Effects of Halothane Anesthesia on Renal Function in Normal Man

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Changes in renal hemodynamics, and water and electrolyte excretion were determined during anesthesia with 1.5 per cent halothane in oxygen in 13 hydrated normal human volunteers without preanesthetic medication or operation. Infusions of ethanol were employed to reverse the antidiuresis associated with anesthesia and to obtain urine volumes greater than 2 mL per minute in order to allow the application of clearance techniques for measurement of renal hemodynamics. Glomerular filtration rate decreased 19 per cent and renal blood flow decreased 38 per cent during anesthesia. Sodium excretion decreased 64 per cent. Possible mechanisms by which halothane acted to produce these changes are discussed.

Significant alterations in renal hemodynamics, urinary volume, and sodium excretion have been observed during general anesthesia. Critical inspection of reported studies, however, reveals several variables which in addition to anesthesia, could have played a role in the changes observed. The effects of anesthetics alone were not evaluated. Most investigations were carried out in patients deprived of fluids for varying periods of time prior to induction of anesthesia, so that dehydration, known to influence urinary volume and concentration, could have affected the results obtained. Premedication with narcotics, barbiturates and belladonna drugs also may have exerted an effect. Other studies were performed during operation with attendant factors of painful stimuli, blood loss, and changes in intra-abdominal pressure produced by packs and retractors. These too may affect renal function.

In addition, measurement of clearance of inulin and para-aminohippurate (PAH) were attempted during low urinary flow rates (V) (less than 1 mL/min), during periods of abruptly changing V, and during changing blood concentrations of inulin and PAH. These factors invalidate the use of clearance methods for the measurement of renal hemodynamics.

The present study of renal function before and during halothane anesthesia was undertaken in an effort to eliminate the variables present in previous studies. Experimental subjects received no premedication, were well hydrated, and were studied in the absence of operative stimuli. Intravenous infusions of ethanol, a potent inhibitor of antidiuretic hormone (ADH) secretion* were given to evaluate the role of ADH in the antidiuresis following the administration of halothane, and to obtain V greater than 2 mL/minute. Sufficient time was allowed for attainment of a relatively steady state of anesthesia, of blood inulin and PAH levels and urine volume, to permit the proper application of clearance techniques. In addition, following renal venous catheterization, PAH extraction was determined before and during anesthesia. This was necessary to assess the validity of the use of PAH clearance as an estimate of effective renal plasma flow.

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Methods

Thirteen healthy male volunteers ranging in age from 22 to 29 years reported to the laboratory, having fasted for 8 to 12 hours. Details of the experimental procedure were explained to the subjects on two occasions prior to the study period and a written informed consent obtained. Subjects were studied in the recumbent position except when they stood to void during the control period. After obtaining a control blood sample and emptying of the bladder, priming doses of inulin and PAH were administered intravenously. Thereafter, a sustaining intravenous infusion of inulin and PAH in physiological saline was maintained at a rate of 1 ml. per minute throughout the experiment with a Holter constant infusion pump. An acute fluid load of 1,000 ml. of 4 per cent fructose in water was administered intravenously over a 30- to 40-minute period. For the remainder of the study, a sustaining infusion of 4 per cent fructose and water was given to each subject at a rate equal to the volume of urine excreted during each collection period, plus 0.8 ml./minute for estimated insensible water loss. Urine was collected every 15 to 20 minutes, and blood specimens drawn every 60 minutes at the midpoint of a collection period.

In 2 subjects following control clearance periods and after V was stable for 3 consecutive periods, ethanol was administered to one orally, and to the other intravenously in order to study the effects on renal function. An equivalent of 30 ml. of absolute alcohol was administered orally as bourbon whisky and in the other subject intravenously, as a 5 per cent solution in 4 per cent fructose and water over a 50-minute period.

In 2 subjects following attainment of a steady state of hydration, a No. 7 Courand venous catheter was inserted via cutdown in an antecubital vein, into the right renal vein under fluoroscopic guidance. In these subjects a Courand needle was also inserted into a femoral artery. Renal extraction of inulin and PAH was determined in these subjects before and during anesthesia.

During the control period subjects breathed room air without a mask in order to avoid emotional stimuli known to affect renal function.

Following establishment of stable V in each subject, anesthesia was induced with 75 per cent nitrous oxide in 25 per cent oxygen. Halothane vaporized in a previously calibrated Fluotec vaporizer was gradually increased to 3 per cent. When the subjects were judged to be in the first phase of surgical anesthesia, nitrous oxide was discontinued and orotracheal intubation was performed following the administration of 60 to 80 mg. of succinylcholine intravenously. Halothane was thereafter delivered at a concentration of 1.5 per cent in oxygen, in a non-rebreathing system. Respiration was assisted in order to maintain the end-expired CO₂ monitored by an infrared analyzer, at a level less than 45 mm. of mercury. A thermistor probe was inserted into the esophagus and body temperature was maintained ±0.5° C. by means of a thermostatically controlled electric blanket.

