THE EFFECT OF REGIONAL MYOCARDIAL ISCHEMIA ON SERIES
ELASTIC AND CONTRACTILE ELEMENTS OF GLYCERINATED
HEART MUSCLE IN DOGS

YUKIO MARUYAMA, RENATE FISCHER, RICHARD J. BING

The response of the contractile and the series elastic elements to ischemia was studied with isometric contraction and quick release methods after measuring the passive length-tension relationship in glycerinated heart muscle fibers of dogs at resting state. Myocardial infarction was induced by ligating left coronary artery. Muscle fibers taken from the ischemic area three hours after ligation demonstrated reduction in maximal developed tension ($P_0$), the maximal rate of tension development ($dp/dt_{max}$) and $V_{max}$. The time to peak tension ($t_0$) was increased. As in fresh papillary muscle the modulus of elasticity of active glycerinated muscle increased in proportion to load. The stiffness of the series elastic element elevated significantly in ischemic muscle fibers. The passive stiffness in resting state showed a decrease in the slope accompanied by an increase in the intercept in ischemic heart muscle. Therefore, increased stiffness of the series elastic element and diminished contractility are present following acute myocardial infarction.

A loss of contractile force has been reported after myocardial ischemia. However, muscle mechanics under ischemia is poorly understood in the whole heart. First of all, measurement of contractility is complicated by the irregular shape of the heart chambers, variable wall tension due to the Laplace relation, nonuniformity of fiber direction and activation, and the difficulty of defining preload and "isotonic" contractions. Furthermore, steady state is lacking and tetanic contractions cannot be obtained in the whole heart. Even though papillary muscle is used to examine muscle mechanics, this tetanic state is not obtained except with specialized intervention.

Many factors contributing to the depression of contractility after ischemia have been discussed, but relatively few investigations are made concerning the contractile system itself. Thus, glycerinated heart muscle composed of contractile and regulatory proteins were used to clarify the behavior of the contractile system after regional ischemia.

Hitherto, it has been reported that stiffness of the series elastic element is not changed by

Key Words:
- Glycerinated heart muscle
- Myocardial infarction
- Quick release
- Contractility
- Series elastic stiffness
- Passive stiffness

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TABLE 1 THE EFFECT OF REGIONAL ISCHEMIA ON MAXIMAL DEVELOPED TENSION ($P_0$), TIME TO PEAK TENSION ($t_0$), AND MAXIMAL RATE OF TENSION DEVELOPMENT ($\frac{dp}{dt_{max}}$)

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Non-infarcted area</th>
<th>Infarcted area</th>
<th>Non-infarcted area</th>
<th>Infarcted area</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$P_0$ (mg/mm²)</td>
<td>$t_0$ (sec)</td>
<td>max dp/dt (mg/min/mm²)</td>
<td>$P_0$ (mg/mm²)</td>
</tr>
<tr>
<td>1</td>
<td>543</td>
<td>36.9</td>
<td>1428</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>729</td>
<td>97.8</td>
<td>703</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>647</td>
<td>98.4</td>
<td>939</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>980</td>
<td>105.0</td>
<td>858</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>1105</td>
<td>78.0</td>
<td>1405</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>707</td>
<td>100.2</td>
<td>697</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>822</td>
<td>67.2</td>
<td>1963</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>450</td>
<td>97.8</td>
<td>1181</td>
<td>8</td>
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<tr>
<td>9</td>
<td>927</td>
<td>74.0</td>
<td>1001</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td>1092</td>
<td>69.2</td>
<td>1185</td>
<td>10</td>
</tr>
<tr>
<td>11</td>
<td>707</td>
<td>69.6</td>
<td>899</td>
<td>11</td>
</tr>
<tr>
<td>12</td>
<td>503</td>
<td>106.2</td>
<td>625</td>
<td></td>
</tr>
</tbody>
</table>

Mean ± SE 

Significance $P < 0.01$ $P < 0.00125$ $P < 0.0125$

inotropic interventions, hyperthyroidism, or myocardial hypertrophy. Only at low temperatures or hyperosmolar external media has an increase of the series elastic element been observed. Some information has been presented concerning the location of the series elastic element in muscle, and it has been suggested that a large part of the series elasticity may reside in the points of attachment of the muscle. However, it has also been proposed that the series elasticity is associated with the contractile element. Thus, it was thought that an alteration of the contractile element may induce the stiffness of the series elastic element. Accordingly, it is the purpose of this report to investigate the contractile system with particular emphasis on the active stiffness.

