Effect of 1-Arterenol Infusion on "Central Blood Volume" in the Dog

By OSCAR W. SHADEL, M.D., JAMES C. MOORE, M.D. AND DONAL M. BILLIG, A.B.

Infusion of 1-arterenol into anesthetized dogs increased the volume of blood in the heart and lungs, as indicated by an increase in "central blood volume," estimated lung volume and pressure changes in the heart and lungs. An analysis of pressure and flow data in the systemic venous bed during infusion of the drug suggests that important sources of the shifted blood are the peripheral veins and venules.

FOWLER AND COWORKERS have demonstrated that both pulmonary artery and "pulmonary capillary pressures" increase during the continuous infusion of 1-arterenol, in the human. These workers concluded that the pulmonary hypertension was secondary to an increased pulmonary venous pressure; however, the mechanism of this pressure rise was not investigated. With a constant cardiac output, changes in pulmonary vascular pressures occurring during 1-arterenol infusion could be due to either vasomotor activity in the pulmonary vascular bed, or a volume increase in the pulmonary circuit due to the shift of blood from the systemic circuit. Since the resistance across the pulmonary vascular bed did not change in any consistent manner during 1-arterenol infusion, Fowler concluded that the rise in pulmonary artery pressure was not due to constriction of the pulmonary arteries. These data, together with the general lack of evidence for active pulmonary vasomotor changes, make the second possibility the more likely explanation for the increased pulmonary artery pressure.

Work from various laboratories indicates that systemic vasomotor activity can change the volume of blood contained in the heart and lungs. Johnson observed a decrease in this "central blood volume" in human subjects during spinal anesthesia and attributed the fall in volume to a displacement of blood from the lungs into dilated systemic veins. Hamilton and associates determined the size of the dog's heart by x-ray during epinephrine infusion and concluded that the heart is responsible for a great part of the increase in the "central blood volume" which occurs during the infusion of this drug. Medullary stimulation with thrombin or fibrinogen increases the weight of the lungs, inferential evidence of a volume increase in this organ, and this weight increase can be abolished with a ganglionic blocking agent, RO 2-2222.

The evidence cited above suggests that shifts of blood between the systemic and pulmonary circuits may occur secondary to systemic vasomotor activity. This investigation was undertaken to determine the existence of such volume changes in anesthetized dogs during continuous 1-arterenol infusions and to identify the mechanisms responsible for these shifts.

METHODS

All experiments were performed on mongrel dogs premedicated with 3 mg./Kg. of morphine sulfate and anesthetized with a 1:1 mixture of Dial-Urethane* and Nembutal. Cardiac output was determined from the dilution curve of injected Evans Blue Dye or H3O15O, the injections being made through a catheter inserted into the right auricle. A syringe wired in series with a signal magnet marked the time of injection on the kymograph drum carrying the blood sampling tubes. Arterial blood was sampled through a catheter inserted into the aorta via a common carotid artery. "Central blood volume" was calculated as the product of flow

* Kindly supplied by Dr. J. C. Saunders, Ciba Pharmaceutical Products, Inc., Summit, New Jersey.
and mean transit time from the injection site to the sampling site. In twenty-one of the twenty-eight determinations, mean transit time was corrected for the passage time through the sampling catheter. The volume of the sampling catheter was 1.3 cc., and the arterial samples were collected at a known rate (1–2 cc. per sec.). Lung blood volume was calculated by the method of Newman et al., as the flow divided by the exponential slope of the dye dilution curve. Both mean and pulsatile pressures were optically recorded from Gregg manometers. In two experiments the registration of pressures was facilitated by a previous operation in which the apex of the left ventricle was sutured to the chest wall and a plastic needle guide was attached to the pulmonary artery. The venous gradient was measured between a femoral vein and the right auricle. Venous flow was measured with a recording rotameter tied into the inferior vena cava distal to the renal veins. These dogs were heparinized to prevent the formation of fibrin on the rotameter float.

