Cyclopropane Effects on Renal Function in Normal Man

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Renal functional changes resulting from anesthesia with cyclopropane were measured in 9 normal human subjects without preanesthetic medication, or operative stimuli. At steady-state conditions, with partial reversal by infusion of ethanol of the antidiuresis produced by cyclopropane the following were observed: glomerular filtration rate decreased 39 per cent; renal blood flow decreased 42 per cent; and, renal vascular resistance increased 84 per cent. Increased plasma levels of renin were found in the two instances in which measurements were made. Mechanisms by which cyclopropane alters renal function are considered, along with the significance for the clinical situation.

As part of re-assessment of the effects of anesthetics on renal function, a study of renal function before and during cyclopropane anesthesia was performed, with elimination of the variables present in previously reported studies. Subjects received no premedication, were well hydrated and were studied in the absence of operative stimuli. Ethanol was administered intravenously as practiced before, when needed to obtain urinary volumes (V) greater than 2 ml per minute during anesthesia, in order to obtain valid estimates of renal hemodynamics, and to evaluate the role of antidiuretic hormone (ADH) in the antidiuresis produced by cyclopropane. No combined description of changes in renal hemodynamics, and of water and electrolyte excretion has been reported in previous studies. In addition, the concentration of renin in peripheral venous plasma was determined before and during anesthesia in a study of its role, if any, in the renal hemodynamic changes observed during anesthesia.

Methods

Nine healthy male volunteers in their twenties reported to the laboratory early in the morning having abstained from food and fluids from 8 to 12 hours. The experimental procedure was explained in detail to the subjects on two occasions prior to the study and a written consent obtained. Subjects were studied in the recumbent position except when they stood to void during the control period. Three plastic catheters were inserted into peripheral arm veins under local anesthesia, and priming doses of inulin (3.5 g.) and para-aminohippurate (PAH) (600 mg.) were administered intravenously after obtaining a control blood sample and after emptying the bladder. 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 load of 1,000 ml of 4 per cent fructose in water was administered intravenously over a 40 to 60 minute period. For the remainder of the study, a sustaining infusion of 4 per cent fructose in water was administered at a rate equal to the volume of urine excreted during each collection period, plus 0.8 ml/minute for estimated

* Sustaining infusion contained 163 ml. 10 per cent inulin and 30 ml. 20 per cent PAH in 307 ml. physiological saline.
insensible water loss. Urine was collected every 15 to 20 minutes, and peripheral venous blood specimens drawn every 60 minutes at the midpoint of a collection period. Arterial pressure was determined by auscultation during the control period, and during this period subjects breathed room air without a mask in order to avoid emotional stimuli that might affect renal function.

Following a control period with the subjects recumbent, denitrogenation of the subjects’ lungs was begun, using a flow of 7 liters of oxygen per minute in a semi-closed circle absorption system with a soda lime canister. Anesthesia was then induced with a mixture of 50 per cent cyclopropane in oxygen. Mild excitement was observed in 6 of the 9 subjects, with induction of anesthesia. When the subjects were judged to be in the first plane of surgical anesthesia according to clinical signs, orotracheal intubation was performed following the intravenous administration of 60 to 80 mg. of succinylcholine. Cyclopropane was thereafter delivered in volumes that would produce a concentration of 18 to 20 volumes per cent in end-expired gas sampled from the endotracheal tube, as analyzed by absorption in 31N sulphuric acid.6 Depth of anesthesia during the study was judged to be within the first and second planes of surgical anesthesia according to clinical signs. Respiration was assisted by manual pressure on the reservoir bag in order to maintain the end-expired CO2 level less than 45 mm. of mercury as monitored by an infra-red analyzer. A thermistor probe was placed in the esophagus after induction of anesthesia and the body temperature was maintained at ±0.6° C. by means of warm blankets when necessary.

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

Lead 2 of the electrocardiogram was recorded continuously just prior to induction and throughout the anesthetic period. A Courand needle was inserted into a femoral artery following induction of anesthesia for recording arterial pressure and sampling for analysis of blood gases and pH.

