Anesthesiology
V 37, No 6, Dec 1972

# *Lactic Acidemia during Hemorrhagic Hypotension and Cyclopropane Anesthesia*

*Douglas H. Arbon, M.D.,* and Richard A. Theye, M.D.†*

**Whole-body, skeletal muscle, and splanchnic bed responses to progressive hemorrhagic hypotension were determined in dogs during cyclopropane anesthesia (22 per cent, MAC 1.3). These were compared with responses previously observed during anesthesia with halothane (1.1 per cent, MAC 1.3). In both groups, control observations were followed by three successive episodes of bleeding and observations for one hour or until death. Major differences in responses were confined to the period following removal of 40 ml/kg of blood when, with cyclopropane anesthesia, more profound metabolic acidosis and lactic acidemia developed and the splanchnic region produced significant amounts of lactate. Skeletal muscle produced lactate throughout. There was a direct qualitative relationship between blood catecholamine and lactate levels during hemorrhagic hypotension and anesthesia with either cyclopropane or halothane. (Key words: Catecholamine; Cyclopropane; Excess lactate; Halothane; Hemorrhagic hypotension; Lactic acidemia.)**

IN A PREVIOUS STUDY,[1] we were unable to demonstrate significant shifts from aerobic to anaerobic metabolic pathways while delivery of oxygen to the tissues became progressively compromised during halothane anesthesia. Arterial lactate levels did not increase with increased depth of anesthesia, arterial hypoxemia, or hemorrhagic hypotension, and only insignificant anaerobic metabolic activity was detected prior to death. We ascribed these findings to the relative absence of increased catecholamine release under stress, due to suppression of sympathetic nervous system activity during anesthesia with halothane. The present study was designed to test this hypothesis by carrying out similar studies with one form of stress, hemorrhagic hypotension, during anesthesia with cyclopropane, an agent known to enhance rather than suppress sympathetic nervous system activity.[2]

## Material and Methods

Staged, progressive hemorrhagic hypotension during cyclopropane anesthesia was designed to duplicate the stress previously studied during halothane anesthesia.[1] Each of 12 unpremedicated, fasted dogs weighing 19 ± 4 kg was anesthetized with nitrous oxide (75 per cent), and the trachea was intubated with the aid of succinylcholine (20 mg), which was continued at 150 mg/hr. After a catheter had been passed into a hepatic vein under fluoroscopic guidance, cyclopropane was introduced into a nonrebreathing system containing nitrogen and oxygen. The inspired concentration of cyclopropane was maintained at 22 per cent in order to achieve approximately the same relative minimal alveolar concentration (MAC) for cyclopropane (1.3) as had been previously achieved with 1.1 per cent halothane in dogs.[3] The concentration of inspired $O_2$ was adjusted to provide a $Pa_{O_2}$ of 150 (±10) mm Hg. Ventilation with a Bird ventilator (Mark IV/VIII) was adjusted to maintain a $Pa_{CO_2}$ of 40 (±2) mm Hg. The carotid artery was cannulated for sampling, measurement of blood pressure, and subsequent blood-letting. Satisfactory whole-body and splanchnic preparations were obtained in ten dogs.

In each dog, either the gastrocnemius or the gracilis muscle group was isolated and prepared for collection and measurement of venous outflow, as previously described.[4] Satis-

* Resident in Anesthesiology, Mayo Graduate School of Medicine (University of Minnesota), Rochester, Minnesota.

† Professor of Anesthesiology, Mayo Graduate School of Medicine (University of Minnesota).

Received from the Department of Anesthesiology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. Accepted for publication June 19, 1972. Supported in part by Research Grant HE-4881 from the National Heart Institute, Public Health Service.

factory muscle preparations were obtained in nine dogs. Collected blood was returned to the contralateral femoral vein, which was also used for infusion of heparin and succinylcholine. Esophageal and muscle temperatures were maintained at 37.0 ± 0.2 C. Wet muscle weight was determined and hepatic catheter placement verified at autopsy.

After the initial preparation and control measurements, each dog was studied during three periods of progressive hemorrhagic hypotension, which was induced by blood-letting of accumulated totals of 20, 30, and 40 ml/kg, respectively, during a period of 5 minutes. Observations were made 15 minutes after initiating each of the three episodes of blood-letting and continued for 45 minutes, or until death occurred. No therapy was given.

