Circulatory Response to Release of Chronic Pulmonary Artery Constriction

By John R. Tobin, Jr., M.D., G. C. Rastelli, M.D., Peter E. Blundell, M.D., and H. J. C. Swan, M.B., Ph.D., M.R.C.P.

During investigations of the effects of exercise and sympathomimetic amines on right ventricular function in unanesthetized dogs with normal or hypertrophied right ventricles, a circulatory state characterized by a supernormal stroke volume and cardiac output and by a decreased systemic vascular resistance was demonstrated in dogs studied 10 to 14 days after the release of chronic pulmonary artery constriction. The purpose of this report is to record this phenomenon and to discuss its nature and possible significance.

Methods

Eleven mongrel dogs (12 to 20 kg body weight) were used. After preliminary observations (study I*), the main pulmonary artery of each dog was tightly banded as described previously2 for a minimal period of three months. Each animal was reinvestigated while its pulmonary artery was constricted (study II). Then, the constricting bands were removed, and observations were made two weeks (study III) and two months (study IV) later.

After study IV, each animal was killed and necropsy was performed. The cleaned and fixed ventricular muscle mass was separated by Herrmann's method,18 and the right ventricular weight was expressed as a ratio of right ventricular weight (RVW) to left ventricular weight (LVW). In 11 dogs, two months or more after the release of pulmonary artery constriction, the mean ratio of RVW to LVW of 0.885 exceeded significantly the ratio, 0.715, derived from Herrmann's data for 200 normal dogs.

PREPARATION OF DOGS

No general anesthetic or premedication was used. Dogs were familiarized with the laboratory, restrained on an animal board, and trained to run without restraint on a horizontal treadmill on several occasions before the experiments. Only those animals who tolerated the animal board and were able to run freely were selected. With the dog under generous local anesthesia (2% lidocaine (Xylocaine) in saline), one carotid artery and one jugular vein were exposed. Size 6F Lehman catheters were introduced and manipulated under fluoroscopic and manometric control into the pulmonary artery, right ventricle, right atrium, and aortic arch, as required. Size 5F Lehman catheters were introduced into the superior vena cava for the injection of indocyanine green and into the jugular vein for the infusion of drugs.

INSTRUMENTATION

Simultaneous pressures were recorded from the same base line by means of Statham strain gauge transducers with equal sensitivities. The zero reference level was fixed at midthorax. The catheter-manometer systems had frequency responses uniform to between 15 and 20 cycles/sec.

Cardiac output was measured by the indicator dilution technic. Indocyanine green (Cardio-Green) concentration 1.25 mg/ml and volume 1.0 to 1.5 ml, was injected into the superior vena cava. Arterial blood was sampled continuously from the aortic arch by a vacuum suction system and was drawn through a densitometer* for the recording of the dilution curves. After the experiment, the densitometer was calibrated with aliquots of the animal’s blood containing known concentrations of indocyanine green. Cardiac outputs were calculated by standard methods, and stroke volume was obtained by dividing the cardiac output by the heart rate.

Lead II of the electrocardiogram was recorded and used to time events with the cardiac cycle.

PROCEDURE

After all catheters had been placed properly,
they were fixed in position firmly with rubber bands. The neck wound was closed and covered with an elastic dressing under slight tension. The catheters emerged from the superior edge of the dressing. The dog was allowed to stand and was restrained without discomfort in this position by a collar and an abdominal sling. When relative stability of heart rate and of intravascular pressures was attained, control observations, including records of indicator dilution curves and pressure pulses, were made during a 10-minute period. Norepinephrine* was then infused at a constant rate of 10.0 \( \mu \)g per minute by means of a Harvard syringe. After six minutes of infusion, indocyanine green dye curves and pressure pulses were recorded again.

**EXERCISE STUDIES**

These experiments were done in a manner identical to that described previously. Dogs were exercised on a horizontal treadmill that was maintained at different but constant speeds for two or three successive intervals of three minutes each, without intervening rest periods. The treadmill speed was increased by increments of 2 to 3 km per hour to a maximal speed of between 9 and 10 km per hour. After each dog had been exercised for three minutes at a given treadmill speed, indocyanine green dye curves and pressure pulses were recorded again. The maximal speed for two dogs in study II was 7 km per hour.

