

# Pulmonary Vasomotor Tone during General Anesthesia and Deliberate Hypotension in Man

Nabil R. Fahmy, M.D., F.F.A.R.C.S.,\* Adrian S. Selwyn, M.D., F.F.A.R.C.S.,†  
Dinesh Patel, M.D.,‡ Demetrios G. Lappas, M.D.\*

Pulmonary and systemic hemodynamic responses to administration of pentolinium (0.3 mg/kg) were studied in eight patients undergoing total hip replacement during N<sub>2</sub>O-halothane anesthesia with PaO<sub>2</sub> maintained at 35–40 mm Hg. Measurements were made prior to induction of anesthesia; 20 minutes after induction; 45 minutes after induction but prior to pentolinium administration; 10, 20, and 60 minutes after administration of pentolinium; 15 minutes after  $\bar{A}P$  recovered to within 10 per cent of baseline values. The reduction in  $\bar{A}P$  produced by pentolinium was associated with significant decreases in both SVR and LVFP (estimated by measuring  $\bar{P}A_u$  via a Swan-Ganz catheter). The profound and significant reductions in calculated PVR were more pronounced than those in SVR. Since PVR decreased in the face of reductions in both pulmonary arterial and left atrial pressures despite a significant increase (at 10 minutes) or no change (at 20 and 60 minutes) in pulmonary blood flow, the results suggest an active decrease in pulmonary vascular tone, presumably due to autonomic inhibition by pentolinium. Both LVSWI and RVSWI decreased significantly following injection of pentolinium. HR  $\times$  SAP, an indirect index of  $\dot{M}V_{O_2}$ , decreased

significantly following an initial increase at 10 minutes. Presumably these effects of pentolinium were conspicuous because N<sub>2</sub>O-halothane anesthesia altered the baseline of pulmonary vascular tone. (Key words: Anesthetic techniques, hypotension, induced; Lung, vasomotor tone; Sympathetic nervous system, pentolinium.)

THE NORMAL pulmonary vasculature is believed to be under little, if any, autonomic control and, therefore, not susceptible to pharmacologic manipulation. Routine monitoring of pulmonary arterial pressures during general anesthesia in patients with and without pulmonary vascular disease has suggested that this attitude requires modification. We present data to show that commonly used anesthetic drugs, nitrous oxide and

## ABBREVIATIONS

$\bar{A}P$	= mean arterial blood pressure
CO	= cardiac output
HR	= heart rate
HR $\times$ SAP	= heart rate $\times$ systolic arterial pressure product
$\bar{L}AP$	= mean left atrial pressure
LVFP	= left ventricular filling pressure
LVSWI	= left ventricular stroke work index
$\dot{M}V_{O_2}$	= myocardial oxygen consumption
$\bar{P}A_u$	= mean balloon-occluded pulmonary arterial pressure
PADP	= pulmonary arterial diastolic pressure
$\bar{P}AP$	= mean pulmonary arterial pressure
PASP	= pulmonary arterial systolic pressure
PVR	= pulmonary vascular resistance
$\bar{R}AP$	= mean right atrial pressure
RVSWI	= right ventricular stroke work index
SI	= stroke index
SV	= stroke volume
SVR	= systemic vascular resistance
$\dot{V}_{O_2}$	= whole-body oxygen consumption

\* Assistant Professor of Anaesthesia, Harvard Medical School; Assistant Anesthetist, Massachusetts General Hospital.

† Instructor in Anaesthesia, Harvard Medical School; Assistant Anesthetist, Massachusetts General Hospital. Present address: University of Massachusetts, Worcester, Massachusetts.

‡ Instructor in Orthopaedic Surgery, Harvard Medical School; Assistant Orthopaedic Surgeon, Massachusetts General Hospital.

Received from the Anaesthesia Laboratories of the Harvard Medical School at Massachusetts General Hospital, Boston, Massachusetts 02114. Accepted for publication January 29, 1976. Supported in part by Grant GM15904-07 from the National Institute of General Medical Sciences. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, Chicago, Illinois, October 11–15, 1975.

Address reprint requests to: Nabil R. Fahmy, M.D., Department of Anesthesia, Massachusetts General Hospital, Boston, Massachusetts 02114.

halothane, do alter tone of pulmonary vessels, which changes can be reversed by ganglion-blocking drugs such as pentolinium tartrate (Ansolsen).

Deliberate hypotension has been employed for more than a quarter-century to provide a relatively bloodless operative field. Although the systemic hemodynamic responses to a deliberate lowering of arterial blood pressure have been adequately delineated,<sup>1-3</sup> changes in pulmonary hemodynamics have not been similarly defined.

### Patients and Methods

Six male and two female patients,§ scheduled for total hip replacement under general anesthesia with induced arterial hypotension, were studied. Their ages ranged from 18 to 48 years (average 38.6 years). All were ASA physical status I or II. None had a history or clinical evidence of cardiovascular, pulmonary or metabolic disease.

All patients were premedicated with morphine sulfate (0.1 mg/kg) and scopolamine hydrobromide (5 µg/kg) intramuscularly, 60 minutes before the anticipated induction of anesthesia. Diazepam (5-10 mg) was administered intravenously in 2.5-mg increments if the patient appeared apprehensive during insertion of intravascular cannulas and preparation for anesthesia.

A 14-gauge polyethylene cannula was inserted into a dorsal hand vein for fluid and drug administration; an 18-gauge cannula was placed in a radial artery for measurement of systemic arterial blood pressure and for blood sampling. Under continuous electrocardiographic and intravascular pressure monitoring, a No. 7 Fr triple-lumen, flow-directed thermodilution catheter\* was advanced through an internal jugular vein into a pulmonary artery for recording of pressures in the pulmonary artery, balloon-occluded pulmonary artery, and right atrium, and for the withdrawal of blood samples. The position of the catheter was confirmed by chest x-ray.

