Effects of Hypertrophy and Allylamine-induced Fibrosis on Mechanical Properties of Isolated Rat Heart Muscles with References to the Pumping Function of the Intact Heart in the Same Models

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To examine the effects of hypertrophy and fibrosis on myocardial mechanics, we studied isolated left ventricular papillary muscles from 6-month-old male SHR and allylamine-fed rats. In SHR, the peak developed tension (DT) and the maximum rate of tension development (dT/dt) were higher compared to control male Wistar-Kyoto rats (WKY). With 15 min of hypoxia, the DT and the dT/dt declined similarly in both groups and the ratios of DT and dT/dt to their prehypoxic values after 15 min of hypoxia were not different in the two groups. From allylamine-fed rats, only 4 papillary muscles had more than 25% interstitial fibrosis by point-counting (AL-B group), but 9 muscles had no fibrotic involvement and their left ventricular hydroxyproline concentration was normal (AL-A group). The myocardial diameters, the passive stiffness constant and the duration of isometric contractions at Lmax were increased in AL-B group, but the resting tension, the DT at Lmax and the force-velocity relations did not differ from controls. The mechanical properties of the AL-A group muscles were not different from controls. However, when pumping function was examined in the intact heart from the AL-A group, the LVEDP was increased and the peak cardiac output normalized by body weight was decreased. Thus, hypertrophied muscle from SHR shows hyperfunction without an increase in susceptibility to hypoxic stress. Even if fibrosis progresses, hypertrophy can compensate for the reduction in contractile component up to a certain degree. The dissociation of the results between the isolated heart muscle study and the hemodynamics of the non-fibrotic heart from allylamine-fed rats may indicate the importance of impaired myocardial perfusion for the genesis of heart failure, since allylamine is known to damage medium-size coronary vessels.

Key Words:

Hypertrophy
Spontaneously hypertensive rat
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MYOCARDIAL hypertrophy and interstitial fibrosis are the major structural processes found in various forms of chronic heart disease of different etiological bases. These two processes interact each other and are thought to play an important role in cardiac adaptation against increased loading conditions and in subsequent

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heart failure.

In the present study, we used the spontaneously hypertensive rat (SHR)¹ as a model of hypertrophy and examined the contractile performance of its isolated heart muscle preparations under normal and hypoxic conditions. As a model of interstitial fibrosis, we used allylamine-induced lesions of rat myocardium and examined the contractile performance and elastic stiffness of isolated heart muscle preparations from allylamine-fed rats². We also examined the left ventricular performance of intact hearts of anesthetized allylamine-fed rats.

By comparing the results of our isolated SHR heart muscle study with previously reported data on pumping ability of the SHR intact heart, and the results of our isolated heart muscle study with the intact heart study of allylamine-fed rats, we take steps to elucidate what factor leads the heart from adaptation to failure.

MATERIALS AND METHODS

(1) Isolated Heart Muscle Study of SHR

(i) Spontaneously Hypertensive Rats

Male spontaneously hypertensive rats (SHR) and control male Wistar Kyoto rats (WKY) were weaned, housed in groups of 4 to 6 and allowed free access to standard laboratory chow and tap water. Systolic blood pressure, by the tail-cuff method¹, and body weight measured monthly.

(ii) Isolated Heart Muscle Study

The preparation for isolated heart muscle study has been described in detail elsewhere.³ In brief, trabeculae carneae and papillary muscles were dissected from the rat left ventricles after decapitation, and mounted vertically between two spring clips in a chamber containing oxygenated Krebs-Henseleit solution⁴ ($\text{Ca}^{2+} = 2.5 \text{ mM}$, Glucose = 5.5 mM) at a temperature of 28°C . The muscle preparations were electrically stimulated 12 times per minute, with 5 msec rectangular pulses at voltages approximately 10% greater than the threshold which were delivered through parallel platinum electrodes. After an equilibration period of 45 min, the muscles were made to contract isometrically at L_{max} .

Hypoxia was then induced by vigorously gassing the solution with 95% N_2 and 5% CO_2 . Reoxygenation following a 15 min period of hypoxia was allowed to take place by replacing the original gas mixture (95% O_2 and 5% CO_2). The PO_2 of the bath fell from over 550 mmHg to $36 \pm 5 \text{ mmHg}$ 5 min after hypoxia was initiated.

With reoxygenation, the PO_2 of the bath solution was greater than 500 mmHg within 5 min. Mechanical events were recorded on a multichannel recorder (San-Ei Instrument, Rectigraph-8S) at a paper speed of 100 mm/sec.