Urine samples were collected every 15 to 20 minutes during anesthesia following insertion of a small indwelling bladder catheter. Careful aseptic technique was employed for insertion and maintenance of the catheter. Suprapubic pressure and bladder washout with air were used to insure emptying of the bladder during anesthesia.

Arterial pressure was determined by auscultation during the control period in 9 subjects who did not have femoral arterial needles inserted while awake. In 2 subjects, in whom femoral arterial needles and renal venous catheters were inserted while awake, arterial and renal venous pressures were measured by means of a Statham strain gauge transducer and recorded continuously on a Grass Polygraph. Following induction of anesthesia, femoral arterial needles were inserted in 8 subjects to monitor arterial pressure and periodically to collect blood for analysis of arterial pH, P O₂, and P CO₂.

Three subjects serving as controls were observed for periods from 220 to 236 minutes following induction of anesthesia. This was done to assess the effects of halothane alone for prolonged periods on urinary flow.

The remaining 10 subjects were observed for 50 to 145 minutes after induction of anes-
HALOTHANE ANESTHESIA AND RENAL FUNCTION

Thesia. Following this an intravenous infusion of 3 or 5 per cent ethanol in 4 per cent fructose and water was administered at a rate of 5 or 10 ml. per minute to 9 subjects. One subject received an infusion of 4 per cent fructose and water at a rate of 10 ml. per minute, instead of ethanol. Seven of the 9 receiving ethanol were given continuous infusions until the end of the experiment; 2 were given ethanol intravenously until V had increased to 3.0 ml. per minute or more; ethanol was then discontinued. Ethanol in fluid volumes of 129 and 148 ml. were administered to these 2 subjects.

Chemical Analyses and Calculations

Insulin in plasma and urine was determined by the method of Walser, Davidson, and Orloff. PAH in plasma and urine was determined by the method of Brun. Specimens of urine and blood were analyzed for sodium by means of flame photometry and osmolality by means of a Fiske osmometer. Ethanol concentration in serum and urine were determined by the method of Conway. Serum and urine osmolalities were corrected for alcohol levels when appropriate. Arterial and renal venous PO₂, PCO₂, and pH were determined by means of an Instrumentation Laboratories electrode system, Model No. 102.

Insulin and PAH clearances were calculated in the usual manner.

\[
C_{\text{osm}} = \frac{U_{\text{osm}} \times V}{P_{\text{osm}}}
\]

\[
C_{\text{H₂O}} = V - C_{\text{osm}}
\]

where \( U_{\text{osm}} \) = osmolality of urine (mOsm./kg.), \( P_{\text{osm}} \) = osmolality of serum (mOsm./kg.), \( V \) = urine flow (ml./min.)

PAH extraction ratios (E) were calculated as:

\[
E = \frac{A - V}{A}
\]

where \( A = \) PAH concentrate in arterial blood (mg./100 ml.)

\( V = \) PAH concentrate in renal venous blood (mg./100 ml.)

Filtration fraction (FF) was calculated as:

\[
FF = \frac{C_{\text{plasma}}}{C_{\text{PAH}}}
\]

Effective renal blood flow (ERBF) was calculated as:

\[
ERBF = \frac{C_{\text{PAH}}}{1 - \text{Hematoeit}}
\]

Renal vascular resistance (RVR) was calculated as:

\[
RVR = \frac{\text{Mean arterial pressure or perfusion pressure (mm. Hg)}}{\text{ERBF ml./min.}}
\]

Perfusion pressure was calculated in the 2 subjects with renal vein catheters as: mean arterial pressure (mm. Hg) minus mean renal venous pressure (mm. Hg).

Mean arterial pressure was calculated as one-third pulse pressure plus diastolic pressure or by electrical damping of the recorded arterial trace.

All clearances, urine volumes, and sodium excretion rates were corrected to 1.73 sq. m. of body surface area.

Statistical analyses were performed using Student's t test.

