The Effect of Vasodilatation on Metabolic and Hemodynamic Parameters During and After Cardiopulmonary Bypass

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WITH THE TECHNICAL ASSISTANCE OF VERNON ORWIG

The effects of active vasodilatation with an infusion of trimethaphan camphorsulfonate (2.3 ± 0.9 mg./kg.) were studied in four dogs undergoing hypothermic (32° C.), constant flow (2.35 liters/m.²/minute) cardiopulmonary bypass for 60 minutes. Four control dogs were treated identically, but were not actively vasodilated. Despite identical oxygen consumption and Pa_{CO_2} values, the treated animals showed a greater metabolic acidosis at the end of bypass. When compared to control animals, the treated group demonstrated a greater oxygen consumption (115–119 per cent, $P < 0.05$) and difference in arterio-venous oxygen content (154–173 per cent, $P < 0.001$); with a lesser cardiac index (70–75 per cent, $P < 0.01$) during the post-bypass period (180 minutes). This was accompanied by a greater urinary output and a more rapid correction of metabolic acidosis. However, the actively vasodilated animals showed grossly abnormal pulmonary ventilation-perfusion ratios (compared to control animals) as demonstrated by lower Pa_{O_2} values (21–29 per cent, $P < 0.001$) and higher Pa_{CO_2} values (142–187 per cent, $P < 0.05$). This relative carbon dioxide retention resulted in a consistently lower arterial pH despite the tendency towards correction of metabolic defects.

SINCE the increased efficiency of extracorporeal oxygenators has resulted in satisfactory hemoglobin oxygen saturation at high flow rates, effective perfusion of peripheral tissue beds has become one of the prime determinants of safe clinical bypass. Certain tissue beds may be completely deprived of blood flow, while in other portions of the circulation, flow remains normal.[1]

The reduction in oxygen consumption during hypothermic cardiopulmonary bypass, therefore reflects not only a depression of metabolism, but also an impairment of tissue blood flow. Metabolic products of these tissues are not present in the general circulation during this period, and acidosis appears later, when the general circulation has improved. This explains the apparent paradox of satisfactory acid-base and oxygen content parameters during bypass, with the subsequent development of post-perfusion acidosis. Since active vasodilatation during bypass modifies the peripheral vascular response to factors affecting redistribution of blood flow, the correlation of changes in oxygen consumption, acid-base and hemodynamic parameters was studied in dogs during and after bypass. If active vasodilatation can improve blood flow in peripheral tissue beds, not only would there be an increase in oxygen consumption, but there would also be a closer correlation of cardiac index, oxygen consumption and metabolic acidosis, due to the prevention of metabolite retention in peripheral tissues.

Method

Without premedication, 8 mongrel dogs weighing 11–16 kg. were anesthetized with an intravenous dose of pentobarbital (20 mg./kg.). Their tracheas were intubated and the lungs ventilated (100 per cent O_2) with a volume-limited piston ventilator, at a tidal volume of 15 ml./kg. and a rate of 20 per minute. Four to six hyperinflations (45 ml./kg.) were performed every 30 minutes. Muscle

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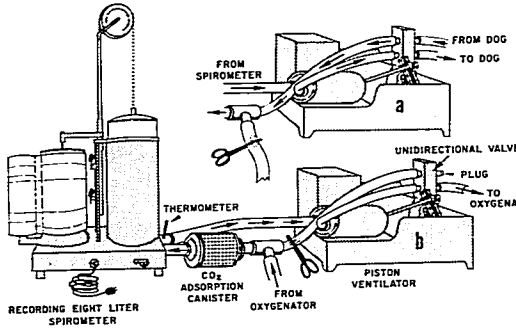

FIG. 1. Closed system spirometer and ventilatory unit used to measure oxygen consumption from (a) dog and (b) extracorporeal oxygenator.

tremors were eliminated (verified by ECG tracing) with a 0.2 per cent infusion of succinylcholine in 5 per cent dextrose/water. The following parameters were monitored before, during and after bypass at identical times (relative to the induction of anesthesia) in each animal:

(1) Esophageal temperature (°C.).