Three subjects who served as controls were observed from 202 to 238 minutes following the induction of anesthesia in order to assess the effects of cyclopropane alone on renal function. The remaining 6 subjects were observed for 64 to 130 minutes after induction of anesthesia: however, following this period an intravenous infusion of 5 per cent ethanol in 4 per cent fructose in water was administered at a rate of 5 ml. per minute in order to reverse the antidiuresis produced by anesthesia. Four of the 6 who were given ethanol received continuous infusions of 500 ml. until the termination of the experiment; two received ethanol until V had increased to 3 ml. per minute or more, whereupon ethanol was discontinued. In the latter, volumes of fluid of 305 ml. and 410 ml., respectively, were administered.

Femoral arterial blood was sampled periodically and analyzed for pH, PO2, and PCO2. In 2 subjects (J. H. and J. M.) peripheral venous blood was sampled before and during anesthesia just prior to the administration of ethanol, and at the termination of the study, for renin assay by the method of Boucher et al.8

Analyses and Calculations. Inulin in plasma and urine was determined by the method of Walser, Davidson and Orloff 8; PAH in plasma and urine was determined by the method of Brun.9 Urine and blood specimens were analyzed for sodium and potassium by means of flame photometry, and osmolality by means of an Advanced Osmometer. Concentrations of ethanol in serum and urine were determined by the method of Nickolls.10 Serum and urine osmolalities were corrected for ethanol levels when appropriate. Arterial PO2, PCO2, and pH were determined by means of an Instrumentation Laboratories electrode system, Model no. 113.

Inulin and PAH clearances were calculated in the usual manner, and were used to determine glomerular filtration rate (GFR), and effective renal plasma flow (ERPF), respectively.
Cyclopropane effects on renal function

Fig. 1. Effect of cyclopropane anesthesia on renal function. Subject from Group I—Control Group. \( U_{osm} \), osmolality of urine, milliosmoles per kg. \( P_{osm} \), osmolality of serum, milliosmoles per kg. \( V \), urine volume ml. per minute. \( C_{osm} \), osmolar clearance ml. per minute = \( U_{osm} \times V/P_{osm} \). \( C_{H_2O} \), free water clearance ml. per minute = \( V - C_{osm} \). \( C_{inulin} \), inulin clearance ml. per minute. \( C_{PAH} \), PAH clearance ml. per minute. The shaded area indicates free water excretion (water in excess of solute). The unshaded area between \( V \) and \( C_{osm} \), represents water absorption in excess of solute (negative free water clearance or \( T_{\text{O}_{2}} \)). All values are corrected to 1.73 m² B.S.A.

\( C_{osm} \) and \( C_{H_2O} \) were calculated by the following formulas:

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

\[ C_{H_2O} = V - C_{osm}, \text{ where } U_{osm} = \text{osmolality of urine (mOsm./kg.), } P_{osm} = \text{osmolality of serum (mOsm./kg.), and } V = \text{urine flow (ml./min.).} \]

Filtration fraction (FF) was calculated as:

\[ FF = \frac{C_{inulin}}{C_{PAH}} \]

† \( C_{osm} \) = osmolar clearance. The volume necessary to excrete all the urinary solutes in isosmotic proportion to plasma.

† \( C_{H_2O} \) = free water clearance. The volume of solute free water excreted. This is an expression of urinary dilution.

Effective renal blood flow (ERBF) was calculated as:

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

Renal vascular resistance (RVR) was calculated as:

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

Mean arterial pressure was calculated as: \( \frac{3}{2} \) pulse pressure + diastolic pressure, or by electrical damping of the recorded arterial trace. All clearances, urine volumes, and sodium ex-
### Table 1. Effects of Cyclopropane Alone on Renal Function (Group I, Controls)*

#### A. Hemodynamic Changes

<table>
<thead>
<tr>
<th>Subject</th>
<th>C1* (mL/min.)</th>
<th>C2* (mL/min.)</th>
<th>FF CIN / CFAH</th>
<th>RV * (mm Hg/L/min.)</th>
<th>MAP (mm Hg)</th>
<th>HR (beats/min.)</th>
<th>Cyclopropane Concentration Vol % End-Expired</th>
</tr>
</thead>
<tbody>
<tr>
<td>J. C.</td>
<td>147 41 69</td>
<td>579 135 311</td>
<td>0.25 0.30 0.22</td>
<td>78 389 167</td>
<td>86 100 99</td>
<td>61 64 68</td>
<td>0 20 19</td>
</tr>
<tr>
<td>J. B.</td>
<td>100 57 70</td>
<td>606 330</td>
<td>0.17 0.18 0.21</td>
<td>83 185 158</td>
<td>101 118 108</td>
<td>65 72 72</td>
<td>0 17 18</td>
</tr>
<tr>
<td>Mean % from control</td>
<td>124 49 70</td>
<td>593 223 -62</td>
<td>0.21 0.24 0.22</td>
<td>81 287 162</td>
<td>94 109 104</td>
<td>63 68 70</td>
<td>18.5 18.5</td>
</tr>
</tbody>
</table>