Results

Subjects were divided into 3 groups for purposes of description and data analysis. Group I (controls) consisted of 3 subjects who received no alcohol during anesthesia and who were studied for periods of 220 to 236 minutes following induction of anesthesia. The data from a typical study (D. G.) are depicted in figure 1. Halothane was administered following achievement of a steady state of water diuresis during which V reached a mean value of 7.3 ml./minute, \( U_{\text{osm}} \) was 85 mOsm/kg., \( U/P \) ratio was 0.3, and \( C_{\text{H₂O}} \) was 5.0 ml./minute. Induction of anesthesia was associated with a sharp reduction in V to 0.3 ml./minute and a rise in U/P ratio to hypertonic values, 2.86. During this acute unsteady state, values for \( C_{\text{H₂O}} \) were negative. As anesthesia was continued up to 220 minutes, the urine re-
Fig. 1. Effect of halothane anesthesia on renal function. Subject D. G. from Group I, control group.

\[ \frac{U_{\text{osm}}}{P_{\text{osm}}} \]

- \( U_{\text{osm}} \): Osmolality of urine, milliosmoles per kg.
- \( P_{\text{osm}} \): Osmolality of serum, milliosmoles per kg.
- \( V \): Urine volume ml per minute
- \( C_{\text{osm}} \): Osmolar clearance ml/minute = \( \frac{U_{\text{osm}} \times V}{P_{\text{osm}}} \)
- \( C_{\text{H}_{2}\text{O}} \): Free water clearance ml. per minute = \( V - C_{\text{osm}} \)
- \( C_{\text{IN}} \): Inulin clearance ml. per minute
- \( C_{\text{PAH}} \): PAH clearance ml. per minute

The shaded area indicates free water excretion (water in excess of solute). The unshaded area between \( V \) and \( C_{\text{osm}} \) represents water absorption in excess of solute (negative free water clearance of \( T_{\text{H}_{2}\text{O}} \)). All values are corrected to 1.73 sq. m. B.S.A.

mained persistently hypertonic. Qualitatively similar results were seen in the other 2 subjects (table 1). Because of the persistent anti-diuresis (low \( V \)), valid conclusions regarding hemodynamic data could not be made.

Group II comprised 6 subjects who received intravenous alcohol during anesthesia and one who received a rapid infusion of fructose in water, all of whom responded with an increase in urine volume of 2 ml./minute or greater. All data presented, except those obtained during the period designated as "unsteady state" (U), represent values obtained during constant blood levels of inulin, PAH,
A. Hemodynamic Changes

<table>
<thead>
<tr>
<th>Subject</th>
<th>(C) ml/min.</th>
<th>(U) ml/min.</th>
<th>(T)</th>
<th>(C) ml/min.</th>
<th>(U) ml/min.</th>
<th>(T)</th>
<th>(C) ml/min.</th>
<th>(U) ml/min.</th>
<th>(T)</th>
<th>(C) ml/min.</th>
<th>(U) ml/min.</th>
<th>(T)</th>
<th>(C) ml/min.</th>
<th>(U) ml/min.</th>
<th>(T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D. P.</td>
<td>120</td>
<td>80</td>
<td>40</td>
<td>250</td>
<td>185</td>
<td>175</td>
<td>0.17</td>
<td>0.20</td>
<td>0.21</td>
<td>61</td>
<td>218</td>
<td>104</td>
<td>80</td>
<td>75</td>
<td>73</td>
</tr>
<tr>
<td>D. G.</td>
<td>124</td>
<td>86</td>
<td>80</td>
<td>200</td>
<td>160</td>
<td>160</td>
<td>0.18</td>
<td>0.20</td>
<td>0.21</td>
<td>70</td>
<td>167</td>
<td>104</td>
<td>88</td>
<td>77</td>
<td>71</td>
</tr>
<tr>
<td>W. H.</td>
<td>108</td>
<td>57</td>
<td>68</td>
<td>520</td>
<td>190</td>
<td>178</td>
<td>0.21</td>
<td>0.27</td>
<td>0.30</td>
<td>70</td>
<td>211</td>
<td>108</td>
<td>75</td>
<td>65</td>
<td>74</td>
</tr>
<tr>
<td>Mean</td>
<td>121</td>
<td>60</td>
<td>90</td>
<td>158</td>
<td>217</td>
<td>312</td>
<td>0.20</td>
<td>0.25</td>
<td>0.27</td>
<td>71</td>
<td>200</td>
<td>120</td>
<td>81</td>
<td>72</td>
<td>70</td>
</tr>
<tr>
<td>S.D.</td>
<td>13</td>
<td>22</td>
<td>22</td>
<td>120</td>
<td>64</td>
<td>110</td>
<td>0.03</td>
<td>0.05</td>
<td>0.06</td>
<td>9</td>
<td>28</td>
<td>36</td>
<td>7</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>%Δ from control</td>
<td>-51</td>
<td>-25</td>
<td>-61</td>
<td>-13</td>
<td>-30</td>
<td>+30</td>
<td>+181</td>
<td>+78</td>
<td>-11</td>
<td>-13</td>
<td>+7</td>
<td>+1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