(2) Urine output (ml./hour).

(3) Heart rate (lead 2 ECG).

(4) Pa_{O_2}, Pa_{CO_2}, *p*H. All blood samples were collected anaerobically and analyzed immediately in duplicate with an Instrumentation Laboratories Inc. model no. 113 blood gas analyzer (glass *p*H, Severinghaus P_{CO_2}, and Clark P_{O_2} electrodes). Values were corrected to esophageal temperature.

(5) Hemoglobin content of arterial blood (gm.%): colorimetric method.[2]

(6) Microhematocrit.[3]

(7) Supravalvular aortic pressure (mm. of mercury) and thoracic inferior vena cava (IVC) venous pressure (cm. of water). These pressures were transmitted via Lehman catheters to Statham P23D transducers and recorded on a Grass model 5 polygraph.

(8) Cardiac index (liters/meter^2/minute): a technique employing planimetric analysis of the supravalvular aortic pressure curve was used (Hamilton and Remington[4]). In our laboratory, cardiac index derived from measured oxygen consumption and A-V_{O_2} difference correlated well ($n = 18$, $r = 0.92$, $P < 0.01$) with that obtained by the method of Hamilton *et al.*[*]

(9) Oxygen consumption (liters/meter^2/minute): a recording eight liter Collins spirometer with a carbon dioxide adsorption canister was used. This was connected in series to a piston ventilator so that a predetermined minute volume of 100 per cent O_2 could be delivered to the animals or to a disk oxygenator (fig. 1). Each determination represented an average value obtained over a 15 minute period. The system was tested before each determination and was considered satisfactory if less than 2 ml. of oxygen were lost per minute.

(10) A-V_{O_2} difference (volume per cent): calculated by the direct Fick method using measured oxygen consumption and cardiac index.

(11) Plasma standard bicarbonate and base deficit (mEq./liter): calculated from Pa_{CO_2}, *p*H and hemoglobin content.

After placement of recording cannulas and control measurements, two groups of animals (4 dogs/group) were subjected to right anterolateral thoracotomy through the fourth or fifth interspace. Clotting was prevented by the administration of heparin (3 mg./kg. intravenously). Both right and left auricular appendages were cannulated with a ¼ inch (inside diameter) plastic cannula. These cannulas were passed into the ventricles at the start of bypass and returned venous drainage

[*] Unpublished data.

to the inflow side of the oxygenator; gravity drainage was used. Arterialized blood was returned to the animal by a no. 14 French plastic cannula inserted into the abdominal aorta via the left femoral artery. Total cardiopulmonary bypass was conducted for 60 minutes, using a rotating disk oxygenator and an occlusive, load-insensitive pump. Perfusion was maintained at 100 ml./kg./minute (2.34 ± 0.11 liters/m.^{2}/minute) at an esophageal temperature of 32° C. (± 1.3° C.). In order to maintain a constant perfusate level in the oxygenator (volume 1,300 ml.), a calibrated reservoir containing 1,000 ml. of perfusate was incorporated into the venous side of the system. The intravascular volume take-up or release by each animal could be accurately determined.

The extrocorporeal system was primed with 1,200 ml. of fresh homologous blood and 1,800 ml. of dextran 75 (average molecular weight 75,000—6 per cent in isotonic saline). The perfusate was buffered to *p*H 7.39–7.42 (at P_{CO_2} 40 mm. of mercury, temperature 37° C.) with a 0.3 molar tris (hydroxymethyl) aminomethane (THAM). The hematocrit of the perfusate showed moderate variation (23–29 per cent).

