2.8*
At 90% Imax	14.1±2.3	11.5±1.0	11.5±1.9
Resting tension, mN/mm ²			
At I _{max}	11.3±1.3	16.7±1.1†	15.8±1.5†
At 90% Imax	4.2±0.6	7.0 ± 1.0	6.7±1.1

*P<.001 compared with peak developed tension at 90% I_{max}; †P<.0 compared with donor.

Table 1. Number of Preparations and Hearts, Preparation Dimensions, Peak Developed Tension, and Resting Tension at l_{max} and 90% l_{max}

Isolated Muscle Strip Protocol

The muscle strip preparations were placed into the muscle bath, which was constantly perfused (7 mL/min) with Krebs-Ringer solution without BDM, and attached to an isometric force transducer. The muscle preparations were initially prestretched so that active tension was developed at minimal diastolic tension (slack length). Preparations were stimulated at 30 bpm throughout the whole experiment with end-to-end stimulation. Stimulation duration was 5 ms, and voltage was set to 25% above threshold. Isometric active tension and passive tension were measured by an isometric force transducer (Scientific Instruments; resonance frequency, 600 Hz) and recorded on a Lineacorder WR 3310 (Graphtec Corp). After steady-state conditions were obtained at slack length (time duration at slack length was between 5 and 15 minutes), the preparations were carefully stretched to L_{max} , the length at which maximum force is developed. Depending on absolute muscle length, we used either 0.10- or 0.05-mm stretches. After each stretch, a period of 5 to 10 minutes allowed the muscle to stabilize with respect to viscoelastic diastolic properties as well as actively developed tension. Resting tension and peak developed tension were measured from the ascending length-tension relationship at least 5 minutes after the last stretch. L sub max was defined as the length of the muscle before the final stretch, which did not either induce an increment or even cause a small decrease in peak developed tension. Bath temperature was regulated at 37 degrees Celsius by means of an electronic feedback system. After each experiment, the weight of the muscle preparation was determined after it was blotted three times. Cross-sectional area was calculated from the muscle length at L_{max} and the muscle weight, assuming a specific gravity of 1. In part of the preparations, we measured force-frequency relationships by increasing the stimulation rate from 0.5 to 1.0 and 2.0 Hz. In some other experiments, isoproterenol (3 x 10 sup -8 mol/L) was applied at the end of the experiment to define betaadrenoceptor-dependent contractile reserve.

Skinned Fiber Preparations

Muscle fibers were prepared with a length of 5 to 6 mm and a weight of 0.25 to 0.35 mg from explanted hearts of patients with DCM. Transport circumstances were the same as indicated above.

The preparations were skinned by incubation in a solution containing EGTA (5 mmol/L), imidazole (20 mmol/L), saccharose (150 mmol/L), KCl (50 mmol/L), and TES (N-tris[hydroximethyl]methyl-2aminoethanesulfonic acid) (1.3 mmol/L)for 30 minutes and a second incubation in a solution containing EGTA (4.4 mmol/L), imidazole (25 mmol/L), KCl (20 mmol/L), TES (1.3 mmol/L), MgCl sub 2 (4 mmol/L), Triton X-100 (1%), Na₂ ATP (1.1 mol/L), and glycerin (50%) for 60 minutes. Thereafter, the skinned fibers were stored in the same solution but without Triton X-100 at a temperature of -78 degrees C for up to 7 days.

For the actual experiments, activation solutions were prepared according to Smith and Martell [23]: EGTA (4 mmol/L), imidazole (10 mmol/L), MgCl₂ (12 mmol/L), KCl (180 mmol/L), NaN₃ (5 mmol/L), Na₂ ATP (5.1 mmol/L), and CaCl₂ (up to 2 mmol/L). Ionic strength was 0.20. A variety of solutions were prepared so that the pCa was 8, 6.5, 6.25, 6, 5.75, 5.25, and 4. We accomplished measurements of force by using the same force transducer mentioned above. Sarcomere length was measured by diffraction of a 670-nm laser (Scientific Instruments). The EC₅₀ values were calculated from the respective Hill plots.

Statistics

Values are given as mean +/- SE in the text and Table 1. Comparison between different groups of experiments was accomplished with the use of ANOVA and the Student-Newman-Keuls test. [24] For comparison within one group of experiments, the paired t test was applied.

Results

Whole Heart Preparations

The impact of a gradual change in intraventricular balloon volume on isovolumic left ventricular pressure from DCM patients is shown in Figure 1(A). As seen in this typical example, both diastolic and systolic pressures increased with ventricular volume. The plots of diastolic and systolic pressures as a function of volume (Figure 1 (B)) and the relationship between volume and developed pressure (Figure 1(C)) indicate that contractile strength of the intact heart varies directly with ventricular volume.