Blood $P_{O_2}$, $P_{CO_2}$, and *p*H were determined by electrodes at 37.0 C during the control and each of the three succeeding periods. Buffer base was estimated from the Singer-Hastings nomogram. Blood $O_2$ content was calculated from $P_{O_2}$ and oxyhemoglobin concentration (I-L, Co-Oximeter), as previously described.[5] Muscle $V_{O_2}$ was calculated from muscle venous flow rate and A-$V_{O_2}$. Arterial and venous (muscle and hepatic) blood lactate (L) and pyruvate (P) concentrations were determined by enzymatic methods. Excess lactate (XL) was calculated as suggested by Huckabee.[6]

$$XL = (L_E - L_C) - (P_E - P_C)\ (L_C/P_C)$$

where the subscripts E and C refer to experimental and control conditions, respectively. For whole-body XL, only arterial values were used. Control values were those of the initial control period and experimental values were those of each subsequent period. For muscle and splanchnic XL, control and experimental values were those of arterial and either muscle or hepatic venous blood, respectively, for that particular period.[7] Statistical significance was determined by Student's t tests for paired and unpaired data, $P < 0.05$ being considered significant.

Arterial blood lactate and total plasma catecholamine levels were determined, under conditions similar to those described above, in a separate group of dogs anesthetized with either 1.1 per cent halothane (three dogs) or 22 per cent cyclopropane (three dogs). In these studies, after control determinations, blood was removed continuously at 10 ml/kg/hr rather than only during the first 5 minutes of each hour-long period; the overall relations of total accumulated rate of blood removed, however, were preserved. For catecholamine determinations, 20 ml of removed blood were transferred into ice-chilled tubes and centrifuged for 15 minutes at 1 C. Sodium metabisulfite was then added to the separated plasma, which was frozen by immersion in a Dry Ice–alcohol slush (−70 C). Total plasma catecholamine content of these samples was determined on the day of collection by the method of Renzini and associates.[8] Logistical considerations limited the scope of this study and prevented differentiation of epinephrine and norepinephrine in the plasma samples. However, many studies have, by using more sophisticated analytical procedures, indicated that increase in the epinephrine component makes the greatest contribution to the total catecholamine content of plasma in stressed, anesthetized dogs.[2, 9, 10]

## Results

### Whole-body, Splanchnic, and Muscle Responses

Progressive stepwise removal of blood from dogs during anesthesia with cyclopropane was associated with progressive reduction in systemic arterial blood pressure and the eventual development of lactic acidemia and metabolic acidosis (table 1). Significant biochemical changes appeared following removal of 30 ml/kg of blood and progressed with further blood removal. The increase in arterial blood lactate levels was paralleled by significant increases in the arterial L/P ratio and whole-body XL value. Splanchnic blood flow rates were not determined, but overall handling of lactate in the splanchnic region can be estimated from the difference between lactate levels of hepatic venous and arterial blood; positive and negative values indicate net production and consumption of lactate, respectively. By this measure, the splanchnic region produced some

lactate initially, became a consumer of lactate at a blood loss of 30 ml/kg, and a producer of lactate again during the final, preterminal period (fig. 1). At this time, the arterial blood pressure averaged 25 mm Hg, hepatic venous L/P ratio was greater than that of arterial blood, splanchnic XL was increased, and hepatic venous $P_{O_2}$ was reduced to an average value of 11 mm Hg.

The responses of the gastrocnemius and gracilis muscles were qualitatively similar and were pooled. Although blood flow and muscle venous $P_{O_2}$ decreased progressively with successive stages of blood-letting, muscle $\dot{V}_{O_2}$ did not become significantly decreased until the final, preterminal period. Skeletal muscle was, overall, a producer of lactate throughout the study (fig. 1). However, in the final period, despite a reduction in $\dot{V}_{O_2}$ related to inadequate $O_2$ transport to the muscle, the muscle venous L/P ratio had become less than that of arterial blood, muscle (V-A) lactate had decreased to approximately control values, and muscle XL had become a negative value.

