The Cardiovascular Effects of Cyclopropane in Man

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The cardiac and peripheral vascular effects of 15–20 per cent, 25–30 per cent, and 35–40 per cent alveolar concentrations of cyclopropane were determined in each of 11 nonmedicated human volunteers at normal Pa_{CO_2} and body temperature during controlled ventilation. Compared with awake values during controlled ventilation, cyclopropane caused little change in cardiac output ($\dot{Q}$), heart rate (HR) or stroke volume (SV), while mean right atrial pressure (MRAP) increased markedly. Large increases in mean arterial pressure ($\overline{AP}$), total peripheral resistance and forearm vascular resistance suggested arterial constriction. A profound decrease in venous compliance contributed to the elevated MRAP. Cutaneous blood flow increased 560 per cent. Rapid reduction of cyclopropane led to immediate increase in $\dot{Q}$, SV, and $\overline{AP}$ at a lower MRAP within two minutes. After eight additional minutes at the lower cyclopropane concentration, $\dot{Q}$, SV, and $\overline{AP}$ returned to the previous values (i.e., before reduction of cyclopropane), but at even lower MRAP. (Key words: Cyclopropane; Controlled ventilation; Cardiovascular effects of cyclopropane; Pa_{CO_2}; Muscle blood flow; Skin blood flow.)

THE CARDIOVASCULAR EFFECTS of an inhaled anesthetic may be modified by premedication, induction agents, surgical stimulation, body temperature and, most importantly, by anesthetic depth and Pa_{CO_2}. No study has eliminated all of these modifying factors to permit both a quantitative evaluation of the effects of the anesthetic agent itself on cardiovascular function and a quantitative comparison of one anesthetic with another. This report describes unmodified cardiac and peripheral vascular effects of cyclopropane in man.

Methods

Eleven healthy, nonmedicated, young adult male volunteers were studied (table 1). With the subjects under local anesthesia, catheters were placed in the radial or brachial artery, right atrium or central vein, and forearm vein. Whitney strain gauges were placed on the terminal phalanx of the third or fourth finger and the fleshy portion of the forearm. Occlusion cuffs were located on the proximal phalanx of the same finger, the wrist, and the arm. A skin-temperature thermistor was taped onto the forearm or dorsum of the hand. Sublingual temperature was measured prior to induction with a thermistor probe. After induction, the probe was inserted into the esophagus. EKG leads were located on both arms and the right leg.

End-tidal cyclopropane was measured with a Beckman LB-1 end-tidal ether analyzer. End-tidal CO_2 was measured with the Beckman LB-1 infrared CO_2 analyzer. Arterial, right atrial, and peripheral venous pressures were measured with Statham strain gauges. Mean values were obtained by electrical damping. Forearm and finger Whitney mercury strain gauges were calibrated against a millimeter ruler. With the gauge on the finger or forearm, the amount of stretch produced by occluding venous return from the finger or forearm was recorded directly. Prior to venous occlusion of the forearm, the cuff at the wrist was inflated to isolate the circulation of the hand from that of the forearm. Considering the arm or finger as a cylinder,

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flow/100 ml tissue/min ($\dot{Q}_m$) was calculated as 200 $\Delta C/C$, where C is the circumference.[1] Peripheral venous pressure was measured simultaneously during occlusion of venous return. Venous compliance was then calculated as $\dot{Q}_m$/MAP-MRAP, where MAP is mean arterial pressure and MRAP, mean right atrial pressure.

Arterial and right atrial P_{O_2}, P_{CO_2} and *p*H were measured with appropriate electrodes and corrected for temperature. Base excess was derived from the Siggaard-Andersen nomogram. Arterial oxygen saturation was always 100 per cent. Venous oxygen saturation was calculated from venous P_{O_2}, *p*H, and base excess using the Severinghaus slide rule.[2] Hematocrits were measured frequently, and hemoglobin concentration was assumed to be a third of the hematocrit. Oxygen consumption was calculated from arteriovenous oxygen difference multiplied by cardiac output. We realize that the use of right atrial or central venous blood limits the value of $\dot{V}_{O_2}$ data, but believe that a right ventricular or pulmonary-artery catheter would have introduced an unnecessary hazard. Although our measure of oxygen consumption was indirect, both control and anesthetic values compare well to results noted previously by others, and we believe absolute accuracy is less important than relative accuracy in determination of the percentage change from the awake to the anesthetized state. Cardiac output was measured with a Beckman Cardiodensitometer equipped with a mechanical integrator. Cardiogreen dye was injected into the right atrium and sampled from the arterial catheter by continuous withdrawal with a Harvard pump. The densitometer was calibrated using three known concentrations of dye in the subjects' blood after the experiment was completed. The calibration curve is alinear below 2.5 mg/l of dye, and no attempt was made to correct for this. Continuous recordings of arterial pressure, right atrial pressure, peripheral venous pressure, electrocardiogram, end-tidal CO_2, forearm and finger circulation were obtained using a Grass model 7 polygraph recorder.