At the start of bypass, both venous drainage catheters were inserted into the ventricles. The ventricles were electrically fibrillated. Gas flow (100 per cent O_2) through the oxygenator was maintained at the pre-bypass minute volume, but with the ventilator adjusted to give a tidal volume of 7.5 ml./kg. at a rate of 40 per minute. This adjustment was necessary to prevent excessive gas pressure in the oxygenator. The lungs were not inflated during bypass. Group I animals (untreated) were not actively vasodilated and were used as controls. In Group II animals (treated), vasodilatation was produced during bypass with an infusion of 0.1 per cent trimethaphan camphor-sulfonate (Arfonad) to a mean arterial pressure of 50–60 mm. of mercury. The infusion rate, titrated against mean arterial pressure during bypass, resulted in 2.3 ± 0.9 mg./kg. of vasodilator administered as a total dose. Similar volumes (25–50 ml.) of 5 per cent dextrose/water were used to irrigate the IVC line in the Group I animals.

Volume take-up by the perfused, vasodilated animals was replaced with buffered perfusate (from a volume calibrated venous reservoir), so that a constant fluid level in the oxygenator was maintained. It was possible to add accurately measured (to 10 ml.) increments of perfusate to the oxygenator.

At the conclusion of bypass, the oxygenator fluid level was adjusted to the pre-bypass level, and the net volume change in the venous reservoir was recorded. The heart was electrically defibrillated without correction of acidosis or hypothermia, and heparinization was reversed with protamine sulfate (3 mg./kg.). Post-bypass, controlled pulmonary ventilation (100 per cent O_2) was resumed at a tidal volume of 15 ml./kg. and a rate of 20 per minute. Periodic hyperinflations (45 ml./kg.; × 4–6) were given every ten minutes for the first 60 minutes post-bypass, and every 30 minutes thereafter. The venous drainage and arterial inflow cannulas were removed, the chest closed, and the right pleural cavity connected to water seal within 30 minutes post-bypass. The animals were allowed to rewarm spontaneously without blood volume replacement or administration of drugs. Drainage from the chest tube was measured but not replaced. Monitoring was continued for 180 minutes post-bypass. All animals were sacrificed at the end of the observation period.

Students paired "*t*" test was used to analyze the data obtained on temporally equivalent parameters in treated and untreated animals.[5] Correlation analysis was used to express concomitant variation between: (1) oxygen consumption and cardiac index, (2) oxygen consumption and standard bicarbonate, and (3) standard bicarbonate and cardiac index. Linear regression (least squares method) was used to establish regression lines for these relations, and analysis of variance (of the linear regression) was used to verify the significance of the linearity.[6]

Results

The hemodynamic and metabolic parameters before, during and after bypass are summarized in table 1. Only temporally equivalent parameters between the two groups of animals were compared. In all animals, thoracotomy was associated with an increase in heart rate and a decrease in blood pressure,

TABLE 1. Hemodynamic and Metabolic Parameters of Dogs Undergoing Cardiopulmonary Bypass (Mean±Standard Deviation)

