Altered Myocardial Force–Frequency Relation in Human Heart Failure

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Background. In congestive heart failure (idiopathic dilated cardiomyopathy), exercise is accompanied by a smaller-than-normal decrease in end-diastolic left ventricular volume, depressed peak rates of left ventricular pressure rise and fall, and depressed heart-rate-dependent potentiation of contractility (bowditch treppe). We studied contractile function of isolated left ventricular myocardium from New York Heart Association class IV-failing and nonfailing hearts at physiological temperature and heart rates in order to identify and quantitate abnormalities in myocardial function that underlie abnormal ventricular function.

Methods and Results. The isometric tension-generating ability of isolated left ventricular strips from nonfailing and failing human hearts was investigated at 37°C and contraction frequencies ranging from 12 to 240 per minute (min⁻¹). Strips were dissected using a new method of protection against cutting injury with 2,3-butanedione monoxime (BDM) as a cardioplegic agent. In nonfailing myocardium the twitch tension–frequency relation is bell-shaped developing 25±2 mN/mm² at a contraction frequency of 72 min⁻¹ and peaking at 44±3.7 mN/mm² at a contraction frequency of 174±4 min⁻¹. In failing myocardium the peak of the curve occurs at lower frequencies between 6 and 120 min⁻¹, averaging 81±22 min⁻¹, and it develops 48% (p<0.001) and 80% (p<0.001) less tension than in nonfailing myocardium at 72 and 174 min⁻¹, respectively. Between 60 and 150 min⁻¹ tension increases by 107% in nonfailing myocardium, but it does not change significantly in failing myocardium. Peak rates of rise and fall of isometric twitch tension vary in parallel with twitch tension as stimulation frequency rises in nonfailing myocardium but not in failing myocardium.

Conclusions. The quantitative agreement between these results from isolated myocardium and those from catheterization laboratory measurements on intact humans suggest that alterations of myocardial origin, independent of systemic factors, may contribute to the above mentioned abnormalities in left ventricular function seen in dilated cardiomyopathy. (Circulation 1992;85:1743–1750)

KEY WORDS • force–frequency relation • idiopathic dilated cardiomyopathy • myocardial twitch tension • tachycardia

In congestive heart failure, exercise is accompanied by a smaller-than-normal decrease in end-systolic ventricular volume and a smaller-than-normal increase in stroke volume.¹² In addition, peak rates of left ventricular pressure rise and fall are depressed and the heart rate–dependent potentiation of these parameters is greatly reduced or absent.³ Evidence suggesting that these deficiencies in cardiac performance in heart failure result from depressed contractility of the myocardium arises from observations of reduction or reversal of the normal positive inotropic response of isolated myocardium to increased stimulation frequency (frequency treppe).⁴⁻⁵

The present study was undertaken to extend these observations by covering a wider range of stimulation frequencies at 37°C to better approach physiological conditions. This was made possible by using a newly developed method of obtaining very thin muscle strip preparations from left ventricular epicardial or endocardial myocardium of patients undergoing open-heart surgery or heart transplantation.⁶

The results show that an even greater disparity in force generation in failing compared with nonfailing myocardium exists at exercise levels of heart rate than has previously been observed at low contraction frequencies.

Methods

General Procedure

Failing myocardium. Left ventricular tissue was obtained from the explanted hearts of six patients (43±5 years old; four men, two women) undergoing cardiac transplantation surgery following a protocol approved by the Committee for the Protection of Human Subjects at Brigham and Women’s Hospital, Boston, Mass. These patients were diagnosed as having end-stage New York Heart Association class IV heart failure (ejection fraction, 0.13±0.01 SEM) because of idiopathic dilated
cardiomyopathy (DCM). Excised hearts were cooled and washed of blood with chilled saline solution. The left ventricular myocardium was dissected into 2- to 4-g sheets from the inner or outer walls of the left ventricle within 15 minutes of cardiectomy.

**Nonfailing myocardium.** Biopsy strips of left ventricular myocardium (1.5×1.5×12 mm long) were dissected with a scalpel from infarct-free regions of the epicardial surface of hearts immediately after cardiac arrest for coronary artery bypass surgery at the Medical Center Hospital of Vermont, Burlington, Vt. All biopsies were cut parallel to the muscle fiber direction that was visible to the surgeon using surgical loupes. These patients (60±4 years old; four men, two women) were selected as having normal left ventricular wall motion and left ventricular function (ejection fraction, 0.66±0.03).

