Hemodynamics in Normal Cattle

By John T. Reeves, M.D., Robert F. Grover, M.D., Ph.D., Donald H. Will, M.S., D.V.M., and Archibald F. Alexander, M.S., D.V.M.

Large animals have been used on numerous occasions by investigators pioneering in the field of cardiovascular research. The first recorded measurement of arterial blood pressure was made in the horse by Stephen Hales in 1733. Cardiac catheterization was first performed in a horse by Chauveau and Marey in 1861. One of the earliest applications of the Fick principle to the measurement of cardiac output was by Zuntz and Hagemann, also in the horse, in 1898. In recent years, cardiovascular studies in large animals have been extended to include the giraffe and cattle, with further observations in the horse.

Hemodynamic measurements in cattle are of particular interest since it has been shown that members of this species living at high altitude may develop severe pulmonary hypertension and even heart failure. In order to examine more fully the circulatory response in cattle exposed to high altitude, it was necessary to carry out extensive studies in normal cattle. Many unusual problems confront the investigator attempting hemodynamic measurements in large animals. Experimental techniques have not been standardized, and normal hemodynamic values are not clearly established. While tranquilizing drugs have been employed by some investigators studying cattle, the hemodynamic effects of these drugs have not previously been evaluated. For these reasons, the details of the methods which we have found satisfactory in more than 100 cardiac catheterizations of cattle are presented in this report. The normal data thus obtained provided baseline information for use in further studies in this species.

Methods

Twenty normal yearling Hereford steers were obtained from a single herd native to an altitude of 3,600 feet. After initial cardiac catheterization studies were made in each animal in June and July 1958, at Fort Collins, Colorado (elevation 5,000 feet), 10 steers were transferred to an altitude of 10,000 feet for a parallel and concurrent study of the effect of high altitude. The remaining 10 steers, the subject of the present report, were maintained at 5,000 feet elevation where cardiac catheterization was repeated in each animal in August, October, and December. They were confined within a corral and exposed to a climate changing from summer to winter. Shortly after the December measurements, the animals were sacrificed and postmortem examinations were performed.

Premedication with sedative or tranquilizing drugs was deliberately avoided after preliminary experience revealed marked alterations in the circulatory and respiratory systems attendant upon chlorpromazine hydrochloride administration. To permit cardiac catheterization, each steer was confined in a standard cattle chute and remained in a normal standing position, with minimal lateral compression by the chute. A foam rubber blindfold was placed over the eyes to eliminate excitement caused by visual stimuli. A halter was used to restrain the head to the right, thereby exposing the left side of the neck. Thus prepared, the animal would usually stand quietly throughout the procedure.

After clipping and cleansing the left side of the neck, a 12-gauge needle was thrust percutaneously into the external jugular vein. Blood samples were then collected for analysis of hemoglobin, hematocrit, serum proteins, serum sodium, and potassium. Next, a GF, 150-cm. cardiac catheter was passed through the needle into the vein and advanced to the heart. The location of the catheter tip could be determined at all times by monitoring the pressure. As the catheter was advanced, the characteristic pressure patterns of right atrium, right ventricle, pulmonary artery, and often the pulmonary arterial “wedge” were obtained. Pressures were recorded using an E & M p500 strain-gauge pressure transducer (Electrical and Circulation Research. Volume X. February 1962

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HEMODYNAMICS IN NORMAL CATTLE

TABLE 1
Circulatory and Ventilatory Measurements in Ten Normal Steers

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Weight (Kg.)</td>
<td>305 ± 28</td>
<td>320 ± 28</td>
<td>306 ± 33</td>
<td>407 ± 33</td>
</tr>
<tr>
<td>Ambient temper.</td>
<td>61 - 74</td>
<td>78 - 87</td>
<td>41 - 50</td>
<td>19 - 50</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>35 ± 2 f</td>
<td>36 ± 4</td>
<td>40 ± 3</td>
<td>41 ± 3</td>
</tr>
<tr>
<td>Minute ventilation (L/min. BTPS)</td>
<td>62 ± 10 f</td>
<td>95 ± 58</td>
<td>76 ± 24</td>
<td>77 ± 19</td>
</tr>
<tr>
<td>Arterial O₂ saturation (%)</td>
<td>89 ± 3 f</td>
<td>93 ± 1</td>
<td>94 ± 3</td>
<td>94 ± 3</td>
</tr>
<tr>
<td>Arterial CO₂ content (vol. %)</td>
<td>49 ± 5 f</td>
<td>48 ± 11</td>
<td>48 ± 11</td>
<td>50 ± 5</td>
</tr>
<tr>
<td>Mean vascular pressures (mm. Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right atrium</td>
<td>5 ± 3</td>
<td>7 ± 4</td>
<td>4 ± 2</td>
<td></td>
</tr>
<tr>
<td>&quot;Wedge&quot;</td>
<td>13 ± 3</td>
<td>13 ± 3</td>
<td>12 ± 5</td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>26 ± 2</td>
<td>28 ± 4</td>
<td>25 ± 5</td>
<td>27 ± 4</td>
</tr>
</tbody>
</table>