**CALCULATIONS**

Since pulmonary artery pressure was not measured in the exercising dog and since high heart rates were encountered, right ventricular systolic mean pressures (RV_{sm}) during the total duration of systole were obtained by planimetry. Mean right atrial pressures were recorded. For studies during rest and during norepinephrine infusions, the mean right ventricular pressures (RV_{sm}) and the mean pulmonary artery pressures (PA_{sm}) were calculated by conventional planimetry during systolic ejection. The end of systole was defined by the dicrotic notch on the pulmonary artery pressure pulse. The maximal rate of rise of the ventricular pressure was calculated from the most rapidly increasing portion of the ventricular pressure pulse. The aortic mean pressure (Ao_{m}) was calculated by the addition of one-third of the pulse pressure to the diastolic pressure. The systemic resistance was calculated in mm Hg/liter/min from aortic mean pressure divided by the cardiac output.

Right ventricular stroke work and right ventricular work per minute were calculated from the following equations.

1. Ventricular stroke work (gram meters) = \( RV_{sm} - (RV_{ed} or RA_{m}) \times S.V. \times 0.0144 \):

   where
   - \( RV_{sm} \) = right ventricular systolic mean pressure.
   - \( RV_{ed} \) = right ventricular end diastolic pressure.
   - \( RA_{m} \) = right atrial mean pressure.
   - \( S.V. \) = stroke volume.
   - 0.0144 = a constant correcting for the density of blood and for the conversions of mm Hg to cm water, and cm to meters.

2. Ventricular work per minute (kilogram meters) = \( \frac{VSW \times \text{heart rate}}{1000} \):

   where
   - \( VSW \) = ventricular stroke work.

**IN RESTING DOGS**

Table 1 lists the hemodynamic variables that describe the circulatory state and right ventricular function in four sets of studies of dogs standing awake and at rest. For each set of studies, all observations (20 to 23) made on six animals were averaged.

The cardiac outputs and stroke volumes that were found two weeks after the release of chronic pulmonary artery constriction (study III) exceeded significantly the values for any other study. Right ventricular pressures, rates of rise of the right ventricular pressures, and systolic ejection periods were maximal in study II (dogs with constricted artery), and values regressed progressively toward normal after removal of the constriction. Pulmonary artery pressures in study III, despite slight residual pulmonary artery constriction exceeded significantly the values found in studies I and IV. Neither calculated pulmonary vascular resistances nor aortic pressures differed between the studies. Systemic vascular resistance was significantly less in study III than in any other study. Right ventricular stroke work was greatest in study II and returned progressively toward normal (study I) by declining stages (studies III and IV).

**NOREPINEPHRINE INFUSION**

Table 2 lists hemodynamic variables per-
TABLE I
Circulatory Effects of Releasing Chronic Pulmonary Artery Constriction in Six Dogs Standing at Rest

<table>
<thead>
<tr>
<th>Study</th>
<th>Heart rate</th>
<th>Cardiac output</th>
<th>Stroke volume</th>
<th>RVsm</th>
<th>RVed</th>
<th>PAsm</th>
<th>AOm</th>
<th>Systemic resistance</th>
<th>RV stroke work</th>
<th>Peak rate of rise RV pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>beats/min</td>
<td>ml/min</td>
<td>ml</td>
<td>mm Hg</td>
<td></td>
<td></td>
<td></td>
<td>mm Hg/liter/min</td>
<td>gram meters</td>
<td>mm Hg/sec</td>
</tr>
<tr>
<td>I. Normals (21)*</td>
<td>132</td>
<td>2.51</td>
<td>20.3</td>
<td>28</td>
<td>4</td>
<td>21</td>
<td>119</td>
<td>50</td>
<td>6.7</td>
<td>536</td>
</tr>
<tr>
<td>II. Pulmonary artery constriction (23)</td>
<td>117</td>
<td>2.38</td>
<td>20.7</td>
<td>73</td>
<td>6</td>
<td>24</td>
<td>122</td>
<td>56</td>
<td>21.1</td>
<td>1236</td>
</tr>
<tr>
<td>III. Constriction released, 2 weeks (20)</td>
<td>121</td>
<td>3.26</td>
<td>27.4</td>
<td>47</td>
<td>7</td>
<td>27</td>
<td>122</td>
<td>39</td>
<td>16.5</td>
<td>877</td>
</tr>
<tr>
<td>IV. Constriction released, 2 months (23)</td>
<td>125</td>
<td>2.70</td>
<td>21.6</td>
<td>37</td>
<td>5</td>
<td>23</td>
<td>121</td>
<td>47</td>
<td>10.8</td>
<td>718</td>
</tr>
</tbody>
</table>