Informed consent was obtained from all tissue donors and consent forms, tissue biopsy techniques, and experimental protocols were approved by the University of Vermont Committee on Human Research. There were no complications (bleeding, arrhythmias) in any of the patients participating in this study.

**Protection of tissue from deterioration.** All excised tissue was immediately submerged in 2,3-butanedione monoxime (BDM)-Krebs protective solution6 at room temperature and oxygenated by bubbling with 95% O2–5% CO2.

Tissue from explanted hearts was transported by car from Boston to Burlington within 5 hours in continuously gassed jars at 20°C. Nonfailing tissue arrived in the laboratory within 15 minutes of excision and was usually used within 2 hours after excision (except in control experiments for the effect of soak time).

**Solutions.** Krebs-Ringer solution7 was modified by doubling the glucose concentration and adding insulin to improve viability and long-term survival of the myocardial tissue. It contained (in mmol/l): Na 152, K 3.6, Cl 135, HCO3⁻ 25, Mg²⁺ 0.6, H2PO4⁻ 1.3, SO4²⁻ 0.6, Ca²⁺ 2.5, glucose 11.2, and insulin 10 IU/l. The BDM-Krebs protective solution consists of this Krebs-Ringer solution to which 30 mmol/l BDM was added. BDM was obtained from Sigma. Glass-distilled water was used for all solutions.

**Muscle strip preparation.** A biopsy strip (diameter, 1–3 mm) of myocardial tissue was clamped between the ends of plastic rods submerged in protective solution in a dissection chamber at room temperature (21°C). The strip could be rotated axially to facilitate dissection on all surfaces using microdissection scissors (6-mm blade) and forceps under a ×10 binocular microscope. The endocardium or epicardium plus a few layers of underlying myocytes were removed from all strip preparations obtained from both failing and nonfailing hearts. Strips of muscle tissue free of dense necrosis or fibrosis were dissected from the biopsy strip and transferred to a similar but smaller dissection chamber also filled with protective solution in which the removal of remaining connective tissue and skewed or damaged fiber bundles was carried out. The strip was sculpted to final dimensions of 0.3–0.8 mm in diameter by 4–6 mm in length. All strip preparations had parallel muscle bundle orientation as determined by ×10–×20 binocular observation and, in some cases, by ×400 bright-field water-immersion microscopy. Loops of 4–0 noncapillary, braided silk, previously wired with 25-μm-diameter platinum stimulating electrodes, were attached to the ends of the preparation with silk ligatures.8 Upon completion of the preparation, the muscle strip was allowed to rest for 15–30 minutes and then transferred to the experimental chamber and submerged in normal oxygenated Krebs-Ringer solution to wash out the BDM. In some cases, the fully prepared muscle strip remained in the protective solution for later use (up to 10 hours).

Preparations were judged “intact” if they exhibited all-or-none twitch responses to electrical stimulation, maintained a steady threshold voltage (i.e., within 20% of initial value), and did not exhibit “rundown” of peak twitch tension during the entire experiment.

**Experimental Procedure**

Isometric twitch tension was measured with a capacitance-type force gauge (model 400, Cambridge Technologies) and displayed, signal averaged, and stored by a digital oscilloscope (model 4094, Nicolet). Longitudinally propagated excitation was evoked by end-to-end stimulation of the muscle strips using 3-msec rectangular pulses 20% above threshold voltage.

Muscle strip preparations were stimulated continuously at 1 to 2 Hz at 37°C during a 60-minute equilibration period after BDM washout. Then they were gradually stretched (in 0.05-mm increments) to Lmax, the length at which active twitch tension was maximum. The steady-state force–frequency relation was obtained at 37°C by recording and measuring the twitch after stimulation for 5 minutes at each frequency starting at 0.2 Hz and increasing in 0.2-Hz increments until the twitch declined by 30% to 40% on the descending limb of the curve. Peak twitch tension and rates of tension rise and fall and timing parameters of the isometric myogram were measured by digital readout from the oscilloscope.