The awake subject, lying supine, breathed pure oxygen from a mouthpiece. Ventilation was controlled with an Air Shields volume-limited ventilator. End-tidal CO_2 was maintained at the value observed during spontaneous breathing of oxygen or slightly below it.

TABLE 1. Physical Characteristics of Volunteer Subjects (±1 SD)

Number	11
Age (years)	24.5 ± 3.4
Height (cm)	179 ± 5.7
Weight (kg)	74.3 ± 17.7
BSA (m^2)	1.92 ± 0.18

After measurement of cardiovascular functions, anesthesia was induced with cyclopropane and oxygen, and endotracheal intubation accomplished without muscle relaxants or topical anesthesia. Anesthesia was maintained with cyclopropane in oxygen at approximately 1 l/min total inflow, using a circle system and a CO_2 absorber. End-tidal cyclopropane was held at 15 per cent or 20 per cent for ten minutes, whereupon all measurements were repeated. End-tidal cyclopropane concentration was raised to 25 or 30 and then to 35 or 40 per cent, and maintained for ten minutes following each change, after which each set of measurements was redetermined. The same sequence was repeated two and four hours following induction to permit observation of the effect of duration of anesthesia on cardiovascular function. Ventilation was controlled to maintain Pa_{CO_2} at or near the awake value. No other drugs were used during the study. Statistical comparisons were made using paired t tests, with each subject serving as his own control.

Results (Table 2)

The cardiac index was 2.5 l/min/m^2, as opposed to 3.0 l/min/m^2 for young healthy males.[3] The difference was due solely to the lower heart rate in our subjects (64 *vs.* 74 beats/min), perhaps the result of positive-pressure ventilation with 100 per cent oxygen.

At 15 to 30 per cent cyclopropane, cardiac output, heart rate and stroke volume were unchanged from awake values (fig. 1), while mean right atrial pressure increased markedly (fig. 2). Additional changes included signifi-

TABLE 2. The Effects of Cyclopropane on the Cardiovascular System in Man†

	Control	First Hour			Fourth Hour		
		15–20 Per Cent	25–30 Per Cent	35–40 Per Cent	15–20 Per Cent	25–30 Per Cent	35–40 Per Cent
$\dot{Q}$ (l/min)	4.57 ±0.23	99 ±5.7	91 ±6.5	85* ±7.8	110 ±6.9	107 ±7.5	100 ±9.4
Heart rate (beats/min)	64 ±2.4	99 ±5.4	92 ±5.7	91 ±5.3	95 ±3.7	94 ±3.4	97 ±7.1
SV (ml)	71 ±3.2	101 ±4.4	98 ±6.1	92 ±6	115** ±4.1	109 ±5.4	102 ±4.2
MRAP (mm Hg)	0 ±0.96	6.2** ±0.84	9.4** ±1.2	10.4** ±0.96	3.3** ±1	6.1** ±1	9.3** ±1.4
$\overline{AP}$ (mm Hg)	90 ±2.9	131** ±5.3	132** ±5.4	131** ±8.4	111* ±3.8	124** ±5.7	132** ±7
TPR (dyne-sec/cm^5)	1589 ±73	132** ±11	142** ±15	151** ±11	102 ±8.5	116 ±11	133* ±14
Muscle blood flow (ml/min/100 ml tissue)	3.3 ±0.48	93 ±11.4	100 ±24	70* ±11.3	147 ±25	121 ±23.4	108 ±21
FVR dyne-sec/cm^5 × 10^6	2.7 ±0.39	162** ±22.8	179** ±30.2	212** ±37.5	96 ±15.3	129 ±21.2	165 ±35.3
FVC	0.16 +0.03	41** ±5.4	37** ±8.4	30** ±4.6	84 ±25.4	39** ±6.2	28** ±4.3
Cutaneous blood flow (ml/min/100 ml tissue)	7.3 ±3	48** ±9.3	46** ±9.7	48** ±14	60** ±10	67** ±11	69** ±16
Skin temperature (C)	30.8 ±0.32	33.7** ±0.4	34.2** +0.42	34** ±0.55	34.7** ±0.33	34.7** ±0.46	34.2** ±0.78
Body temperature (C)	36.5 ±0.11	36.3 ±0.15	36.4 ±0.19	36.6 ±0.18	36.5 ±0.09	36.5 ±0.08	36.5 ±0.09
$\dot{V}_{O_2}$ (ml/min)	221 ±29	79* ±7.2	74* ±3.9	65* ±5.4	101	85 ±8.8	80
$P_{a_{CO_2}}$ (mm Hg)	34 ±1.3	38 ±1	37 ±0.95	38 ±0.96	38 ±1.5	37 ±0.96	37 ±1.6
Base excess (mEq/l)	−1.5 ±0.73	−3.2** ±0.9	−3.5** ±0.79	−4.4** ∞0.74	−2.7 ±0.57	−3 ±0.66	−2.8 ±0.76
Hct (per cent)	42.1 ±0.95		44.4 ±0.99		43.6 ±0.84		