§ This investigation was approved by the Human Studies Committee at the Massachusetts General Hospital, and informed consent for the study was obtained from each patient.

\* Edwards Laboratory, Santa Ana, California.

Peripheral arterial, right atrial, and pulmonary arterial pressures were measured by transducers (Hewlett-Packard type 267 BC) and recorded continuously, together with lead II of the ECG, on a Sanborn multichannel recorder and display oscilloscope. Mean pressures were obtained by electronic integration. The baseline for the transducers was taken as the level of the right atrium.

Induction of anesthesia was achieved with sodium thiopental (3-5 mg/kg), followed by succinylcholine chloride (1 mg/kg) for endotracheal intubation. Anesthesia was maintained with halothane (0.5-1 per cent, inspired concentration) in nitrous oxide and oxygen (3:2 l/min) using a semiclosed system with a CO<sub>2</sub> absorber. The halothane vaporizer (Fluotec Mark II) was placed outside the circle. Ventilation was controlled throughout the investigation to maintain Pa<sub>CO<sub>2</sub></sub> within the range 35-40 mm Hg, as determined by repeated measurements. Pentolinium tartrate (0.3 mg/kg) was administered intravenously over a period of 5 minutes after a steady state was established (45 minutes after induction of anesthesia) as judged by constant heart rate and arterial blood pressure. Lactated Ringer's solution was infused at a rate of 5 ml/kg/hr. Blood loss was estimated by weighing of sponges and measurement of suction loss. Blood loss did not exceed 750 ml and was replaced by both albumin (5 per cent in saline solution) and packed erythrocytes.

Seven sets of measurements were made: before induction of anesthesia; 20 minutes after induction of anesthesia; 45 minutes after induction of anesthesia but prior to administration of pentolinium; 10, 20, and 60 minutes after intravenous injection of pentolinium; 15 minutes after AP had returned to within 10 per cent of pre-pentolinium values. The latter occurred 95 to 135 minutes (average: 110 minutes) following administration of pentolinium. Each set of observations included measurement of CO, HR, and pressures in the pulmonary artery, occluded pulmonary artery, radial artery, and right atrium. For each observation, blood samples were withdrawn for measurement of arterial and mixed venous blood pH, P<sub>O<sub>2</sub></sub>, P<sub>CO<sub>2</sub></sub>, and O<sub>2</sub> content. Hematocrit, plasma proteins and hemoglobin concentration of arterial

blood were also measured. All measurements were recorded at end-expiration with zero end-expiratory pressure. Recordings were taken with the patients in the lateral decubitus position, except before and 20 minutes after induction of anesthesia, at which times the subjects were supine.

CO was determined by the thermodilution technique,<sup>8</sup> wherein a bolus of cold liquid (10 ml of 5 per cent dextrose at 2–5 C) is injected rapidly into the right atrium and the resultant change in temperature detected by a thermistor embedded in the catheter wall located in the pulmonary artery. A temperature–time curve similar in configuration to a dye-dilution curve except for the absence of recirculation peaks and a more protracted downslope is recorded. The area under the resulting temperature–time curve is determined by planimetry, and cardiac output is calculated by the Stewart-Hamilton indicator dilution equation. All measurements were performed in duplicate in less than a minute; the average value of each pair of measurements is presented. HR was calculated from the ECG tracing.

Derived variables were obtained as follows: pulmonary (PVR) and systemic vascular resistance (SVR) in dynes. sec. cm<sup>-5</sup>:

$$PVR = \frac{\overline{PAP} - \overline{PA}_0}{CO} \times 80$$

$$SVR = \frac{\overline{AP} - \overline{RAP}}{CO} \times 80$$

where

$\overline{PAP}$  = mean pulmonary arterial pressure;

$\overline{PA}_0$  = mean balloon-occluded pulmonary arterial pressure;

$\overline{RAP}$  = mean right atrial pressure;

and

CO = cardiac output.

Cardiac index (CI) was calculated by dividing CO by the estimated body surface area, and SI by dividing CI by HR. Because of the absence of pulmonary vascular or cardiac valvular disease,  $\overline{PA}_0$  was utilized to estimate left ventricular filling pressure<sup>7,8</sup> and  $\overline{RAP}$  as indicative of right ventricular filling pressure. Right (RVSWI) and left ventricular stroke work

indices (LVSWI) in gram-meters/m<sup>2</sup> were calculated using the formulas:

$$RVSWI = \frac{1.36(\overline{PAP} - \overline{RAP})}{100} \times SI$$

$$LVSWI = \frac{1.36(\overline{AP} - \overline{PA}_0)}{100} \times SI$$

The heart rate–systolic pressure product (HR × SAP) was employed to evaluate relative changes in myocardial oxygen consumption (MV<sub>o2</sub>). This product has been shown to provide a satisfactory predictor of MV<sub>o2</sub> in subjects with<sup>9</sup> and without<sup>10</sup> coronary-artery disease.

Blood gases and pH were analyzed with standard electrodes at 37 C, and values were corrected to measured body temperature.<sup>11</sup> The O<sub>2</sub> content of whole blood was determined by the manometric method of Van Slyke and Neill.<sup>12</sup> Whole-body oxygen consumption ( $\dot{V}_{O_2}$ ) was derived from the product of the cardiac output and arteriovenous O<sub>2</sub> content difference ( $\overline{Ca}_{O_2} - \overline{Cv}_{O_2}$ ). Hematocrit and hemoglobin concentration were measured using the Coulter Counter Model S; plasma proteins concentration was measured by refractometry.

Esophageal temperature was measured with a thermistor probe; body temperature was maintained constant by adjusting ambient temperature.