The muscle length was measured at L_{max} . At the end of each experiment, the portion of the muscle between the spring clips was blotted and weighed and the muscle cross sectional area was calculated assuming cylindrical uniformity and a specific gravity of 1.00. Values for tension were normalized for the muscle cross sectional area.

Each portion of the heart was blotted and weighed. Left ventricular weight was defined here as the sum of the weights of the free left ventricular wall and of the interventricular septum. Right ventricular weight was defined here as the weight of the free wall of the right ventricle.

(iii) Data Analyses

The following measurements were made during the control period, every 3 min during 15 min of hypoxia and at 1, 2, 3, 5, 10, 30 and 45 min during reoxygenation: (1) peak developed tension (DT), in g/mm^2 ; (2) maximum rate of tension development (dT/dt), in $\text{g/mm}^2/\text{sec}$; (3) time from onset of tension to peak isometric tension (TPT), in msec; and (4) time for tension to fall to 50% of the peak value ($\text{RT}_{1/2}$), in msec. All values were expressed as mean $\pm$ S.E.M..

(2) Isolated Heart Muscle Study of Allylamine-Induced Myocardial Lesions

(i) Animals and Allylamine Administration

Male Charles River CD rats initially weighing 150 to 180g were housed in groups of 3 or 4 and allowed free access to standard laboratory chow. Eighteen rats, selected at random, were given 0.1% allylamine (Pfaltz and Bauer Inc., Stamford, Conn.) in drinking water, ad libitum. Six control rats were given tap water. Rats administered allylamine were sacrificed between 4 and 8 weeks after onset of drug administration. At least one control rat was studied each week during the same experimental period.

(ii) Isolated Heart Muscle Study

Isolated heart muscles were prepared same way as in the above described SHR study; however, the study equipment used in this protocol was one with which either the force or the length of the preparation could be specified by means of an electronic servosystem⁵ under the control of a Nova 2 digital computer (Data

TABLE I

	WKY (<i>n</i> = 9)	SHR (<i>n</i> = 9)	<i>p</i>
<i>L</i> _{max} (mm)	11.1 ± 0.5	10.7 ± 0.4	NS
CSA (mm ²)	0.97 ± 0.05	0.82 ± 0.06	NS
RT (g/mm ²)	0.78 ± 0.06	0.91 ± 0.10	NS
DT (g/mm ²)	5.52 ± 0.39	7.72 ± 0.72	< 0.05
<i>dT/dt</i> (g/mm ² /sec)	50.0 ± 3.2	66.9 ± 7.0	< 0.05
TPT (msec)	195 ± 5	221 ± 3	< 0.05
RT _{1/2} (msec)	203 ± 7	244 ± 10	< 0.01

Values are mean ± S.E.M.. *n* = number of animals; CSA = cross sectional area; RT = resting tension; DT = isometric peak developed tension; *dT/dt* = maximum rate of isometric tension development; TPT = time from onset of contraction to peak isometric tension; RT_{1/2} = time for tension to fall to 50% of the peak value; *p* = *p* value; NS = not significant.

General Corp), so that force-velocity relation as well as elastic stiffness of the preparation could be studied. Details of this system have been described elsewhere.⁶

Following are the methods specific to this protocol: The entire study was carried out at the temperature of 30°C. Force-velocity relations for each muscle were studied with a preload equal to that measured at *L*_{max} and afterloads between 0 and maximum (isometric) with step size selected to obtain an average of seven to nine steps per muscle. Passive stiffness was measured by slow release (0.01 mm/sec) of resting muscle from *L*_{max}, and fitting the equation $\sigma = A + B e^{C\epsilon}$, where σ = stress, ϵ = natural strain (= $\ln l/l_0$) and A, B, and Cp are constants. Stiffness is then given by $d\sigma/d\epsilon = C_p\sigma - AC_p$, where *C_p* is a passive stiffness constant.

At the end of each experiment, the muscle was removed from the bath and immersed vertically in 10% buffered formalin with a preload of 2.0g. After 48 hours of fixation, the muscle was cut from the spring clip and weighed. Preliminary studies showed the muscle weight after 48 hours of formalin fixation to be approximately 3% less than the muscle weight prior to fixation. Therefore, the initial muscle weight was estimated by dividing the fixed muscle weight by 0.97.

