Physiologists are agreed that muscular activity increases the blood flow of the active muscles approximately in proportion to the increase in muscle metabolism. However, this metabolically induced increase in flow is a delayed reaction, the blood flow increasing gradually over a period of 15 to 60 seconds after muscle activity begins. Yet, different investigators have presented recordings showing that the cardiac output increases almost instantly after exercise begins (reviewed in reference 3).

Rushmer, particularly, has shown that cardiac stroke excursions (and presumably also the cardiac output) can increase literally within the next heart beat after exercise begins, thus supplying the extra blood flow required by the active muscles. He has emphasized the importance of an increased heart rate in this reaction. However, to increase the output significantly, there must be other effects besides increased heart rate, because studies by Holt, Duomarco, and ourselves have all demonstrated that increased pumping ability of the heart is not sufficient by itself to increase the cardiac output significantly. The reason for this is that blood flow around the circulation is limited by collapse of the veins entering the chest when the pumping action of the heart becomes too great. Furthermore, all of these studies have demonstrated that the normal circulatory system operates near this limit so that an increase in efficacy of the heart as a pump cannot by itself increase the cardiac output more than a few per cent, unless some simultaneous effect takes place in the peripheral circulatory system at the same time to translocate blood from the peripheral vessels to the heart.

In the present studies, muscular activity has been induced by stimulation of both sciatic nerves, by stimulation of the lower segment of the transected spinal cord, or by direct muscular stimulation. These experiments have demonstrated that widespread muscular contraction compresses the enclosed blood vessels and thereby elevates the mean circulatory pressure, sometimes to over three times normal; this, in turn, is accompanied by immediate translocation of blood from the peripheral vascular system toward the heart, which appears to be one of the major factors that increases the cardiac output at the onset of muscular activity.

**Methods**

Thirty-three dogs, anesthetized with 25 mg/Kg. of sodium pentobarbital given intravenously and heparinized with 5 mg/Kg. of heparin, were used in these experiments.

Two different basic experimental procedures were used: (1) an open-chest procedure in which cardiac output could be measured and recorded continuously; the response time of the cardiac output recorder (a rotameter) was only a fraction of a second; (2) a closed-chest method utilizing a continuous cardiac output recorder developed in this laboratory. The open-chest procedure has been described previously, the essential techniques of which are the following: A large glass cannula is inserted into the wall of the right atrium, and blood is pumped from this cannula through (a) an external pump, (b) a heater circuit, and (c) a Shipley-Wilson rotam-
eter to measure blood flow, thence back into the pulmonary artery. At the input to the external circuit is a segment of thin rubber tube which can be raised or lowered. The pump is always adjusted to keep this thin segment collapsed. Therefore, the pressure of the blood as it enters the thin segment is exactly equal to the atmospheric pressure at that level. Raising and lowering the thin segment of tube increases or decreases the hydrostatic pressure in the right atrium and, therefore, sets the right atrial pressure. In this preparation, the external pump controls the output of the heart because within physiological limits the left heart pumps whatever amount of blood is put out by the external pump. Therefore, the effect of peripheral circulatory conditions on blood flow around the circulatory pathway can be studied independently of cardiac action.

The closed-chest procedure for recording cardiac output is based on the Fick principle. A special apparatus continuously records arteriovenous (A-V) oxygen difference; an oxygen consumption recorder continuously records oxygen usage by the animal, and an analogue computer continuously computes the cardiac output from these other two values. This method for recording cardiac output is limited to steady state conditions, as is true of all Fick cardiac output methods. However, it allowed corroboration in closed-chest animals of most of the results obtained by the open-chest procedure.

Three different methods were used to cause muscular activity. First, the spinal cord was sectioned in the midthoracic region, and four 2-inch needle electrodes were inserted on each side of the spinal column approximately 10 cm. below the transected point of the cord. Sixty-cycle sinusoidal current was used to stimulate the lower segment of the cord. The voltage was adjusted to give maximal muscular response. Second, both sciatic nerves were sectioned shortly after leaving the spinal canal, and the distal stumps of the nerves were stimulated by theratron discharge stimuli at frequencies up to 60 c.p.s. and at voltages which always gave maximal responses. Third, the anterior abdominal muscles were stimulated for maximal response in a few experiments by using diffuse needle electrodes in the muscles themselves.