*The values for each measurement are the mean values and one standard deviation for 10 animals during each period of observation. The range of ambient temperature is given for each period of observation.

†Data from six animals.

Mechanical Instrument Company, Houston, Texas) and a direct writing multichannel recorder, the entire system being optimally damped. The zero reference point for all pressures was 16 to 18 cm. above the ventrum of the sternum at the level of the olecranon in the standing animal. Using this reference point, the optimally damped right ventricular end-diastolic pressure proved to be near zero in the normal animal. Mean pressures were determined with a planimeter.

For the determination of blood volume, a known amount of Evans blue dye (T 1824) was injected through the catheter into the pulmonary artery, and blood samples were drawn from the jugular vein after 15 and 20 minutes. The Evans blue was extracted from the plasma and brought into aqueous solution for the determination of optical density, according to the method of Campbell et al.

A lightweight mask with an attached high-velocity Rudolph valve was fitted snugly over the muzzle of the steer. This permitted collection of the respiratory gases in a Douglas bag and the measurement of minute ventilation. The oxygen and carbon dioxide concentrations in the expired air were determined by duplicate micro-Scholander analysis. Oxygen uptake and the respiratory quotient were then calculated.

For the determination of blood volume, a known amount of Evans blue dye (T 1824) was injected through the catheter into the pulmonary artery, and blood samples were drawn from the jugular vein after 15 and 20 minutes. The Evans blue was extracted from the plasma and brought into aqueous solution for the determination of optical density, according to the method of Campbell et al.14

Results and Discussion

Hemodynamic data were obtained from each of the 10 normal steers remaining at 5,000 feet on four occasions during the six months of the experiment. Over this time, certain measurements remained relatively stable, while others showed a progressive change. The changes may have been associated with the variation in environmental temperature and/or with the growth in each animal.
Effects of Chlorpromazine Hydrochloride

| Table 2 |

| Table 2 Effects of Chlorpromazine Hydrochloride* |
|-----------------|-----------------|-----------------|-----------------|
|                  | Nontranquilized | Tranquilized    | Probability     |
| Hematocrit (%)  | 37 ± 3          | 34 ± 3          | <0.05           |
| Plasma volume (cc./Kg.) | 44 ± 4          | 48 ± 5          | —               |
| Serum proteins (Gm. %) | 6.8 ± 0.5       | 6.4 ± 0.4       | <0.05           |
| Respiratory rate (R./min.) | 27 ± 14         | 24 ± 11         | —               |
| Minute ventilation (L./min. BTPS) | 68 ± 20         | 64 ± 18         | —               |
| O₂ uptake (cc./min. STPD)  | 1,690 ± 380     | 1,490 ± 330     | —               |
| Arterial O₂ saturation (%) | 91 ± 4          | 90 ± 4          | —               |
| Arterial CO₂ content (vol. %) (whole blood) | 49 ± 5          | 54 ± 5          | <0.01           |
| A-V O₂ difference (cc./L.) | 48 ± 1          | 38 ± 1          | <0.005          |
| Pulmonary arterial O₂ saturation (%) | 61 ± 5          | 65 ± 4          | <0.01           |
| Cardiac output (L./min.) | 37 ± 3          | 39 ± 3          | —               |
| Pulmonary arterial pressure (mm. Hg) | 25 ± 3          | 27 ± 6          | —               |

*These data compare the cardiopulmonary state using t-test for paired data before and 45 minutes after chlorpromazine administration for nine pairs of observations in eight animals. Whether or not a statistically significant change occurred is shown in the third column.

during the experiment (table 1). The average individual weight gain was about 100 Kg.