B. Changes in Water and Electrolyte Excretion

| Subject | \(V\) ml/min. | \(U_{\text{Na}}\) mEq/l. | \(T\) | \(P_{\text{Na}}\) mEq/l. | \(U_{\text{Na}}/P_{\text{Na}}\) | \(C_{\text{Na}}\) mEq/l. | \(U_{\text{Na}}/C_{\text{Na}}\) | \(C_{\text{K}}\) mEq/l. | \(U_{\text{K}}/C_{\text{K}}\) | \(C_{\text{Cl}}\) mEq/l. | \(U_{\text{Cl}}/C_{\text{Cl}}\) | \(U_{\text{K}}/C_{\text{K}}\) | \(U_{\text{K}}/C_{\text{Cl}}\) | \(U_{\text{Cl}}/C_{\text{Cl}}\) | \(\%\text{Δ}\) from control |
|---------|--------------|----------------|------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| D. P.   | 8.6          | 0.2           | 2.0  | 81            | 712           | 223           | 285           | 285           | 0.3           | 2.0           | 0.8           | 3.2           | 1.0           | 8.0           | 1.0           | -90            |
| D. G.   | 7.3          | 0.3           | 0.3  | 85            | 804           | 781           | 287           | 284           | 0.3           | 2.0           | 0.9           | 2.0           | 0.9           | 1.0           | 0.9           | -88            |
| W. H.   | 10.6         | 0.0           | 1.0  | 90            | 572           | 320           | 290           | 282           | 0.3           | 2.0           | 1.7           | 3.4           | 1.2           | 7.3           | 1.2           | -86            |
| Mean    | 8.8          | 0.3           | 0.3  | 89            | 766           | 400           | 280           | 283           | 0.3           | 2.0           | 1.8           | 2.7           | 0.8           | 1.7           | 0.8           | -90            |
| S.D.    | 1.7          | 0.2           | 0.7  | 3             | 120           | 60            | 2             | 3             | 0.0           | 0.4           | 1.0           | 0.6           | 0.4           | 1.3           | 0.2           | -89            |

*Subjects who received no ethanol and manifested persistent oliguria during anestheisa.
†All data except osmolalities and pressure measurements are corrected to 1.73 m., body surface area.
*U = Data obtained during unstable state following induction of anestheisa during which clearance measurements are invalid. These data are presented merely for purposes of comparison.
*T = Mean values of 2-3 urine periods approximately 105 to 236 minutes after induction during which V was stable.
### A. Hemodynamic Changes

<table>
<thead>
<tr>
<th>Subject</th>
<th>CUF † ml/min.</th>
<th>CPRµ † ml/min.</th>
<th>FF CF/Grail</th>
<th>RVR min, Hg/l/min.</th>
<th>MAP min, Hg</th>
<th>HR beats/min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>W, D.</td>
<td>113</td>
<td>513</td>
<td>0.22</td>
<td>84</td>
<td>178</td>
<td>78</td>
</tr>
<tr>
<td>J, M.</td>
<td>111</td>
<td>478</td>
<td>0.23</td>
<td>95</td>
<td>171</td>
<td>80</td>
</tr>
<tr>
<td>J, L.</td>
<td>104</td>
<td>525</td>
<td>0.18</td>
<td>71</td>
<td>292</td>
<td>77</td>
</tr>
<tr>
<td>J, G.1</td>
<td>97</td>
<td>452</td>
<td>0.22</td>
<td>107</td>
<td>194</td>
<td>80</td>
</tr>
<tr>
<td>J, G.</td>
<td>140</td>
<td>550</td>
<td>0.24</td>
<td>69</td>
<td>156</td>
<td>58</td>
</tr>
<tr>
<td>O, W.</td>
<td>88</td>
<td>501</td>
<td>0.19</td>
<td>70</td>
<td>91</td>
<td>60</td>
</tr>
<tr>
<td>Mean</td>
<td>109</td>
<td>533</td>
<td>0.21</td>
<td>80</td>
<td>105</td>
<td>70</td>
</tr>
<tr>
<td>S.D.</td>
<td>16</td>
<td>49</td>
<td>0.03</td>
<td>16</td>
<td>50</td>
<td>12</td>
</tr>
<tr>
<td>% A from control</td>
<td>-42</td>
<td>-19</td>
<td>+10</td>
<td>70</td>
<td>70</td>
<td>70</td>
</tr>
</tbody>
</table>

\[ P < 0.001 \]

