Rats anesthetized with ethyl ether were compared with rats anesthetized with sodium pentobarbital from the standpoint of cardiac output, peripheral resistance and regional blood flow. Cardiac output was measured by the indicator-dilution technic; regional blood flow was determined by the indicator-fractionation technic employing Rb 85 or I 131-antipyrine. The cardiac output is one and a half times as great in ether anesthesia as in pentobarbital anesthesia; the peripheral resistance is about two-thirds as great with ether. Compared to pentobarbital, ether increases myocardial, cerebral, and carcass blood flow, while decreasing renal, splanchnic and cutaneous blood flow. The pronounced difference in the cardiovascular effects of the two agents indicates the need for caution in the interpretation of experiments in which cardiovascular measurements are made under anesthesia.

ETHER anesthesia results in increased cardiac output in dogs. Less regular increases in cardiac output are observed in human subjects. On the other hand, the renal blood flow is reduced by ether anesthesia, and the splanchnic blood flow is said to decrease with either cyclopropane or ether anesthesia in the human subject.

The present studies were designed to compare the cardiac output and the distribution of blood flow in rats subjected to ether and pentobarbital anesthesia. The results are of particular methodologic interest because of the fact that anesthesia is employed in some methods for the measurement of blood pressure in this species. If the cardiac output and its distribution are altered by the anesthetic, it may be questioned whether blood pressure measurements made in anesthetized animals correctly describe the basal condition.

METHODS

Female rats of the Sprague-Dawley strain were used in all experiments. The animals weighed 180 to 230 Gm. after an 18 hour fast during which water was allowed ad libitum. Ether anesthesia was induced in a covered beaker and was maintained by a paper nose cone containing a pledget of ether moistened cotton. The animals were maintained in stage 3 of anesthesia for at least 15 min. before any measurement. The plane of anesthesia was judged by observation of the abdominal and thoracic respiration. An attempt was made to keep the animals between plane 2 and plane 3. Pentobarbital anesthesia was induced with pentobarbital sodium, 40 mg./Kg.; by the intraperitoneal route 10 to 15 min. before measurements were made.

The cardiac output was measured by the indicator-dilution method using Rb 85 as the indicator. Approximately 15 min. after the induction of anesthesia, the indicator was injected in a volume of 0.2 ml. in an exposed femoral vein. Blood samples were collected at 0.93 sec. intervals from a cannulated carotid artery. The cardiac output was calculated in the usual manner from the real and extrapolated curves of arterial indicator concentration.

Blood pressures were recorded in 6 ether anesthetized rats and in 6 animals anesthetized with pentobarbital sodium. The pressures were recorded directly from a carotid cannula with a Statham strain-gage manometer which recorded through a Sanborn oscillograph.

Other animals were used for the determination of regional blood flow by the indicator-fractionation-
tion technic. Rb86 was used for the measurement in all organs other than the brain. I131-antipyrine was used in the cerebral blood flow measurement. The basis of the method and the reasons for the choice of these indicators have been reviewed previously. The method requires an extrapolation of observations made at various times after injection of the labeling substance to zero time. The "zero time" situation corresponds to that which would have existed if the indicator had been delivered to but not removed from each organ. The extrapolated organ content of indicator at zero time, therefore, describes the fraction of the cardiac output which it received. The fact that most organs maintain their content of Rb86 essentially constant during the first minute, and that the brain maintains its content of I131-antipyrine nearly constant for the same period, simplifies the extrapolation.

The animals were killed with a mallet-driven axe which transected the thorax. The timing was accurate to within 0.5 sec. Observations were made at 10 to 15, 20, 30, and 60 sec. following injection.

RESULTS

The cardiac output of 12 ether anesthetized rats averaged 350 ± 36 ml./Kg./min. The value in pentobarbital anesthesia in 12 rats was 230 ± 41 ml./Kg./min.

The mean blood pressure in 6 rats anesthetized with ether averaged 107 mm. Hg. Twelve pentobarbitalized rats had a mean blood pressure which averaged 115 mm. Hg. These average values showed the peripheral resistance of a 200 Gm. rat anesthetized with ether to be approximately 1.2 × 10^5 dynes sec. cm^-5. The peripheral resistance is, thus, substantially lower in ether anesthesia than in pentobarbital anesthesia.