RIGHT HEART PRESSURES

The mean pulmonary arterial pressure for 36 measurements in 10 normal steers was 27 ± 5 mm. Hg. The pressure variation between animals was therefore relatively small, and there was no consistent or significant change during the course of the experiment despite the changes in body weight and environmental temperatures. This consistency within the pressure measurements implies that the method of study was uniform, and the absence of extremely high or labile pressures suggests that the animals were in a reasonably quiet state. These pressures agree with those reported for cattle by Doyle et al. In 45 determinations of pulmonary arterial pressure before and after application of the face mask in these animals, the average change in mean pulmonary arterial pressure was an increase of only 2 mm. Hg.

The right atrial pressures were similarly consistent, with a mean value of 5 ± 3 mm. Hg. The magnitude of this mean pressure indicated that the zero reference point was reasonable. Right ventricular pressures were consistent with the foregoing measurements, and the pulmonary arterial wedge pressure was 13 ± 4 mm. Hg.

BLOOD FLOW

The arteriovenous oxygen difference showed a progressive and significant increase (P < 0.05) from a mean of 48 to 62 cc./L. over the course of the experiment. The basis for this widening is not clear, but a redistribution of blood flow in adapting to colder weather may be a partial explanation. Thus, to conserve body heat, a reduction of blood flow to skin (a tissue with a narrow A-V oxygen difference), with an increase in flow to muscle (a tissue with a wide A-V oxygen difference), would tend to widen the A-V difference for the body as a whole. A proportional increase in oxygen uptake (metabolic rate) would then permit such a redistribution with no net change in cardiac output. Adequate investigation of the effect of prolonged cold on the total circulation of intact healthy mammals has not been reported, and this problem would appear to merit further attention.

Other factors possibly bearing on the observed increase in the total tissue oxygen extraction are the increasing blood oxygen capacity and the increasing maturity of the animal. However, the A-V oxygen difference in normal man is relatively constant from the ages of 5 to 45 years.15

Over the six months of the experiment, the
Effects of Chlorpromazine Hydrochloride

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Nontranquilized</th>
<th>Tranquilized</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>36 ± 4</td>
<td>31 ± 2</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Plasma volume (cc./Kg.)</td>
<td>45 ± 4</td>
<td>47 ± 4</td>
<td>—</td>
</tr>
<tr>
<td>Serum proteins (Gm. %)</td>
<td>7.1 ± 0.4</td>
<td>6.7 ± 0.3</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Respiratory rate (R./min.)</td>
<td>33 ± 12</td>
<td>29 ± 11</td>
<td>—</td>
</tr>
<tr>
<td>Minute ventilation (L./min. BTPS)</td>
<td>83 ± 16</td>
<td>58 ± 15</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>O2 uptake (cc./min. STPD)</td>
<td>1,740 ± 510</td>
<td>1,380 ± 320</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Arterial O2 saturation (%)</td>
<td>92 ± 2</td>
<td>89 ± 3</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Arterial CO2 content (vol. %) (whole blood)</td>
<td>49 ± 9</td>
<td>57 ± 4</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>A-V O2 difference (cc./L.)</td>
<td>52 ± 9</td>
<td>35 ± 8</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Pulmonary arterial O2 saturation (%)</td>
<td>66 ± 6</td>
<td>65 ± 3</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Cardiac output (L./min.)</td>
<td>34 ± 10</td>
<td>40 ± 11</td>
<td>—</td>
</tr>
<tr>
<td>Pulmonary arterial pressure (mm. Hg)</td>
<td>28 ± 4</td>
<td>26 ± 4</td>
<td>—</td>
</tr>
</tbody>
</table>

*These data compare the cardiopulmonary state using t-test for unpaired data of unequal number of 20 animals which received chlorpromazine with 16 animals of comparable age and weight to which premedication had not been given. Whether or not a statistically significant difference was observed in the parameters measured is shown in the third column.

Oxygen uptake in these animals tended to increase. However, because there was a parallel increase in the A-V oxygen difference, the net effect was no increase in calculated cardiac output despite the obvious growth of these steers. For all measurements the mean cardiac output was 33 ± 9 L./min.