Arterial pressure was recorded from a catheter in the femoral artery by use of a Statham transducer, and right atrial pressure was recorded similarly through a catheter inserted by way of the external jugular vein into the right atrium.

Obviously, when stimulating either the sciatic nerves or the spinal cord, both skeletal and autonomic nerve fibers were excited simultaneously. To separate the effects of these two types of stimulation on the circulatory responses, hexamethonium was given in one series of animals and decamethonium in another series, the first drug blocking all autonomic effects and the second blocking all skeletal nerve effects. The dosage of the hexamethonium was adjusted to the point that no carotid sinus reflex could be elicited from the animal (approximately 1.5 mg./Kg.), and the dosage of decamethonium was adjusted to the point that no skeletal muscular response occurred upon stimulation of the sciatic nerves or the spinal cord (approximately 0.6 mg./Kg.).

Results

EFFECT OF SUDDEN MUSCLE STIMULATION ON CARDIAC OUTPUT IN OPEN-CHEST PREPARATION

Figure 1 illustrates the effects in the open-chest preparation of suddenly stimulating the spinal cord with maximal 60-cycle stimuli applied intermittently approximately two times per second. Note that immediately after onset of stimulation the cardiac output rose from a control value of 1,500 cc. per minute to 2,060 cc. per minute. The initial rise occurred actually during the first three heartbeats after stimulation began, thus illustrating the immediacy of the reaction. As illustrated in the figure, there was a simultaneous, though less pronounced, elevation of arterial pressure. In 11 experiments of this type, summarized in table 1, the immediate rise in cardiac output averaged 40 per cent.

Table 1 also summarizes the effects, first, of stimulating both sciatic nerves and, second, of stimulating the anterior abdominal musculature with maximal stimuli. In one-half of the experiments, intermittent stimuli were used and, in the other half, continuous stimuli. This table shows that all types of muscular activity caused an immediate increase in cardiac output, although stimulation of the legs or anterior abdominal muscles caused far less increase than did excitation of the entire lower body by means of spinal cord stimulation.

Figure 1 and table 1 also demonstrate an additional important fact: After the initial acute rise in cardiac output, the output then rose still further during the next 30 seconds to one minute to an average value 86 per cent above the control. Thus, the record dem-
demonstrates two phases in the cardiac output response: (a) an acute phase occurring literally in the first second after onset of muscular activity, and (b) a delayed phase requiring 30 seconds to one minute to develop fully.

In our earlier studies, especially when stimulating only the sciatic nerves, we used several types of stimuli, such as (a) different frequencies of stimulation, (b) continuous stimulation, (c) intermittent tetanizing stimuli with the intervals of intermittence varying from once every few seconds up to two times per second, and so forth. Of all these different types of stimuli, the intermittent tetanizing stimuli applied approximately two times per second gave the most persistent effect on cardiac output, whereas continuous stimuli usually gave a greater immediate effect but a less persistent one, as is evident from the data in table 1.

**EFFECT OF SUDDEN MUSCLE STIMULATION ON CARDIAC OUTPUT IN CLOSED- CHEST PREPARATION**

Figure 2 illustrates recordings of A-V oxygen difference, rate of oxygen utilization, and cardiac output as measured by the continuous Fick cardiac output recorder in the closed-

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**TABLE 1**

_Effect of Muscle Stimulation on Cardiac Output and Arterial Pressure in the Open-Chest Preparation*