† The upper figure in each row is the mean value; the lower is the standard error. Cardiac output ($\dot{Q}$), heart rate (HR), stroke volume (SV), mean arterial pressure ($\overline{AP}$), total peripheral resistance (TPR), muscle flow, forearm vascular resistance (FVR), forearm venous compliance (FVC), and oxygen consumption ($\dot{V}_{O_2}$) during anesthesia are expressed as percentages of the awake values. MRAP is mean right atrial pressure.

*P <0.05 compared with the awake value.

** P <0.005 compared with the awake value.

cant increases in total peripheral resistance, mean arterial pressure, and forearm vascular resistance, and a decrease in forearm venous compliance (fig. 3). Cutaneous blood flow increased 560 per cent, and skin temperature rose 3 C (fig. 4). Oxygen consumption was reduced by anesthesia.

The differences between cardiovascular function at the three different alveolar concentrations of cyclopropane were small. At 35–40 per cent cyclopropane, cardiac output was 85 per cent of the awake value, a small but significant difference ($P < 0.05$). Total peripheral resistance, forearm vascular resistance, and mean right atrial pressure increased, and forearm venous compliance decreased, while heart rate and blood pressure remained constant as anesthesia deepened.

Prolongation of anesthesia had little effect on cardiovascular function (table 2). Although cardiac output during 35–40 per cent cyclopropane was significantly higher after five hours than after one hour of anesthesia, the mean difference was only 15 per cent ($P < 0.005$) (fig. 5). The peripheral circulation showed less vasoconstriction as time progressed, since muscle blood flow increased and forearm vascular resistance decreased. Forearm venous compliance did not change significantly. Mean cutaneous blood flow was higher after five hours than after one hour at all three levels of anesthesia, but the differences were not significant.

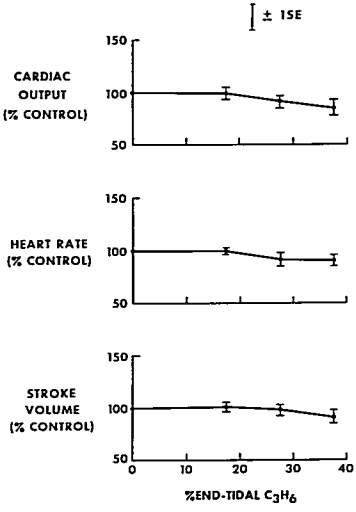

FIG. 1. Effects of cyclopropane on cardiac output, heart rate, and stroke volume.

An acute reduction in cyclopropane concentration produced immediate increases in car-

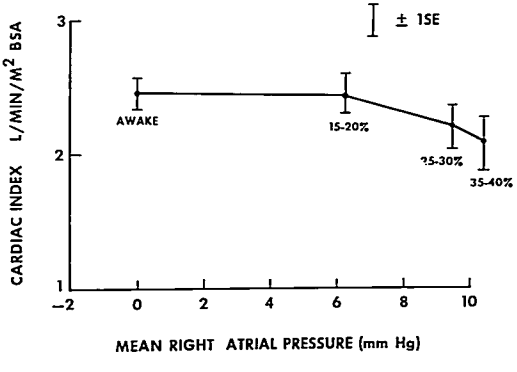

FIG. 2. Effects of cyclopropane on MRAP and Q. Note profound increase in MRAP with small change in Q as cyclopropane concentration is elevated.