The experiments reveal that disturbances in the contractile element occur in the increased stiffness of the series elastic element without significantly increased passive stiffness throughout various loads used in this experiment.

MATERIALS AND METHODS

Experiments on ischemic myocardium of dogs

Ten mongrel dogs were studied three hours after ligation of the left coronary artery. The dogs were anesthetized intravenously with sodium pentobarbital (30 mg/kg weight). The chest was opened and the anterior descending coronary artery was ligated distal to the origin of the septal arteries. epicardial ST elevations and the degree of visible cyanosis were used to differentiate non-ischemic myocardium from borderline and ischemic regions. The heart was excised and washed in ice-cold saline and two samples were removed, one from the center of the ischemic region, and the other from the non-ischemic region. Each specimen weighed about 2 grams, and consisted primarily of trabecular or papillary muscle. A small section of the muscle was placed in the glycerol solution. The method for glycerinization was identical to previous reports.

One hour prior to the experiment the muscle fibers were removed from the solution and immersed into a relaxation solution containing 100 mM KCl, 5 mM MgCl₂, 5 mM disodium ATP, 5 mM EDTA, 5 mM NaH₄ and 20 mM imidazole, pH 7.0. The muscle bundle was placed under the dissecting microscope (Zeiss, Model 3, Wild-Heerbrugg, Ltd., Switzerland). and smaller fiber bundles were dissected from the central core of the muscle. Most of the fibers were almost parallel. In animals exposed to ischemia for three hours, 12 observations were made from ischemic and 11 from non-ischemic regions (Table I). The cross-sectional area of the muscle bundles was 0.164 ± 0.014 mm² in non-ischemic region and 0.160 ± 0.010 mm² in ischemic region.
mm² in ischemic region, respectively.

Passive length-tension relationship in resting state

The ends of the muscle bundle were tied to a stainless steel wire (0.0045 inches in diameter) with a series of three half-hitches of monofilament nylon 10-0 Ethilon (Ethilon, Inc., Sommerville, N. J.). One wire was connected to the servo arm which has been fixed during the measurement of the length-tension relationship of glycerinated heart muscle. The other wire was connected to the force transducer. This can be moved using a micrometer system which adjusts the distance between the wires (Fig. 1). The passive length-tension relationship was measured prior to inducing the contraction.

First, the muscle fiber was stretched 20 to 30% above the length at zero load, then stretch was released stepwise by 50 to 70 μm, each step lasting about 30 seconds. The length of the muscle bundle was observed employing a microscope (objective 2.5X, eyepiece 10X) (Standard WL Research Microscope, Carl Zeiss, West Germany); the force was measured with a force transducer (a variable capacitance type, Lion-Precision Co., Newton, Mass.) and recorded on a strip chart recorder (Soltex Corp., North Hollywood, Ca.). The number of observations three hours after ligation of the left coronary artery was 10 from ischemic, and 9 from non-ischemic regions. (Figs. 2 a, b and Table II).
TABLE II PASSIVE STIFFNESS OF HEART MUSCLE

<table>
<thead>
<tr>
<th></th>
<th>Non-Infarcted Area (n = 9)</th>
<th>Infarcted Area (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( a ) Slope: % ML(^{-1} )</td>
<td>0.0557 (0.0460 &lt; a &lt; 0.0632)</td>
<td>0.0346 (0.0251 &lt; a &lt; 0.0423)</td>
</tr>
<tr>
<td>( b ) Y intercept</td>
<td>3.79 (3.07 &lt; b &lt; 4.51)</td>
<td>6.35 (5.38 &lt; b &lt; 7.32)</td>
</tr>
</tbody>
</table>