Difference III and I | d | -11 | 0.75* | 7.1* | 19* | 3* | 6* | 3 | -11* | 9.8* | 341* |
Difference III and II | d | 4 | 0.88* | 6.7* | -26* | 1 | 3 | 0 | -17* | -4.6 | -359* |
Difference III and IV | d | -4 | 0.56* | 5.8* | 10* | 2 | 4* | 1 | -8* | 5.7* | 159* |

*Total number of observations can be found in parentheses (3 or 4 per animal).
†P < 0.05. Significance of differences are based on the differences between the means of all available data in six dogs.
TABLE 2

**Circulatory Response During Infusions of Norepinephrine to Release of Chronic Pulmonary Artery Constriction in Six Dogs Awake and Standing**

<table>
<thead>
<tr>
<th>Study</th>
<th>Heart rate</th>
<th>Cardiac output</th>
<th>Stroke volume</th>
<th>RV sm</th>
<th>RV ed</th>
<th>PAsm</th>
<th>AOm</th>
<th>Systemic resistance</th>
<th>RV stroke work</th>
<th>Peak rate of rise RV pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>beats/min</td>
<td>ml/min</td>
<td>ml</td>
<td>mm Hg</td>
<td>mm Hg</td>
<td>mm Hg/liter/min</td>
<td>gram meters</td>
<td>mm Hg</td>
<td>mm Hg/sec</td>
<td></td>
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<tr>
<td>I. Normals</td>
<td>85</td>
<td>1.90</td>
<td>24.6</td>
<td>34</td>
<td>9</td>
<td>27</td>
<td>154</td>
<td>90</td>
<td>9.3</td>
<td>853</td>
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<tr>
<td>Difference*</td>
<td>d</td>
<td>-48*</td>
<td>-0.53†</td>
<td>4.6</td>
<td>7†</td>
<td>5†</td>
<td>5†</td>
<td>36†</td>
<td>40†</td>
<td>2.7†</td>
</tr>
<tr>
<td>II. Pulmonary artery constricted</td>
<td>97</td>
<td>2.53</td>
<td>27.0</td>
<td>119</td>
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<td>27</td>
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<td>64</td>
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<tr>
<td>Difference*</td>
<td>d</td>
<td>-24</td>
<td>-0.29</td>
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<td>4</td>
<td>1</td>
<td>34†</td>
<td>18†</td>
<td>17.3†</td>
</tr>
<tr>
<td>III. Constriction released, 2 weeks</td>
<td>104</td>
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<td>30</td>
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<td>0.07</td>
<td>6.0†</td>
<td>17†</td>
<td>4†</td>
<td>2</td>
<td>27†</td>
<td>4</td>
<td>10.6†</td>
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<tr>
<td>IV. Constriction released, 2 months</td>
<td>97</td>
<td>2.88</td>
<td>32.7</td>
<td>60</td>
<td>11</td>
<td>32</td>
<td>163</td>
<td>58</td>
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<td>1025</td>
</tr>
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<td>-31†</td>
<td>0.23</td>
<td>9.3†</td>
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<td>6†</td>
<td>10†</td>
<td>42†</td>
<td>11†</td>
<td>12.3†</td>
</tr>
</tbody>
</table>