Figure 1. Results from a heart with DCM. A, Changes in ventricular pressure resulting from a gradual increase in ventricular volume. B, ESP and EDP are plotted as a function of volume. C, Developed pressure (defined as ESP minus EDP) increases as volume is increased.

ESPVRs, EDPVRs, and LVDPVRs from all hearts studied are shown in Figure 2. In comparison to the normal hearts, all of these relations are shifted toward larger volumes in the DCM hearts. These data indicate that maximum ventricular performance is reached at much higher volumes compared with normal ventricles.



Figure 2. Results from 5 hearts with DCM (filled symbols) and 2 normal hearts (open symbols). A, End-systolic pressure-volume relations; B, end-diastolic pressure-volume relations; and C, impact of volume on developed pressure.

Left Ventricular Strip Preparations: The Frank-Starling Mechanism

Typical examples of the length-tension relationship for failing human myocardium are demonstrated in Figure 3 and Figure 4. Isometric peak developed force gradually increases in the failing preparations when the muscle is stretched to l_{max} . For pooling of the data and statistical purposes, peak developed tension and diastolic tension were evaluated at 100% and 90% l_{max} (Figure 4 and Figure 5). On average, peak developed force increased from 14.1 +/- 2.3 mN/mm² (90% l_{max}) to 21.7 +/- 2.6 mN/mm² (100% l_{max}) in preparations from donor hearts (P < .01), from 11.5 +/- 1.9 mN/mm sup 2 (90% l_{max}) to 19.3 +/- 2.8 mN/mm² (100 l_{max}) in preparations from failing ventricles with ICM (P < .01), and from 11.5 +/- 1.0 mN/mm² (90% l_{max}) to 19.4 +/- 1.8 mN/mm sup 2 (100% l_{max}) in preparations from failing left ventricles with DCM (P < .01; Table 1 and Figure 5).



Figure 3. Original record of a typical experiment. Isolated muscle strip preparation of a failing left ventricle (DCM; NYHA IV). Muscle length was 5.4 mm and cross-sectional area 0.46 mm² at l_{max} . The muscle was gradually stretched from slack length to l_{max} with the use of 0.05-mm stretches. Arrow indicates a change in amplification.



tension (right). Donor indicates left ventricular muscle strip preparations from donor hearts. Values are mean +/- SE. *P < .05, **P < .01.

(Figure 5 and Table 1) also present data on diastolic properties of isolated human myocardium. Whereas no significant differences of resting tension are seen between failing and nonfailing myocardia at 90% l_{max} , average diastolic tension at l_{max} is only 11.3 +/- 1.3 mN/mm² in nonfailing myocardium, 15.8 +/- 1.5 mN/mm² in ICM, and 16.7 +/- 1.1 mN/mm² in DCM (P < .05). Therefore, myocardium from failing left ventricles is considerably stiffer than that from normal left ventricles (Figure 5).

Left Ventricular Strip Preparations: Force-Frequency Relationships and beta-Adrenergic Response

In some of the preparations given in Table 1, additional experiments were performed: When stimulation rate was increased in preparations from donor hearts, peak developed force increased significantly by 32% (1 Hz) and 74% (2 Hz). In contrast, the force-frequency relationship was inverse in DCM and ICM, as shown in Table 2. The observed decrease in peak developed tension with increasing stimulation rate was significant in DCM (P < .05) but not in ICM.

	Stimulation Rate, Hz		
	0.5	1.0	2.0
Donor (n=8 hearts)	100	132±7*†	174±8*†
DCM (n=14 hearts)	100	88±4†	76±4†
ICM (n=5 hearts)	100	95±5	81±3

*P<.01 compared with DCM and ICM; †P<.05 compared with basal values at 0.5-Hz stimulation rate.

Table 2. Force-Frequency Relationship Obtained at l_{max} : Developed Force Is Normalized to Basal Values at 0.5-Hz Stimulation Rate (%)

Isoproterenol (3 x 10 sup -8 mol/L) was highly effective in donor heart preparations. In contrast, isoproterenol had only little effect on contractile performance in DCM and ICM myocardia (Table 3).

	Basal	ISO, 3×10 ⁸ mol/L
Donor (n=7 hearts)	100	308±46*†
DCM (n=11 hearts)	100	119±2†
ICM (n=4 hearts)	100	123±11

*P<.01 compared with DCM and ICM; †P<.05 compared with basal values.