Numbers in parenthesis: 95% confidence limits

RESTING LENGTH-TENSION

(a) NON-ISCHEMIC DOG HEART MUSCLE

(b) ISCHEMIC DOG HEART MUSCLE

Fig. 2. Computer plot of passive length-tension relationship in resting state of non-ischemic area (Fig. 2a) and ischemic area (Fig. 2b) obtained three hours after left coronary artery ligation. The exponential solid line is obtained by plotting resting tension against its corresponding % change in muscle length (non-linear least-squares method). There is no significant difference between both groups throughout any given stress.

Isometric contraction and isotonic quick release

Maximal developed tension (\( P_0 \)), maximal rate of tension development (dp/dt\(_{\max} \)), time to peak tension (\( t_0 \)) and shortening velocity at zero load (\( V_{max} \)) were estimated, as described previously. In brief, a servo programmer was utilized which permitted recording both of isometric and isotonic contractions. Figure 1 illustrates the servo system. Monitoring of shortening of the muscle fiber was accomplished by an electro-optical system as previously described.

The operating sequence consists of an isometric phase at initial length followed by three successive isotonic phases at force levels of \( P_1 \), \( P_2 \) and \( P_3 \) (Figs. 3 a, b).

After the muscle has been suspended between hooked wires (Fig. 1), and the experimental trough filled with relaxation solution, initial tension was 142.3 ± 3.5 mg/mm\(^2\) of the cross-sectional area of the fiber. This corresponded to an average sarcomere length of 2.23 ± 0.02 µm. Sarcomere length was measured by directly photographing the fiber with a Polaroid camera with a 40X water-immersion objective and 8X eyepiece (Fig. 4). The relaxation solution was then replaced with the contraction solution (100 mM KCl, 5 mM MgCl\(_2\), 5 mM Na\(_2\)ATP, 5 mM EGTA, 5 mM NaN\(_3\), 20 mM imidazole and 5 mM CaCl\(_2\), pH 7.0). The servo system maintained constant length, while increases of tension were recorded. When tension reached a plateau, the program sequence of shortening (Fig. 3b) was activated by pushing the start button on the programmer. This permitted the muscle fiber to contract isotonically at about 60, 30 and 15% levels of the total tension. Figures 3a, b illustrate \( P_0 \), dp/dt\(_{\max} \) and \( t_0 \) in isometric contraction, and the three different isotonic contractions at three different tensions after quick release. Figures, 5 a, b show isometric contraction by a chart recording and quick release steps by a photographic recording. Sarcomere length was also measured at \( P_0 \) (maximal developed tension) and \( P_3 \) (the lowest load after quick release). No significant difference in sarcomere length during muscle shortening was observed between both non-ischemic and ischemic groups (Table III).

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TABLE III  SARCOMERLE LENGTH AT PRELOAD (P_r) IN THE RELAXATION, MAXIMAL DEVELOPED TENSION (P_0) AND THE SMALLEST FORCE (P_3) AFTER QUICK RELEASE

<table>
<thead>
<tr>
<th></th>
<th>non-infarcted area (n = 12)</th>
<th>infarcted area (n = 11)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>P_r (μm)</td>
<td>2.24 ± 0.02</td>
<td>2.22 ± 0.04</td>
<td>n.s.</td>
</tr>
<tr>
<td>P_0 (μm)</td>
<td>2.19 ± 0.02</td>
<td>2.20 ± 0.02</td>
<td>n.s.</td>
</tr>
<tr>
<td>P_3 (μm)</td>
<td>2.05 ± 0.03</td>
<td>2.11 ± 0.02</td>
<td>n.s.</td>
</tr>
<tr>
<td>% decrease from P_r to P_0</td>
<td>2.2 ± 0.3</td>
<td>0.7 ± 2.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>% decrease from P_0 to P_3</td>
<td>6.9 ± 1.0</td>
<td>3.6 ± 0.5</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

(a)  
relaxation  \hspace{1cm} \text{isometric}  \hspace{1cm} \text{contraction}  \hspace{1cm} \rightarrow

Fig.3a: Schematic diagram of a typical experiment shows a slow sweep recorder tracing of a glycerinated muscle fiber. Maximal developed tension, P_0, total tension, P_t, maximal rate of tension development, dp/dt_max, the time to peak tension, t_0.