After preliminary manipulations were completed, control measurements of the various parameters were made. Three to six minutes later all determinations were repeated during a continuous infusion of 3.3 cc. of saline per minute containing I-arternol to result in a dose of either 0, 0.5, 1.0, 1.5, 2.0, or 2.5 mg per Kg per minute. The infusions were made with a motor-driven syringe into a peripheral vein. In seven dogs, two such observations were made, separated by an interval of 15 to 20 minutes, with the dog receiving the same concentration of I-arternol the second time.

In addition to this series, two similar experiments were done, one after removal of the spleen, and one in which the variables were measured at frequent intervals, early during infusion of the drug.

RESULTS

Figure 1 presents the effect of I-arternol infusion on cardiac output. Each solid circle represents the per cent change in cardiac output caused by an infusion of one of the doses of I-arternol. Only one dosage was infused in any particular dog. The open circles represent the average per cent change in all dogs receiving the same concentration of I-arternol. Changes in cardiac output show no consistent trend relating to increasing concentrations of infused drug.

The percentage change in estimated lung volume is given in figure 2. As the concentration of infused I-arternol increased, the volume of blood in the lungs, as calculated by the method of Newman, also increased up to an infusion concentration of 2.0 mg per Kg per minute. The changes measured by this method were not as consistent as the changes in the "central blood volume." Figure 3 shows that during the infusion of various concentrations of the drug the volume of blood between the injection and sampling catheters increased at all concentrations infused. Changes in both estimated lung volume and "central blood volume" showed poor corre-

![Fig. 1. Effect of I-arternol infusion on cardiac output (ordinate). Per cent change in cardiac output was calculated as 
\[ \frac{CO_{\text{infused}} - CO_{\text{control}}}{CO_{\text{control}}} \times 100 \]

Details in text.](http://circres.ahajournals.org/)

![Fig. 2. Effect of I-arternol infusion on estimated lung volume (ordinate). Construction as in Fig. 1. Details in text.](http://circres.ahajournals.org/)

![Fig. 3. Effect of I-arternol infusion on "central blood volume" (ordinate). Construction as in Fig. 1. Details in text.](http://circres.ahajournals.org/)
Table 1 summarizes the data on two dogs in which pulmonary artery and left ventricular pressures were recorded. Mean arterial pressure and left ventricular end-diastolic pressures increased in both dogs during the infusion. Pulmonary artery systolic pressure rose and diastolic pressure fell, while mean pressure in the pulmonary artery rose in one dog and showed no change in the other. Estimated lung volume and "central blood volume" increased in both animals. The post-infusion determinations were made 20 minutes following cessation of the infusion in dog 1 and five minutes in dog 2.

Table 1 (dog 3) demonstrates that acute splenectomy does not prevent the increases in "central blood volume" and estimated lung volume which occur during the infusion of 2.0 μg/m per Kg per minute of 1-arterenol.

Figure 4 shows the results in one of the experiments in which arterial pressure, inferior vena cava flow, peripheral venous pressure, and central venous pressure were measured. Control values taken six minutes before the 1-arterenol infusion began are plotted at "C." Early during the infusion the rotameter flow spiked very high, in phase with the venous pressure gradient but completely out of phase with the changes in arterial pressure. This phasic increase in venous gradient was due largely to an increased peripheral venous pressure. The increase in rotameter flow preceded the increase in mean arterial pressure. As the infusion continued the arterial pressure rose, the rotameter flow returned near the control value, and the venous pressure gradient decreased largely because of a rising central venous pressure. One hundred and twenty seconds after the beginning of the 1-arterenol infusion the rotameter flow again increased, even in the face of the decreased venous pressure gradient.