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Number of dogs</th>
<th>Increase in cardiac output (per cent of control)</th>
<th>Increase in arterial pressure (mm. Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulate spinal cord intermittently</td>
<td>11</td>
<td>40 ± 3, 86 ± 8.5</td>
<td>1 ± 3.5, 16 ± 5.5</td>
</tr>
<tr>
<td>Stimulate spinal cord intermittently after decamethonium</td>
<td>4</td>
<td>0 ± 0, 22 ± 6.0</td>
<td>0 ± 0, 16 ± 10</td>
</tr>
<tr>
<td>Stimulate spinal cord intermittently after hexamethonium</td>
<td>5</td>
<td>30 ± 6.7, 45 ± 6.2</td>
<td>13 ± 7.8, 26 ± 9.4</td>
</tr>
<tr>
<td>Stimulate abdominal muscles continuously</td>
<td>5</td>
<td>22 ± 7.5, 10 ± 5.4</td>
<td>5 ± 6.5, 3 ± 3.8</td>
</tr>
<tr>
<td>Stimulate abdominal muscles intermittently</td>
<td>5</td>
<td>12 ± 2.5, 9 ± 3.7</td>
<td>−4 ± 4.3, −3 ± 5.0</td>
</tr>
<tr>
<td>Stimulate sciatic nerves continuously</td>
<td>5</td>
<td>16 ± 4.8, 7 ± 3.2</td>
<td>2 ± 4.5, 3 ± 3.7</td>
</tr>
<tr>
<td>Stimulate sciatic nerves intermittently</td>
<td>5</td>
<td>14 ± 2.5, 11 ± 2.6</td>
<td>−5 ± 4.5, −2 ± 3.4</td>
</tr>
</tbody>
</table>

*Variance is expressed as standard error of the mean.

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_Circulation Research, Volume XI, September 1968_
EFFECT OF HEXAMETHONIUM AND DECAMETHONIUM ON THE CARDIAC OUTPUT RESPONSE TO MUSCLE STIMULATION

Stimulation of the nerves or the spinal cord excites both sympathetic and skeletal nerve fibers. Therefore, it was necessary to differentiate between the effects on cardiac output of stimulating these two types of fibers. To separate these effects, five open-chest and five closed-chest animals were given sufficient decamethonium to paralyze the entire skeletal nervous system (as tested by response of muscles to nerve stimulation), and four open-chest and five closed-chest animals were given hexamethonium in large enough dosage to paralyze completely the sympathetic nerves (as tested by response of the animal to the carotid sinus reflex). The results of stimulat-
### TABLE 2

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Number of dogs</th>
<th>Increase in cardiac output (percent)</th>
<th>Increase in arterial pressure (percent)</th>
<th>Increase in right atrial pressure (mm. Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulate spinal cord intermittently</td>
<td>12</td>
<td>149 ± 25.9</td>
<td>67 ± 10.9</td>
<td>1.2 ± 0.4 (P = 0.002)</td>
</tr>
<tr>
<td>Stimulate spinal cord intermittently after hexamethonium</td>
<td>5</td>
<td>67 ± 17.7</td>
<td>143 ± 43</td>
<td>2.2 ± 1.2 (P = 0.07)</td>
</tr>
<tr>
<td>Stimulate spinal cord intermittently after hexamethonium</td>
<td>5</td>
<td>89 ± 26.5</td>
<td>71 ± 20.7</td>
<td>−0.3 ± 1.38 (P = 0.8)</td>
</tr>
<tr>
<td>Stimulate abdomen continuously</td>
<td>13</td>
<td>10 ± 4.5</td>
<td>0 ± 7.3</td>
<td>1.5 ± 0.47 (P = 0.001)</td>
</tr>
<tr>
<td>Stimulate abdomen intermittently</td>
<td>13</td>
<td>15 ± 3.4</td>
<td>−4 ± 7.6</td>
<td>1.4 ± 0.66 (P = 0.03)</td>
</tr>
<tr>
<td>Stimulate both sciatic nerves continuously</td>
<td>13</td>
<td>30 ± 8.2</td>
<td>−8 ± 6.8</td>
<td>0.2 ± 0.38 (P = 0.6)</td>
</tr>
<tr>
<td>Stimulate both sciatic nerves intermittently</td>
<td>13</td>
<td>43 ± 9.4</td>
<td>−4 ± 7.5</td>
<td>0.6 ± 0.66 (P = 0.4)</td>
</tr>
</tbody>
</table>

*Variance is expressed as standard error of the mean.

Overall average rise in right atrial pressure = 1.05 ± 0.346 (P = 0.003).

In substance, these results illustrate that stimulation of the peripheral nervous system can increase the cardiac output either by stimulation of the skeletal nerves or by stimulation of the autonomic nervous system (table 2).
intermittent compression caused about the same immediate increase in cardiac output as did continuous compression, but it caused a more sustained increase in cardiac output than did continuous compression. Figure 4 illustrates typical results, 4 (A) showing the effect of continuous compression and 4 (B) the effect of intermittent compression. Note that the cardiac output tends to fall considerably more rapidly following continuous compression than following intermittent compression.