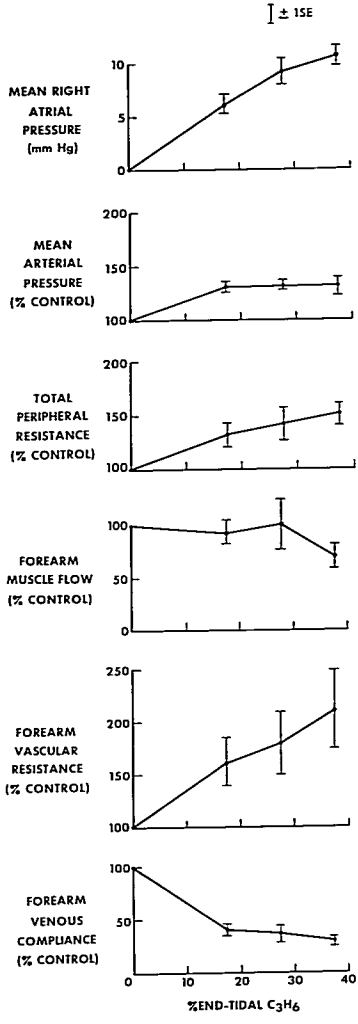

FIG. 3. Effects of cyclopropane on the arterial and venous circulation.

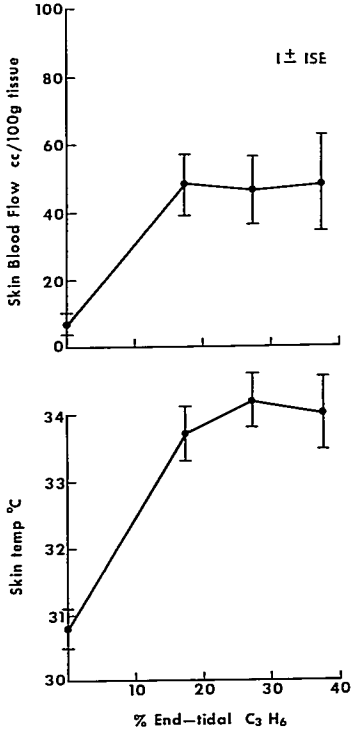

FIG. 4. Effects of cyclopropane on cutaneous blood flow and skin temperature.

diac output, stroke volume and mean right atrial pressure (fig. 6) (table 3). Two minutes after cyclopropane was reduced from 35–40 per cent to 15–20 per cent, cardiac output and stroke volume were higher, while mean right atrial pressure was 3 mm. Hg lower. After eight additional minutes at 15–20 per cent cyclopropane, cardiac output returned to normal, but at an even lower mean right atrial pressure.

Arrhythmias occurred during deep cyclopropane anesthesia while Pa_{CO_2} was normal.

These ranged from a wandering pacemaker and nodal rhythm to multifocal premature ventricular contractions and ventricular tachycardia. Immediate reduction of cyclopropane restored cardiac rhythm to normal. Experimental conditions remained constant, as demonstrated by normal Pa_{CO_2} values and body temperatures (table 2). A minimal metabolic acidosis following induction did not progress during the experiment.

Discussion

The awake measurements which served as control values for this study were obtained in unstimulated unexcited subjects during controlled positive-pressure ventilation. In addition to their outward calm appearance, the subjects' low-normal cardiac indexes, low heart rates, normal stroke volumes, normal mean arterial pressures, and normal forearm blood flows confirmed our evaluation of their basal condition. The variations in finger blood flow were the only measurements which suggested that our clinical observations of the subjects' emotional state might be in error. Therefore, we measured cutaneous blood flow and skin temperature in ten anesthesiologists, including the authors (table 4). The same degree of variability was observed, and mean finger blood flow measurements were not significantly different from those obtained in the subjects. However, our skin temperatures were 2 C higher than those of the volunteers ($P < 0.001$). This was the one and only indication that the data were not truly baseline.

All anesthetics except ether elevate resting Pa_{CO_2} as anesthetic depth increases.[4] In view of the well-known cardiovascular effects of hypercarbia,[5] it was essential to maintain normal Pa_{CO_2} during this experiment, hence the need for controlled positive-pressure ventilation. This introduced a new variable, increased mean intrathoracic pressure. By obtaining our awake control data during controlled ventilation, we eliminated this potential source of error, while allowing deep cyclopropane anesthesia at normal Pa_{CO_2}. Our results, obtained in a rigidly controlled experiment, confirm those of previous studies during light cyclopropane anesthesia in man.[6, 7, 8] By avoiding