In Table 2 are the data from an experiment in which the various parameters were measured at more frequent intervals. The cardiac output and "central blood volume" show a continuous rise throughout infusion of the drug. Early

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Experiment</th>
<th>Cardiac Output cc./min</th>
<th>Estimated Lung Volume cc</th>
<th>&quot;Central Blood Volume&quot; cc</th>
<th>Mean Arterial Pressure mm. Hg</th>
<th>Pulmonary Artery Pressure mm. Hg</th>
<th>S</th>
<th>D</th>
<th>M</th>
<th>Heart Rate</th>
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<tbody>
<tr>
<td>1</td>
<td>Control</td>
<td>2690</td>
<td>101</td>
<td>345</td>
<td>72</td>
<td>17</td>
<td>4.0</td>
<td>10.5</td>
<td>-3.0</td>
<td>124</td>
</tr>
<tr>
<td></td>
<td>1-arterenol</td>
<td>2340</td>
<td>117</td>
<td>411</td>
<td>110</td>
<td>20</td>
<td>3.0</td>
<td>11.5</td>
<td>2.7</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>Post-infusion</td>
<td>2295</td>
<td>99</td>
<td>354</td>
<td>61</td>
<td>10</td>
<td>2.3</td>
<td>6.3</td>
<td>-3.0</td>
<td>121</td>
</tr>
<tr>
<td>2</td>
<td>Control</td>
<td>1304</td>
<td>66</td>
<td>214</td>
<td>124</td>
<td>23</td>
<td>9</td>
<td>16</td>
<td>1.9</td>
<td>123</td>
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<tr>
<td></td>
<td>1-arterenol</td>
<td>1434</td>
<td>79</td>
<td>255</td>
<td>135</td>
<td>24</td>
<td>8</td>
<td>16</td>
<td>3.8</td>
<td>112</td>
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<tr>
<td></td>
<td>Post-infusion</td>
<td>1022</td>
<td>44</td>
<td>207</td>
<td>95</td>
<td>15</td>
<td>7</td>
<td>11</td>
<td>1.9</td>
<td>128</td>
</tr>
<tr>
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<td>2610</td>
<td>68</td>
<td>274</td>
<td>278</td>
<td>15</td>
<td>2</td>
<td>22</td>
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<td>82</td>
<td>328</td>
<td>328</td>
<td>15</td>
<td>7</td>
<td>22</td>
<td>1.0</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Post-infusion</td>
<td>2490</td>
<td>73</td>
<td>296</td>
<td>296</td>
<td>15</td>
<td>7</td>
<td>22</td>
<td>1.0</td>
<td>22</td>
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</tbody>
</table>

Fig. 4. Effect of 1-arterenol infusion on arterial pressure, rotameter flow, and venous pressure gradient. CO, cardiac output. PVP, peripheral venous pressure. CVP, central venous pressure. Details in text.
ARTERENOL AND CENTRAL BLOOD VOLUME

Table 2

<table>
<thead>
<tr>
<th>Time from Beginning of 1-arterenol Infusion</th>
<th>CO cc/min.</th>
<th>&quot;CVP&quot; mm. Hg</th>
<th>&quot;TVP&quot; mm. Hg</th>
<th>Heart Rate</th>
<th>TPR PDU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control I</td>
<td>1017/228</td>
<td>97.3.2</td>
<td>-0.55.7</td>
<td>116</td>
<td>9.55</td>
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</table>

<table>
<thead>
<tr>
<th>Time sec.</th>
<th>CO cc/min.</th>
<th>&quot;CVP&quot; mm. Hg</th>
<th>&quot;TVP&quot; mm. Hg</th>
<th>Heart Rate</th>
<th>TPR PDU</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 sec.</td>
<td>1131/276</td>
<td>97.3.2</td>
<td>-0.55.5</td>
<td>123</td>
<td>8.56</td>
</tr>
<tr>
<td>30 sec.</td>
<td>1213/276</td>
<td>103.4.0</td>
<td>-0.55.1</td>
<td>117</td>
<td>8.50</td>
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<td>65 sec.</td>
<td>1273/316</td>
<td>115.5.6</td>
<td>-0.55.9</td>
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<td>8.45</td>
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<tr>
<td>95 sec.</td>
<td>1377/316</td>
<td>115.5.9</td>
<td>-0.55.3</td>
<td>117</td>
<td>8.45</td>
</tr>
<tr>
<td>120 sec.</td>
<td>1113/264</td>
<td>95.3.1</td>
<td>-0.55.9</td>
<td>134</td>
<td>7.72</td>
</tr>
<tr>
<td>4 min.</td>
<td>1017/228</td>
<td>97.3.2</td>
<td>-0.55.7</td>
<td>116</td>
<td>9.55</td>
</tr>
</tbody>
</table>