Adequate oxygenation of the entire cross section of the muscle strips was confirmed by applying the oxygen tension reduction test.9 This test was performed on each ventricular strip during stimulation at the highest frequency (fmax) giving maximal twitch tension. The gas bubbling through the muscle bath at four times normal rate (60 ml/min) was changed from the normal 95% O2–5% CO2 to 80% O2–15% N2–5% CO2 for a period of 30 minutes with continuous stimulation at fmax ranging from 6 to 180 contractions per minute (min−1). If the twitch force fell by 10% or more by the end of this period, the experiment was discarded. Four strip preparations were rejected on this basis, and for the muscle strips included here the average decline was 5±2%.

After completion of the experiments, length and bled weight of the portion of the muscle strip extending between the ligatures were measured. Cross-sectional areas used for normalization of twitch force were calculated by division of bled weight by length at Lmax.

**Statistics.** Comparison of tension–frequency curves for nonfailing myocardium with those of failing myocardium was made by two-factor ANOVA with repeated measures on one of the factors (stimulation frequency). Analysis of data was also performed by t tests at selected stimulation frequencies with Bonferroni correction. The Wilcoxon rank sum test was used to test for significance of the difference between optimum stimulation frequencies of the two groups. Maximal values of twitch tension
and rates of tension rise and fall and corresponding optimal stimulation frequencies were compared across groups by Student’s t test. All values are expressed as mean±SEM.

**Results**

**Time Course of Isometric Twitch**

Isometric twitch myograms from individual failing and nonfailing preparations are shown normalized to 100% in Figure 1 to facilitate waveform comparison. The complete frequency dependence of the timing parameters of the twitch, pooled for each group, is shown in Figure 2. All of the timing parameters have a statistically significant dependence on stimulation frequency in both nonfailing and failing myocardium (p<0.001). The total duration of the twitch is reduced by 50% (contraction phase by 30%, relaxation phase by 60%) when stimulation frequency is increased from 60 to 180 min⁻¹ (Figure 1 inset and Figure 2). The twitch durations in failing myocardium are only slightly longer (10%, NS) than in nonfailing myocardium even though some have a slower “tail” on the relaxation phase (Figure 1, DCM).

**Steady State Isometric Twitch Tension Versus Frequency**

Individual tension–frequency curves from left ventricular myocardial strips of failing and nonfailing hearts are shown in Figure 3. The curves from nonfailing myocardium peak in a narrow range of frequencies between 156 and 180 min⁻¹, but in the failing myocardium the peaks occur between 12 and 120 min⁻¹. Two-factor ANOVA (with repeated measures on frequency) indicates a highly significant difference between the two groups (p<0.0009). The Wilcoxon rank sum test

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<th>TABLE 1. Isometric Twitch Parameters at 72 min⁻¹ and 37°C</th>
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P₁₇, peak isometric twitch tension; TPT, time to peak twitch tension; RT, time from peak of twitch to complete relaxation; T½ R, time from peak of twitch to 50% relaxation; DCM, dilated cardiomyopathy.

*p<0.001.
showed a significant difference in $f_{\text{max}}$ (frequency at which curve peaks) between failing and non-failing myocardium ($p=0.001$).

Table 1 gives twitch tension and timing parameter values for the two groups at normal resting heart rate. The mean value of twitch tension at this frequency (72 min$^{-1}$) is reduced by 48% ($p<0.001$) in the failing myocardium, and the timing parameters are different than in nonfailing myocardium. Table 2 gives maximal values of peak twitch tension and the optimal stimulation frequencies at which they occur in the nonfailing and failing myocardium. When compared at nonfailing optimal frequency (174 min$^{-1}$) the tension developed by the failing myocardium is reduced by 80% compared with the nonfailing myocardium ($p<0.001$).

The mean values of peak twitch tension at all frequencies for the two groups are plotted in Figure 4. The averaged curve for the nonfailing preparations peaks at 180 min$^{-1}$, whereas in the failing preparations the peak is at 84 min$^{-1}$. At these frequencies the maximal twitch tensions are 43.7±3.7 mN/mm$^2$ and 11.9±1.4 mN/mm$^2$, respectively. To determine if the curve through the pooled data of the failing myocardium reasonably represents the wide array of individual curves in Figure 3, we compared these values of maximal tension and optimal frequency obtained from the curve in Figure 4 with the averages of the values obtained from the individual tension–frequency curves in Figure 3. The averaged values are: $f_{\text{max}}=81±22$ min$^{-1}$ and maximal peak twitch tension $=14.2±2.4$ mN/mm$^2$ (Table 2). Therefore, even though the averaged tension–frequency curve for failing myocardium is flatter than the individual curves in Figure 3 because of the wide range of $f_{\text{max}}$ values between these preparations, the similarity of these mean values to the ones obtained from the averaged curve in Figure 4 supports the validity of the pooled-data curve.