After removal of the papillary muscle and trabeculae carneae, the left ventricle and the septum were dissected from the remainder of the heart, blotted and weighed. Hydroxyproline was determined from samples of left ventricle utilizing the method of Prockop and Underfriend.⁷

(iii) Quantitative Assessment of Interstitial

Fibrosis and Myocardial Fiber Diameter of the Isolated Heart Muscle

Interstitial fibrosis was evaluated by using a point-counting method similar to that of Hess et al.¹⁸ A total of 600 points were measured for each muscle stained with Mason-trichrome.

Myocardial fiber diameters were measured directly with an ocular micrometer calibrated with an objective micrometer. For each muscle specimen, the shortest diameter at the level of the cell nucleus in cross section was measured. This diameter was obtained from an average of 39 myocyte measurements.

(3) Hemodynamic Measurement of the Allylamine-fed Rats

Hemodynamic measurements were performed on six allylamine-fed rats and six control rats which were fed the same way as the rats in the isolated muscle study protocol described above.

The basic surgical preparation has been described elsewhere in detail.^{9,10} Briefly, after induction of anesthesia with ether, a tracheostomy was performed and ventilation was maintained by a positive pressure respirator connected in series to an ether drip apparatus. The right carotid artery and jugular vein were cannulated and their catheters connected to a high fidelity Millar catheter-tip transducer for measurements of systemic arterial and right atrial pressures and heart rate. After a midsternal thoracotomy, the ascending aorta was exposed and fitted with an electromagnetic flow probe for measurements of aortic blood flow.

Tyrod's solution was infused into a femoral vein at a rate of 40 ml/min per kg for 45 seconds

Fig.1. Mean changes in isometric peak developed tension produced by 15 min of hypoxia, then 45 min of reoxygenation, from 9 SHR and 9 WKY cardiac muscles. Values are shown as mean $\pm$ S.E.M..
* $p < 0.05$, ** $p < 0.01$

to produce an increase to a plateau in cardiac output, even though right atrial pressure continued to rise. The maximum cardiac output and stroke volume attained during this volume loading served as indices of the peak pumping ability of the left ventricle.

Upon return of all hemodynamic parameters to baseline levels, the flow probe was removed and the carotid arterial catheter advanced to the left ventricle for continuous monitoring of end-diastolic pressure. The ascending aorta was then occluded briefly with a suture to produce isovolumic (except for coronary flow) contractions. Developed pressure was calculated from measurements of peak left ventricular systolic and end-diastolic pressures obtained during the first 7 beats of aortic occlusion.

The passive pressure-volume relation was examined in each heart after cardiac arrest in diastole by potassium chloride with infusion of saline at a rate of 0.68 ml/min. The index of chamber stiffness, chamber stiffness constant (Kc) was obtained from the slope of the chamber

stiffness-pressure relation over 2.5–30 mmHg (i.e., $dP/dV = KcP$).

Histological examination was done on all hearts studied.

Statistical Analyses

All values were expressed as mean $\pm$ S.E.M.. Student's t-test was used to compare single measurements between the two groups. Two-way analysis of variance followed by Newman-Keul's test was employed to compare multiple measurements during hypoxia and reoxygenation in the two groups. A significant difference was said to exist when p was less than 0.05.

RESULTS

(1) Isolated Heart Muscle Study of SHR

(i) Blood pressure, Body Weight and Heart Weight

The blood pressure of the SHR at 6 months was 179 ± 4 mmHg and that of the WKY was 117 ± 2 mmHg. The whole body weight at the

TABLE II

	Controls (n = 8)	AL-A (n = 9)	AL-B (n = 4)	ANOV
CSA (mm ²)	0.92 ± 0.13	1.22 ± 0.13	1.33 ± 0.18	NS
mean myocyte diameter (μ)	12.1 ± 0.6	12.7 ± 0.57	18.0 ± 0.6	**
PT (g/mm ²)	1.70 ± 0.19	1.44 ± 0.17	1.48 ± 0.32	NS
DT (g/mm ²)	4.96 ± 0.43	4.45 ± 0.52	4.75 ± 0.96	NS
TPT (msec)	105.6 ± 2.6	109.3 ± 3.6	118.8 ± 9.4	NS
RT _{1/2} (msec)	121.0 ± 7.0	121.4 ± 4.7	156 ± 7.7	**
Cp	34.1 ± 2.5	35.9 ± 1.6	43.3 ± 1.2	*

CSA = muscle cross sectional area; RT = resting tension at Lmax; DT = peak developed tension at Lmax; TPT = time to peak tension; EM delay = electromechanical delay time; RT_{1/2} = time for tension to fall from peak to 50% of the peak value; Cp = passive stiffness constant; ANOV = analysis of variance.
 *p < 0.05, **p < 0.01, mean ± S.E.M.

time of sacrifice was lower in the SHR than in the WKY (278 ± 10 vs. 347 ± 15g). The ratio of left ventricular weight to whole body weight was significantly increased in the SHR (320 × 10⁻⁵ ± 8 × 10⁻⁵ vs. 245 × 10⁻⁵ ± 7 × 10⁻⁵), whereas the ratio of right ventricular weight to whole body weight was not different in the two groups.