Operation began after the 20-minute post-pentolinium measurements were made; manipulations were interrupted 3 minutes before each set of observations subsequently obtained.

A two-way analysis of variance using patients by time was employed to test whether the variables, measured and derived, changed over time. Comparisons were computed by Student's *t* test for paired data; *P* < 0.05 was considered significant.

## Results

### EFFECT OF ANESTHESIA

Prior to pentolinium administration, anesthesia with N<sub>2</sub>O–O<sub>2</sub>–halothane for 45 minutes (table 1) produced significant decreases in  $\overline{AP}$  (*P* < 0.01), CO (*P* < 0.01), SI (*P* < 0.01) LVSWI (*P* < 0.01), HR × SAP (*P*

< 0.005) and  $\bar{V}_{O_2}$  ( $P < 0.001$ ), and significant increases in  $\bar{PAP}$  ( $P < 0.05$ ),  $\bar{P\bar{A}_a}$  ( $P < 0.05$ ),  $PVR$  ( $P < 0.01$ ),  $\bar{RAP}$  ( $P < 0.005$ ) and  $P_{a_{O_2}}$  ( $P < 0.01$ ). HR, RVS<sub>WI</sub>, SVR, and other blood-gas variables were not significantly altered by anesthesia. The changes observed following induction of anesthesia were not related to change in position because the values obtained 45 minutes after induction of anesthesia, with the patients in the lateral decubitus position, were not significantly different from those recorded 20 minutes after induction, with the patients supine (data not shown in table 1).

#### MEAN ARTERIAL BLOOD PRESSURE ( $\bar{AP}$ )

$\bar{AP}$ 's ranged from 55 to 93 mm Hg ( $72.2 \pm 4.6$ , mean  $\pm$  SE) during the control period. Following pentolinium administration, the average decreases from control values were 20.2, 21.5, and 21.9 per cent at 10, 20, and 60 minutes, respectively; all changes were

significant (table 1). The decrease in mean arterial pressure was associated with significant reductions in SVR and LVFP.

#### CARDIAC OUTPUT (CO), HEART RATE (HR) AND STROKE VOLUME (SV)

CO increased significantly ( $P < 0.05$ ) 10 minutes after injection of pentolinium; subsequent changes were not significant. As SV was not significantly reduced from baseline, the changes in CO were related to increases in HR, which were 28.5, 23.1, and 18.5 per cent above control values at 10, 20, and 60 minutes, respectively. CO was significantly increased ( $P < 0.02$ ) when  $\bar{AP}$  returned to pre-pentolinium values.

#### PULMONARY ARTERIAL SYSTOLIC (PASP), DIASTOLIC (PADP), MEAN ( $\bar{PAP}$ ) AND OCCLUDED ( $\bar{P\bar{A}_a}$ ) PRESSURES

A significant reduction in  $\bar{PAP}$  occurred in every patient within 10 minutes of pento-

TABLE 1. Measured Hemodynamic Values (Means  $\pm$  SEM) before and after Pentolinium (0.3 mg/kg) in Eight Patients Anesthetized with Nitrous Oxide-Halothane

	Pre-induction	Pre-pentolinium (Control)	Minutes after Pentolinium			15 Minutes after Arterial Pressure Returned to Control
			10	20	60	
Cardiac output (l/min)	5.48 $\pm$ 0.33	3.39 $\pm$ 0.20	3.88* $\pm$ 0.28	3.43 $\pm$ 0.24	3.45 $\pm$ 0.19	4.16† $\pm$ 0.40
Heart rate (beats/min)	68.6 $\pm$ 4.6	60.7 $\pm$ 3.3	77.6* $\pm$ 3.9	74.3 $\pm$ 3.8	71.6 $\pm$ 3.5	70.3 $\pm$ 3.4
Mean arterial blood pressure (mm Hg)	98.1 $\pm$ 6.8	72.2 $\pm$ 4.6	59.1‡ $\pm$ 2.6	55.1§ $\pm$ 2.1	56.0§ $\pm$ 3.5	76.1 $\pm$ 3.9
Pulmonary arterial pressures (mm Hg)						
Systolic	20.3 $\pm$ 2.3	24.3 $\pm$ 2.6	17.8‡ $\pm$ 2.1	15.7§ $\pm$ 2.2	16.4§ $\pm$ 2.3	21.7* $\pm$ 1.6
Diastolic	9.6 $\pm$ 0.9	13.5 $\pm$ 1.8	9.3‡ $\pm$ 1.2	8.0‡ $\pm$ 1.5	8.6‡ $\pm$ 1.4	10.3* $\pm$ 0.9
Mean	12.9 $\pm$ 1.0	18.6 $\pm$ 2.3	12.4‡ $\pm$ 1.3	11.0‡ $\pm$ 1.6	12.1‡ $\pm$ 1.8	15.5 $\pm$ 1.3
Occluded	7.8 $\pm$ 1.0	13.1 $\pm$ 1.9	9.0‡ $\pm$ 1.2	7.8‡ $\pm$ 1.5	8.8‡ $\pm$ 1.5	10.0* $\pm$ 0.9
Mean right atrial pressure (mm Hg)	4.6 $\pm$ 0.9	8.2 $\pm$ 1.7	5.5 $\pm$ 1.3	6.3 $\pm$ 1.0	7.1 $\pm$ 1.3	6.7 $\pm$ 1.0

\*  $P < 0.05$ ; †  $P < 0.02$ ; ‡  $P < 0.01$ ; §  $P < 0.005$ .

Significance was determined by comparison of values obtained before with those after pentolinium using Student's *t* test for paired data. Comparisons were made only for values that showed a significant change in a two-way analysis of variance.