#### B. Changes in Water and Electrolyte Excretion

<table>
<thead>
<tr>
<th>Subject</th>
<th>V** (mL/min.)</th>
<th>Uosm (mOsM/kg.)</th>
<th>P*osm (mOsM/kg.)</th>
<th>Uosm/P*osm</th>
<th>C**osm (mL/min.)</th>
<th>C*osm (mL/min.)</th>
<th>C**osm / P*osm</th>
<th>UNaV† (sEq/min.)</th>
<th>UKV† (sEq/min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>J. C.</td>
<td>7.5 0.2 1.1</td>
<td>80 449 345</td>
<td>298 290 293</td>
<td>0.3 1.6</td>
<td>1.2 0.3 1.3</td>
<td>5.5 0.1 0.2</td>
<td>0.2 60 160</td>
<td>80 6 16</td>
<td>30 15 7</td>
</tr>
<tr>
<td>J. B.</td>
<td>7.7 0.2 0.9</td>
<td>47 670 255</td>
<td>255 315 315</td>
<td>0.1 2.1</td>
<td>0.6 0.7 0.7</td>
<td>6.6 0.2 0.2</td>
<td>0.2 103 25</td>
<td>60 5 25</td>
<td>79 2 7</td>
</tr>
<tr>
<td>Mean % from control</td>
<td>7.0 0.2 1.0</td>
<td>64 560 300</td>
<td>272 303 304</td>
<td>0.2 1.9</td>
<td>1.0 0.3 1.0</td>
<td>6.1 0.2 0.2</td>
<td>0.2 94 21</td>
<td>55 9 11</td>
<td>-84 -80 -80</td>
</tr>
</tbody>
</table>

* Subjects who received no ethanol and manifested persistent oliguria during anesthesia.
† All data except osmolalities and pressure measurements are corrected to 1.73 m² body surface area.
‡ C = Mean values of 2-3 urine collection periods prior to induction of anesthesia. 
§ U = Data obtained during unsteady state following induction of anesthesia during which clearance measurements are invalid. These data are presented merely for purposes of data presentation. 

T = Mean values of 2-3 urine collection periods approximately 200 to 238 minutes after induction during which V was stable.
cretion rates were corrected to 1.73 m$^2$ of body surface area.

Statistical analyses were performed using Student's $t$ test.

**Results**

As in the previous study $^1$ the subjects fell into distinct groups: (1) those showing persistent antidiuresis with or without ethanol; and (2) those without persistent diuresis.

*Group I.* This comprised 2 of the 3 subjects who received no ethanol during anesthesia, and who maintained a persistent antidiuresis (low V) from 213 to 238 minutes following induction of anesthesia. The data from a typical member of this group (J. C.) are depicted in figure 1. In this individual following the institution of a steady-state of water diuresis, V reached a mean level of 7.5 mL/minute, $U_{\text{osm}}$ was 80 mOsm./kg, mean, the U/P ratio was 0.3 mean, and the mean $C_{\text{H}_2\text{O}}$ was 5.5 mL/minute. Induction of anesthesia was associated with a sharp reduction in V to 0.2 mL/minute and a rise in U/P ratio to hypertonic values, 1.6, within 60 minutes. During this acute unsteady state V, blood and urine inulin and PAH levels changed continuously and values for $C_{\text{H}_2\text{O}}$ were negative ($-0.1$). Urine remained persistently hypertonic during the 238 minutes of observation. Quantitatively similar results were seen in J. B., and the data from both of these subjects are presented in table 1B. Because of the persistent antidiuresis (low V) valid estimations of hemodynamic changes could not be made, and are included in table 1A for purposes of data presentation.