(ii) Muscle Mechanics

Table I shows baseline mechanical parameters of isolated cardiac muscles from SHR and WKY. The Lmax muscle length and the cross sectional area, and the resting tension are comparable in the two groups.

The peak developed tension (DT) and the maximum rate of tension development (dT/dt) are significantly increased in the SHR cardiac muscles, indicating a hypercontractile state. The TPT and the RT_{1/2} are both prolonged in the SHR cardiac muscle.

(iii) Effect of Hypoxia on Muscle Mechanics

The DT and the dT/dt declined precipitously during hypoxia in both groups. In the SHR, the DT declined from 7.72 ± 0.72 to 2.65 ± 0.31 g/mm², and in the WKY from 5.51 ± 0.39 to 2.01 ± 0.18 g/mm². The time course of the decline of dT/dt during hypoxia was similar to that of DT. The ratios of DT and dT/dt to their prehypoxic values after 15 min's hypoxia did not differ in the two groups (DT, 34 ± 2% in the SHR vs. 36 ± 2% in the WKY, and dT/dt: 41 ± 2% in the SHR vs. 43 ± 3% in the WKY). Thus, although the cardiac muscle of SHR was in a

state of hyperfunction, its susceptibility to hypoxia was not different from that of WKY cardiac muscle.

Reoxygenation resulted in gradual recovery of the DT and the dT/dt, and after 30 min of reoxygenation, the DT and the dT/dt returned to their prehypoxic values in both groups. Although the prehypoxic control TPT and RT_{1/2} were prolonged in the SHR, no significant differences in the TPT and the RT_{1/2} were seen when these parameters were analysed over the entire experimental period by means of analysis of variance. Reoxygenation produced a similar degree of tension prolongation in both groups.¹¹

(2) Isolated Heart Muscle Study of Allylamine-Induced Myocardial Changes

(i) Body and LV Weight

The initial body weights of control rats and those receiving allylamine were comparable (control rats (n = 6), 167 ± 5g vs. allylamine treated rats (n = 18), 168.2 ± g; mean ± S.E.M.). After four weeks, allylamine-treated rats had gained considerably less weight compared to control rats drinking plain tap water (gain in weight of controls: 176 ± 13g vs allylamine treated rats 99 ± 7g p < 0.01). These findings are similar to those reported by Boor et al.²

(ii) The Left Ventricular Hydroxyproline and Interstitial Fibrosis

Left ventricular hydroxyproline concentration was significantly increased in the allylamine treated group (p < 0.01). When the interstitial

fibrosis for each papillary or trabecular muscle (measured by point-counting) was plotted against the hydroxyproline concentration of the left ventricle from which each muscle was taken it was found that many muscles from animals in the allylamine-treated groups had no increase in fibrosis, and there was no relation between the degree of fibrosis of the isolated heart muscle studied and the hydroxyproline concentration of the left ventricle after removal of the papillary muscle and the trabeculae carnaeae. Because of this variable involvement of the isolated muscle by fibrosis, the allylamine-treated muscles were broken down into two subgroups for analysis of mechanical and contractile properties. Four muscles from allylamine-treated rats had a high degree ($> 25\%$) of interstitial fibrosis (mean $34.9 \pm 1.2\%$) and were called allylamine B (AL-B). A second sub-group of 9 muscles from allylamine-treated rats with normal LV hydroxyproline concentration and no increase in interstitial fibrosis was selected to serve as a second control group (AL-A group).

(iii) Isolated Muscle Mechanics

As shown in Table II, there were no significant differences in the contractile or mechanical properties of the control group and allylamine-treated muscles without fibrosis (AL-A group).