		Chest Closed	Chest Open	After 60 Min. Bypass	60 Min. Post-Bypass	120 Min. Post-Bypass	180 Min. Post-Bypass
Anesthesia Time (minutes)	I	50	100	210	280	345	400
	II	55	110	210	285	345	405
Esophageal temperature (°C.)	I	38.3±0.4	37.9±0.3	32.1±0.6	31.9±0.5	32.2±0.5	33.1±0.4
	II	38.0±0.2	37.8±0.4	32.4±0.4	32.0±0.4	32.0±0.6	32.5±0.3
Urine output (ml./hour)	I	18.1±3.1	12.1±5.3	QNS	3.2±1.8	2.1±1.8	2.9±1.9
	II	18.9±2.7	13.0±6.1	4.3±2.7	4.1±2.0	4.0±2.1	4.9±1.3
Heart rate	I	176±30	204±21		135±12	148±36	142±28
	II	168±34	192±28		156±22	172±41	166±30
Systolic B. P. (mm. Hg)	I	190±47	160±39		100±19	72±22	99±30
	II	187±38	165±33		70±9	67±16	82±21
Diastolic B. P. (mm. Hg)	I	125±31	110±22		65±21	45±14	66±20
	II	132±36	122±31		33±14	33±16	36±21
Mean B. P. (mm. Hg)	I	152±34	132±29	95±18	75±19	55±14	80±14
	II	147±32	141±31	54±4	50±12	48±12	55±16
Central venous pressure (cm. H_2O)	I	6.0±3.1	2.5±1.1	1.0±0.6	5.5±1.3	4.5±1.6	3.5±0.9
	II	6.8±2.8	1.9±0.9	2.1±1.1	3.5±1.0	3.5±1.3	3.0±0.6
Hemoglobin (g./100 ml.)	I	13.4±0.9	13.3±1.2	9.6±4.4	10.4±3.7	10.8±4.0	10.2±3.3
	II	15.2±2.4	14.5±2.4	11.5±1.6	13.2±2.8	13.3±2.4	13.3±2.4
Hematocrit	I	39.6±2.4	40.1±3.7	28.8±13.3	31.3±11.3	32.1±11.7	30.1±9.6
	II	47.5±5.9	45.1±6.7	34.6±5.1	40.4±8.2	40.1±7.2	39.8±7.0
Arterial Po_2 (mm. Hg)	I	493±43	463±6	110±40	342±41***	327±38***	326±23***
	II	522±55	429±60	87±11	109±70	70±37	85±43
Arterial Pco_2 (mm. Hg)	I	32.9±6.6	27.0±3.2	22.7±4.5	20.4±5.9	17.2±4.0*	18.2±3.6*
	II	33.6±4.2	28.1±9.3	22.9±4.6	29.0±5.0	31.9±8.3	32.3±10.2
Arterial pH	I	7.407±0.058	7.414±0.047	7.329±0.136	7.338±0.129*	7.322±0.146*	7.255±0.120*
	II	7.415±0.035	7.429±0.057	7.249±0.091	7.190±0.070	7.182±0.110	7.197±0.132
Standard bicarbonate (mEq./L)	I	22.0±0.9	19.9±1.1	13.8±1.6	11.4±1.2	13.1±0.9	12.4±1.7
	II	22.6±0.9	20.8±1.0	12.0±0.8	11.8±1.1	12.5±0.9	13.2±0.7
Base deficit (mEq. /L)	I	2.9±0.2	5.5±0.3	14.2±2.9	14.4±3.1	15.5±2.2	16.6±2.9
	II	2.2±0.4	4.6±0.4	17.3±1.9	17.8±1.7	16.8±1.1	15.8±0.9
Cardiac index (L./m.²/min.)	I	3.50±0.41	3.18±0.62	2.31±0.11		3.19±0.30**	3.22±0.42**
	II	3.39±0.38	3.21±0.32	2.36±0.08		2.39±0.24	2.24±0.28
Oxygen consumption (L./m.²/min.)	I	0.182±0.015	0.164±0.023	0.131±0.022	0.105±0.016***	0.096±0.017	0.089±0.018*
	II	0.179±0.009	0.159±0.030	0.128±0.010	0.124±0.019	0.110±0.007	0.106±0.007
A−V_{O_2} difference (vol. %)	I	5.28±0.14	5.34±0.17	5.73±1.01		3.00±0.45***	2.75±0.19***
	II	5.22±0.12	5.10±0.11	5.31±0.24		4.62±0.18	4.77±0.35

* Group I, Nontreated animals; Group II, treated animals (actively vasodilated with Arfonad during bypass). Significant difference of the means, Group I versus Group II, * $p < .05$; ** $p < .01$; *** $p < .001$.

central venous pressure (reflecting diminution of mean intrathoracic pressure), cardiac index and oxygen consumption. Urinary output, Pa_{O_2} and plasma standard bicarbonate were similarly reduced.

Pump output and esophageal temperature during bypass were similar in both groups of animals. This resulted in essentially identical oxygen consumption and A-V_{O_2} differences, despite marked differences in mean aortic pressure and intravascular fluid volume (as measured by volume take-up from the venous reservoir to maintain a constant perfusate level in the oxygenator) between the two groups. Although all animals had a positive fluid balance at the end of bypass, the treated animals had a significantly ($P < 0.001$) greater net positive balance (385 ± 52 ml.) than did the untreated animals (106 ± 35 ml.).