Rates of Rise and Fall of Twitch Tension

The frequency dependence of the peak rates of tension rise and fall is summarized in Figure 5. There was a statistically significant dependence on stimulation frequency of both $+dT/dt$ ($p<0.001$) and $-dT/dt$ ($p<0.001$) in the nonfailing myocardium. This was not the case in the failing myocardium.

In the nonfailing control, the maximal peak rates of rise and fall of twitch tension occur at a slightly higher frequency than $f_{\text{max}}$ for the maximal peak twitch tension (Table 2), and they increase by approximately 210% with an increase in stimulation frequency from 60 to 180 min$^{-1}$, whereas peak twitch tension increases 115% in this range (Figures 4 and 5).

In failing myocardium, the maximal peak rates of tension rise and fall are lower than in nonfailing myocardium by about 75%, and the frequencies at which they occur are reduced by 30% to 45% compared with the nonfailing myocardium.
The frequency-dependent potentiation of rate of tension rise and fall is essentially absent in the failing myocardium (Figure 5).

Control Experiments

To control for possible influences of differences of from 1 to 10 hours in duration of soak in the protective solution and of aging per se, separate control experiments were carried out on muscle strips from nonfailing left ventricles. After soaking the left ventricular biopsy specimen in the protective solution for 30 minutes, the first of a matched pair (matched dimensions and adjacent location within biopsy specimen) of ventricular strip preparations was dissected. This required an additional 30 minutes in the protective solution, and it was therefore used for a force–frequency experiment as described above after a total soak time of 1 hour. The dissection of the second strip was completed after 2 or 10 hours of soaking in the oxygenated protective solution, and it was subsequently used for an identical force–frequency experiment. Figure 6 shows force–frequency curves obtained after 1, 2, and 10 hours’ soak. Twitch parameter values obtained from the strip soaked for 10 hours were divided by the values obtained from the matching strip soaked for 1 hour. The average ratios for optimal stimulation frequency, maximal twitch tension, and resting tension were 0.99 ± 0.06, 0.99 ± 0.2, and 0.63 ± 0.18, respectively. The average ratios for time-to-peak twitch tension, time-to-half relaxation, and total twitch time were 0.96 ± 0.03, 1.02 ± 0.04, and 0.99 ± 0.003, respectively (all at a stimulation frequency of 72 min⁻¹). None of the average differences between these parameters from the 1-hour versus 10-hour soaked pairs of muscle strips were significant (p > 0.4, n=8).

Six additional control experiments were performed to determine if there are differences in the force–frequency curves obtained from subendocardial muscle strips as compared with subepicardial muscle strips from failing hearts. Peak twitch tensions at 60 min⁻¹ for six epicardial and six endocardial strips averaged 11.5 ± 1.3 and 12.9 ± 3.5 mN/mm² (p = 0.7), respectively, whereas optimal stimulation frequency (tested in only three of the pairs) ranged between 72 and 132 min⁻¹ in the epicardial strips and between 36 and 144 min⁻¹ in the endocardial strips. Therefore, no clear differences in performance were observed between the two biopsy sites.

Discussion

In this article we report measurement of isometric twitch tension in isolated left ventricular strips of non-failing and failing adult human myocardium at 37°C over a range of stimulation frequencies from 12 to 240 min⁻¹. Although portions of the low frequency end of the tension–frequency relation have been explored in isolated human myocardium before,⁴⁻⁷,¹⁰⁻¹² the frequency range has never been extended to high enough frequencies to demonstrate either the entire ascending limb or the peak of the curve in nonfailing adult human myocardium at 37°C (see below).

Of major interest are the findings that in failing myocardium, peak twitch tension is depressed by 48% at a stimulation frequency of 72 min⁻¹ and by 80% at 174 min⁻¹ and that the ascending limb and peak of the tension–frequency curve are shifted leftward from 174 min⁻¹ to subphysiological heart rates as low as 12 min⁻¹.

Although peak twitch tensions are similar in failing and nonfailing myocardial strips in the low frequency range (12–40 min⁻¹), the present study reveals this is not true at higher stimulation frequencies. In nonfailing myocardium, increasing the stimulation frequency from 60 to 150 min⁻¹ causes a doubling of twitch tension and a 2.6-fold increase in peak rates of twitch tension rise and fall.