Cogent comparisons of these findings with those previously obtained at an equivalent concentration of halothane are presented in table 2. Control values were not remarkably different in the two studies. Arterial blood pressure was initially better maintained with cyclopropane, but in the final stage it was greater with halothane. Metabolic acidosis appeared earlier with cyclopropane than with halothane, and, in the final stage, there was a greater degree of metabolic acidosis and lactic acidemia, and a greater increase in arterial L/P ratio, with cyclopropane than with halothane (fig. 2).

TABLE 1. Whole-body, Splanchnic, and Skeletal Muscle Responses to Staged Hemorrhagic Hypotension during Cyclopropane Anesthesia

| | Blood Removed | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 | | 20 ml/kg | | 30 ml/kg | | 40 ml/kg | |
| | Mean | SE | Mean | SE | Mean | SE | Mean | SE |
| Arterial blood | | | | | | | | |
| Mean pressure, mm Hg | 111 | 5 | 88* | 7 | 57* | 5 | 25* | 3 |
| pH | 7.41 | 0.01 | 7.40 | 0.01 | 7.33* | 0.02 | 7.25* | 0.01 |
| $P_{CO_2}$, mm Hg | 40 | 1 | 40 | 1 | 40 | 1 | 31* | 2 |
| Buffer base, mEq/l | 49 | 0 | 48* | 1 | 44* | 1 | 36* | 1 |
| Lactate, μmol/ml | 3.63 | 0.21 | 3.29 | 0.25 | 5.34* | 0.67 | 11.0* | 0.92 |
| Lactate/Pyruvate | 14.2 | 1.0 | 14.7 | 0.9 | 21.8* | 3.0 | 46.3* | 5.6 |
| Excess lactate, whole-body, μmol/ml | 0 | 0 | 0.13 | 0.30 | 2.26* | 0.79 | 7.52* | 0.90 |
| Hepatic venous | | | | | | | | |
| Lactate, μmol/ml | 3.83 | 0.22 | 3.36 | 0.22 | 4.98 | 0.66 | 12.85* | 1.16 |
| V-A lactate, μmol/ml | 0.21 | 0.18 | 0.07 | 0.16 | −0.35* | 0.14 | 1.68* | 0.54 |
| Lactate/pyruvate | 13.1 | 2.0 | 12.2 | 1.1 | 23.3* | 5.2 | 147.2* | 55.3 |
| Excess lactate, splanchnic, μmol/ml | −0.84 | 0.54 | −0.99 | 0.52 | −0.30 | 0.6 | 6.91* | 2.12 |
| $P_{O_2}$, mm Hg | 51 | 1 | 37* | 3 | 23* | 3 | 11* | 2 |
| Skeletal muscle | | | | | | | | |
| Blood flow, ml/min/100 g | 16.9 | 3.2 | 7.9* | 1.4 | 5.4* | 1.1 | 2.8* | 0.8 |
| $P_{VO_2}$, mm Hg | 53 | 1 | 36* | 2 | 27* | 2 | 24* | 1 |
| $\dot{V}_{O_2}$, ml/min/100 g | 0.91 | 0.14 | 0.89 | 0.14 | 0.82 | 0.14 | 0.50* | 0.11 |
| Venous lactate, μmol/ml | 3.86 | 0.25 | 4.02 | 0.33 | 6.77* | 0.77 | 11.35* | 1.41 |
| V-A lactate, μmol/ml | 0.30 | 0.25 | 0.72* | 0.45 | 1.49* | 0.43 | 0.30 | 0.70 |
| Lactate/pyruvate | 16.3 | 1.6 | 18.2 | 1.0 | 22.2* | 2.4 | 31.3* | 3.2 |
| Excess lactate, μmol/ml | 0.46 | 0.13 | 0.77 | 0.18 | −0.29 | 0.38 | −5.05* | 1.68 |

* Significantly different ($P < 0.05$) from control value by t test for paired data.