At the end of bypass, both groups had developed a marked metabolic acidosis as evidenced by decreased plasma standard bicarbonate and increased base deficit. The treated animals showed a greater decrease in titratable base. The difference between the groups was not significant. Since the Pa_{O_2} values during bypass should have given hemoglobin saturations greater than 95 per cent, oxygen content was not a limiting factor in oxygen availability to tissues. Urinary output decreased markedly during cardiopulmonary bypass in both groups, but was greater in the treated animals. Both

groups of animals were easily defibrillated at the end of bypass.

The post-bypass period was marked by a slow, but progressive recovery from metabolic acidosis in the treated animals, while the course of the untreated animals was less consistent. The degree of metabolic acidosis at the beginning of the post-bypass period was greater in the treated than the untreated animals, in spite of a significantly greater oxygen consumption in the former (table 1). However, at the end of the post-bypass observation period (180 minutes), the standard bicarbonate was higher and the base deficit was lower in the treated animals. The treated animals continued to have a greater oxygen consumption (115–119 per cent, $P < 0.05$), a lower cardiac index (70–75 per cent, $P < 0.01$) throughout the post-bypass period, as compared to the untreated animals. This resulted in an A-V_{O_2} difference that was greater (154–173 per cent, $P < 0.001$) in the treated than in the untreated animals. Urinary output was persistently higher in the treated animals, despite the lower cardiac index, blood pressure and central venous pressure. The magnitude of the differences in esophageal temperature, hemoglobin and hematocrit between the two groups was relatively constant during the 500 minutes of observation. Post-bypass blood loss, as judged by volumetrically measuring drainage from the surgical field, was similar in both groups of animals.

As compared to the untreated animals, the slightly lower Pa_{O_2} of the treated animals during bypass, became much lower (21–29 per cent, $P < 0.001$) after bypass with the chest closed. Despite identical ventilatory management, Pa_{CO_2} values progressively increased in the treated animals, while those of the untreated animals decreased. The higher Pa_{CO_2} values in the treated animals (142–187 per cent, $P < 0.05$) as compared to the untreated animals resulted in a commensurate decrease in arterial *p*H. Spot checks of airway pressure (not included in the protocol) during periods of no-flow at the end of inspiration revealed values of 13–16 cm. of water in all animals. These pressures were transiently lowered after hyperinflations (45 ml./kg.).

The pre-bypass correlation of oxygen consumption to cardiac index showed a wide scatter of values about the regression line. Since analysis of variance showed that the regression formula was not statistically significant, cardiac index (the dependent variable) could not be predicted with any degree of certainty from oxygen consumption (the independent variable). The post-bypass correlation coefficients for both treated and untreated animals were significant, as was the linearity of their respective regression equations (fig. 2).

The correlation of oxygen consumption to standard bicarbonate (fig. 3) showed statistical significance only in the pre-bypass period. In this group of values, the positive correlation was constant, and the linearity of the regression equation was within acceptable confidence limits (95 per cent). Post-bypass, the correlation coefficients of both the treated and untreated animals became negative, and the regression coefficients (slope of the regression line) were identical between the two groups.

Standard bicarbonate did not correlate well with cardiac index in either of the groups. Although post-bypass sign reversal was evident in the regression coefficients of both groups, that of the treated animals was three times that of the untreated animals (fig. 4).

Discussion

Vasodilatation with Arfonad produced many of the expected changes in both metabolic and hemodynamic parameters. By design, the time of observation related to induction of anesthesia and the esophageal temperature remained comparable between both groups of animals before, during and after cardiopulmonary bypass (table 1). Consequently, the effects of pentobarbital anesthesia and body temperature did not influence statistical pairing.