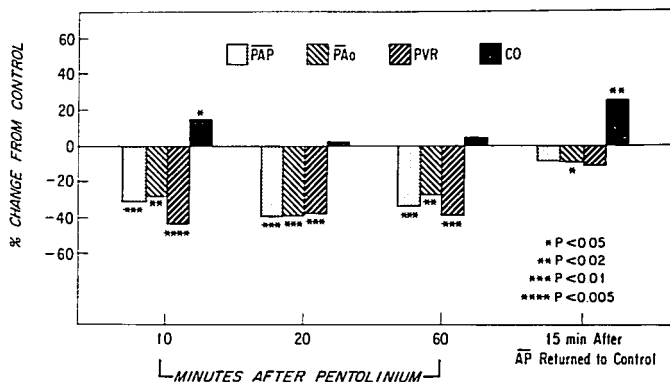


FIG. 1. Average percentile changes of mean pulmonary arterial pressure ( $\bar{PAP}$ ), mean balloon-occluded pulmonary arterial pressure ( $\bar{PA}_o$ ), calculated pulmonary vascular resistance (PVR), and cardiac output (CO) from control values 10, 20, and 60 minutes after administration of pentolinium (0.3 mg/kg) and 15 minutes after mean arterial pressure ( $\bar{AP}$ ) returned to within 10 per cent of pre-pentolinium levels.

TABLE 2. Derived Hemodynamic Data (Means  $\pm$  SEM) before and after Pentolinium (0.3 mg/kg) in Eight Patients Anesthetized with Nitrous Oxide-Halothane

	Pre-induction	Pre-pentolinium (Control)	Minutes after Pentolinium			15 Minutes after Arterial Pressure Returned to Control
			10	20	60	
Stroke index (ml/beat/m <sup>2</sup> )	49.2 $\pm$ 1.3	35 $\pm$ 3.0	32 $\pm$ 3.0	29 $\pm$ 2.5	30 $\pm$ 1.5	36 $\pm$ 3.0
Systemic vascular resistance (dynes.sec.cm <sup>-2</sup> )	1,373 $\pm$ 79	1,543 $\pm$ 132	1,136† $\pm$ 83.5	1,163† $\pm$ 92	1,130† $\pm$ 78.5	1,428 $\pm$ 166.5
Pulmonary vascular resistance (dynes.sec.cm <sup>-2</sup> )	74 $\pm$ 11	132 $\pm$ 18.1	65‡ $\pm$ 9.7	75† $\pm$ 8.1	79† $\pm$ 11.7	116 $\pm$ 21.2
Left ventricular stroke work index (g-m/beat/m <sup>2</sup> )	60 $\pm$ 3.7	28.1 $\pm$ 2.7	21.7 $\pm$ 2.1	18.8* $\pm$ 1.8	18.6* $\pm$ 1.2	31.9 $\pm$ 1.9
Right ventricular stroke work index (g-m/beat/m <sup>2</sup> )	5.5 $\pm$ 0.3	5.0 $\pm$ 1.3	2.8† $\pm$ 0.5	1.9‡ $\pm$ 0.3	2.2† $\pm$ 0.3	4.3 $\pm$ 0.6
Heart rate-pressure product	10,794 $\pm$ 1,608	5,782 $\pm$ 509	5,834 $\pm$ 448	4,529† $\pm$ 763	5,094* $\pm$ 517	7,097* $\pm$ 666
Oxygen consumption (derived) (ml/min STPD)	219 $\pm$ 23	127 $\pm$ 9.3	136 $\pm$ 13.7	132.5 $\pm$ 9.5	134.5 $\pm$ 7.6	155* $\pm$ 10.2

\*  $P < 0.05$ ; †  $P < 0.02$ ; ‡  $P < 0.01$ ; §  $P < 0.005$ .

Significance was computed by comparison of data obtained before with those after pentolinium using Student's *t* test for paired data. Specific comparisons were made only for variables that showed a significant change in a two-way analysis of variance.

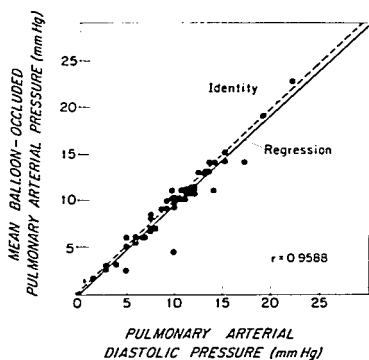


FIG. 2. Scattergram of the relationship of pulmonary arterial diastolic and mean balloon-occluded pulmonary arterial pressures. Each dot represents one measurement.

linium administration, concomitant with the decrease in  $\overline{AP}$ .  $\overline{PAP}$  continued to decrease thereafter (table 1, fig. 1);  $\overline{PASP}$  was more affected than  $\overline{PADP}$ . With pentolinium, the

average decrease in  $\overline{PAP}$  (30.6, 38.4, and 33 per cent at 10, 20, and 60 minutes, respectively) was greater than that in  $\overline{AP}$  (20.2, 21.5, and 21.9 per cent, respectively).

The pressure gradient across the pulmonary vascular bed ( $\overline{PAP} - \overline{PA}_o$ ) narrowed because  $\overline{PAP}$  decreased more than  $\overline{PA}_o$  (table 1): it was 5.5 mm Hg before pentolinium, compared with 3.4, 3.2, and 3.3 mm Hg 10, 20, and 60 minutes, respectively, after pentolinium.