The results of the compression studies in the open-chest preparation are given in table 3, showing that intermittent compression of both the abdomen and the two hind legs increased the cardiac output an average of 30 per cent immediately after onset of the compression and that this could be sustained at a level of 21 per cent above the control value for many minutes at a time.

In the closed-chest preparation, the quantitative results were essentially the same as those in the open-chest preparation; however, because of the inherent lag in the Fick method for recording cardiac output, the effect did not occur instantaneously but built up slowly over a period of one to two minutes following the onset of muscle compression.

**EFFECT OF MUSCLE ACTIVITY ON RIGHT ATRIAL PRESSURE**

If the mechanism by which muscle activity increases cardiac output is purely a mechanical compression of the peripheral vasculature, then it follows that muscle compression must cause a translocation of blood into the heart. This, in turn, should be reflected by an increase in right atrial pressure. In our open-chest preparation, muscle stimulation in the periphery invariably elevated the right atrial pressure 1 to 3 mm. Hg immediately following the onset of muscular activity. However, because the pump in the external circuit altered the normal dynamics of right atrial function, attention was given mainly to the immediate effect of muscle stimulation on the right atrial pressure in the closed-chest preparation. The alterations of right atrial pressure in these experiments are shown in the last column of table 2. This table illustrates that in essentially all of the experiments, the right atrial pressure rose. Statistical analysis of the rise in right atrial pressure from all the experiments, as illustrated in the lowest line of table 2, gave a \( P \) value of 0.003. This degree of significance demonstrates almost certainly that peripheral muscular activity does indeed cause an instantaneous increase in right atrial pressure, the increase averaging in these studies 1.05 mm. Hg.

Manual compression of the peripheral musculature also increased the right atrial pressure, as summarized in the last column of table 3. Here again, we find a very significant elevation of right atrial pressure following muscle compression, averaging 1.00 mm. Hg and having a \( P \) value for significance of \( 10^{-4} \). The degree of significance was so great that there is no real doubt about the effect.

**EFFECT OF MUSCULAR CONTRACTION ON MEAN CIRCULATORY PRESSURE**

Previous studies from this laboratory have emphasized the importance of the mean circulatory pressure as one of the major determinants of cardiac output. In many instances, the cardiac output increases almost directly in proportion to the rise in mean circulatory pressure. Therefore, it was important in the present studies to determine how much muscular compression of the peripheral vasculature can increase the mean circulatory pressure.

The mean circulatory pressure was deter-
MUSCULAR ACTIVITY

mined in two different series of open-chest preparations both before and after muscular contraction began. In the first series, 11 dogs were used, and the control mean circulatory pressure averaged 8.7 mm. Hg. Following stimulation of the spinal cord in the usual manner, the mean circulatory pressure rose to an average of 19.0 mm. Hg with a P value for significance of less than 10^-20.

In still a second series of eight dogs, the mean circulatory pressure was studied before and after muscular stimulation, and the results were repeated again after administration of either decamethonium or hexamethonium. A typical experiment in these studies is illustrated in figure 5. Figure 5 (A) shows the results from a control study in an open-chest dog and figure 5 (B) the results in the same dog after administration of hexamethonium to block the autonomic nervous system. In figure 5 (A), at point 1 the pump of the external circuit was suddenly stopped, which caused all circulation to cease and caused the right atrial pressure to begin rising. At point 2, approximately eight seconds later, the right atrial pressure had risen as high as it would go, to 7 mm. Hg, or in other words, up to the level of the normal mean circulatory pressure. At this point, the lower spinal cord was stimulated in the usual manner, causing within the next few seconds an additional rise in mean circulatory pressure from its control value of 7 mm. Hg up to 17 mm. Hg. Figure 5 (B) illustrates similar effects after hexamethonium, the control mean circulatory pressure being 3.5 mm. Hg and this rising to 8 mm. Hg during muscular contraction. This figure illustrates particularly that stimulation of the skeletal musculature alone, without concurrent stimulation of the sympathetic nerves...