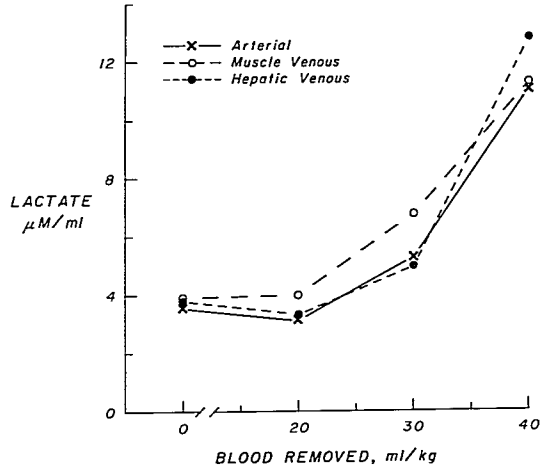


FIG. 1. Lactate levels in arterial (X), muscle venous (O), and hepatic venous (●) blood before and after induction of hypotension by progressive removal of blood during cyclopropane anesthesia.

### ARTERIAL CATECHOLAMINE AND LACTATE LEVELS

The levels of total catecholamine and blood lactate in arterial plasma before and after progressive blood removal are presented in table 3 and figure 3. Although the small number of observations limits extensive analysis of these data, several generalizations may be justified. With the same hemorrhagic stress, catecholamine levels increased earlier and achieved a greater final value during cyclopropane anesthesia. With both anesthetics, there were crude, but qualitatively similar, direct relationships between increases in blood lactate and catecholamine levels.

## Discussion

We recognize the many limitations of the present study. The blood loss occurred during and not before anesthesia in dogs and not in man. Observations following hemorrhage were made during an essentially unsteady, physiologic state in the presence of continuous succinylcholine, which is known to increase muscle $\dot{V}_{O_2}$. Cardiac output, hepatic blood flow, and actual tissue $O_2$ levels were not measured. Only total catecholamines were determined, and the relative contribution of epinephrine and norepinephrine to the total increase can only be conjectured. Blood was removed rapidly over a short period in the primary studies and slowly but continuously in the studies yielding plasma catecholamine values. Finally, and perhaps most importantly, the reliability of changes in blood lactate levels as prognosticators of bad events was not established.

It is clear, however, that the same hemorrhagic hypotensive stress resulted in a more severe lactic acidemia during cyclopropane than during halothane anesthesia. Furthermore, this difference appeared to reflect primarily the degree to which the stress evoked increased activity of the sympathetic nervous system and the consequent increase in levels of circulating catecholamines. The degree to which altered organ and whole-body blood flows influenced these findings cannot be defined except for skeletal muscle. While skeletal muscle blood flow rates decreased more during hemorrhage with cyclopropane, actual flow rates were greater at each stage than with halothane. In the previous studies with halothane, each tissue hypoxic stress (increased

TABLE 2. Responses to Staged Hemorrhagic Hypotension during Halothane Anesthesia (1.1 Per Cent)*

| | Blood Removed | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 | | 20 ml/kg | | 30 ml/kg | | 40 ml/kg | |
| | Mean | SE | Mean | SE | Mean | SE | Mean | SE |
| Arterial blood | | | | | | | | |
| Mean pressure, mm Hg | 102 | 4 | 70† | 1 | 53 | 3 | 37† | 2 |
| $P_{CO_2}$, mm Hg | 37 | 1 | 37 | 1 | 39 | 1 | 39† | 1 |
| *p*H | 7.43 | 0.01 | 7.42 | 0.01 | 7.39† | 0.01 | 7.34† | 0.01 |
| Buffer base, mEq/l | 50 | 1 | 49 | 0 | 48† | 1 | 44† | 1 |
| Lactate, μmol/ml | 3.33 | 0.62 | 3.09 | 0.50 | 3.51† | 0.43 | 4.94† | 0.69 |
| Lactate/pyruvate | 15.8 | 0.9 | 14.3 | 0.8 | 18.4 | 1.5 | 27.8† | 3.1 |
| Excess lactate, whole-body, μmol/ml | 0 | 0 | −0.35 | 0.16 | 0.48 | 0.20 | 2.08† | 0.49 |

* Modified from Theye RA: Effects of halothane, anoxia, and hemorrhage upon canine whole-body, skeletal muscle, and splanchnic excess lactate production. ANESTHESIOLOGY 35:394–400, 1971.