A significant ( $P < 0.01$ ) positive correlation between pulmonary arterial diastolic and occluded pressures,  $r = 0.9588$ , was observed (fig. 2), corroborating the findings of other investigators.<sup>7,8</sup>

#### PULMONARY VASCULAR RESISTANCE (PVR)

Calculated PVR's were reduced consistently in all patients following pentolinium administration (table 2, fig. 1). The average decreases from control were 50, 37, and 37 per cent at 10, 20, and 60 minutes, respectively. All changes were significant. Although the reduction in SVR was significant (24, 22, and 24 per cent at 10, 20, and 60 minutes,

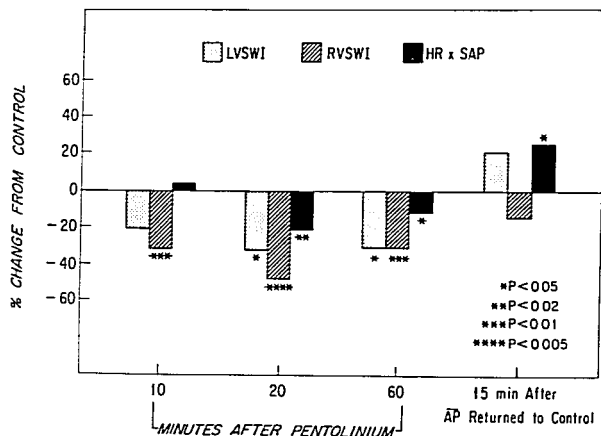


FIG. 3. Average percentile changes of left (LVS WI) and right (RVS WI) ventricular stroke work indices, and heart rate-systolic pressure product (HR  $\times$  SAP) from control values 10, 20, and 60 minutes after administration of pentolinium (0.3 mg/kg) and 15 minutes after mean arterial pressure ( $\overline{AP}$ ) returned to within 10 per cent of pre-pentolinium levels.

respectively), it was less pronounced than that of PVR. On return of  $\bar{A}P$  to pre-pentolinium values, PVR was 12 per cent and SVR was 7 per cent lower than control levels (not significant).

LEFT AND RIGHT VENTRICULAR STROKE  
 WORK INDICES (LVS<sub>W</sub>, RVS<sub>W</sub>) AND  
 HEART RATE-SYSTOLIC PRESSURE  
 PRODUCT (HR × SAP)

Both LVS<sub>W</sub> and RVS<sub>W</sub> decreased significantly following injection of pentolinium; however, the reduction in RVS<sub>W</sub> was more pronounced (table 2, fig. 3). HR × SAP

decreased significantly following an initial increase at 10 minutes.

MEAN RIGHT ATRIAL PRESSURE ( $\bar{R}A\bar{P}$ )

Although  $\bar{R}A\bar{P}$  decreased to below control values, the changes were small and not significant.

OXYGEN CONSUMPTION ( $\dot{V}O_2$ ) AND  
 BLOOD-GAS STUDIES

The small increases in  $\dot{V}O_2$  observed after administration of pentolinium were not significant. These changes were associated with

TABLE 3. Blood-Gas Data (Means  $\pm$  SEM) before and after Pentolinium (0.3 mg/kg) in Eight Patients Anesthetized with Nitrous Oxide-Halothane

	Pre- induction	Pre- pentolinium (Control)	Minutes after Pentolinium			15 Minutes after Arterial Pressure Re- turned to Control
			10	20	60	
Arterial blood						
P <sub>a</sub> O <sub>2</sub> (mm Hg)	90.6 $\pm$ 2.3	183 $\pm$ 8.6	178 $\pm$ 16.2	167 $\pm$ 10.1	159* $\pm$ 11.3	176 $\pm$ 1.3
P <sub>a</sub> CO <sub>2</sub> (mm Hg)	41 $\pm$ 0.7	37.5 $\pm$ 1.4	37.6 $\pm$ 0.4	37.7 $\pm$ 0.8	38.1 $\pm$ 0.5	39.8 $\pm$ 1.3
pH	7.4 $\pm$ 0.0	7.4 $\pm$ 0.01	7.42 $\pm$ 0.01	7.41 $\pm$ 0.01	7.4 $\pm$ 0.01	7.4 $\pm$ 0.0
O <sub>2</sub> content (ml/100 ml) STPD	17.4 $\pm$ 0.4	17.4 $\pm$ 0.4	16.2 $\pm$ 0.6	15.6 $\pm$ 0.5	15.3 $\pm$ 0.3	16.4 $\pm$ 0.4
Hematocrit (per cent)	41.4 $\pm$ 0.8	41.1 $\pm$ 0.9	39.6 $\pm$ 0.9	40 $\pm$ 0.9	39.1 $\pm$ 0.6	38.7 $\pm$ 0.5
Hemoglobin (g/100 ml)	12.8 $\pm$ 0.5	12.7 $\pm$ 0.5	11.9 $\pm$ 0.5	11.8 $\pm$ 0.5	11.8 $\pm$ 0.5	11.9 $\pm$ 0.5
Plasma proteins (g/100 ml)	7 $\pm$ 0.2	6.9 $\pm$ 0.2	6.8 $\pm$ 0.2	6.7 $\pm$ 0.2	6.6 $\pm$ 0.2	6.6 $\pm$ 0.2
Mixed venous blood						
P <sub>v</sub> O <sub>2</sub> (mm Hg)	41.2 $\pm$ 0.2	47.6 $\pm$ 2.7	44.7 $\pm$ 1.8	41.7 $\pm$ 1.9	42.1 $\pm$ 1.7	43.5 $\pm$ 1.7
P <sub>v</sub> CO <sub>2</sub> (mm Hg)	45.5 $\pm$ 0.7	43 $\pm$ 1.7	43 $\pm$ 0.4	42 $\pm$ 1	42 $\pm$ 0.8	42.3 $\pm$ 0.8
pH	7.37 $\pm$ 0.01	7.37 $\pm$ 0.01	7.4 $\pm$ 0.01	7.39 $\pm$ 0.01	7.39 $\pm$ 0.01	7.38 $\pm$ 0.01
O <sub>2</sub> content (ml/100 ml) STPD	13.5 $\pm$ 0.5	13.5 $\pm$ 0.6	12.7 $\pm$ 0.6	11.7 $\pm$ 0.6	11.4 $\pm$ 0.4	12.5 $\pm$ 0.4

\*  $P < 0.02$ .