![Figure 5](http://circres.ahajournals.org/)

**FIGURE 5**

Effect of spinal cord stimulation on the mean circulatory pressure (as measured by changes in right atrial pressure after stopping all cardiac output) in the control condition (A) and after blocking the sympathetics with hexamethonium (B). Open-chest animals were used in these experiments. (See explanation in text.)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Increase in venous return (percent of control)</th>
<th>Increase in arterial pressure (mm Hg)</th>
<th>Increase in right atrial pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Immediate Sustained</td>
<td>Immediate Sustained</td>
<td>Immediate Sustained</td>
</tr>
<tr>
<td>Compress abdomen continuously</td>
<td>22 ± 6.7 -1 ± 1.8</td>
<td>12 ± 7.4 4 ± 9.6</td>
<td>0.6 ± 1.52 0 ± 1.31</td>
</tr>
<tr>
<td>Compress abdomen intermittently</td>
<td>23 ± 3.7 15 ± 1.5</td>
<td>2 ± 5.2 8 ± 7.1</td>
<td>1.2 ± 1.14 1.2 ± 1.14</td>
</tr>
<tr>
<td>Compress legs continuously</td>
<td>14 ± 4.2 6 ± 1.3</td>
<td>10 ± 8.3 13 ± 7.9</td>
<td>0.4 ± 1.03 0.2 ± 0.91</td>
</tr>
<tr>
<td>Compress legs intermittently</td>
<td>11 ± 5.1 9 ± 1.4</td>
<td>-2 ± 6.7 5 ± 8.5</td>
<td>0.6 ± 1.03 0.4 ± 0.89</td>
</tr>
<tr>
<td>Compress abdomen and legs continuously</td>
<td>20 ± 7.1 15 ± 8.2</td>
<td>10 ± 4.5 17 ± 9.2</td>
<td>1.5 ± 1.27 1.25 ± 1.20</td>
</tr>
<tr>
<td>Compress abdomen and legs intermittently</td>
<td>30 ± 4.0 21 ± 3.4</td>
<td>7 ± 7.9 13 ± 11.7</td>
<td>1.6 ± 1.08 1.4 ± 0.99</td>
</tr>
</tbody>
</table>

**TABLE 3**

Effect of Muscle Compression on Venous Return and Arterial Pressure in the Open-Chest Preparation

- Variance is expressed as the standard error of the mean. Number of dogs = 5.
- Overall average rise in right atrial pressure: immediate = 0.99 ± 0.2 (P = 22 × 10^-4); sustained = 0.7 ± 0.2 (P = 64 × 10^-4).
GUYTON, DOUGLAS, LANGSTON, RICHARDSON

TABLE 4

Effect of Spinal Stimulation on Mean Circulatory Pressure

<table>
<thead>
<tr>
<th>Condition of nervous system</th>
<th>Number of dogs</th>
<th>Control value (mm. Hg)</th>
<th>After stimulation (mm. Hg)</th>
<th>Average per cent increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>6</td>
<td>7.3 ± 0.2</td>
<td>24.3 ± 1.6</td>
<td>233</td>
</tr>
<tr>
<td>After decamethonium</td>
<td>3</td>
<td>3.3 ± 0.3</td>
<td>5 ± 0.0</td>
<td>52</td>
</tr>
<tr>
<td>After hexamethonium</td>
<td>5</td>
<td>3.8 ± 0.3</td>
<td>11.3 ± 1.4</td>
<td>107</td>
</tr>
</tbody>
</table>

*Variance is expressed as standard error of the mean.

ous system, can elevate the mean circulatory pressure instantaneously.

Table 4 summarizes the results from eight studies performed in the manner illustrated in figure 5, showing a mean increase in mean circulatory pressure in the six control animals from 7.3 mm. Hg up to 24.3 mm. Hg. After administration of decamethonium, that is, after the skeletal nervous system had been knocked out but with the sympathetic system still active, the average mean circulatory pressure rose from 3.3 to 5 mm. Hg during stimulation. After hexamethonium, that is, after the sympathetic nervous system had been knocked out but with the skeletal system still active, the average mean circulatory pressure rose from 3.8 to 11.3 mm. Hg.