In myocardium from failing hearts, this frequency-dependent potentiation is either entirely absent or it is greatly attenuated. At a contraction frequency of 120 min⁻¹ the amplitude and rate of rise of twitch tension are only one third of the values generated by the nonfailing myocardium. These results closely parallel previously observed differences in the responses of left ventricular function to atrial pacing tachycardia in patients with DCM heart failure compared with patients without heart failure.³ In these catheterization laboratory studies in nonfailing subjects, ventricular pacing between 80 and 120 min⁻¹ caused the peak rate of left ventricular pressure development to increase by 30%. Over this same range of stimulation frequencies the present nonfailing ventricular strip preparations exhibit a 46% rise in peak twitch tension (Figure 4) and a 54% increase in peak rate of tension rise (Figure 5). In subjects with DCM heart failure, pacing tachycardia produced no changes in peak rate of left ventricular pressure rise. This lack of frequency treppe is also seen in the isolated myocardium from failing hearts in Figures 4 and 5.

This suggests that the alterations in myocardial tension generation observed here in isolated myocardium from failing hearts may be of myocyte origin and may contribute significantly to the depressed response to tachycardia observed with left ventricular catheterization and to the inadequate cardiac output during resting conditions as well as the inadequate increase in cardiac output during physical activity in patients with DCM heart failure. With moderate to extreme upright exercise in normal subjects, end-systolic volume decreases as much as 20% to 50%, whereas end-diastolic volume remains unchanged or increases. This stroke–volume enhancing effect may generate as much as 40% of the

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**Figure 6.** Steady-state isometric tension vs. stimulation frequency in human left ventricular muscle strips. Tissue from nonfailing left ventricles dissected after 1, 2, or 10 hours soaking in BDM-Krebs protective solution. The 1- and 10-hour strips were prepared from the same heart.
threefold increase in cardiac output that occurs during exercise.\textsuperscript{1,2} Although the increased contractility needed to compensate for the decreased end-systolic volume and to bring about the increased stroke volume is commonly attributed to increased sympathetic stimulation,\textsuperscript{3} the present data suggest that the large positive slope of the tension–frequency relation intrinsic to nonfailing myocardium may also contribute significantly to enhancement of contractility during exercise tachycardia. Its absence in failing hearts may contribute, over and above the decrease in maximal twitch tension, to the poor exercise tolerance of patients with DCM.

The present studies are in qualitative agreement with previous studies of tension production in human myocardium isolated from normal and failing hearts in showing that twitch tension is normal in failing myocardium at low (12–20 min\textsuperscript{-1}) stimulation frequencies,\textsuperscript{2} and that there is a positive frequency treppe in normal myocardium but not in failing myocardium.\textsuperscript{4,5,13,14}

Our methods have allowed an expanded examination of the tension–frequency relation of left ventricular myocardium at 37°C. We were able to cover a wider range of stimulation frequencies because we could dissect left ventricular myocardial strip preparations that were thin enough to pass a test confirming that adequate oxygenation existed during the measurements. We believe that this criterion plus the careful dissection procedure, which reduces myocyte damage, maximizes the ability to produce strips with myocytes oriented along the length of the strip, and minimizes the amount of noncontractile tissue in the preparations, accounts for our excellent values of isometric twitch tension in human myocardium (44±3.7 mN/mm\textsuperscript{2} at optimal stimulation frequency of 174±4 min\textsuperscript{-1}, 2.5 mmol/l Ca\textsuperscript{2+}).