![Diagram](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931617/)  

**Fig. 2.** Subject D. G. who exhibited spontaneous reversal of the antidiuresis associated with cyclopropane anesthesia and therefore hemodynamics before and during anesthesia may be compared. Symbols same as figure 1.
Group II. This comprised a total of 6 subjects; 5 subjects who received ethanol intravenously during anesthesia, all of whom responded with an increase in V of 3 ml./minute or greater; and, one subject who did not receive ethanol (D. G.); the latter spontaneously exhibited reversal of antidiuresis. All data presented, except those obtained during the period designated as "unsteady state," represent values obtained during constantly maintained levels of inulin, PAH, and stable V. Table 2 contains a summary of the data from all of the 6 subjects in this group. The results of two representative experiments from this group are illustrated in figures 2 and 3.

Group II, Effects on Water and Electrolyte Excretion (table 2B). As found in Group I with the induction of anesthesia, V decreased sharply from 15.6 to 0.3 ml./minute (P < 0.001). \( U_{\text{osm}} \) increased from 80 to 569 mOsm./kg. (P < 0.001). The \( U_{\text{osm}}/P_{\text{osm}} \) ratio increased from 0.29 to 2.0 (P < 0.001), and \( C_{\text{osm}} \) was reduced from 4.3 to 0.6 ml./minute (P < 0.001). \( C_{\text{H}_2\text{O}} \) during the control period, averaged 11.5 ml./minute. Following induction of anesthesia a negative free water clearance (\( T'_{\text{H}_2\text{O}} \)) was observed (-0.3 ml./minute) (P < 0.001), again representing an antidiuresis. Urinary sodium was reduced from

\[ (T'_{\text{H}_2\text{O}}) \] = negative free water clearance. The net amount of free water reabsorbed to produce a urine more concentrated than the GFR. This is an index of the concentrating activity of the kidney.
### Table 2. Effects of Cyclopropane Following Ethyl Alcohol (Group II)*

#### A. Hemodynamic Changes

<table>
<thead>
<tr>
<th>Subject</th>
<th>$C_{in}$† (ml./min.)</th>
<th>$C_{par}$† (ml./min.)</th>
<th>FF $C_{in}$</th>
<th>$C_{par}$</th>
<th>RVR (mm Hg/l./min.)</th>
<th>MAP (mm Hg)</th>
<th>HR (beats/min.)</th>
<th>Cyclopropane Concentration Vol.%</th>
<th>End-expired</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>U</td>
<td>S</td>
<td>C</td>
<td>U</td>
<td>S</td>
<td>C</td>
<td>U</td>
<td>S</td>
<td>C</td>
</tr>
<tr>
<td>J. M.</td>
<td>119</td>
<td>49</td>
<td>77</td>
<td>507</td>
<td>24</td>
<td>291</td>
<td>0.21</td>
<td>2.00</td>
<td>0.30</td>
</tr>
<tr>
<td>R. T.</td>
<td>116</td>
<td>39</td>
<td>33</td>
<td>480</td>
<td>194</td>
<td>381</td>
<td>0.24</td>
<td>0.20</td>
<td>0.10</td>
</tr>
<tr>
<td>R. G.</td>
<td>123</td>
<td>29</td>
<td>86</td>
<td>509</td>
<td>190</td>
<td>343</td>
<td>0.21</td>
<td>0.29</td>
<td>0.25</td>
</tr>
<tr>
<td>W. R.</td>
<td>114</td>
<td>55</td>
<td>96</td>
<td>501</td>
<td>191</td>
<td>281</td>
<td>0.21</td>
<td>0.29</td>
<td>0.34</td>
</tr>
<tr>
<td>J. H.</td>
<td>109</td>
<td>26</td>
<td>67</td>
<td>572</td>
<td>35</td>
<td>310</td>
<td>0.19</td>
<td>0.75</td>
<td>0.22</td>
</tr>
<tr>
<td>D. G.§</td>
<td>108</td>
<td>63</td>
<td>62</td>
<td>568</td>
<td>330</td>
<td>283</td>
<td>0.19</td>
<td>0.19</td>
<td>0.22</td>
</tr>
<tr>
<td>Mean</td>
<td>116</td>
<td>44</td>
<td>70</td>
<td>543</td>
<td>146</td>
<td>317</td>
<td>0.21</td>
<td>0.62</td>
<td>0.24</td>
</tr>
<tr>
<td>S.D.</td>
<td>5.8</td>
<td>15.4</td>
<td>6.9</td>
<td>3.9</td>
<td>36.9</td>
<td>39.5</td>
<td>0.02</td>
<td>0.70</td>
<td>0.67</td>
</tr>
<tr>
<td>% from control P</td>
<td>&lt;0.005</td>
<td>&lt;0.001</td>
<td>&lt;42</td>
<td>+14</td>
<td>+14</td>
<td>+8</td>
<td>+8</td>
<td>+8</td>
<td>+8</td>
</tr>
<tr>
<td>R. W. G.§</td>
<td>116</td>
<td>44</td>
<td>70</td>
<td>543</td>
<td>146</td>
<td>317</td>
<td>0.21</td>
<td>0.62</td>
<td>0.24</td>
</tr>
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<td>% from control P</td>
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<td>&lt;42</td>
<td>+14</td>
<td>+14</td>
<td>+8</td>
<td>+8</td>
<td>+8</td>
<td>+8</td>
</tr>
</tbody>
</table>