(b)  
isotonic quick release

Fig.3b: Schematic diagram of a typical fast sweep oscillographic tracing showing a sequence of isotonic shortenings of the glycerinated muscle fiber at three different loads (P_1, P_2, and P_3). \( \Delta P_{1,2} \) and \( \Delta L_{1,2} \) and \( \Delta P_3 \) are shown after quick release. \( P_t \) = total tension, \( L_0 \) = initial and maximal length, \( L_5 \) = minimum allowed length.

Calculations: Isometric contraction and force-velocity relationship

Maximal developed tension (P_0) was calculated as described previously from this laboratory.\(^{20}\) Force-velocity curves were obtained by plotting shortening velocity in muscle lengths/second versus relative force P/P_total, where P represents force levels at different isotonic shortening steps and P_total represents total force of preload plus maximal developed tension. Thus, relative force was expressed as P_1, P_2, P_3, P/P_total force. The pooled data from each group were fitted into a hyperbola by the least-squares method, using a modified equation of Hill, as published previously.\(^{20-22}\)

\[
(V + b)(P/P_{\text{total}} + b/V_{\text{max}}) = (1 + b/V_{\text{max}})b
\]

where \( V \) = shortening velocity/muscle lengths/second; \( V_{\text{max}} \) = maximal shortening velocity corresponding to zero load; b = constant (Figs. 6a, b). This particular form of Hill's equation was employed because on this case, the computer was programmed to yield not only estimates of the projected value of \( V_{\text{max}} \), but also its 95% confidence limits.
Passive length-tension relationship (passive stiffness in resting state)

Individual tensions were converted to g/mm² of muscle cross-sectional area and length data calculated as % change of the muscle length at zero tension. Passive length-tension curves obtained from glycerinated heart muscle were fitted to exponential curves (Figs. 2a, b). According to Covell and Ross²³ in resting cardiac muscle the relation between the length extension and tension is exponential. Also, there was the same trend in glycerinated muscle as found in excised papillary muscle (Fig. 7); the resulting linear relation between passive stiffness (dP/dL) and tension (P) can be expressed as

\[ \frac{dP}{dL} = aP + b \]

where \( \frac{dP}{dL} \) is referred to as the passive stiffness of the muscle in resting state, P is tension (g/mm²), L is the corresponding relative length (% change) and a and b are constants (a is the slope, and b is the intercept with the Y axis (Figs. 2a, b, Table II). Non-linear least-squares method was employed to determine a and b from the experimental data by using the computer.

Stiffness of series elastic element

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According to Edman and Nilsson, the series compliance is defined as a drop in tension (ΔP) that occurs in response to a quick control release (ΔL) during isometric contraction of the muscle. In our experiments, as in those of Jewell and Wilkie, tension was controlled and length was permitted to change. There is a rapid change in length due to shortening of the series elastic element when the force of the muscle is suddenly reduced by the quick release method. From the oscilloscope tracing obtained, the ratio ΔP/ΔL is calculated (Fig. 3b), and its value was plotted against individual loads (P₁, P₂, P₃) (Fig. 8). As seen from Fig. 8 the relation between stiffness (dP/dL) and load was linear, so that the stiffness of the muscle could be represented as the modulus of elasticity

\[ \text{dP/dL} = K P + C, \]

where dP/dL is the muscle stiffness in the series elastic element, P is the load, K and C are constants (K is the slope, C is the intercept with the y axis). The linear relations between stiffness and tension make it possible to compare the slope and intercept of non-ischemic data with those observed in ischemic data.