*Difference = value during norepinephrine infusion minus value during pre-infusion period (average for 6 dogs).
†P < 0.05. Significance of differences are based on paired values.
taining to the circulatory state and right ventricular function in four sets of studies in awake, standing dogs during the infusion of norepinephrine at the rate of 10 μg per minute. Norepinephrine infusion decreased average heart rate and increased average stroke volume. Cardiac output declined in studies I and II and increased slightly in studies III and IV. Stroke volume and cardiac output were highest in study III. The right ventricular systolic pressure and the rate of rise of this pressure were increased in all studies. The right ventricular end diastolic pressure increased in all studies with the exception of study II (dogs with pulmonary artery constricted). In these animals, the end diastolic pressures were high in the control state, and norepinephrine infusion did not produce further increases.

Aortic pressures increased significantly in all studies and, with the exception of study III, these increases in aortic pressures were accompanied by significant increases in the systemic vascular resistance. In study III, the systemic vascular resistance was unaltered by norepinephrine infusion (fig. 1). Right ventricular stroke work increased in all animals, but effective ventricular work (based on systolic mean pressure in pulmonary artery) increased only after pulmonary artery constriction was released (studies III and IV).

EXERCISE

Table 3 lists the hemodynamic variables describing the circulatory state and right ventricular functions in three groups (studies II, III, and IV) of dogs during exercise at 9.0 km per hour. Figure 2 illustrates graphically some of these hemodynamic variables at exercise rates of 7.0 and 9.0 km per hour.

Exercise increased heart rate in all animals. Most of the increase in heart rate was

![Figure 1](http://circres.ahajournals.org/)

Effects of norepinephrine on circulation (average six dogs) before and after pulmonary artery banding and release. In each instance the mean and standard deviation are given for the control state and for the period during infusion of norepinephrine. Cardiac output and stroke volume values were greatest in animals two weeks after release of constriction from the pulmonary artery (study III). Also in these animals, systemic vascular resistance was lowest and showed smallest response to infusion of norepinephrine. Right ventricular systolic pressure was greatest when the pulmonary artery was constricted, but a significant increase still remained after removal of constricting band.
observed between the resting and 7.0 km per hour values, and a smaller increment of heart rate appeared when the level of exercise was increased to 9.0 km per hour. Stroke volumes and cardiac outputs during exercise were greatest in study III. In study II, the increases in cardiac output that occurred with exercise were attributable entirely to increases in heart rate, since stroke volume did not change. The right ventricular pressure increased with exercise in all animals; the greatest increases were found in study II.

**Discussion**

An increase of myocardial mass (cardiac hypertrophy) is the response of the ventricular myocardium to chronic increase in work load. These increases of myocardial mass result primarily from enlargement of individual muscle fibers rather than from multiplication of myocardial cells. Since fiber enlargement increases the diffusion distance for essential metabolites, it has been suggested that myocardial hypertrophy is detrimental rather than beneficial. The conclusion that hypertrophy enables the myocardium to perform more work has been questioned, but other studies have indicated that increased myocardial mass may enhance work capacity.

In our studies, a chronic work load was imposed by placing a tight band around the pulmonary artery for a minimal period of three months. The mean cross-sectional area of the pulmonary artery at the point of constriction measured by angiocardiograms was $0.42 \text{ cm}^2$ (SD ± 0.19). The magnitude of the imposed work load is revealed by the values for right ventricular stroke work in study II (Tables 1, 2, and 3). At rest, the right ventricular stroke work increased from 6.7 to 21.1 gram meters (315% of normal control). During norepinephrine infusion, right ventricular stroke work reached an average value of 44.1 gram meters (658% of normal resting control), and during exercise at 9.0 km per hour, right ventricular stroke work reached an average value of 28.5 gram meters (425% of normal resting control). After the observations of study IV were completed, necropsies were done on the 11 animals and the right