Both groups of animals showed the pre-bypass parameters suggestive of intense sympathetic system activity, such as high cardiac index, heart rate and blood pressure. The large variance in correlation of cardiac index to oxygen consumption during the pre-bypass period, was in marked contrast to the same animals post-bypass (figure 2). This would imply that an indeterminate fraction of the cardiac output was not being used to prefuse tissue capillaries (owing to precapillary arterial to venous shunting) during the pre-bypass

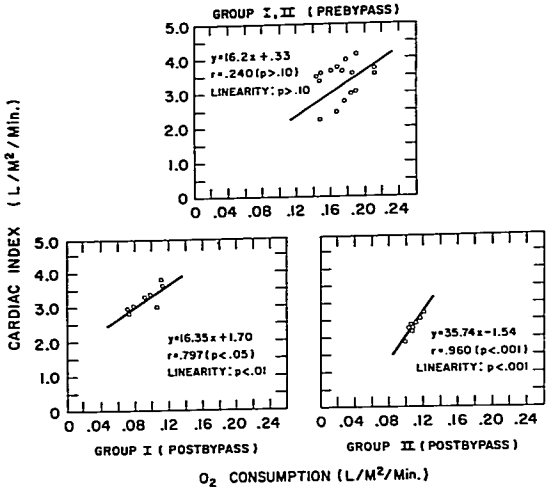

FIG. 2. Correlation of oxygen consumption and cardiac index in Group I and Group II (actively vasodilated) animals.

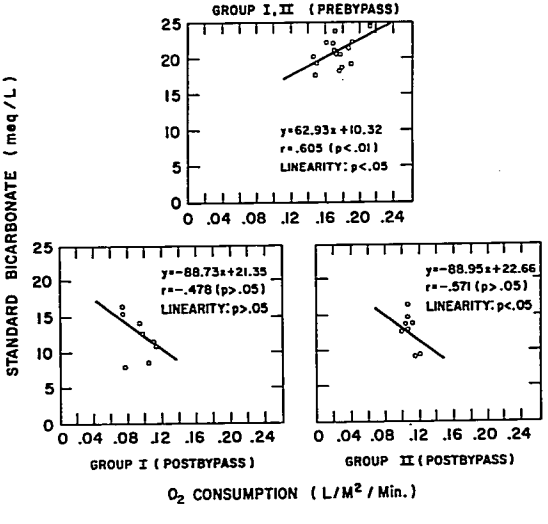

FIG. 3. Correlation of oxygen consumption and standard bicarbonate in Group I and Group II (actively vasodilated) animals.

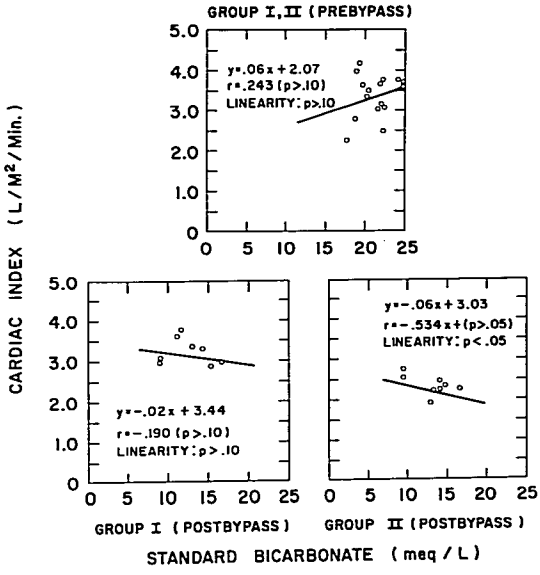

FIG. 4. Correlation of standard bicarbonate and cardiac index in Group I and Group II (actively vasodilated) animals.

period. The lack of significant retention of acid metabolites in peripheral tissue beds is suggested by the statistically significant correlation of oxygen consumption with standard bicarbonate. However, the positive correlation of oxygen consumption with standard bicarbonate in the pre-bypass animals does not represent conclusive evidence of anaerobic metabolism, without the washout of previously formed acid metabolites.

Although the pump output (100 ml./kg./minute) was intended to represent high flow perfusion,[7] this perfusion rate was associated with a mean aortic pressure of 50–65 mm. of mercury during normothermia (38° C.). This pressure subsequently decreased to 20–30 mm. of mercury with minimal amounts (less than 1 μg./kg./minute) of Arfonad.[9] Therefore, a temperature (32° C.) was chosen that is commonly encountered in clinical hypothermic perfusions. This high flow, hypothermic technique was still not satisfactory, since treated and untreated animals developed what would be clinically unacceptable metabolic acidosis after 60 minutes of extracorporeal circulation.