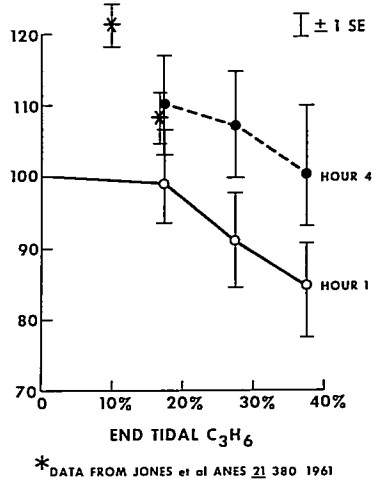

FIG. 5. The effect of duration of cyclopropane anesthesia on Q. The asterisk denotes data recalculated from those of Jones *et al.*[10] The point at 10 per cent cyclopropane refers to non-intubated subjects whose mean end-tidal P_{CO_2} was 40 mm Hg. The point at 17 per cent cyclopropane refers to intubated subjects. There is no significant difference between his results in spontaneously-breathing subjects (Pa_{CO_2} 38 mm Hg) and our results during controlled ventilation (Pa_{CO_2} 38 mm Hg) at either one or four hours.

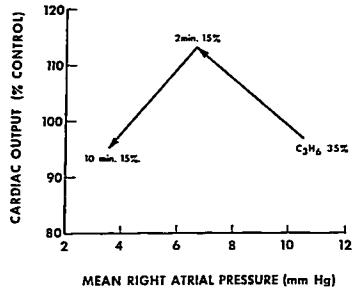

FIG. 6. The overshoot produced by an acute reduction in cyclopropane concentration.

hypoxia and hypercarbia, we were able to observe that deep cyclopropane anesthesia intensified the potent vasoconstriction noted at light anesthetic levels.

Cardiac output was well maintained during cyclopropane anesthesia in man, a finding which agrees with that of Jones.[6] Recalculation of his results and their expression as percentages of the awake control values (fig. 5) result in a mean cardiac output that is 108 per cent of the mean control value in his intubated subjects at 17 per cent cyclopropane, breathing spontaneously ($P_{A_{CO_2}}$ −38). This was not significantly different from mean cardiac output in our subjects at either one hour (99 per cent of control) or five hours (111 per cent of control).

The elevation of mean right atrial pressure probably reflected an increase in venous return owing to peripheral venoconstriction, an increase in ventricular end-diastolic pressure from a less compliant ventricle,[9] or a combination of both. Maintenance of stroke volume, hence cardiac output, in the presence of higher combinations of cyclopropane is due at least in part to increased filling pressure (fig. 2). This implies a shift in the position of the ventricular function curve to the right, although we cannot define the shape or slope of that curve. One can speculate that if filling pressure had not been elevated 6–10 mm Hg, stroke volume would have decreased as cyclopropane concentration was raised.

Heart rate was unaltered by changes in cyclopropane concentration or duration of anesthesia. This may have been the result of balancing opposing stimuli. In man, cyclopropane stimulates norepinephrine release by increased sympathetic activity.[10] Tachycardia might result unless the associated hypertension stimulated reflex bradycardia. In addition, the data of Jones *et al.*[11] suggest parasympathetic stimulation by cyclopropane, since heart rate increased markedly following administration of atropine (0.4 mg iv) during cyclopropane anesthesia.

The peripheral circulation is important in maintaining cardiac output during cyclopropane anesthesia. Resistance vessels constrict to maintain arterial pressure, while capacitance vessels constrict to raise the filling pressure of the heart. The finding of profound forearm arterial and venous constriction agrees with the observations of others. In unmedicated patients, Caffrey[7] found decreased forearm blood volume, decreased venous compliance and increased venous pressure, results similar to those of infusion of norepinephrine. The strong sympathetic stimulation observed by Price *et al.*[12] and Ngai *et al.*[13] caused periph-

TABLE 3. Cardiovascular Effects of Acute Reduction in Cyclopropane Concentration

	35 Per Cent End-tidal C_3H_6	2 Min after Reduction to 15 Per Cent, End-tidal C_3H_6	10 Min after Reduction to 15 Per Cent, End-tidal C_3H_6
Cardiac output, per cent of control	97	113*	98*
MRAP (mm Hg)	10.6	6.7*	3.7**
$\overline{AP}$ per cent of control	137	146	123**
Heart rate, per cent of control	102	93	92
Stroke volume, per cent of control	93	115*	105*
Total peripheral resistance, per cent of control	139	129	120

* $P < 0.05$ compared with the previous value.
** $P < 0.01$ compared with the previous value.

eral constriction and elevation of plasma catecholamines. The synergism of cyclopropane with norepinephrine[14, 15] adds to the effective vasoconstrictor action.