### Table 3

<table>
<thead>
<tr>
<th>Study</th>
<th>Constriction released, 2 weeks</th>
<th>Constriction released, 2 months</th>
<th>Constriction released, 2 months</th>
<th>d</th>
<th>94t</th>
<th>2.0</th>
<th>+1</th>
<th>+13</th>
<th>+6.9t</th>
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<td>218</td>
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<td>±0</td>
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<td>±2.5t</td>
</tr>
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<td>+4.78t</td>
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<td>(0.39, 0.45)</td>
<td>(0.39, 0.45)</td>
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<td>±0</td>
<td>±0</td>
<td>±0</td>
<td>±2.5t</td>
</tr>
</tbody>
</table>

†Only three dogs capable of exercise at 9 km per hour for study II. Five dogs reached this level of exercise for studies III and IV.

*Significance of differences based on paired values.

**Difference** = value during exercise at 9.0 kilometers per hour minus value during pre-exercise period (average for five dogs).
ventricular weight was expressed as a ratio of right ventricular weight (RVW) to left ventricular weight (LVW). This ratio, according to Herrmann’s data for 200 normal dogs, is 0.715. We found an average of 0.885 for the 11 animals studied at necropsy two months or more after the release of chronic pulmonary artery constriction. The ratio of RVW to LVW for six animals used in another investigation was 0.926 after their pulmonary arteries had been constricted for three to fourteen months and after they were sacrificed with the bands in place. These weight ratios are consistent with the concept of a slow regression of an increased muscle mass after a chronic increase in pressure load is removed.

Tables 1, 2, and 3 and figure 3 indicate that ventricular stroke work does not decrease abruptly after removal of a chronic increase in work load. Study III showed a relatively small decrease of stroke work. There is considerable decrease in right ventricular pressure, but the stroke volume has concomitantly increased (fig. 3). At study period IV, there is a significant decrease in ventricular stroke work from the peak values but not to the range of normal, particularly during infusion of norepinephrine. It is probable that the decline of ventricular stroke work and the regression of myocardial mass are related phenomena.

The data in tables 1, 2, and 3 and the variables in figures 1, 2, and 3 demonstrate that a unique circulatory state existed during study III. This state was characterized by increased stroke volume, increased cardiac output, and decreased systemic vascular resistance both at rest and during stress imposed by norepinephrine or exercise. Since circula-
tory studies after sham thoracotomy have demonstrated a return to normal values within 48 hours, this consistent circulatory response pattern cannot be attributed to the effects of the surgical procedure.

The relation of ventricular stroke work to

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure3}
\caption{Stroke volume, right ventricular systolic mean pressure, and right ventricular stroke work plotted sequentially for studies I, II, III, and IV at rest (left panel), during norepinephrine infusion (center panel), and during exercise at 9 km per hour (right panel). Greatest values for right ventricular systolic mean pressure were obtained when the pulmonary artery was banded (study II). However, stroke volume values for study III exceeded those for studies I, II, or IV under all circumstances.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure4}
\caption{Effect of exercise at different levels on right ventricular function after release of chronic pulmonary artery constriction. Stroke work is plotted against right atrial mean pressure. Exercise levels 1 through 4 indicate running speeds of 3, 5, 7, and 9 km per hour, respectively. Values for 9 km per hour for the three dogs in study II (pulmonary artery band in place) are not included. It is evident that in study III (constriction released for two weeks) for a given right atrial pressure, stroke work response of the right ventricle was greatest.}
\end{figure}
filling pressure for the exercise studies is shown in figure 4, from which it is evident that the greatest stroke work for a given filling pressure was attained during study III. Although it is evident that right ventricular stroke work for study III should exceed levels attained in study IV, the comparison with study II also showed a significant difference. The occurrence of pulsus alternans at peak exercise stress has been interpreted as an effect of relative coronary insufficiency. In study II (banded animals) mean aortic pressure did not change but systemic vascular resistance was substantially reduced with exercise. Right ventricular systolic mean pressure and aortic mean pressure approached equality. In study III, a similar decrease in systemic vascular resistance was found but, owing to greater cardiac output, the aortic mean pressure increased substantially, maintaining a gradient of approximately 70 mm Hg between aortic and right ventricular systolic pressure. Greater coronary blood flow may be a factor in the greater stroke work found in study III.