EFFECT OF MUSCULAR ACTIVITY ON VENOUS RETURN CURVE

Since the very early studies of Starling and Bolton and the more recent studies of Starr, it has been recognized that the peripheral circulatory system plays a major role in the regulation of cardiac output, and in our laboratory we have worked out a graphical method for simultaneous analysis of the peripheral and cardiac factors in the regulation of cardiac output. The peripheral factors for a given animal, under a given set of conditions, can be represented in the form of a "venous return curve," which expresses the relationship between venous return and right atrial pressure. Figure 6 illustrates by the lower curve, labeled I, the average control venous return curve in 11 dogs, as determined in the open-chest preparation. This was determined by progressively elevating the right atrial pressure until all cardiac output ceased. Then, the lower spinal cord was stimulated by maximal tetanizing stimuli applied intermittently two times per second. After 45 seconds of this stimulation, the cardiac output had increased to an average of 150 per cent of the control value, and a second venous return curve was determined. The average curve for the 11 animals is the one labeled II in figure 6. The point at which each venous return curve reaches zero venous return is equal to the mean circulatory pressure for that particular set of conditions. Note that the mean circulatory pressure increased from 8.7 to 19 mm. Hg following muscle stimulation. This was the dominant factor influencing the venous return curve, causing it to be elevated at all right atrial pressures.

ESTIMATION OF CARDIAC OUTPUT CURVE DURING THE COURSE OF SPINAL CORD STIMULATION

In the closed-chest experiments, conditions were ideal for estimating the average cardiac output curve (effect on cardiac output of changes in right atrial pressure) of the dogs used in these experiments. Data from the different stimulation experiments are depicted by the X's in figure 6. X no. 1 represents the average of 38 separate control determinations; X no. 2 represents the average of 13 separate determinations after stimulating both sciatic nerves continuously; X no. 3 represents the average of 13 determinations after stimulating both sciatic nerves intermittently; and X no. 4 represents the average of 12 determinations after stimulating the lower spinal cord intermittently. A curve is drawn through these points and then extrapolated both above and below by dashed lines, these extrapolations being based on complete curves that we have run by changing the blood volume while recording cardiac output.

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GRAPHICAL ANALYSIS OF CARDIAC OUTPUT AND RIGHT ATRIAL PRESSURE CHANGES FOLLOWING THE ONSET OF MUSCULAR ACTIVITY

In figure 6, the combination of the venous return curves I and II and the cardiac output curve gives a graphical analysis of the effects on cardiac output found in the present experiments when the lower spinal cord was stimulated. Point A in figure 6 illustrates the equilibrium point between the cardiac output curve and the control venous return curve, representing an analysis of the cardiac output and right atrial pressure prior to stimulation of the lower spinal cord. After 45 seconds stimulation of the cord, the venous return curve had increased to curve II. This curve crossed the cardiac output curve at point B, predicting the expected changes in right atrial pressure and cardiac output following the onset of muscular activity. Thus, we find an increase in right atrial pressure averaging 0.9 mm Hg and an increase in cardiac output of 82 per cent. These were almost exactly the values found in other experiments of this study (1.05 mm Hg and 80 per cent, respectively).

It should be noted particularly that, because of the conditions of these experiments, reflex cardiac stimulation was prevented during the muscular activity. In normal exercise, the heart does become stimulated which would have shifted the cardiac output curve to the left, as has been demonstrated by Sarnoff and his associates. Such a shift would have moved point B in figure 6 to the left perhaps as much as 2 to 3 mm Hg, thus giving a decrease in right atrial pressure. Rushmer, in particular, has emphasized this decrease in right atrial pressure during moderate exercise.

Discussion

Other acute effects besides this one have been shown by other investigators also to contribute to the increase in cardiac output at the onset of exercise. For instance, Rushmer has demonstrated that an increase in heart rate contributes to the increased cardiac output, this effect beginning about one to two seconds after the onset of muscular activity and becoming fully developed within 5 to 10 seconds. Even though an increase in heart rate alone cannot increase the cardiac output significantly because of collapse of the veins entering the thorax, an increased heart rate can be a particularly valuable stimulant to cardiac output when combined with simultaneous translocation of large amounts of blood from the peripheral circulation.

Also, it is possible that acute respiratory changes at the onset of exercise cause still additional increase in cardiac output. Krug and Schlicher have summarized the possible mechanisms for such an effect, including most importantly (a) a decreased mean intrapleural pressure which could help translocate blood into the intrathoracic portion of the circulation, and (b) an increased intra-
abdominal pressure which could help increase the mean circulatory pressure and thereby translocate still additional amounts of blood into the heart. Unfortunately, we have little quantitative information which will allow us to assess the relative value of these respiratory effects.