Table 1 illustrates the distribution of the injected Rb86 in the organs of ether anesthetized rats at 10 to 15, 20, 30, and 60 sec. after injection of the label. It will be noted that there is no consistent change with time in any of the values. Values for all rats killed at these times were, therefore, averaged to determine the fraction of the cardiac output which perfused each area under study.

The fractional uptake of I131-antipyrine by brain in ether anesthesia is shown in table 1. The fairly consistent decline in the cerebral uptake fraction with time suggests that the zero time situation requires extrapolation, or else that the average cerebral uptake of the label throughout the period of observation should be taken as representing the minimum fraction of the cardiac output which perfused the brain. Since the manner in which these data should be extrapolated has not, as yet, been clarified, the latter was done.

Table 2 shows the values for the fraction of the cardiac output and organ blood flow in animals anesthetized with ether and pentobarbital. The blood flow values, which are expressed as milliliter/organ in a 200 Gm. rat are obtained by multiplying the cardiac output fraction for the organ by the cardiac output of a 200 Gm. rat in the condition described. The flow fraction values are based on aver-

---

### Table 1.—Distribution of Rb^{86} and I^{131}-antipyrine as a Function of Time After A Single Intravenous Injection (Percentages of Injected Dose)

<table>
<thead>
<tr>
<th>Organs</th>
<th>10-15 (10 rats)</th>
<th>20 (6 rats)</th>
<th>30 (6 rats)</th>
<th>60 (6 rats)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rb^{86} Heart</td>
<td>2.53± .35</td>
<td>2.41± .28</td>
<td>2.50± .32</td>
<td>2.99± .27</td>
</tr>
<tr>
<td>Kidney</td>
<td>5.57±1.54</td>
<td>6.88±2.50</td>
<td>7.96±1.91</td>
<td>7.67±1.41</td>
</tr>
<tr>
<td>Liver</td>
<td>4.61±.99</td>
<td>5.25± .97</td>
<td>6.14± .76</td>
<td>5.80± .93</td>
</tr>
<tr>
<td>Gut</td>
<td>7.16±1.97</td>
<td>8.91±1.42</td>
<td>9.15±1.25</td>
<td>8.09±1.21</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.47± .23</td>
<td>0.64± .26</td>
<td>0.52± .13</td>
<td>0.41± .08</td>
</tr>
<tr>
<td>Skin</td>
<td>5.54± .71</td>
<td>6.23±1.47</td>
<td>5.43± .65</td>
<td>4.39± .58</td>
</tr>
<tr>
<td>Carcass</td>
<td>67.05±4.36</td>
<td>64.74±5.93</td>
<td>60.34±3.12</td>
<td>66.42±4.14</td>
</tr>
<tr>
<td>I^{131}-antipyrine Brain</td>
<td>2.50± .64</td>
<td>1.94± .28</td>
<td>1.92± .32</td>
<td>1.05± .30</td>
</tr>
</tbody>
</table>
CIRCULATION IN ETHER ANESTHESIA

TABLE 2.—Distribution of Blood Flow and Perfusion Rates of Organs of Anesthetized Rats

<table>
<thead>
<tr>
<th>Organ</th>
<th>Cardiac output (vol.)</th>
<th>Blood flow (ml./organ/min.)</th>
<th>Cardiac output (vol.)</th>
<th>Blood flow (ml./organ/min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ether</td>
<td></td>
<td>Pentobarbital</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>2.60±0.28</td>
<td>1.8</td>
<td>2.60±0.28</td>
<td>1.2</td>
</tr>
<tr>
<td>Kidney</td>
<td>6.81±1.84</td>
<td>4.8</td>
<td>14.86±2.04</td>
<td>6.9</td>
</tr>
<tr>
<td>Liver</td>
<td>5.33±1.35</td>
<td>3.7</td>
<td>7.31±1.45</td>
<td>3.4</td>
</tr>
<tr>
<td>Gut</td>
<td>8.8±1.60</td>
<td>5.8</td>
<td>19.19±1.70</td>
<td>8.9</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.50±0.22</td>
<td>0.4</td>
<td>0.81±0.32</td>
<td>0.4</td>
</tr>
<tr>
<td>Total splanchnic</td>
<td></td>
<td></td>
<td>9.9</td>
<td>12.7</td>
</tr>
<tr>
<td>Skin</td>
<td>5.54±0.71</td>
<td>3.8</td>
<td>10.43±1.95</td>
<td>4.8</td>
</tr>
<tr>
<td>Carcass</td>
<td>64.9±4.4</td>
<td>46.0</td>
<td>45.4±4.55</td>
<td>21.0</td>
</tr>
<tr>
<td>Brain</td>
<td>2.05±0.45</td>
<td>1.4</td>
<td>1.58±0.20</td>
<td>0.73</td>
</tr>
</tbody>
</table>