Fibrotic muscle preparations (AL-B) had similar muscle cross sectional areas. Resting tension (RT) at L_{max} and peak developed tension (DT) were not significantly different among groups. However, passive stiffness constants (C_p) were significantly increased in AL-B in comparison with both control groups. Although time from the onset of tension to peak tension (TPT) was unchanged, the relaxation time ($RT_{1/2}$) of isometric contractions at L_{max} was prolonged in fibrotic muscle preparations. Force-velocity data from fibrotic muscles (AL-B) were not different from controls as a group. Although the AL-B group appears to show a trend to lower velocities, this reflects one muscle with particularly low velocities; the velocity of the other 3 AL-B preparations were equal to or exceeded controls.

(iv) Myocardial Fiber Diameters

The fiber diameters of the control and the AL-A group were similar; $12.1 \pm 0.9\mu$ and $12.7 \pm 0.6\mu$, respectively (Table II). The AL-B group (muscles with fibrosis) had significantly larger myocyte diameters ($18.0 \pm 0.4\mu$) than either the control or AL-A group. That is to say, the remaining myocytes of muscle preparations

with a high degree of interstitial fibrosis demonstrated hypertrophy.

(3) Hemodynamic Measurement of Allylamine-fed Rats.

Histological examination after hemodynamic measurement showed none of the six hearts of allylamine-fed rats had fibrotic changes in the myocardium. Therefore, these six hearts are comparable to AL-A heart muscles of the above isolated heart muscle study. The developed pressure during ligation of the aorta was not different in the two groups (control, 230 ± 7.7 mmHg ($n = 6$) vs. allylamine-fed rat, 214 ± 6.9 mmHg ($n = 6$). However, the baseline left ventricular end-diastolic pressure was increased in the allylamine-fed group (control, 3.4 ± 0.7 mmHg vs. allylamine group, 6.2 ± 0.4 mmHg, $p < 0.01$), and the peak cardiac index (the peak cardiac output during volume loading divided by the body weight) was diminished in the allylamine group (control, 438 ± 11.9 ml/min/kg vs. allylamine group, 370 ± 20.6 ml/min/kg, $p < 0.01$), indicating pumping dysfunction of the allylamine-fed rat hearts despite the absence of fibrotic process in these hearts. The chamber stiffness constant, K_c , was not different in the two groups (control, 5.33 ± 0.40 vs. allylamine group, 5.54 ± 0.40).

DISCUSSION

Contractile Performance of Hypertrophied Myocardium and Its Susceptibility to Hypoxia.

The results of the isolated heart muscle studies on the function of hypertrophied myocardium have varied depending on the duration and the amount of the applied load, and how abruptly or gradually the load was applied.¹²⁻¹⁵ In the present study, we found that hypertrophied cardiac muscle of 6 month SHR was in a state of hyperfunction, reflected by increases in the prehypoxic peak developed tension and the peak rate of tension development. In a recent study by Capasso and coworkers in rats in which hypertension developed gradually after constriction of the left renal artery,¹⁵ active and totally developed isometric tension increased throughout the 30 week period, although the force-velocity relations demonstrated a significant decrease in peak velocity of muscle shortening at all relative loads. Similarly, Bing and coworkers showed an increase in active tension in the cardiac muscles of 6-, 12- and 18-month old SHR.¹⁶ Functional

differences between the hypertrophied myocardium of SHR and of other experimental models may be due in part to the fact that the degree of hypertrophy in SHR hearts is less than in the other models, reflected in only about a 30% increase in LV to whole body weight ratio, whereas in studies using other models of hypertrophied ventricle to whole body weight can be over 50% higher than in the controls.¹⁷ As mentioned by Capasso and coworkers,¹⁵ a gradual increase in load in hypertensive animals may be another reason for increased isometric tension, since an abrupt increase in load as applied in the other experimental models might damage the myocardium.

Generally, cardiac muscles which show hyperfunction are more susceptible to hypoxic stress. For instance, after the application of isoproterenol, muscles at high temperatures or in alkaline solutions show hyperfunction when enough oxygen is supplied, but hypoxia increases the decline in contractility, and with reoxygenation these muscles recover poorly.^{18,19} Similar results were found with a hyperthyroid myocardium.²⁰ Therefore, the general rule governing these situations is that factors which increase the utilization of limited stores of aerobic substrate facilitate deterioration of myocardial performance during hypoxia. However, the findings in the present study of SHR's hypertrophied myocardium do not follow this rule. That is, although the SHR cardiac muscle was in a state of hyperfunction indicated by an increase in the peak developed tension and the maximum rate of tension development, its susceptibility to hypoxic stress was similar to that of the control cardiac muscles. The reason for the difference in susceptibility to hypoxic stress between the hyperfunctioning muscle of the SHR heart and that of cardiac muscles with induced hyperfunctioning may be due to a higher efficiency in energy utilization in the SHR cardiac muscle. Recent studies on the energy efficiency in hypertrophy support this idea.²¹