Table 3. Beta-Adrenoceptor Stimulation: Developed Force Is Normalized to Basal Values Obtained at l_{max} and 0.5-Hz Stimulation Rate (%)

Skinned Fiber Preparations

A typical example of an experiment in a skinned fiber preparation is shown in Figure 6. Sarcomere lengths were 1.9 micro meter, 2.4 micro meter, and 2.05 micro meter as measured by laser diffraction. It is clear that the muscle fiber is much more sensitive to pCa 6 at a sarcomere length of 2.4 micro meter compared with 2.05 micro meter or even 1.9 micro meter.



Figure 6. Original record of a typical skinned fiber experiment. Top, At a sarcomere length of 1.9 micro meter, the fiber was activated with pCa = 6 and pCa = 4. After calcium concentration was reduced to pCa = 8, the fiber was stretched (sarcomere length [SL], 2.4 micro meter) and activated again using pCa = 6 and pCa = 4 (middle). To demonstrate reversibility of the stretch effect, the calcium concentration was reduced to pCa = 8 and the fiber released to a sarcomere length of 2.05 micro meter. The activation procedure was performed again (bottom). Note that at pCa = 6, force is highest at a sarcomere length of 2.4 micro meter. Fiber preparation was obtained from the left ventricte of a DCM heart, NYHA III-IV.

In the same way as demonstrated in Figure 6, pCa-force relations were analyzed for 9 preparations obtained from the right ventricle (n = 4) as well as the left ventricle (n = 3) of end-stage failing hearts. No differences were found between right and left ventricular preparations. Figure 7 and Table 4 clearly demonstrate a significant leftward shift of the pCa-force relation for all studied preparations with increasing sarcomere length. The EC₅₀ value at 1.9 micro meter was 5.56 + /-0.06 and at 2.3 micro meter was 5.70 + /-0.05 (P < .01).



Figure 7. Force plotted as a function of pCa for different sarcomere lengths. Force was expressed as percent of maximum force at pCa = 4. An increase in sarcomere length leads to a leftward shift of the activation curve. Pooled data from 7 failing hearts with DCM (n = 9 preparations).

	Sarcomere Length, µm		
pCa	1.9±0.1	2.3±0.1	
8	0	0	
6.5	0.27±0.20	1.17±0.36	
6.25	1.11±0.30	3.11±0.92*	
6.00	6.62±2.32	14.96±3.58*	
5.75	31.95±9.10	48.10±7.64*	
5.25	89.21±3.15	93.52±2.16	
4.00	98.41±1.59	97.98±1.31	

n=4 right ventricles and n=3 left ventricles. Mean \pm SEM values of force are given; force is expressed as percent of maximum force (pCa=4). *P<.01 compared with 1.9 \pm 0.1- μ m sarcomere length. Absolute max-

imum force per cross-sectional area was 30.98±5.26 mN/mm². Table 4. Skinned Fiber Experiments: Force Measured in DCM Preparations of Right and Left Ventricles

In addition, skinned fibers were activated with a solution of pCa = 6 and stepwise stretched to greater sarcomere lengths. As shown in Figure 8, there is a clear increase in developed force for all preparations of the



left and right ventricles at greater sarcomere lengths.

Figure 8. Force plotted as a function of sarcomere length at a constant pCa = 6. Sarcomere length was directly measured by laser diffraction. Developed force is expressed as a fraction of maximum force development at pCa = 4.

Discussion

There are at least three basic mechanisms that regulate contractile strength of the heart in vivo: the Frank-Starling mechanism, [1-3] the force-frequency relationship, [4-7] and the sympathetic and vagal nervous systems. [8,12,13] Significant alterations of the failing human myocardium already have been described in detail for the force-frequency relationship [5-7] and the beta-adrenoceptor system. [11-13] Recently, it also has been suggested that the length dependence of contractile performance in failing human myocardium is also absent. [14,15,25] Because of its primary importance, the purpose of the present study was to clarify whether loss of the Frank-Starling mechanism represents a third major defect in advanced heart failure.

Studies performed in intact hearts revealed that end-systolic and end-diastolic pressures increased when volume was increased. Both end-systolic and end-diastolic pressure-volume relations were shifted toward much larger volumes in cardiomyopathic hearts compared with normal hearts, reflecting the large degree of structural remodeling that is typical for this disease. Nevertheless, the effect of volume was greater on ESP than EDP, as revealed by the fact that developed pressure (ESP minus EDP) also varied directly with ventricular volume. Thus, there is clear evidence that preload influences ventricular performance at the whole heart level. These findings are consistent with results of previous clinical studies in patients with chronic heart failure demonstrating that end-systolic pressure and stroke volume decrease as preload is abruptly curtailed by inferior vena caval occlusion. [16,26,27].