#### B. Changes in Water and Electrolyte Excretion

<table>
<thead>
<tr>
<th>Subject</th>
<th>$V$† (ml./min.)</th>
<th>$U_{com}$ (mOsm./kg.)</th>
<th>$P_{com}$ (mOsm./kg.)</th>
<th>$U_{com}/P_{com}$</th>
<th>$C_{com}$† (ml./min.)</th>
<th>$C_{tio}$† (ml./min.)</th>
<th>$U_{NaV}$ (mEq./min.)</th>
<th>$U_{Kv}$ (mEq./min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>U</td>
<td>S</td>
<td>C</td>
<td>U</td>
<td>S</td>
<td>C</td>
<td>U</td>
<td>S</td>
</tr>
<tr>
<td>J. M.</td>
<td>14.4</td>
<td>0.2</td>
<td>4.7</td>
<td>92</td>
<td>739</td>
<td>118</td>
<td>275</td>
<td>273</td>
</tr>
<tr>
<td>R. T.</td>
<td>12.4</td>
<td>0.5</td>
<td>6.0</td>
<td>80</td>
<td>422</td>
<td>105</td>
<td>291</td>
<td>285</td>
</tr>
<tr>
<td>R. G.</td>
<td>11.4</td>
<td>0.5</td>
<td>6.3</td>
<td>92</td>
<td>502</td>
<td>110</td>
<td>282</td>
<td>280</td>
</tr>
<tr>
<td>W. R.</td>
<td>12.4</td>
<td>0.4</td>
<td>8.6</td>
<td>70</td>
<td>522</td>
<td>78</td>
<td>293</td>
<td>286</td>
</tr>
<tr>
<td>J. H.</td>
<td>17.7</td>
<td>0.3</td>
<td>6.4</td>
<td>71</td>
<td>651</td>
<td>84</td>
<td>287</td>
<td>274</td>
</tr>
<tr>
<td>D. G.§</td>
<td>15.9</td>
<td>0.3</td>
<td>5.2</td>
<td>76</td>
<td>547</td>
<td>109</td>
<td>287</td>
<td>285</td>
</tr>
<tr>
<td>Mean</td>
<td>15.6</td>
<td>0.4</td>
<td>5.4</td>
<td>80</td>
<td>569</td>
<td>101</td>
<td>286</td>
<td>282</td>
</tr>
<tr>
<td>S.D.</td>
<td>4.5</td>
<td>0.1</td>
<td>1.5</td>
<td>9.8</td>
<td>36.1</td>
<td>18</td>
<td>6.5</td>
<td>6.8</td>
</tr>
<tr>
<td>% from control P</td>
<td>&lt;0.005</td>
<td>+0.000</td>
<td>&lt;0.005</td>
<td>+0.000</td>
<td>+0.000</td>
<td>+0.000</td>
<td>+0.000</td>
<td>+0.000</td>
</tr>
<tr>
<td>R. W. G.§</td>
<td>10.6</td>
<td>0.1</td>
<td>0.4</td>
<td>81</td>
<td>456</td>
<td>709</td>
<td>284</td>
<td>286</td>
</tr>
</tbody>
</table>

*Abbreviations as in table 1.
†See table 1.
‡C = As in table 1. U = Anesthesia "Steady State"—urine volume increased greater than 3 ml./min., with urine flow for 2–3 consecutive periods, and stable plasma inulin and PAH concentrations.
§D. G. received no ethanol and had spontaneous reversal of the diuresis.
¶R. W. G. received ethanol, but did not respond with reversal of diuresis and therefore hemodynamic data are not valid.
#Statistical analysis comparing C versus S.
207 to 8 µEq./minute (P < 0.001) and urinary potassium was not significantly changed.