### B. Changes in Water and Electrolyte Excretion

<table>
<thead>
<tr>
<th>Subject</th>
<th>X † ml/min.</th>
<th>U1 † mOsm/l</th>
<th>P1 † mOsm/kg.</th>
<th>U2 † mOsm/kg.</th>
<th>U1/U2 *</th>
<th>Cme † ml/min.</th>
<th>Cme † ml/min.</th>
<th>UNAV * μEq/min.</th>
<th>U † ml/min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>W, D.</td>
<td>7.6</td>
<td>6</td>
<td>3.9</td>
<td>111</td>
<td>0.6</td>
<td>3.9</td>
<td>3.9</td>
<td>1.0</td>
<td>-0.8</td>
</tr>
<tr>
<td>J, M.</td>
<td>11.9</td>
<td>4</td>
<td>5.7</td>
<td>98</td>
<td>1.5</td>
<td>5.7</td>
<td>5.7</td>
<td>0.6</td>
<td>-0.8</td>
</tr>
<tr>
<td>J, L.</td>
<td>11.8</td>
<td>5</td>
<td>4.1</td>
<td>50</td>
<td>2.0</td>
<td>4.1</td>
<td>4.1</td>
<td>1.0</td>
<td>-0.4</td>
</tr>
<tr>
<td>J, G.1</td>
<td>12.2</td>
<td>7</td>
<td>5.1</td>
<td>71</td>
<td>0.9</td>
<td>5.1</td>
<td>5.1</td>
<td>2.0</td>
<td>-1.0</td>
</tr>
<tr>
<td>J, G.</td>
<td>12.2</td>
<td>8</td>
<td>2.8</td>
<td>88</td>
<td>2.8</td>
<td>2.8</td>
<td>2.8</td>
<td>1.0</td>
<td>-1.0</td>
</tr>
<tr>
<td>O, W.</td>
<td>13.6</td>
<td>9</td>
<td>1.5</td>
<td>99</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.0</td>
<td>-1.0</td>
</tr>
<tr>
<td>Mean</td>
<td>11.0</td>
<td>8</td>
<td>1.1</td>
<td>85</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td>1.0</td>
<td>-1.0</td>
</tr>
<tr>
<td>S, D.</td>
<td>2.4</td>
<td>20</td>
<td>1.0</td>
<td>20</td>
<td>2.0</td>
<td>1.0</td>
<td>1.0</td>
<td>2.0</td>
<td>-1.0</td>
</tr>
<tr>
<td>% A from control</td>
<td>-91</td>
<td>-63</td>
<td>+563</td>
<td>-2</td>
<td>563</td>
<td>4.57</td>
<td>563</td>
<td>-53</td>
<td>-106</td>
</tr>
</tbody>
</table>

\[ P < 0.001 \]
and stable V. By “unsteady state” we mean periods of low or abruptly changing V, and changing levels of inulin and PAH. Since valid hemodynamic measurements were obtained only in this group of subjects the remainder of the presentation and the discussion will pertain mainly to the experimental data from Group II.

Effects on V, \( U_{osm} \), \( U_{osm}/P_{osm} \), \( C_{osm} \), \( C_{H_2O} \) and Sodium Excretion (\( U_{Na}V \)). Data from all 7 subjects in Group II are summarized in table 2 and 2 representative experiments are illustrated in figures 2 and 3. As in the control group, with induction of anesthesia, V decreased sharply from 11.9 to 1.0 ml per minute \((P < 0.001)\); \( U_{osm} \) increased from 85 to 562 mOsm./kg. \((P < 0.001)\); the \( U_{osm}/P_{osm} \) ratio increased from 0.3 to 2.1 \((P < 0.001)\), and \( C_{osm} \) was reduced from 4.4 to 1.6 ml per minute \((P < 0.001)\). During the control period \( C_{H_2O} \) averaged 8.4 ml./minute. Following induction of anesthesia a negative free water clearance \((T_{H_2O})\) was observed in 6 of the 7 subjects. The average free water clearance during this unsteady state was \(-0.5\) ml./minute \((P < 0.001)\). Urinary sodium excretion was reduced from 167 to 54 \(\mu\)Eq. minute \((P < 0.005)\).

Administration of ethanol and in one instance fructose in water intravenously, resulted in an increase in V from mean values of 1.1 to 4.4 ml./minute \((P < 0.001)\). The volume of ethanol and of fructose and water required to increase the urine volume during anesthesia was 227 ml. (mean) with a range from 95 to 463 ml. The infusion time required for the ethanol to initiate an increase in V was 32.6 minutes (mean) with a range of 10 to 58 minutes.

Administration of ethanol resulted in a reduction in \( U_{osm} \) to 132 mOsm./kg. \((P < 0.001)\); \( U_{osm}/P_{osm} \) ratio was reduced to 0.47 ml after ethanol administration \((P < 0.001)\), a value not significantly different from the control. \( C_{osm} \) changed only slightly following ethanol administration while \( C_{H_2O} \) in-
creased from negative values to 2.2 ml/minute ($P < 0.001$). No significant change in $U_{Na} \cdot V$ was observed with ethanol administration.