Myocardial Mechanical Properties and Pumping Function of Allylamine-fed Rat Heart

Allylamine as used in the present study effects medium sized coronary vessels which presumably result in microcirculations and the development of subsequent fibrosis. Despite our initial expectation, the prevalence of fibrotic changes produced by allylamine was relatively low. Papillary muscles and trabeculae carneae were

spared in many rats even though the free left ventricular walls showing significant fibrosis so that fibrotic muscles that we could study (AL-B) were limited in number. On the other hand, the larger group of treated animals with limited myocardial fibrosis (AL-A) provided a valuable second control group to demonstrate that allylamine, in the absence of fibrosis, had no effect on mechanical properties or performance.

In the present study, we found increased passive stiffness constant and $RT_{1/2}$ in fibrotic muscle preparations (AL-B) compared to controls, yet the resting tension at L_{max} , the maximum developed tension and the force-velocity relations of these muscles were not different. The mean myocyte diameter in fibrotic muscles was significantly larger than the control groups and it appears that the contractile component spared from fibrosis has undergone compensatory hypertrophy. Therefore, observed changes in mechanical properties of fibrotic muscles are the result of combined effects of fibrosis and hypertrophy. Since it has been shown that myocardial hypertrophy itself does not induce a change in stiffness,^{8,23} the observed increase in stiffness of fibrotic muscles is thought to be the result of fibrosis, whereas the prolonged relaxation is the result of hypertrophy since similar changes have been noted in isolated heart muscle studies of the hypertrophied heart.^{13,15} The preserved isometric developed tension and almost normal shortening velocity is thought to be the compensatory effect of hypertrophy.

Non-fibrotic muscles, despite feeding the rats with allylamine (AL-A), did not differ in any respect from control muscles; however, the pumping ability of these heart, was impaired when they were examined in situ. The reason for this dissociation of results may be due to damage of the medium sized coronary vessels which has been reported to occur in the allylamine-fed heart. This kind of damage to the coronary vessels probably does not interfere with the performance of the isolated heart muscle, since oxygen is delivered by diffusion in the experimental system for the isolated heart muscle study.

Factors Leading Heart from Adaptation to Failure in Cardiac Hypertrophy

For many years, extensive investigations have been carried out in order to elucidate the mechanism which leads the hypertrophied heart

from compensation to subsequent heart failure; and a number of mechanisms have been postulated to be the cause. For instance, abnormalities of mitochondrial respiratory function,^{23,24} shift in myosin isoenzyme pattern,^{25,26} abnormality in excitation-contraction coupling,²⁷ myocardial depletion of catecholamine²⁸ and reduction in beta-adrenergic receptor density²⁹ found in hypertrophied cardiac muscles are postulated to be related to heart failure. However, almost all of them seem to be the result but not the cause of heart failure and some of them can explain the adaptive processes in cardiac hypertrophy.

Hypoxia and ischemia are well known to induce profound reduction in cardiac performance and myocardial contractility. When myocardial perfusion is impaired without reduction in basic myocardial contractility, pumping impairment of the in situ heart is seen, but the contractile performance of the isolated heart muscle can remain normal. This is shown in the present study of isolated heart muscle contractility and hemodynamics of allylamine-fed rats. Similar dissociation of the results of myocardial function has been seen in the studies of isolated heart muscle performance¹⁶ and of hemodynamics of old SHR.³¹

Recent histometrical studies have shown that the capillary growth in myocardial hypertrophy is less than the growth of myocardium, so that relative ischemia is present in cardiac hypertrophy.^{31,32} These studies support the hypothesis that the late progression of heart failure in cardiac hypertrophy is caused by the impairment of perfusion present in the hypertrophied myocardium. Study of the human hearts of recipients of cardiac transplantation has also shown that the basic contractility of the isolated right ventricular heart muscle of patients with severe heart failure requiring cardiac transplantation is normal, although the response to extrinsic catecholamine is impaired.²⁹ This study is also in step with our hypothesis about the pathogenesis of heart failure.

In conclusion, myocardial hypertrophy is the adaptive process against increased loading conditions to myocardium. Even if interstitial fibrosis proceeds, hypertrophy can compensate for the reduction in contractile component up to a certain degree. Relative impairment of myocardial perfusion present in cardiac hypertrophy is important to account for the pathogenesis of late heart failure in hypertrophy.

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