Despite essentially identical oxygen consumption and Pa_{CO_2} values during bypass, the treated animals showed a greater (but not significant) decrease in standard bicarbonate and increase in base deficit at the end of bypass, than did the untreated animals. Arfonad has been shown to either have no effect, or to cause a slight reduction in oxygen consumption in both awake and anesthetized subjects.[8, 9, 10] Therefore, there is no reason to believe that more acid metabolites (secondary to anaerobic metabolism) were produced in the treated than in the untreated animals. The more severe metabolic acidosis in the treated group probably represents an earlier and more complete expression of byproducts of anaerobic metabolism incurred during a bypass that did not adequately perfuse tissues in either group of animals.

[9] Unpublished data.

Although both groups of animals displayed a significant positive correlation of oxygen consumption with cardiac index in the post-bypass period, the relation was most nearly linear in the treated group ($r = 0.960$, $P < 0.001$ versus $r = 0.797$, $p < 0.05$). This close association of oxygen consumption with cardiac index would suggest that the post-bypass cardiac output was more effective in perfusing tissue capillary beds. The post-bypass cardiac indexes of the treated animals (2.24 – 2.39 liters/m.²/minute) were similar to the extracorporeal pump output (2.34 ± 0.11 liters/m.²/minute), and may have limited both the rate and extent to which the metabolic acidosis could be corrected. This was not true for the untreated animals, whose post-bypass cardiac indexes (3.19 – 3.22 liters/m.²/minute) were similar to the pre-bypass value (3.18 ± 0.62 l/m.²/minute). The treated animals did, however, consistently display a higher oxygen consumption, urinary output and acid washout, despite the lower cardiac index. This resulted in a progressive improvement in all metabolic parameters, as opposed to signs of eventual deterioration in the untreated animals. An extension of the post-bypass observation period may have more clearly delineated these differences.

An interpretation of the negative correlation of standard bicarbonate with oxygen consumption or cardiac index must be tempered by the large variance and lack of statistical significance demonstrated in both groups for post-bypass values. The provocative, but tenuous implications of previously formed acid metabolite washout may be another manifestation of post-ischemic augmentation of tissue perfusion.

Prolonged periods (30 minutes) between hyperinflations, ventilation with 100 per cent O_2, and lung collapse during bypass were important factors contributing to the post-bypass atelectasis seen in both groups of animals. However, the ventilatory management was identical in each animal, and does not explain the significantly greater Pa_{CO_2} values and smaller Pa_{O_2} values seen in the treated animals (compared to untreated animals) during the post-bypass period. These values would suggest a greater right-to-left intrapulmonary shunting of blood and a greater physiological dead space in the treated animals.

Although more effective peripheral tissue perfusion resulted in metabolic improvement, the animals given Arfonad displayed a consistently lower post-bypass arterial *p*H. Since the standard bicarbonate values were similar in the two groups, the post-bypass *p*H differences could be attributed primarily to the greater Pa_{CO_2} values evident in the treated animals.

Although the effects of Arfonad on pulmonary vascular perfusion and/or surfactant activity were not delineated by this study, increased peripheral and central blood volumes may have influenced ventilation-perfusion ratios in the treated animals. The hemodynamic effects of drug induced vasodilatation during hypothermic cardiopulmonary bypass must also be delineated from those of acidosis *per se* before this technique is used for clinical bypass procedures.

Summary

The effect of active vasodilatation with trimethaphan camphorsulfonate has been studied in dogs undergoing hypothermic cardiopulmonary bypass. The rheological benefits of this technique on certain hemodynamic and metabolic parameters demonstrated by this study include: (1) improved oxygen consumption despite marginal cardiac output, presumably due to increased peripheral tissue perfusion, (2) less acid metabolite hold-up in peripheral tissue beds, with subsequent washout acidosis. Blood values thus more accurately reflect the current status of peripheral tissue perfusion, and (3) more rapid correction of the existing hypoxic metabolic acidosis.