**Effect on GFR, ERBF, FF and RVR.** Under steady state conditions with $V$ greater than 2 ml/minute, a comparison of hemodynamics before and during anesthesia was made. A reduction in GFR from 109 to 88 ml/minute ($-19$ per cent) was observed ($P < 0.005$). PAH clearance was reduced from 533 to 332 ml/minute ($-35$ per cent). When expressed as ERBF a reduction from 967 to 596 ml/minute was found ($P < 0.01$). An increase in FF from 0.21 to 0.29 was observed ($P < 0.01$), and the calculated RVR increased from 80 to 135 units. MAP decreased from 77 to 71 mm. of mercury and heart rate increased from 70 to 80/minute. Renal venous pressure was 9.6 mm. of mercury in both subjects during renal venous catheterization.

PAH extraction was 0.88 before and 0.87 during anesthesia in subject R. R., and 0.92 in subject O. W. during anesthesia. The catheter had inadvertently slipped from the renal vein in the latter subject during the control period. These values for PAH extraction both before and during anesthesia are within normal limits for man.$^{12}$ From these few observations it would appear that PAH extraction is not altered by halothane, and therefore $C_{PAH}$ during the "steady state" is a valid estimate of ERBF.

Administration of ethanol did not alter renal hemodynamics during the control period (fig. 2).

**Arterial $P_{O_2}$, $P_{CO_2}$, and pH During Halothane Anesthesia.** In 9 subjects arterial blood samples were analyzed for $P_{O_2}$, $P_{CO_2}$, and pH. Mean $P_{O_2}$ for all subjects was 545 mm. of mercury, $P_{CO_2}$ was 38.7 mm. of mercury, and pH was 7.385. One can, therefore, rule out hypoxia and respiratory and metabolic acidosis as factors producing the changes observed during anesthesia.
A. Hemodynamic Changes

<table>
<thead>
<tr>
<th>Subject</th>
<th>Cml/min.</th>
<th>Amin.</th>
<th>Creat</th>
<th>ml/min.</th>
<th>FF</th>
<th>Cml/</th>
<th>Creat</th>
<th>mm. Hg.</th>
<th>L/min.</th>
<th>MAP</th>
<th>mm. Hg.</th>
<th>HR</th>
<th>beats/min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. H.</td>
<td>107</td>
<td>50</td>
<td>77</td>
<td>540</td>
<td>267</td>
<td>361</td>
<td>0.20</td>
<td>0.20</td>
<td>0.22</td>
<td>72</td>
<td>118</td>
<td>92</td>
<td>76</td>
</tr>
<tr>
<td>M. D.</td>
<td>115</td>
<td>55</td>
<td>71</td>
<td>550</td>
<td>255</td>
<td>236</td>
<td>0.20</td>
<td>0.21</td>
<td>0.29</td>
<td>81</td>
<td>145</td>
<td>117</td>
<td>80</td>
</tr>
<tr>
<td>T. H.</td>
<td>120</td>
<td>51</td>
<td>47</td>
<td>570</td>
<td>255</td>
<td>314</td>
<td>0.20</td>
<td>0.17</td>
<td>0.23</td>
<td>99</td>
<td>114</td>
<td>111</td>
<td>94</td>
</tr>
<tr>
<td>Mean</td>
<td>116</td>
<td>55</td>
<td>60</td>
<td>573</td>
<td>282</td>
<td>301</td>
<td>0.29</td>
<td>0.10</td>
<td>0.22</td>
<td>84</td>
<td>126</td>
<td>126</td>
<td>85</td>
</tr>
<tr>
<td>S. D.</td>
<td>10</td>
<td>4</td>
<td>24</td>
<td>21</td>
<td>11</td>
<td>76</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%∆ from control</td>
<td>-52</td>
<td>-10</td>
<td>-51</td>
<td>-17</td>
<td>-5</td>
<td>+10</td>
<td>+50</td>
<td>+50</td>
<td>-24</td>
<td>-20</td>
<td>+10</td>
<td>+10</td>
<td></td>
</tr>
</tbody>
</table>