*Fractional flows from values in table 1, cardiac outputs adjusted to 200 Gm. rat.

ages obtained in 52 animals, 28 of which were anesthetized with ether, while 24 received pentobarbital.

Two areas other than the brain showed a significant increase in the blood flow values in ether as compared with pentobarbital anesthesia. The coronary flow rose from 1.2 ml./heart in the pentobarbital anesthetized animal to 1.8 ml./heart in ether anesthesia. Carcass perfusion increased from about 21 ml./carcass with pentobarbital to more than twice this value with ether.

Cerebral perfusion, 0.73 ml./min. in pentobarbital anesthesia, rose to at least 1.4 ml./min. in ether anesthesia. This value, based on observations, which decline with time, is the average of all observations, and no attempt was made to extrapolate to zero time.

Ether reduced the fractional perfusion rate of the kidney to about half the pentobarbital value. The greater cardiac output in the etherized animal makes the absolute reduction in renal blood flow less impressive, though it remains appreciable. The same is noted of the splanchnic bed and the skin; a reduction of 50 per cent in the flow fraction represents a 25 per cent reduction in the flow value in both cases.

**DISCUSSION**

In the interpretation of the present experiments, it should be remembered that no unanesthetized controls were available. There does, however, seem to be some justification for assuming that the circulatory status of the animal just previously anesthetized with pentobarbital approximates that of the unanesthetized animal. For example, the cardiac output in dogs anesthetized with pentobarbital is not significantly different from that of the trained unanesthetized animal, the renal plasma flow in the trained unanesthetized dog is not altered by pentobarbital anesthesia; splanchic blood flow measured in unanesthetized dogs does not differ substantially from that observed in animals anesthetized with pentobarbital.

On the other hand, in prolonged anesthesia with pentobarbital, the cardiac output and the renal plasma flow are known to fall from control levels. In the case of the cardiac output, there is a 10 per cent fall from control values after 30 min. of anesthesia; the renal plasma flow falls after two hours of anesthesia.

Whether every vascular bed shares the insensitivity of the splanchic and renal vascular beds and the circulation as a whole to pentobarbital anesthesia of short duration and whether 10 to 15 min. is a short period in the rat is uncertain. It should be borne in mind that the effects of ether are described here in terms of the actions of pentobarbital and cannot rigorously be considered to represent changes from the "normal." The total peripheral resistance is markedly decreased in ether anesthesia compared to pentobarbital anesthesia. The resistance in the renal, splanchnic, and cutaneous vascular beds is increased slightly; this is more than
made up by decreases in the vascular resistances of the coronary, cerebral and carcass (skeletal and skeletal muscular) vascular beds.

The observation that cardiac output increases in ether anesthesia in the rat is similar in kind and degree to observations made on humans and dogs. In some studies it has been found that the human cardiac output is decreased in prolonged ether anesthesia; this finding is exceptional. Again, it must be emphasized that the increases seen in cardiac output observed with ether in the present experiments are increases relative to pentobarbital. In short periods of anesthesia, however, it seems probable that the total cardiac output is not affected very greatly by pentobarbital.

The renal blood flow of pentobarbital anesthetized rats was 6.9 ml./min./200 Gm. rat. Assuming a 40 per cent hematocrit, this corresponds to a renal plasma flow of 2.1 ml./100 Gm. body weight/min. This figure is remarkably close to the "best figure" for renal plasma flow of the unanesthetized rat quoted by Smith of 2.2 ml./100 Gm. body weight and suggests that in the rat as in the dog, the renal plasma flow is not greatly affected by pentobarbital anesthesia. Our finding of a smaller renal blood flow in the ether anesthetized animal is consistent with those of Habif et al. and de Wardener who found diminished renal plasma flow during anesthesia.