The findings of increases in cutaneous blood flow and skin temperature confirm Thomson's results[8] with cyclopropane, halothane, and thiopental. He noted an immediate increase in cutaneous blood flow following induction of anesthesia, or prior to induction if the subject merely fell asleep. He suggested that the mechanism responsible was the central inhibition of vasoconstrictor tone. It is surprising that cyclopropane did not attenuate the increase in cutaneous blood flow, because cutaneous vessels have only vasoconstrictor sympathetic innervation,[16] and cyclopropane is a potent sympathetic stimulant.

The 5.6-fold increase in cutaneous blood flow may have clinical significance in the redistribution of cardiac output during anesthesia. Assuming that skin is 1.2 mm thick[17] with a surface area of 1.8 m^2, the estimated volume of skin is 2.04 l. Our control cutaneous blood flow was 7.3 ml/100 ml tissue/min. Total cutaneous flow is calculated at 146 ml/min, or 3.1 per cent of the control cardiac output. The increase in cutaneous blood flow after induction of anesthesia represents 16 per cent of the cardiac output. Inherent in this calculation is the assumption that all cutaneous blood vessels react like those in digital skin, an assumption which has not yet been proven.

The immediate increases in cardiac output and blood pressure which occurred as cyclopropane concentration was reduced probably reflected improved ventricular function occurring before mean right atrial pressure had fallen. When ten minutes had elapsed, cardiac output decreased to its previous value, while mean right atrial pressure had fallen further. The removal of cyclopropane from the blood in the heart is more rapid than removal from the peripheral venous bed because blood flow to heart muscle is far greater. Hence, depression of the heart is reversed more rapidly than constriction of the peripheral bed. Alternatively, Price *et al.*[18] recently have shown in the cat that sympathetic discharge continues for several minutes after cyclopropane is discontinued, possibly maintaining peripheral vasomotor tone. A high peripheral venous tone due to this prolonged sympathetic effect could maintain the filling pressure of a more active myocardium (since elimination of cyclopropane has commenced). By ten minutes, sympathetic tone returns to a lower level, allowing peripheral venous tone to fall; the filling pressure falls further, and cardiac output returns to normal.

TABLE 4. Finger (Skin) Blood Flow and Temperature of Naive Subjects and of Anesthesiologists (±1 SE)

	Subjects (n = 7)	Anesthesiologists (n = 10)
Cutaneous blood Flow, ml/100 ml tissue/min	7.3 ± 3	11.4 ± 3.5, NS
Skin temperature (C)	30.8 ± 0.32	32.2 ± 0.36, $P < 0.001$

The minor recovery of cardiovascular function with time during cyclopropane anesthesia contrasts with the recovery seen during halothane anesthesia by McGregor *et al.*,[19] Deutsch *et al.*,[20] and Eger *et al.*[21] In the last-mentioned study, marked recovery of cardiovascular depression occurred within five hours. The minimal recovery of cardiac output and oxygen consumption we observed was due to an increase in heart rate and a slight increase in stroke volume. Slight decreases in mean right atrial pressure and total peripheral resistance also occurred.

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Kidney

DRUG NEPHROPATHY Salicylate and phenacetin were administered to 19 hydropenic dogs and the renal accumulation and distribution of the major metabolic products, salicylate and N-acetyl-p-aminophenol (APAP) were studied. During peak blood levels of salicylate and/or APAP, the kidneys were rapidly removed, frozen, sliced from the cortex to the papillary tip, and analyzed for water, urea, APAP and salicylate. No renal medullary gradient for salicylate was found during either dry or hydrated states. In contrast, both free and conjugated APAP concentrations increased sharply in the inner medulla during hydropenia, reaching at the papillary tip a maximal value exceeding ten times the cortical concentration, a distribution similar to that of urea. Salicylate had no effect on the APAP gradient, but hydration markedly reduced both the APAP and urea gradients in the medulla. The data indicate that APAP probably shares the same renal mechanisms of transport and accumulation as acetamide and urea, and that papillary necrosis from excessive phenacetin may be related to high papillary concentration of APAP. (*Bluemle, L. W., Jr., and Goldberg, M.: Renal Accumulation of Salicylate and Phenacetin: Possible Mechanisms in the Nephropathy of Analgesic Abuse, J. Clin. Invest. 47: 2507 (Nov.) 1968.*)