In the animals with hypertrophied right ventricle during study period III, the capacity for increased stroke work at a given filling pressure is translated apparently into an increased flow when the outflow resistance is reduced. From this viewpoint, the work capacity of the right ventricular myocardium relative to its outflow resistance determines stroke volume and cardiac output. Such a concept requires that the work capacity of the hypertrophied right ventricle is increased, possibly in proportion to the increased muscle mass as suggested by the work of Beznak. The concepts of heterometric and homometric autoregulation, although based on analogous observations, pertain to the responses to acutely imposed stress and do not seem relevant to the chronic state reported here. The increased cardiac output declined over several weeks, probably in parallel with the resolving myocardial hypertrophy.

Guyton and associates demonstrated the importance of blood volume and circulatory reflexes in ventricular response to acute pulmonary artery occlusion. Small increases in filling pressure (1 to 3 mm Hg) were found in resting dogs between study I and studies II, III, and IV. The difference (plus 3 mm Hg) between filling pressures in studies I and III was significant. The increases in filling pressure may have resulted from small increases of blood volume, but Holman and Beck and Beznak did not record such increases. The contribution of venoconstrictor tone to venous return cannot be evaluated from the data.

Table 1 reveals that aortic pressures were similar in all study periods but the systemic vascular resistance was greatest in study II. Alden et al. induced chronic right ventricular hypertension in dogs by constricting the infundibulum. Such animals had aortic pressures and calculated systemic vascular resistances that were higher than normal, but their differences were such that these data were regarded as suggestive and not confirmatory evidence of a pressor reflex. In their study, Alden et al. suggested that the receptors for this pressor reflex reside in the right ventricle. The report of Pinkerson and Kot tends to confirm the presence of a systemic pressor reflex over vagal afferent fibers from the right ventricle. A pressor response to partial pulmonary artery occlusion has been noted by others, and Guyton and associates suggest that decreased pressure (negative feedback) distal to the occlusion is the stimulus to pressor response. The release of chronic pulmonary artery constriction by decompression of the right ventricle or by restoration of a more normal pulsatile wave form in the pulmonary artery may induce a decrease in systemic vascular resistance which is reinforced by systemic baroreceptors sensing a supernormal stroke volume from the hypertrophied heart. In our experiments, the effect of infusion of norepinephrine revealed differing responses in the several studies. In study I, norepinephrine infusion decreased heart rate and cardiac output while increasing aortic pressure and calculated systemic vascular resistance. In study III, the large stroke volume increased further by 22%, and the calculated systemic vascular resistance was unchanged. These results suggest
relative insensitivity of systemic vasoreceptors to norepinephrine.

Summary

The imposition of a chronic work load (pulmonary artery constriction) on the right ventricle increases ventricular muscle mass. This is associated with increased ventricular stroke work when the animal is standing awake, during infusions of norepinephrine, and under conditions of exercise (running on a horizontal treadmill). Studies two weeks after release of chronic pulmonary artery constriction reveal stroke volume and cardiac output are increased during standing at rest, during norepinephrine infusion, and during exercise. Studies eight weeks after removal of pulmonary artery bands show that stroke volume and cardiac output are approaching the normal range. Right ventricular hypertrophy and right ventricular stroke work decline progressively and apparently in parallel in the weeks following release of chronic pulmonary artery constriction.

The stroke work capacity of the ventricle seems related to the presence of right ventricular hypertrophy. With a reduction in outflow tract resistance, the stroke volume for a given set of circumstances is markedly increased. From this standpoint, the work capacity of the right ventricle may be taken as a determinant of stroke volume and cardiac output.

Decrease of systemic vascular resistance and relative insensitivity of systemic vasoreceptors to norepinephrine were observed after the release of chronic pulmonary artery constriction. These phenomena have roles in the production of the observed hyperdynamic circulatory state, but their contributions to its genesis are secondary to the major role of the hypertrophied right ventricle.

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