Two possible mechanisms may be considered to account for the observed changes in contractility accompanying DCM. First, the 68% reduction (14.2/43.7) in maximal twitch tension may be partly attributable to differences in myofilament protein content. This has been reported to be from 45%/15 to 20%/16 lower than normal in DCM. The failure to observe a significant depression in maximally activated contracture tension in skinned preparations from failing hearts\textsuperscript{17} favors the 20% figure, however. More likely, the tension deficit and altered frequency dependence of the twitch in DCM myocardium may be caused predominantly by reduced activation of contractile proteins. This is suggested by the recent observation of a 68% reduction in tension-independent heat in left ventricular strip preparations from some of the same hearts used in the present study.\textsuperscript{18} Although direct measurements of peak intracellular calcium concentration in normal and myopathic myocardium do not indicate reduced values,\textsuperscript{12} these measurements were made at low stimulation frequency and temperature (30°C) in which the differences in peak twitch tensions of the failing and control preparations\textsuperscript{19} are much smaller than they are at 37°C. Assuming calcium sensitivity of the myofilaments,\textsuperscript{17} Ca\textsuperscript{2+}-release channels,\textsuperscript{20} and specific Ca\textsuperscript{2+} uptake by sarcoplasmic reticulum vesicles\textsuperscript{21} are normal, other possibilities for the mechanism of altered tension–frequency relation are: 1) a reduced number of sarcoplasmic reticulum Ca\textsuperscript{2+} pumps\textsuperscript{22}; 2) a reduced production of cyclic AMP\textsuperscript{23}; and 3) intracellular aci-
In nonfailing fetal papillary muscles, the peak of the tension–frequency curve occurs at the same frequency (180 min⁻¹) and the time-to-peak twitch tension (152.7±10.7 msec at 120 min⁻¹) is the same as the present values observed in BDM-pretreated nonfailing myocardium (174±4 min⁻¹ and 137±9 msec, respectively).

Moreover, the slope of the positive frequency treppe of twitch tension between stimulation frequencies of 20 and 60 min⁻¹ in nonfailing, BDM-treated myocardium (60% increase in peak tension) of the present study agrees well with the slope observed in normal untreated myocardium (71%) over this same frequency range.³

The present observation of a diminished or negative frequency treppe in BDM-pretreated failing myocardium has also been observed previously in studies that covered the lower frequency portion of the tension–frequency curve in untreated myocardium. The slope of the present curve for BDM-treated failing myocardium (10%) in the 10- to 60-min⁻¹ range of stimulation frequencies agrees well with the previously observed slope (3% to 4%) in this frequency range using untreated failing myocardium.⁵

The present mean values of peak twitch tension at 20 min⁻¹ in nonfailing and failing myocardium (14 and 10 mN/mm², respectively, Figure 4) are comparable with the highest values reported by others (20 and 23 mN/mm², respectively)³⁰,³¹ under the same conditions if correction is made for the 33% decrease expected in going from 30°C to 37°C.

Third, as discussed earlier, the present results from BDM-treated nonfailing and failing isolated myocardium are in good quantitative agreement with the degree of frequency potentiation of left ventricular peak rates of pressure rise and fall in both normal and heart failure human subjects.³

These agreements between the present results and those of others using isolated myocardial preparations or intact human subjects that were not pretreated with BDM argue very strongly against there being a significant influence of 30-mmol/L BDM pretreatment on the present results in either the nonfailing or the failing myocardium.

Summary

The use of the BDM protective solution method of preparing very thin and viable left ventricular myocardial strips from nonfailing and failing human myocardium has enabled the complete tension–frequency relation to be obtained at 37°C.

In nonfailing myocardium the ascending limb of the tension–frequency curve peaks at a stimulation frequency of 174 min⁻¹, whereas in failing myocardium the peak occurs at 6 to 120 min⁻¹ (average, 81 min⁻¹).

Between 60 and 150 min⁻¹, twitch tension increases 107% in nonfailing myocardium, but it does not change significantly in failing myocardium, causing peak twitch tension to be 48% lower than the nonfailing value at 72 min⁻¹ and 80% lower at 174 min⁻¹.

Maximal rates of tension rise and fall vary similarly as does twitch tension with stimulation frequency, and they show similar degrees of depression in the failing preparations.

The qualitative and quantitative accord between these results and those from catheterization laboratory measurements on intact humans suggests that myocardial origins independent of systemic factors may account for abnormalities seen in left ventricular function in human DCM.

Preliminary reports of some of the findings reported here have been presented previously.³²,³³

Acknowledgments

We thank Richard Lachapelle for assistance with the apparatus; Dr. Bryan K. Slinker, Dr. Elizabeth Low, and Tom Haviland for assistance with statistics and programming; Dr. James P. Morgan and Cynthia L. Perreault for obtaining tissue biopsies for us; and Drs. Martin LeWinter, Frederick Schoen, Rosemarie Maddi, and John Fox for liaison with surgery and advice concerning the use of human tissue. We also thank Julie Lovelette for preparing the manuscript.

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Circulation. 1992;85:1743-1750
doi: 10.1161/01.CIR.85.5.1743

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