**RESULTS**

**Experiments on ischemic heart muscle of dog: Isometric contraction and force-velocity relationship**

Table I and Figs. 6a, b illustrate the maximal developed tension (Pₒ), the maximal rate of tension development (dp/dt max), the time to peak tension (tₒ) and the force-velocity relationship (V_max). Ischemic heart muscle three hours after left coronary artery ligation showed a marked decline in maximal developed tension (Pₒ) and in maximal rate of tension development (dp/dt max). A significant increase in tₒ was observed. The relationship between P/total load and shortening velocity of contractile element is illustrated in Figs. 6a, b. A significant difference in V_max between ischemic and non-ischemic areas is noticeable, with no overlapping of confidence limits.

**Passive stiffness**

The slope was lower in infarcted area, although the intercept was higher. Therefore, when small loads were used, passive stiffness of the ischemic muscle was increased (Figs. 2a, b, Table II). However, passive stiffness was not significantly increased throughout any loads investigated in the experiment.

**Stiffness of series elastic element**

The changes in the stiffness of the series elastic element (dP/dL) are illustrated in representative experiments after three hours of left coronary artery ligation (Fig. 8). Mean values for slopes (K) using fibers from non-ischemic and ischemic regions were 0.284 ± 0.030 and 0.355 ± 0.022/% length, respectively (p < 0.05). C was not significantly different in both groups (non-
The mechanisms by which the contractility is depressed after ischemia have been discussed from different points of view.\textsuperscript{25-28} However, data concerning the contractile machinery itself is poor. Although several problems for using a glycerinated muscle have been pointed out\textsuperscript{22} its preparation was used because it eliminated systems of activation related in membrane activities, and serves as a model of the contractile elements.\textsuperscript{20,22,29} In the present study, the main concern was to compare the characteristics of the contractile element and series elastic element of ischemic muscle with those of non-ischemic muscle. Comparing our values of $P_0$ with those of glycerinated rabbit heart, much difference was not found.\textsuperscript{19} The reason why the pooled data in each group were used for the calculation of $V_{\text{max}}$ is indicated in the previous report.\textsuperscript{20} Since the main purpose is to compare the $V_{\text{max}}$ in each group, this method is likely to be reasonable. Although data of $V_{\text{max}}$ using glycerinated heart muscle are not available, our value of non-ischemic region is higher than that of a glycerinated psoas muscle of a rabbit.\textsuperscript{30} Reported values of $V_{\text{max}}$ in normal papillary muscle were different between species.\textsuperscript{31} However, it is interesting to recognize that $V_{\text{max}}$ in glycerinated

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Fig. 7. Resting length-tension relationship from a single muscle preparation of a non-ischemic muscle. Note that there is the exponential relation between the length extension and tension.

Fig. 8. Representative experiments to measure the stiffness of series elastic element in non-ischemic area and ischemic area. Values of the stiffness (ΔP/ΔL) are plotted against individual loads. The relation between stiffness of series elastic elements and loads is linear.

rat heart muscle was not so different from that of dog heart muscle. Moreover, it is noticeable that values of \( V_{\text{max}} \) in normal papillary muscle were considerably higher than those of glycerinated muscle. One reason is probably the difference in temperature (30°C in fresh muscle, as compared to our preparations, 20–22°C). This is in line with observations which showed a decline of \( V_{\text{max}} \) of fresh heart muscle at lower temperature.

As Figs. 6a, b illustrate, another problem is, that force-velocity relationship may not always be represented by a hyperbolic curve. We assumed that this relationship was hyperbolic and programmed the data accordingly. Our confidence values for \( V_{\text{max}} \) were significant within 95% non-linear confidence limits, making comparisons between the two groups possible. However, the possibility that the force-velocity relationship may not be a true hyperbola, represents a possible error in calculation of \( V_{\text{max}} \).

In order to investigate sarcomere shortening during quick release, microscopic pictures of muscle fibers in preload, after maximal force development (\( P_0 \)) and after quick release following the smallest force (\( P_3 \)) were taken.