Significance was computed by comparison of values obtained before with those after pentolinium using Student's t test for paired data. Comparisons were made only when a two-way analysis of variance indicated a significant change.

minimal alterations in esophageal temperature.

A significant decrease ( $P < 0.02$ ) in  $\text{Pa}_{\text{O}_2}$  occurred 60 minutes after pentolinium, probably secondary to ventilation-perfusion inequalities; changes at other times were not significant. No notable change in arterial blood  $\text{P}_{\text{CO}_2}$ , pH,  $\text{O}_2$  content, hematocrit, hemoglobin or plasma protein concentration was detected. Likewise, mixed venous blood  $\text{P}_{\text{O}_2}$ ,  $\text{P}_{\text{CO}_2}$ , pH and  $\text{O}_2$  content were not significantly different from control values.

### Discussion

Our study has demonstrated that the intravenous administration of pentolinium during  $\text{N}_2\text{O}-\text{O}_2$ -halothane anesthesia decreased pulmonary vascular autonomic tone as reflected by reductions in  $\overline{\text{PAP}}$ ,  $\overline{\text{P}\bar{\text{A}}_{\text{m}}}$ , the pulmonary artery-left atrial pressure gradient, and calculated PVR. These changes were associated with a significant increase in CO 10 minutes after pentolinium administration, primarily due to an increase in HR.

According to Fritts *et al.*,<sup>15</sup> drug-induced pulmonary vasodilation can be assumed if pulmonary arterial pressure decreases in the face of the following conditions: 1) a constant or increased cardiac output; 2) a constant pressure in the left atrium; 3) an unchanged extravascular pressure within the lungs and thorax; 4) constant heart rate, systemic pressure, and pulmonary blood volume. According to our data,  $\overline{\text{PAP}}$  decreased more (6.2, 7.6, and 6.5 mm Hg at 10, 20, and 60 minutes, respectively) than  $\overline{\text{LAP}}$  (corresponding values 4.1, 5.3, and 4.3 mm Hg, respectively) in the face of an increased or constant CO. Thus, the gradient between mean pulmonary arterial and left atrial pressures was reduced as required by the above criteria. Since there was no change in ventilatory pattern or airway pressure, we may assume that the extravascular pressure within the lungs and thorax remained constant. The magnitude of the demonstrated vasodilation will depend on the redistribution of blood between the systemic and pulmonary vasculatures. Since pentolinium reduced both systemic and pulmonary pressures, we have no data on the capacitance changes in these circuits. Because at the time

of measurements 1) the patients had received little in the way of blood or colloid, 2)  $\overline{\text{RAP}}$  was essentially unchanged, and 3) CO either increased or remained unchanged, we have assumed that redistribution of intravascular volume was minimal and that pentolinium reversed the anesthetic-induced constriction of the pulmonary vasculature.

A decrease in pulmonary arterial pressure may follow one or more of three changes: 1) decrease in cardiac output; 2) reduction in left atrial pressure; 3) decrease in pulmonary vascular tone. The reduction in  $\overline{\text{PAP}}$  recorded after the administration of pentolinium was not associated with a decrease in pulmonary blood flow. In fact, cardiac output either increased or remained essentially unchanged. A significant fraction of the decline of  $\overline{\text{PAP}}$  resulted from a decrease in  $\overline{\text{LAP}}$  (table 1). However, the reduction in  $\overline{\text{LAP}}$  could not account for the entire decrease in  $\overline{\text{PAP}}$ , since the pressure gradient ( $\overline{\text{PAP}} - \overline{\text{P}\bar{\text{A}}_{\text{m}}}$ ) across the pulmonary vasculature had narrowed, suggestive of a change in vasomotor tone. Ten minutes following pentolinium administration, the drop in pressure gradient was associated with a significant elevation of pulmonary blood flow. At 20 and 60 minutes, however, the pressure gradient continued to fall, while pulmonary blood flow remained essentially unchanged from pre-pentolinium levels. As a consequence, calculated PVR decreased. LVFP fell, presumably because of a diminished workload on the left ventricle.

Data from the experimental animal<sup>11-16</sup> suggest that autonomic tone may alter markedly the physical characteristics of the pulmonary vasculature when studied following sympathetic stimulation. General anesthesia and operation are known to be associated with an increase in autonomic discharge. The ultimate pattern, however, is largely dependent upon the anesthetic and adjuvant drugs used. Our results demonstrate that the pulmonary vessels are responsive to drugs used in anesthesia, and do not necessarily respond in a passive manner to changes in blood flow as generally believed.

Difficulties in the interpretation of changes in calculated PVR are well appreciated.<sup>17,18</sup>



The pulmonary vasculature is exquisitely sensitive to changes in transmural pressure. Thus, a decrease in the distending pressure will diminish the cross-sectional area and calculated PVR will increase.<sup>19</sup> Accordingly, the finding that calculated PVR decreased in the face of reductions in both  $\overline{PAP}$  and  $\overline{LAP}$  despite an increase or no change in pulmonary blood flow may be interpreted as indicating that pentolinium resulted in an "active" change in the pressure-volume characteristics of the pulmonary vascular bed.