The data suggest that by reducing precapillary vasospasm and arterial to venous shunting, not only is the efficiency of cardiac output enhanced, but also the balance of cellular oxygen demand to oxygen availability is stabilized.

The abnormal pulmonary ventilation-perfusion ratios found in those animals vasodilated with Trimethaphan camphorsulfonate produced an unacceptable degree of both right-to-left shunting of pulmonary blood flow and increased physiological dead space. The resulting decrease in Pa_{O_2} values and increase in Pa_{CO_2} values, compared to the un-

treated animals, was impressive. The relative carbon dioxide retention obscured any salutary effect that the correction of metabolic acidosis might have had on arterial *p*H values. The role of pulmonary blood flow during bypass, increased intravascular fluid volume, acidosis, and Trimethaphan camphorsulfonate *per se* in the etiology of these ventilation-perfusion aberrations requires further delineation.

References

1. Nichol, J., Girling, T. F., Jerrard, W., Claxton, E. G., and Burton, A. C.: Fundamental instability of small blood vessels and critical closing pressures in vascular beds, Amer. J. Physiol. 164: 330, 1951.
2. Hawk, P. B., Oser, B. L., and Summerson, W. H.: Practical Physiological Chemistry, ed. 13. New York, The Blakiston Company, Inc., 1954, p. 613.
3. *Ibid.* p. 675.
4. Hamilton, W. F., and Remington, J. W.: The measurement of the stroke volume from the pressure pulse, Amer. J. Physiol. 148: 14, 1947.
5. Batson, H. C.: An Introduction to Statistics in the Medical Sciences. Minnesota, Burgess Publishing Co., 1961.
6. Wilks, S. S.: Elementary Statistical Analysis. Princeton, New Jersey, Princeton University Press, 1961.
7. Galletti, P. M., and Brecher, G. A.: Heart-Lung Bypass. New York, Grune & Stratton, Inc., 1962, pp. 209 and 220.
8. Sobal, B. J., Kessler, R. H., Pader, B., and Eichna, L. W.: Cardiac hemodynamic and renal function in congestive heart failure during induced peripheral vasodilatation. Relationship to Starling's law of the heart in man, J. Clin. Invest. 38: 557, 1959.
9. Tuohy, G. E., and Theye, R. A.: Effects of Arfonad during ether anesthesia in man, Anesth. Analg. 44: 160, 1965.
10. Theye, R. A., and Tuohy, G. E.: Effect of trimethaphan on haemodynamics and oxygen consumption during halothane anesthesia in man, Brit. J. Anaesth. 37: 144, 1965.

Anesthesia

MATERNAL ANESTHETIC DEATH Of 3,104 maternal deaths occurring in North Carolina from 1946 to 1965, 75 were judged to be primarily due to anesthesia. Grouped in 5-year periods, both the maternal death rate and the anesthesia death rate fell during the 20-year period. There was a 29 per cent reduction in general anesthetic deaths over the second decade, and an 87 per cent reduction in conduction and local anesthetic deaths. It was recommended that since an adequate supply of anesthesia personnel cannot be anticipated, obstetricians should receive thorough training in anesthesia, allowing them to become more skilled in selection of anesthesia, with a resultant elimination of maternal anesthetic deaths. *(Greiss, F. C., and Anderson, S. G.: Elimination of Maternal Deaths from Anesthesia, Obstet. Gynec. 29: 677 (May) 1967.)*

PREMIXED GASES FOR OBSTETRICS Premixed nitrous oxide and oxygen in equal proportions v/v in tanks under pressure are used for obstetrical analgesia. Upon cooling tanks to room temperature, partial separation of nitrous oxide and oxygen occurred and on trial runs with gas composition monitored, it was found that markedly reduced oxygen concentrations were sometime obtained. Adequate rewarming and agitation restored the original homogeneity of the mixture. *(Crawford, J. S., and others: Effects of Cooling on the Safety of Premixed Gases, Brit. Med. J. 1: 138 (April) 1967.)*