B. Changes in Water and Electrolyte Excretion

<table>
<thead>
<tr>
<th>Subject</th>
<th>V</th>
<th>ml/min.</th>
<th>Closmal.</th>
<th>mEq/kg</th>
<th>Plosmal.</th>
<th>mEq/kg</th>
<th>Xlos/Plos</th>
<th>Clos</th>
<th>ml/min.</th>
<th>Clos</th>
<th>mEq/ml/min.</th>
<th>UosV</th>
<th>µEq/ml/min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. H.</td>
<td>5</td>
<td>0.1</td>
<td>0.9</td>
<td>158</td>
<td>631</td>
<td>117</td>
<td>290</td>
<td>280</td>
<td>278</td>
<td>0.55</td>
<td>3.0</td>
<td>1.0</td>
<td>1.1</td>
</tr>
<tr>
<td>M. D.</td>
<td>16</td>
<td>1.6</td>
<td>2.5</td>
<td>94</td>
<td>325</td>
<td>159</td>
<td>267</td>
<td>264</td>
<td>263</td>
<td>0.33</td>
<td>1.1</td>
<td>0.6</td>
<td>5.1</td>
</tr>
<tr>
<td>T. H.</td>
<td>15</td>
<td>0.5</td>
<td>0.7</td>
<td>67</td>
<td>162</td>
<td>597</td>
<td>298</td>
<td>282</td>
<td>278</td>
<td>0.23</td>
<td>2.1</td>
<td>2.2</td>
<td>3.3</td>
</tr>
<tr>
<td>Mean</td>
<td>12</td>
<td>0.8</td>
<td>1.1</td>
<td>100</td>
<td>160</td>
<td>401</td>
<td>298</td>
<td>282</td>
<td>280</td>
<td>0.37</td>
<td>2.2</td>
<td>1.5</td>
<td>3.8</td>
</tr>
<tr>
<td>S. D.</td>
<td>6</td>
<td>0.9</td>
<td>1.0</td>
<td>47</td>
<td>256</td>
<td>221</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.16</td>
<td>0.9</td>
<td>0.8</td>
<td>1.2</td>
</tr>
</tbody>
</table>

* Abbreviations and footnotes as in table 1.
C as in table 1.
U as in table 1.
A Period of anesthesia mean of two 3 urine periods with failure of alcohol to produce increased V greater 2 ml./minute.
Concentrations of ethanol in blood in the 6 subjects in Group II ranged from 7.2 to 43.9 mg./100 ml. with a mean of 29.1 mg./100 ml.

Group III contained 3 subjects who received intravenous ethanol who did not respond with increases in urine volume greater than 2 ml. per minute (table 3). No comparison of hemodynamics before and during anesthesia could be made in these subjects.

**Discussion**

Two studies of renal function in man during halothane anesthesia have previously been reported. GFR was reduced 36 to 44 per cent and ERBF decreased 47 to 52 per cent when concentrations of halothane inspired were greater than 1.2 per cent. Hydration with 0.3 per cent saline prior to anesthesia resulted in maintenance of GFR and ERBF at approximately control levels in a lightly anesthetized group (0.5 to 1.0 per cent inspired). Reductions in \( V \) and \( U_{\text{Na}} \) of 64 per cent were observed. Estimated differences in hemodynamic changes between the hydrated and nonhydrated groups were based upon a presumed maintenance of an unchanged central circulatory volume with saline.

The hemodynamic changes in our study, a fall in GFR of 19 per cent and a 38 per cent reduction in ERBF are lower than those just cited. Several reasons for the discrepancies between the studies may be mentioned. In prior studies patients received morphine 10 mg. and scopolamine 0.4 mg. as premedication, and were studied during operation. Anesthetic levels varied in each patient and a period of only 20 to 30 minutes was allowed for attainment of equilibrium before measurements were made. The presence of low \( V \), abrupt changes in \( V \), changing blood levels of inulin, PAH, and halothane are variables which make it difficult to interpret the hemodynamic data obtained in these studies. Evidence for storage of inulin within the kidney and PAH with extremely low \( V \) has been reported by a number of investigators.

Our study was carried out in hydrated subjects who received no premedication, breathed a constant inspired concentration of halothane, did not undergo operation, and who were given ethanol intravenously to increase urine volume in order to allow the valid application of clearance techniques by obviating storage of inulin and PAH within the kidney. In addition, body temperature was maintained constant, and hypoxia and respiratory acidosis were avoided. PAH extraction was found to be unchanged by halothane. From this we may assume that \( C_{\text{PAH}} \) is a true estimate of renal plasma flow when there is a steady state of \( V \), blood PAH, and the absence of PAH storage within the kidney. A 28 per cent increase in the filtration fraction and 41 per cent increase in the calculated renal vascular resistance suggest some degree of efferent arteriolar vasoconstriction.