The effects of pentolinium were conspicuous because  $N_2O$ -halothane anesthesia had altered baseline pulmonary vascular tone. During anesthesia  $\overline{PAP}$ ,  $\overline{PA}$ , and PVR increased significantly from awake values. Price *et al.*<sup>20</sup> have demonstrated that halothane-oxygen anesthesia has no conspicuous effect on these variables. Nitrous oxide, however, was shown by Lappas *et al.*<sup>21</sup> to increase mean pulmonary arterial occluded pressure, left ventricular end-diastolic pressure, and pulmonary vascular resistance in patients with coronary-artery disease during morphine anesthesia. They suggested that these effects of nitrous oxide are mediated by alpha-adrenergic stimulation because administration of phentolamine, an alpha-adrenergic blocker, reversed the changes. By extrapolation we suggest that it was the nitrous oxide, not the halothane, that increased PVR in our patients following induction of anesthesia. Furthermore, we suggest that the observed reduction in calculated PVR without an increase in blood flow resulted from a decrease in autonomic vasoconstrictor tone, secondary to ganglionic blockade by pentolinium, and provides evidence for active vasoconstriction in the normal pulmonary vasculature.

Many studies have been carried out in an effort to establish and delineate a neurogenic control of the pulmonary circulation in man.<sup>22,23</sup> It has been demonstrated that the pulmonary vessels are amply supplied with adrenergic fibers wherever smooth muscle is present; this involves large and small arteries, large arterioles, and the venous compartment.<sup>24</sup> It has proved difficult, however, to demonstrate pulmonary vasocon-

strictor fiber effect in man. Much of the information about man has been obtained from evaluation of the effects of ganglionic-blocking drugs, tetraethylammonium chloride,<sup>25</sup> hexamethonium,<sup>26</sup> and trimethaphan,<sup>27</sup> in patients with pulmonary hypertension secondary to mitral stenosis. In these studies, reductions in both pulmonary arterial pressure and pulmonary vascular resistance were observed. The findings were attributed to a probable "arteriolar dilatation," presumably a consequence of ganglionic blockade. Perfusion experiments of canine lungs show that most ganglioplegic drugs, including pentolinium, do not have a direct dilator action on pulmonary vessels.<sup>28</sup>

Our results are in agreement with several reports that ganglionic blocking drugs reduce pulmonary arterial and pulmonary "capillary" pressures without significantly altering flow. Rakita and Sancetta<sup>29</sup> found a reduction in pulmonary arterial pressure following intravenous administration of hexamethonium in normotensive unanesthetized subjects. In most patients the reduction in pressure, as much as 40 per cent, was accompanied by no change or even an increase of as much as 20 per cent in pulmonary blood flow. Sancetta<sup>29</sup> reported that hexamethonium in five patients in the head-down position caused a decrease of an already elevated pulmonary arterial pressure and resistance. Since wedge pressure did not change, he concluded that pulmonary vasodilation was brought about by the ganglionic blocking drug.

In the present study, measurements were made at end-expiration. The observed changes in  $\overline{PAP}$  and PVR cannot, therefore, be ascribed to changes in intrapleural pressure or the extent of expansion of the lung, factors known to influence these variables.<sup>21,22</sup> Blood viscosity, an important determinant of pulmonary vascular resistance, did not influence our observations, because both hematocrit and plasma protein concentration were unchanged during the study.

Three essential conclusions emerge from this study. First, the effect of pentolinium on pulmonary vascular resistance is mediated by two mechanisms: 1) decrease in preload; 2) reduction of pulmonary vascular tone as a result of sympathetic blockade. Second, anes-

thisa modifies the baseline of pulmonary vascular resistance, which is probably the reason for the conspicuous results with pentolinium. Finally, these data achieve particular importance in view of the fact that the consequences of general anesthetic drugs when administered to patients with pulmonary vascular disease have not been defined.

From a practical standpoint, the data suggest that pentolinium might be useful in the acute management of patients who have acute or chronic pulmonary hypertension. The drug might also provide information regarding the etiology of chronic pulmonary hypertension.

The authors are indebted to André F. Courmand, M.D., Myron B. Laver, M.D., and Leroy D. Vandam, M.D., for their helpful suggestions and criticism during preparation of the manuscript.