Administration of ethanol in 5 subjects resulted in an increase in V whereas in subject D. G., V spontaneously reverted from 0.3 to 3.2 ml./minute. V in the group as a whole showed a mean increase from 0.3 to 5.4 ml./minute (P < 0.001).

Administration of ethanol resulted in a reduction in U_osm to 101 mOsm/kg. (P < 0.001), and the U_osm/P_osm ratio was reduced to 0.37 after ethanol administration (P < 0.001), approximating the control value. C_osm increased from 0.6 to 1.9 following ethanol administration but remained significantly reduced from the control (P < 0.001). C_HCO_3 increased from negative values to 3.5 ml./minute (P < 0.001). Sodium excretion increased following ethanol administration but remained significantly reduced from control level (P < 0.005); potassium excretion increased significantly, but no significant change from control levels was observed at termination of the infusion of ethanol.

**Group II, Effect on Hemodynamics.** With V greater than 3.0 ml./minute and steady state conditions comparison of hemodynamic changes before and during anesthesia can be made.¹ GFR decreased from 116 to 70 ml./minute (−39 per cent) (P < 0.005). PAH clearance was reduced from 543 to 315 ml./minute (−42 per cent), indicating a marked reduction in ERPF. When expressed as ERBF, a reduction from 1,022 to 601 ml/minute was observed (P < 0.001). Filtration fraction (FF) increased in 5 of the 6 subjects; one subject R. T. had a greater reduction in GFR than ERBF resulting in a marked decrease in the FF. The increase in FF for the group as a whole was therefore not significant. Calculated RVR increased from 83 to 153 units (P < 0.005); this together with the changes in FF indicated an increase in overall arteriolar tone. (Mean arterial pressure increased in 5 of the 6 subjects in this group [6 to 27 mm. of mercury] and remained unchanged in one subject.) Heart rate was not significantly altered during anesthesia, and a normal sinus rhythm was present throughout the study in all subjects.

**Arterial P_O_2, P_CO_2, and pH.** Mean P_O_2 and range for all subjects was 350 mm. of mercury (290–452), P_CO_2 was 38.3 (35–46) mm. of mercury and pH was 7.39 (7.34–7.44).

Concentration of ethanol in peripheral venous blood in the 5 subjects in Group II ranged from 23 to 68 mg. per cent with a mean of 36 mg. per cent.

The mean end-expired concentration of cyclopropane for all subjects was 19 volumes per cent.

Subject R. W. G., who received intravenous ethanol, but who did not respond with an increase in V is presented at the bottom of table 2. Valid hemodynamic data cannot be obtained from his experiment. They are included for purposes of data presentation.

**Levels of Renin During Anesthesia.** Assay of renin was performed on the plasma from 2 subjects from Group II, J. M. and J. H. Normal levels of renin (according to the method used) are 400 nanograms per cent, or less. Mean renin concentration during the control period was 235 nanograms per cent. During the “unsteady” period of anesthesia, renin concentration increased significantly in both subjects from 344 and 125 nanograms per cent to 678 and 1,250 nanograms per cent, respectively. During the “steady” state period with ethanol, a further increase in renin level to 870 nanograms per cent was observed in J. M., while renin decreased to 270 nanograms per cent in J. H.

**Discussion**

Four studies of renal functional changes during cyclopropane anesthesia have previously been reported.²-⁵ Reductions in GFR ranging from a mean of 31 to 48 per cent were found and renal plasma flow decreased 44 to 63 per cent. Marked reductions in V and U_Na,V were also noted. Several factors in these studies in addition to the cyclopropane administered could have affected the results obtained. The subjects in 3 of the studies were patients in whom measurements were made during or shortly after termination of operation so that experience of pain, accumulated blood loss, and changes in intra-abdominal pressure might have influenced the results.¹¹,¹² Except in one study,¹ premedication with narcotics and belladonna derivatives was given to most patients. Narcotics are
known to alter the hemodynamic response to cyclopropane \(^{13}\) and to affect renal function.\(^{14}\) Mannitol which is known to lower renal vascular resistance,\(^{15,16}\) was administered in 2 studies\(^ {9,6}\) in order to measure GFR, or to ensure a V during anesthesia, of at least 2 ml per minute. Previous studies have not eliminated respiratory or metabolic acidosis and changes in body temperature as factors which might have influenced the renal response to cyclopropane. Respiratory acidosis as a factor which might have influenced the renal hemodynamic response was mentioned in only one study.\(^ {5}\)

Perhaps the greatest criticism that may be made regarding previous studies is the use of clearance techniques for the quantitation of renal hemodynamics in the presence of: low V; abrupt changes in V; changing blood levels of inulin, PAH; and, changing anesthetic levels; all variables which invalidate the accuracy of hemodynamic data.\(^ {1}\) In the clinical situation, however, the results reported are important and differ only quantitatively from the changes found in the present experiments.