DISCUSSION

These data furnish evidence that both the lung and heart volumes increase during the infusion of 1-arterenol. Such a conclusion is reached not only because the absolute increase in the "central blood volume" was greater than the increase in Newman volume, but from an analysis of the pressure records as well. The left ventricular end-diastolic pressure rose in both dogs in which it was measured. Since there is no evidence to indicate that the drug influences the ventricular relaxation process, the pressure rise affords inferential evidence of a volume increase. Pressure changes in the pulmonary artery are not a reliable index of blood volume changes in the lung because of the occurrence of stress relaxation in this circulatory bed. The pulmonary artery pressure measured after a volume increase is dependent on the slope of the pressure-volume curve, as well as the rate of volume increase. Also the pressure declines with time after the volume increase has occurred. Unless all of these variables are known it is very difficult to predict the relationship between these two parameters.

Although we have no measurement of the volume changes in the great veins, an analysis of the pressure and flow records (fig. 4) indicates that there was a volume increase in these vessels also. The pressure in the right atrium rose during infusion of the drug, and flow through the inferior vena cava increased although the venous gradient was lower than the control gradient. These changes indicate an increased radius of the inferior vena cava and right auricle.

Obviously, if blood is trapped in the left heart and lungs there must have been at some interval a discrepancy between the output of the two ventricles. The increased central volume could conceivably be due to a fall in left ventricular output caused by an increased total peripheral resistance. The data in table 2 indicate such a mechanism is not operative, since the cardiac output was increased and the total peripheral resistance decreased in the early phase of the infusion when the volume shifts were occurring.

A pertinent question raised by these experiments is the source of the blood which is shifted into the pulmonary circuit. One rather obvious source would be the spleen. However, the data in table 1 indicate that the spleen is not essential in this mechanism, since the volume shifts occur after it has been surgically removed. The spiking rotameter flow early during the infusion suggests an alternative mechanism. The increase in inferior vena caval flow, proportionately much greater than the increase in cardiac output (table 2), suggests a decreasing volume in a peripheral vascular bed. Bazett's calculations from Mall's data indicate that about 20 per cent of the total blood volume is in the systemic arterial compartment. It seems unlikely that this volume decrease occurs in the systemic arterial system, since the absolute volume shifted into the heart and lungs alone represents about 20 per cent of the estimated arterial volume in these dogs. Therefore it seems more likely that the increased "central blood volume" represents a passive increase in volume secondary to active changes in volume in peripheral veins and venules.
SUMMARY

I-Arterenol in doses ranging from 0.5 to 2.5 μg. per Kg. per minute was infused intravenously into anesthetized dogs. During these infusions an increase in the volume of blood in the heart and lungs was indicated by measurements of the "central blood volume" and Newman's calculation of lung volume. This increase also occurred in a splenectomized dog. Additional evidence for a shift of blood from the systemic circulation into the pulmonary circulation is afforded by left ventricular enddiastolic and pulmonary artery pressures. Analysis of inferior vena caval flow and venous pressure gradients indicates an increase in volume of the inferior vena cava and right auricle, as well.

Further consideration of pressure-flow relationships suggests that the peripheral venous bed is the source of the blood which is shifted to the heart and lungs.

REFERENCES

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