As can be seen from Figure 2(A and C), the slopes of ESPVRs and LVDPVRs are low in four of five DCM ventricles, which indicates depressed contractile states in these hearts. However, low slopes of ESPVRs and LVDPVRs may be due to geometric factors according to LaPlace, may represent an attenuation of the Frank-Starling mechanism, or both. Therefore, it is necessary to test the preload dependence of force development in isolated muscle preparations obtained from failing hearts. These studies (see Figure 3, Figure 4, and Figure 5) not only reveal that contractile force is clearly preload dependent in preparations from the left ventricles of donor, DCM, and ICM hearts but also demonstrate full effectiveness of the Frank-Starling mechanism in failing myocardium. In addition, depressed myocardial performance is clearly demonstrated in part of the studied

preparations: In DCM as well as ICM left ventricular myocardium, the force-frequency relationship is shown to be inverse (Table 2) and beta-adrenoceptor stimulation is shown to be blunted (Table 3).

The finding of a maintained Frank-Starling mechanism in failing human heart is in clear contrast to recently published data of Bohm et al and Schwinger et al. [14,15] To explain these discrepancies, two possibilities must be discussed: (1) Differences in the study design: First, we used BDM as a protection against cutting injury. Second, in the present study, we used a different stretching protocol in which the muscles were carefully stretched by length changes of 0.05-mm and 0.1-mm steps, creating very little resting tension (Figure 3 and Figure 4). In contrast, the cited authors used fixed and high preloads. [14,15] (2) Differences in properties of isolated myocardium: Maximal developed force values are low in normal myocardium and extremely low in failing myocardium in Schwinger and colleagues' report compared with the present values; we measured greater than threefold higher force values (21.7 mN/mm sup 2 in this study compared with 6.2 mN/mm² in their study [14,15]). In failing human myocardium, peak developed force at 1_{max} was even six times higher in the present study compared with their studies. [14,15] Diastolic tension is clearly demonstrated to be higher in failing myocardium in nonfailing myocardium, which has been attributed to an increased interstitial collagen formation. [28-31] In contrast, Schwinger et al postulated that no differences between the resting tension curves of failing and nonfailing human myocardia were seen.

Regarding diastolic and systolic properties of the present muscle preparations, the measured parameters are very similar to those obtained in animal experiments: For example, peak developed force has been shown to be greater or equal to [nearly equal] 20 mN/mm² in normal ferret, [32] rat, [33] cat, [34,35] rabbit, [36] guinea pig, [37] and human myocardia. [38,39] In failing human myocardium, similar values have been reported. [38,39] To characterize the quality of isolated muscle preparations, the active-to-passive tension ratio often has been used. [40,41] In the present study, this ratio was 1.9 in nonfailing myocardium (see Table 1). In Schwinger and colleagues' [14,15] report, the respective values were calculated to be 0.30 in nonfailing tissues and only 0.12 in failing tissues.

The length dependence of contractile force is brought about mainly by changes in the Calcium²⁺ sensitivity of the myofibrils, possibly as the result of altered Calcium²⁺ affinity of troponin C. [16-19] Therefore, in addition to whole heart and intact muscle strip experiments, we exposed skinned fibers obtained from the right and left ventricles of failing hearts to different calcium concentrations, varying the length of the muscle. It is important to note that sarcomere length measurements were accomplished, which allowed us to correlate developed force directly to sarcomere length. As shown in Figure 6, Figure 7, and Figure 8, increases in sarcomere length lead to significant increases in developed force at calcium concentrations that are equivalent to physiological activation of cardiac muscle. Therefore, these data indicate that the Frank-Starling mechanism is maintained at the sarcomere level in failing myocardium.

Conclusions

We have found that the Frank-Starling mechanism is well preserved in failing human myocardium. This finding has important clinical implications: Left ventricular filling pressure should be kept high enough to reach the benefit of the length dependency of contractile performance but low enough to prevent pulmonary congestion in end-stage heart failure. On the other hand, from the presented data we cannot draw conclusions on sarcomere lengths in decompensated patients with end-stage heart failure. However, it is reasonable to assume that the left ventricle operates near or even beyond the optimal sarcomere lengths, indicating reduced or even no preload reserve. In addition, reduced diastolic compliance has been found in isolated preparations of failing human ventricles. This indicates that higher end-diastolic stresses and pressures are necessary to reach optimal contractile force in failing hearts compared with normal hearts.

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