In the present study the effects of dehydration, premedication, operation, hypoxia, respiratory acidosis, changes in body temperature, and “unsteady state” conditions of V, blood levels of inulin, PAH, and anesthetic concentration, were avoided. Our purpose was to assess the purely pharmacological effects of cyclopropane anesthesia on the kidney. When needed, ethanol was administered intravenously to increase V, thereby obviating storage of inulin and PAH within the kidney in order to allow the valid application of clearance techniques. In addition concomitant changes in renal hemodynamics, and water and electrolyte excretion with cyclopropane are reported here for the first time.

Under “steady state” conditions a 39 per cent reduction in GFR, and 42 per cent reduction in effective renal blood flow were observed, with an 84 per cent increase in calculated renal vascular resistance. These findings suggest both afferent and efferent arteriolar vasoconstriction consistent with the well known sympathetic nervous stimulation resulting from administration of cyclopropane.

Changes in water and electrolyte excretion during induction of cyclopropane anesthesia consisted of: a reduction in V; increased U\(_{\text{osm}}\); increased U\(_{\text{osm}}/P\(_{\text{osm}}\) ratio; and, a change from the excretion of solute free water (C\(_{\text{H}_{2}O}\)) to tubular reabsorption of water (T\(_{\text{H}_{2}O}\)). All these findings are consistent with an intense antidiuresis. Following infusion of ethanol 5 of the 6 subjects excreted solute free water (C\(_{\text{H}_{2}O}\)) as in the control period, indicating partial reversal of the antidiuresis. This suggests an influence of ADH in the antidiuresis associated with anesthesia as previously observed with halothane (Fluothane).\(^ {1}\) One subject, D. G. in the control group, with demonstrated spontaneous reversal of the antidiuresis had hemodynamic alterations and changes in water and electrolyte excretion similar to the others in Group II. It would appear, therefore, that the effects of ethanol in this study were mainly those of inhibition of ADH secretion, as previously reported.\(^ {3,17}\) The volumes of ethanol in solution required to initiate reversal of antidiuresis ranged from 115 to 491 ml suggesting that ethanol did not act merely by expanding the central circulating blood volume.

The effects of cyclopropane on renal function may be explained by one or a combination of mechanisms. Increased afferent and efferent arteriolar vasoconstriction are suggested by the marked reduction in GFR, RPF, and increased renal vascular resistance. Increased sympathetic nervous system activity known to accompany the administration of cyclopropane\(^ {18}\) may be responsible in part for the changes observed. Studies on the renal effects of infusion of epinephrine and norepinephrine in conscious adult volunteers,\(^ {19}\) and in dogs anesthetized with pentobarbital,\(^ {20}\) have demonstrated changes similar to these reported here.

The observed increase in circulating renin during cyclopropane anesthesia suggests still another mechanism which might affect renal hemodynamics. Release of renin from the kidney\(^ {21}\) leads to the formation of angiotensin,\(^ {22,28}\) a potent vasoconstrictor, known to produce increased renal vascular resistance in the intact or isolated kidney,\(^ {24}\) and a resultant decrease in GFR and RPF.\(^ {20,25}\) The possibility that changes in renal arteriolar tone during
cyclopropane anesthesia are a result of the action of angiotensin must therefore be considered.

There are several possible mechanisms by which renin may be liberated during cyclopropane anesthesia. Liberation of renin has been reported following the infusion of catecholamines. Sympathetic innervation as found in the juxtaglomerular apparatus may play a role in the function of the juxtaglomerular apparatus as a renal baroreceptor. Thus increased sympathetic activity during cyclopropane anesthesia may cause the release of renin from the juxtaglomerular apparatus in this manner. The renin-angiotensin system has been implicated in the autoregulation of renal blood flow. It remains to be determined whether the hemodynamic effects of cyclopropane are the result of angiotensin or whether the release of renin is a compensating mechanism for the changes in hemodynamics resulting from the administration of cyclopropane. Further studies of the role of the renin-angiotensin system during anesthesia are in progress.