### References

1. Scott DB, Stephen GW, Marshall RL, et al: Circulatory effects of controlled arterial hypotension with trimetaphan during nitrous oxide/halothane anaesthesia. *Br J Anaesth* 44:523-527, 1972
2. Lynn RB, Sancecchia SM, Simeone FA, et al: Observations on the circulation in high spinal anaesthesia. *Surgery* 32:195-213, 1952
3. Styles M, Coleman AJ, Leary WP: Some hemodynamic effects of sodium nitroprusside. *ANESTHESIOLOGY* 38:173-176, 1973
4. Prys-Roberts C, Lloyd JW, Fisher A, et al: Deliberate profound hypotension induced with halothane: Studies of haemodynamics and pulmonary gas exchange. *Br J Anaesth* 46:105-116, 1974
5. Fahmy NR, Laver MB: Hemodynamic response to ganglionic blockade with pentolinium during N<sub>2</sub>O-halothane anaesthesia in man. *ANESTHESIOLOGY* 44:6-15, 1976
6. Ganz W, Swan HJC: Measurement of blood flow by thermodilution. *Am J Cardiol* 29:241-246, 1972
7. Lappas DG, Lell WA, Gabel JE, et al: Indirect measurement of left-atrial pressure in surgical patients—pulmonary-capillary wedge and pulmonary-artery diastolic pressures compared with left-atrial pressure. *ANESTHESIOLOGY* 38:394-397, 1973
8. Fitzpatrick GF, Hampson LC, Burgess JH: Bedside determination of left atrial pressure. *Can Med Assoc J* 106:1293-1298, 1972
9. Robinson BF: Relation of heart rate and systolic blood pressure to the onset of pain in angina pectoris. *Circulation* 35:1073-1083, 1967
10. Nelson RR, Gobel FL, Jorgensen CR, et al: Hemodynamic predictors of myocardial oxygen consumption during static and dynamic exercise. *Circulation* 50:1179-1189, 1974
11. Kelman GR, Nunn JF: Nomograms for correction of blood P<sub>O<sub>2</sub></sub>, P<sub>CO<sub>2</sub></sub>, pH, and base excess for time and temperature. *J Appl Physiol* 21:1484-1490, 1966
12. Van Slyke DD, Neill JM: The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. *J Biol Chem* 61:523-573, 1924
13. Fritts HW Jr, Harris P, Clauss RH, et al: The effect of acetylcholine on the human pulmonary circulation under normal and hypoxic conditions. *J Clin Invest* 37:99-170, 1958
14. Szidon JP, Fishman AP: Autonomic control of the pulmonary circulation. *The Pulmonary Circulation and Interstitial Space*. Edited by AP Fishman, HH Hecht, Chicago and London, The University of Chicago Press, 1969, pp 239-268
15. Ingram RH, Szidon JP, Skalak R, et al: Effects of sympathetic nerve stimulation on the pulmonary arterial tree of the isolated lobe perfused in situ. *Circ Res* 22:801-815, 1968
16. Porcelli RJ, Bergofsky EH: Adrenergic receptors in pulmonary vasoconstrictor responses to gaseous and lumoral agents. *J Appl Physiol* 34:483-488, 1973
17. Fritts HW Jr, Courmand A: Physiological factors regulating pressure, flow and distribution of blood in pulmonary circulation. *Pulmonary Circulation: An International Symposium*. Edited by WR Adams, I Veith. New York, Grune and Stratton, 1959, pp 62-67
18. Braunwald NS, Braunwald E, Morrow AG: Effects of surgical abolition of left-to-right shunts on pulmonary vascular dynamics of patients with pulmonary hypertension. *Circulation* 26:1270-1278, 1962
19. Borst HG, McGregor M, Whittenberger JL, et al: Influence of pulmonary arterial and left atrial pressures on pulmonary vascular resistance. *Circ Res* 4:393-399, 1956
20. Price HL, Cooperman LH, Warden JC, et al: Pulmonary hemodynamics during general anesthesia in man. *ANESTHESIOLOGY* 30: 629-636, 1969
21. Lappas DG, Buckley MJ, Laver MB, et al: Left ventricular performance and pulmonary circulation following addition of nitrous oxide to morphine during coronary-artery surgery. *ANESTHESIOLOGY* 43:61-69, 1975
22. Courmand A: Some aspects of the pulmonary circulation in normal man and in chronic cardio-pulmonary diseases. *Circulation* 2: 641-657, 1950
23. Fowler N, Wescott R, Hauenstein VD, et al:

- Observations on autonomic participation in pulmonary arteriolar resistance in man. *J Clin Invest* 29:1387-1396, 1950
24. Daly I de B, Hebb C: Pulmonary and bronchial vascular systems. London, Arnold, 1966, pp 289-315
25. Scott RC, Kaplan S, Stiles WJ: Observations on the effect of tetraethylammonium chloride on the pulmonary vascular resistance in mitral stenosis. *Am Heart J* 50:720-730, 1955
26. Balchum OJ, Gensini G, Blount SG, Jr: The effect of hexamethonium upon the pulmonary vascular resistance in mitral stenosis. *J Lab Clin Med* 50:186-198, 1957
27. Sobol BJ, Kessler RH, Rader B, et al: Cardiac, hemodynamic and renal functions in congestive heart failure during induced peripheral vasodilatation: relationship to Starling's law of the heart in man. *J Clin Invest* 38:557-578, 1959
28. Aviado DM: Hemodynamic effects of ganglion blocking drugs. *Circ Res* 8:304-314, 1960
29. Rakita L, Sancecetta SM: Acute hemodynamic effects of hexamethonium in normotensive man. *Circ Res* 1:499-501, 1953
30. Sancecetta SM: Acute hemodynamic effects of total head-down body tilt and hexamethonium in normal and pulmonary emphysematous subjects. *J Lab Clin Med* 49:684-693, 1957
31. Fowler NO: Effects of pharmacologic agents on the pulmonary circulation. *Am J Med* 28:927-942, 1960
32. Roos A, Thomas LJ, Nagel EL, et al: Pulmonary vascular resistance as determined by lung inflation and vascular pressures. *J Appl Physiol* 16:77-84, 1961

### Local Anesthesia

**PLASMA LEVELS OF COCAINE** Cocaine is an extremely useful drug for topical application prior to nasotracheal intubation. As with any topical anesthetic, knowledge of plasma levels is important. The authors studied nine patients undergoing cardiovascular surgery and four patients undergoing dental surgery. A 10 per cent solution of cocaine hydrochloride (1.5 mg/kg) was applied topically to the nasal mucosa prior to nasotracheal intubation. Blood samples were obtained before administration of cocaine as well as 3, 6, 10, 15, 20, and 60 minutes after application. In dental patients, further blood samples were obtained as long as 6 hours after application. Plasma concentrations of cocaine were assayed by gas-liquid chromatography. The plasma concentration increased

rapidly for 15-20 minutes, peaked at 60 minutes, and then gradually decreased over the next 3-5 hours. The drug could be found in blood within 3 minutes and for as long as 6 hours after application. Persistence of cocaine in the plasma for this length of time probably resulted from its vasoconstrictive action. Indeed, cocaine was detectable on the nasal mucosa 3 hours after application. These factors should be considered when repeat application of the drug is proposed, as well as when sympathomimetic amines are administered some time after topical application of cocaine. (*Van Dyke C, et al: Cocaine: Plasma concentrations after intranasal application in man. Science* 191: 859-861, 1976.)