To increase the contrast, computer image contrast enhancement was used. Figure 4 illustrates an example of this pattern at preload. Table III shows sarcomere length changes at each stage. Brutsaert has shown that if sarcomere length is below 87.5% of \( L_{\text{max}} \) (sarcomere length of about 1.9 μm), \( V_{\text{max}} \) is affected and decreases with shortening. In addition, Julian and Sollins have shown that peak active tension in rat papillary muscle decreases as sarcomere length diminishes below approximately 2.0 μm. As Table III illustrates, the sarcomere length at \( P_3 \) (non-ischemic: 2.05 ± 0.03 μm, ischemic: 2.11 ± 0.02 μm) is greater than considered critical by their data.

After myocardial infarction the resulting fibrosis has been thought to change the left ventricular diastolic pressure-volume relationship. However, there are some controversies for diastolic compliance during acute ischemia or hypoxia. Namely, some investigators found increased compliance and others declared little or no change in diastolic compliance. On the other hand, a significant decrease was showed by some reporters. Furthermore, Templeton et al. declared that viscous stiffness was significantly increased, and it lead to the increase in total ventricular stiffness during ischemia without any change in elastic stiffness. Although the precise reason for the discrepancy of previous data is not clear, one possible explanation may be dependent on the severity and duration of the ischemic or hypoxic state. We showed lower values in stiffness constant accompanied with higher values in the intercept with the Y axis 3 hours.
after myocardial infarction (Table II). Little, R. C.\(^{48}\) showed similar results in hypoxia, but he did not find any significant difference in passive stiffness between control and hypoxia. From our results, it was also not concluded that an increase in passive stiffness throughout any given stress was followed after acute myocardial infarction.

The quick release method, which was used by several reporters\(^{3,10}\) was employed in the investigation of the series elastic, as well as the contractile element. The reason using the glyc erinated muscle preparation for this experiment is previously described. In addition, it has been reported recently that the stiffness of the series elastic element varies with time after activation\(^{17,18}\) suggesting that cross-bridge elasticity may be an important component of the series elastic compliance measured in heart muscle, though there are several different reports in which the series elastic stiffness of cardiac muscle varies in a linear way with force and is independent of time\(^{3,49}\). In the glyc erinated muscle preparation the function of membrane structures such as SR is thought to be lost, while the muscle preparation has the ability to generate tension in the presence of Ca\(^{++}\) and ATP. Thus, active state is held constant following the attainment of P\(_0\). Moreover, deactivation during quick release isotonic contraction is not likely to occur as described before (Table III). Therefore, it is possible to study the alteration in the stiffness of the series elastic element without considering the change in active state.

The data presented here indicate that in dog hearts following production of regional ischemia, the series elastic and contractile elements were impaired. Our previous report also showed the depressed contractility in the early stage of ischemia\(^{29}\). It has been demonstrated biochemically that ischemia induced changes in the regulatory proteins and that such changes may have an effect on the interaction of actin and myosin.\(^{50}\) Furthermore, the difference in slope (K) between non-ischemic area and ischemic area is significant, while there is no difference in intercept with y axis (Fig. 8). The similar results showing the changes in active stiffness and contractility have been obtained in rat hearts exposed to alcohol.\(^{22}\) It is also not possible to draw any definite conclusions as to the cause of this increased stiffness of the series elastic element of the muscle. Hitherto, hypoxia has been found to cause no change in the stiffness of the series elastic element\(^{4}\) whereas it became stiffer as contracture in resting state developed.\(^{6}\) The discrepancy between our data and Henderson et al.\(^{6}\) is not clear. Although several workers, particularly Huxley,\(^{15,16}\) have tried to associate the series elastic element with cross bridges, linking actin to myosin, no histological counterpart has been identified in cardiac muscle\(^{16}\) and one would have to conclude that the cross bridges of heart muscle are about four times as compliant as those of skeletal muscle.\(^{17}\)

Therefore, it would be premature to explain the mechanisms underlying the disturbance in the series elastic and contractile elements, as long as so many options exist concerning their structural and biochemical nature. The fact, however, that in the experiments reported here, changes in the series elastic and contractile elements occur together, suggesting some relationship between the two systems.

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