A question arose as to the reliability of the oxygen uptake measurements, since fermentation in the stomach of these ruminants produces large quantities of carbon dioxide and methane which might be expelled into the expired air. Five samples of expired air from these steers were analyzed by a gas chromatograph sensitive to the presence of simple hydrocarbons, and such gases were not detected. However, aspiration of stomach gas from recently killed cattle revealed concentrations of methane which averaged 40 per cent and those of carbon dioxide which averaged 20 per cent, the remainder being oxygen and nitrogen. These data suggest that contamination of the expired air by gases produced in the gastrointestinal tract was probably negligible.

Hematocrit and Plasma Volume

The hematocrit increased progressively from 35 to 41 per cent over the six months of this experiment. Similar changes occurred in the hemoglobin and blood oxygen capacity. Concurrently, there was a tendency for the plasma volume (cc./Kg.) to decrease. These changes may reflect the increasingly cold environmental temperatures to which the animals were subjected. Increased age and body weight appeared to be unlikely causes for the increased hematocrit.

Ventilatory Measurements

The arterial oxygen saturation was relatively constant, the mean of 36 determinations being 94 ± 2 per cent (table 1). This value agrees with that obtained for man at this altitude (94 ± 2 per cent). Minute ventilation (BTPS) was variable, but both respiratory rate and minute volume increased at the higher environmental temperatures. Consequently, the highest values for the ventilatory equivalent for oxygen were obtained during the studies in August. Since there was no associated decrease in arterial carbon dioxide content, this implies an increase in dead space ventilation, probably employed as an aid in regulating body temperature.
Effects of Chlorpromazine

Chlorpromazine-hydrochloride administration did not appear to alter the pulmonary arterial pressure in these steers (tables 2 and 3). However, it has been shown to decrease the pulmonary arterial pressure in anesthetized dogs.\textsuperscript{19}

Chlorpromazine produced hemodilution as evidenced by a decrease in both hematocrit and serum proteins and an increase in plasma volume. These changes were observed 45 minutes after medication, but had disappeared 24 hours later. A similar decrease in hematocrit following chlorpromazine administration has been observed in horses,\textsuperscript{20} cattle,\textsuperscript{21} and dogs,\textsuperscript{22} but not convincingly in man.\textsuperscript{23,24} In sheep in which both hemodilution and trapping of the red cells by the spleen have been demonstrated, the splenic action was considered to be the major factor.\textsuperscript{25}

A striking and consistent increase in arterial carbon dioxide content occurred following chlorpromazine administration. The associated decrease in the ventilatory equivalent for oxygen (table 3) implies a decrease in effective ventilation with this drug. However, direct determination of arterial blood CO\textsubscript{2} tension and pH would be required to establish this firmly. These observed changes following chlorpromazine are consistent with the decrease in respiratory rate in the horse\textsuperscript{26} and the decrease in minute ventilation in man.\textsuperscript{24,26}

Most impressive was the narrowing of the A-V oxygen difference following chlorpromazine administration which was due primarily to an elevation of the venous oxygen saturation. This tended to increase the values for cardiac output, but the changes were not consistent because of the variations in oxygen uptake.

Since satisfactory measurements can be made in cattle without chlorpromazine, extreme caution should be exercised in the use of this drug in investigations of the cardiovascular system.

Summary

A satisfactory method has been described for conducting hemodynamic studies in cattle. With the animals in normal standing position, and without sedation or tranquilization, cardiac catheterization can be readily performed. With a muzzle mask, ventilatory studies are also feasible. Using this method, each of 10 normal steers was studied four times during a six-month period. This permitted the establishment of normal values for a number of circulatory measurements. In addition, an evaluation of chlorpromazine administration in normal cattle demonstrated some of the numerous complex effects of this drug on the cardiovascular and respiratory systems. These included hemodilution, hypoventilation, and a marked reduction of the arteriovenous oxygen difference.

Acknowledgment

We wish to thank Drs. Roy Jensen, S. Gilbert Blount, Jr., Dale D. Mang, and Maxine M. Benjamin for their assistance and helpful criticism of the work in this and the accompanying report.\textsuperscript{26} Our thanks are due also to Margaret Anth, Mrs. Janet Caramas, Mrs. Paul Emroy, Mrs. Dolores Guerue, Jean Lutz, Earl Rumley, George Fayette, and Delbert Ropp for technical assistance. We are grateful to H. J. Dillard, Chief Chemist, Continental Oil Refinery, Denver, Colorado, for the gas chromatographic analysis.

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