Finally, Folkow's demonstration of vasodilator nerves to the muscles that become stimulated at the onset of exercise adds still another possible factor that could acutely increase the cardiac output.

Aside from the acute increase in cardiac output, several delayed effects develop during the ensuing minute. These include (a) an increase in peripheral sympathetic activity which increases the peripheral vascular tone and thereby translocates still more blood into the heart (the data of this study indicated this to begin after a latent period of about six seconds and to reach a maximal effect averaging 22 per cent additional increase in output in about 30 seconds), and (b) a metabolically induced vasodilation of the muscles that allows increased rapidity of blood flow through the systemic circulation. The second of these effects, although not a factor primarily studied in these experiments, became well developed within one minute and was associated with a rise in oxygen utilization.

Especially important in the present study has been the fact that cardiac output increased instantaneously in these experiments even though reflex autonomic excitation of the heart was prevented. To prevent reflex cardiac activity, the spinal cord was transected in the midthorax, thereby preventing passage of impulses from the stimulated or compressed musculature to the central nervous system. Furthermore, in nine separate experiments, hexamethonium was given to the animals in doses large enough to prevent even the slightest inking of cardiovascular reflexes, and still the cardiac output increased immediately when the distal cord was stimulated. In these experiments, the heart could not possibly have responded to nervous stimuli.

If the heart could not be stimulated by nervous activity following the onset of the muscular activity, then the observed increase in cardiac output must be explained on the basis of intrinsic adaptation of the heart to the translocation of blood into its chambers. The studies in the closed-chest animals showed an average rise in cardiac output of 149 per cent with a simultaneous average rise in right atrial pressure of 1.05 mm Hg following onset of muscle activity, and the P value for significance was 0.003, which indicates almost certainly that this was a true effect. Therefore, there seems to be little doubt that muscular compression of the peripheral vasculature did indeed cause enough rise in right atrial pressure to account for the increased pumping by the heart in accordance with Starling's principle of cardiac adaptation. The observed increase in cardiac output in these experiments in relation to the increase in right atrial pressure was approximately the amount that would have been expected from application of cardiac function curves measured by many different investigators, including especially Sarnoff and his co-workers and ourselves.

Finally, these studies have demonstrated that both venous return and cardiac output curves can be determined during various levels of muscular activity, and that the curves can then be equated with each other to analyze what happens to both the cardiac output and right atrial pressure as an animal suddenly changes from a state of no muscular activity to a state of intensive muscular activity (fig. 6). They also illustrate that it is possible to determine in mathematical terms the functions of individual components of the circulation and then to put these together in an analysis of the overall circulatory picture, demonstrating particularly that graphical curves or their equivalent mathematical equations are extremely valuable in predicting the function of the circulation as a whole. Although others, as well as we ourselves, can easily find fault with many portions of the analysis that we have presented in this paper, it will never
be possible to analyze completely the effects of muscular activity (or any other factor that alters the circulatory dynamics) without first analyzing both the cardiac and the peripheral effects simultaneously and then putting these together by some method such as the graphical analysis offered in this paper or the algebraic counterparts of this graphical method offered by Grodins\textsuperscript{22} or Warner.\textsuperscript{23}

**Summary**

In dogs with their spinal cords cut, sudden maximal muscular contraction in the lower half of the body caused the mean circulatory pressure to rise instantaneously to three times normal and the cardiac output to rise to an average of 40 per cent above normal. This instantaneous effect was not blocked by sympathetic blockade with hexamethonium but was blocked by skeletal muscle blockade with decamethonium. Furthermore, because of the transected cord, no cardiac reflex effects were observed. Therefore, it was concluded that skeletal muscle activity compresses the intra-muscular and intra-abdominal vessels and thereby increases the mean circulatory pressure. Evidence is presented to show that this, in turn, translocates blood into the heart and that the heart then responds in conformity with Starling’s principle of cardiac adaptation to increase the cardiac output.

**References**

Instantaneous Increase in Mean Circulatory Pressure and Cardiac Output at Onset of Muscular Activity
Arthur C. Guyton, Ben H. Douglas, Jimmy B. Langston, Travis Q. Richardson and Barry Abernathy

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doi: 10.1161/01.RES.11.3.431

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