A volume stimulus for aldosterone may also be responsible for the liberation of renin and angiotensin formation. Changes in sodium concentration in the renal tubule as a result of reduced GFR may also result in liberation of renin and angiotensin-aldosterone formation, again with a role in the autoregulation of blood flow.

Changes in excretion of water and electrolytes during cyclopropane anesthesia may be explained by one or more mechanisms. An acute reduction in GFR observed in all of the subjects resulted in decreased V, C\text{osm}, and an increase in U\text{osm}. Partial reversal of the antidiuresis of cyclopropane by infusion of ethanol suggests an influence of ADH. Cyclopropane is known to exert central nervous system effect, and may stimulate liberation of ADH. Changes in circulating blood volume may also evoke release of ADH. Likewise a reduction in GFR may explain, in part, the reduction in sodium excretion observed. The observation of increased renal levels during cyclopropane suggests still another mechanism that might effect sodium excretion. Liberation of aldosterone as a result of angiotensin formation and stimulation of the adrenal cortex could result in increased sodium reabsorption from the renal tubule. Potassium excretion increased in 3 of 6 subjects in Group II despite reductions in GFR suggesting a possible aldosterone effect on the renal tubule.

The clinical significance of these results is not easily assessed. In comparison with halothane, cyclopropane produces a far greater reduction in GFR (39 versus 19 per cent) suggesting greater afferent arteriolar vasoconstriction. This could be a reflection of the marked increase in sympathetic venous activity associated with cyclopropane rather than halothane. Administration of cyclopropane in the face of hemorrhage or pre-existing renal disease might be expected to seriously compromise renal function. Whether structural damage would be produced under these conditions remains to be determined.

Summary

Cyclopropane in oxygen administered to hydrated, unpremedicated normal human subjects under conditions of diuresis resulted in a 39 per cent reduction in glomerular filtration rate, and a 42 per cent reduction in effective renal plasma flow. Increased afferent and efferent arteriolar tone is inferred from marked reduction in glomerular filtration rate and the increase in renal vascular resistance. This is consistent with the known increased sympathetic nervous system activity during cyclopropane.

Cyclopropane anesthesia was associated with an intense antidiuresis which could be reversed partially by infusion of ethanol, suggesting an influence of ADH in the production of the antidiuresis. The reduction in glomerular filtration rate and other factors directly increasing tubular reabsorption of sodium resulted in reduced sodium excretion.

The observation of increased plasma renin levels during cyclopropane suggests a possible role of the renin-angiotensin-aldosterone system in the renal response to cyclopropane.

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References


Respiration

THORACIC SURGERY IN THE ELDERLY With careful attention to details of preoperative, operative and postoperative care, intrathoracic procedures can be carried out safely in the elderly patient. The authors describe thoracic procedures in all patients over 60 years of age who presented with a wide variety of primary diseases. Bronchogenic carcinoma, present in 48 patients, was the commonest. One-third of the total group had significant associated disease, usually in the form of coronary artery or chronic respiratory disease. The overall mortality rate was 6.3 per cent. Before surgery, all patients were prophylactically digitalized regardless of their cardiac status. Blood volume estimations were determined in those with excessive weight loss. At operation, measurements of central venous pressure was found to be the best guide to blood replacement. Retention of bronchial secretions was the commonest postoperative complication. This problem can be minimized with intensive chest physiotherapy, adequate hydration, minimal doses of analgesic agents and, when indicated, early tracheostomy. (Wellington, J., and Lynn, R.: Thoracic Surgery in the Elderly, Canad. Med. Ass. J. 95: 252 (Aug.) 1966.)

RESPIRATORY DEPRESSION The respiratory depression caused by meperidine 100 mg. intramuscularly) was studied in 10 male patients using the carbon dioxide response test. Thirty minutes after meperidine administration, there was an average of 28 per cent depression in CO₂ response and after 60 minutes, an average of 29.8 per cent depression. Six of the 10 patients showed respiratory depression (average 18 per cent) even 90 minutes after the opiate. (Ritzow, H., and Barth, L.: On the Extent and Duration caused by Pethidine, German, Der Anaesthesist 15: 300 (Sept.) 1966.)