Habif et al. also noted that the splanchnic blood flow was reduced in man by ether or cyclopropane anesthesia. Our findings similarly suggest that ether reduces splanchnic blood flow, at least in comparison with pentobarbital. The reduction in the splanchnic blood flow appears to occur in the gut; while the hepatic arterial supply and splenic blood flow are not affected. Hershey, Zweifach and Rovenstine have noted diminished blood flow in the mesenteric venules of ether anesthetized animals.

The reduction in the peripheral resistance with ether occurs in the coronary and cerebral circulations and in the carcass. We are not aware of any previous measurements of coronary blood flow in ether anesthesia. The increase in myocardial blood flow is probably associated with the increased work load on the heart as the cardiac output is increased 50 per cent above pentobarbital levels.

Observations on the total cerebral blood flow in ether anesthesia have not been made. Dilation of the meningeal vessels has been observed after ether by Fineman and Cobb. The finding of increased flow is reminiscent of others, in which it has been observed that alcohol in large amounts increases the cerebral blood flow in both man and rat.

The increased cardiac output and decreased peripheral resistance in ether compared to pentobarbital anesthetized rats are associated chiefly with changes in the blood flow to the carcass. In these experiments, the blood flow through the carcass was more than doubled; the resistance was approximately half as great with ether anesthesia. Presumably ether acts as a vasodilator for skeletal muscular arterioles; whether it does so directly or indirectly cannot be determined from these results. The alternative that pentobarbital is a vasoconstrictor cannot be excluded. However, the conclusion that ether is a vasodilator is consistent with the findings of Prime and Gray, who found fivefold increases in forearm blood flow during ether anesthesia. It seems probable that these increases were associated with increases in muscular blood flow, although Abramson's finding that hand blood flow is elevated by ether implicates the skin. Our findings suggest that ether actually reduces the skin blood flow in the rat. Whether the apparent discrepancy reflects a species difference or results from the fact that the intrinsic muscles of the hand contribute substantially to the plethysmographic measurement of hand blood flow is not, at present, clear. It is of interest that ether in quantities sufficient to abolish the corneal reflex produces vasoconstriction in the arterial vessels of the rabbit.
Vasodilation occurs with deeper anesthesia. With respect to the measurement of blood pressure in ether anesthetized rats, these results, as well as others in which ether anesthesia has been shown to produce cardiovascular changes, suggest that the greatest caution should be exercised in interpretation. The cardiovascular changes produced by ether are so great that they may simulate or override those under investigation. Although it has been stated that blood pressure measurements obtained with ether in renal hypertension in the rat are more reliable than those in unanesthetized animals, it is possible that in other circumstances of interest, erroneous values for blood pressure may be given when it is employed.

**SUMMARY**

Ethyl ether increases the cardiac output of rats compared to animals anesthetized with sodium pentobarbital. The total peripheral resistance is decreased by ether while the blood pressure is maintained. The renal, splanchnic and cutaneous resistances are increased, resulting in diminished perfusion of these areas. The cerebral, coronary, and skeletal muscular resistances are decreased. The significance of these results in the estimation of blood pressure in the rat by techniques involving ether administration is indicated.

**SUMMARIO IN INTERLINGUA**

Ethere ethylic augmenta le rendimento cardiae de rattos in comparation con illo de rattos anesthesiate con sodium pentobarbital. Le total resistentia peripheric es reducute per ethere, durante que le tension de sanguine es mantenite. Le resistentias renal, splanchnic, e cutanea es augmentate, con le resultato de un reduce perfusion de iste areas. Le resistentias cerebral, coronari, e skeleto-muscular es reduce. Le signification de iste resultatos in le estimation del tension de sanguine in rattos per medio de technicas que require le administration de ethere es indicate.

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vidt, breDEMeyer, sapiRstein, sapiRstein


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Effect of Ether Anesthesia on the Cardiac Output, Blood Pressure, and Distribution of Blood Flow in the Albino Rat

DONALD G. VIDT, ANTONIE BREDEMEYER, ELIZABETH SAPIRSTEIN and LEO A. SAPIRSTEIN

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