With respect to changes in water and electrolyte excretion during halothane anesthesia, the following were observed: reduction in \( V \), increased \( U_{\text{Na}} \), increased \( U_{\text{Na}}/P_{\text{Na}} \) ratio, and a change from excretion of solute free water (\( C_{\text{H}_{2}O} \)) to tubular re-absorption of water (\( T_{\text{H}_{2}O} \)). These changes represent an antidiuresis, and the reappearance of \( C_{\text{H}_{2}O} \), following the administration of ethanol represents a partial reversal of antidiuresis. The fact that relatively small volumes of ethanol (less than 300 ml.) in 6 of 7 subjects were necessary to initiate reversal of antidiuresis suggests that the infusion of ethanol did not act by increasing central circulatory volume, but exerted its effects primarily by inhibiting the secretion of ADH.

Several mechanisms by which anesthetic agents affect renal function should be noted. An acute reduction in GFR may result in decreased \( V \), decreased \( C_{\text{H}_{2}O} \), and an increase in \( U_{\text{Na}} \). All of our subjects except one (O. W.) had a reduction in GFR. Liberation of ADH during anesthesia is another factor that might contribute to the antidiuresis observed. Partial reversal of the antidiuresis with ethanol in this study strongly suggests a contribution of ADH in the antidiuresis associated with anesthesia. Halothane may act to liberate ADH by a central autonomic effect or by changes in circulating blood volume a stimulus known to evoke ADH release.

Changes in sodium excretion may be explained by the previously mentioned reduction in GFR. In addition, a volume stimulus for aldosterone excretion with resultant in-
creased tubular re-absorption of sodium may reduce sodium excretion. Halothane, a known vasodilator may activate the renin-angiotensin-aldosterone system by producing a transitory reduction in circulating blood volume. Similarly, reductions in perfusion pressure at the juxtaglomerular apparatus may activate this system. Other factors such as the "third factor" proposed by Levinsky and Lalone 22 believed to play a role in tubular re-absorption of sodium may be affected by halothane. This factor supposedly acts to reduce tubular re-absorption of sodium and has been postulated to play a role in the sodium diuresis that follows saline infusions.

Hemodynamic changes observed during halothane anesthesia may represent an attempt by the kidney to compensate for the reduction in perfusion pressure, via efferent arteriolar vasoconstriction, thus maintaining glomerular filtration. The increased FF and increased calculated renal vascular resistance are compatible with efferent arteriolar vasoconstriction. It is generally agreed that the kidney has a well-developed capacity for autoregulation of blood flow and glomerular filtration rate but there is no general agreement regarding the mechanisms involved. 23 One possible explanation invokes the renin-angiotensin system which may be stimulated by changes in sodium concentration at the macula densa. 24 The macula densa is believed to play an important role in the activation of the renin-angiotensin system. Alteration of sodium concentration at this area has been demonstrated to produce changes in renal hemodynamics via a feedback mechanism.

The clinical significance of these findings is speculative. The effects of anesthetics in the presence of renal disease have not been elucidated. Certainly, significant reductions in GFR, ERBF, water and sodium excretion have been demonstrated. It is conceivable that these changes may play a role in rendering the kidney more susceptible to noxious stimuli such as hemorrhage, fluid and electrolyte depletion, or hemolytic transfusion reaction.

Summary

Halothane 1.5 per cent in oxygen administered to hydrated unpremedicated normal human subjects produced a 19 per cent mean reduction in glomerular filtration rate and 38 per cent reduction in effective renal plasma flow. Increased vascular resistance within the kidney was inferred from an observed increase in the filtration fraction and calculation of renal vascular resistance. Antidiuresis was associated with the induction of halothane anesthesia which persisted for long periods of time and was partially reversed in most subjects by the intravenous administration of ethanol. The antidiuresis observed probably was related to both a reduction in glomerular filtration rate and the release of antidiuretic hormone. Sodium excretion was reduced partly as a result of reduction in glomerular filtration rate.

References


MYASTHENIC BLOOD  Blood fractions from 11 of 16 patients with myasthenia gravis, when injected intra-arterially into the rat produced neuromuscular blockade. Blocking activity was not found in the blood of those patients whose symptoms were confined to the extra-ocular muscles. The blocking activity occurred in a globulin fraction of the plasma. These results support previous findings that there is a blocking agent in the blood of some patients with myasthenia. The blocking agent appears to act at the neuromuscular junction as shown by the electrical fatigue between the nerve and the muscle and by the effects of the use of neostigmine and edrophonium. The neuromuscular block provoked in the rat has elements of both competition and depolarization. The disappearance of plasma blocking activity after thymectomy in one case was accompanied by an improvement in muscle weakness. Blood from other post-thymectomy patients continued to show neuromuscular blocking activity. (Parkes, J. D., and McKinna, J. A.: Neuromuscular Blocking Activity in the Blood of Patients with Myasthenia Gravis, Lancet 1: 388 (Feb.) 1966.)