† Significantly different ($P < 0.05$) from comparable observations made during cyclopropane anesthesia in the present study (table 1) (t test for unpaired data).

halothane, decreased $Pa_{O_2}$, hemorrhagic hypotension) was progressively increased until skeletal muscle $\dot{V}_{O_2}$ decreased, and was thereafter continued until death. Despite this extent of compromise of oxygen delivery, shifts to anaerobic metabolic pathways and increases in blood lactate levels were not detected prior to the immediate preterminal period. In the studies with cyclopropane, similar criteria demonstrated a shift to anaerobic pathways prior to an overt reduction in skeletal muscle $\dot{V}_{O_2}$. It is our contention that these changes resulted not from hypoxia, *per se*, but rather from the release of catecholamines in response to various stimuli, including indirect effects of hypoxia, circulatory and metabolic reflexes, and direct and indirect actions of cyclopropane. Epinephrine, the catecholamine presumably released in this circumstance in the dog, is very effective in raising blood lactate

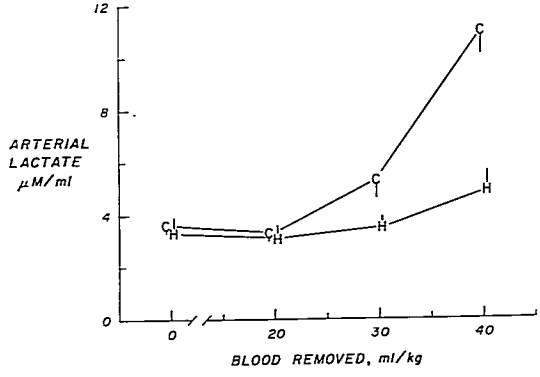


FIG. 2. Arterial blood lactate levels before and after induction of hypotension by progressive removal of blood during halothane (H) and cyclopropane (C) anesthesia.

TABLE 3. Total Arterial Plasma Catecholamine and Blood Lactate Contents before and after Removal of Blood during Halothane (Three Dogs) or Cyclopropane (Three Dogs) Anesthesia

| | Blood Removed | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 | | 20 ml/kg | | 30 ml/kg | | 40 ml/kg | |
| | Mean | Range | Mean | Range | Mean | Range | Mean | Range |
| Halothane | | | | | | | | |
| Catecholamine, μg/l | 0.29 | 0.24–0.38 | 0.33 | 0.18–0.43 | 0.47 | 0.17–0.99 | 1.96 | 0.31–5.20 |
| Lactate, μmol/ml | 2.1 | 1.3–2.6 | 1.5 | 1.0–1.9 | 1.5 | 1.0–1.7 | 2.7 | 1.5–4.3 |
| Cyclopropane | | | | | | | | |
| Catecholamine, μg/l | 0.18 | 0.04–0.34 | 0.53 | 0.18–0.73 | 0.94 | 0.81–1.05 | 9.71 | 5.04–15.60 |
| Lactate, μmol/ml | 1.7 | 1.1–2.9 | 1.4 | 0.9–2.5 | 2.2 | 1.2–3.1 | 6.1 | 3.7–8.8 |

levels, presumably by indirect effects involving the glycolytic pathway.[2, 9, 11]

This viewpoint is supported by the findings and opinions of others using a variety of experimental approaches. Price and associates,[12] studying adult male volunteers, detected production by the splanchnic viscera of XL during cyclopropane but not during halothane anesthesia. XL production apparently did not result from splanchnic ischemia, could be abolished by a β-adrenergic blocking drug, and was therefore ascribed to increased sympathetic nervous activity in these viscera. Drucker and associates[13] studied hypovolemic dogs and detected a greater decrease in arterial blood pH and a greater increase in the L/P ratio when the same degree of hypovolemia was followed by anesthesia with cyclopropane compared with halothane; these differences were ascribed to the relative inhibiting effects of halothane on sympathetic activity. Irving,[14] in an extensive review of the results of his own and other studies concerned with the therapeutic use of α- and β-adrenergic blocking agents in preventing development of irreversibility in hemorrhagic shock, concluded that ". . . the lactic-acidosis of haemorrhagic hypotension results from the action of both circulating and tissue catecholamines upon intracellular enzyme mechanisms

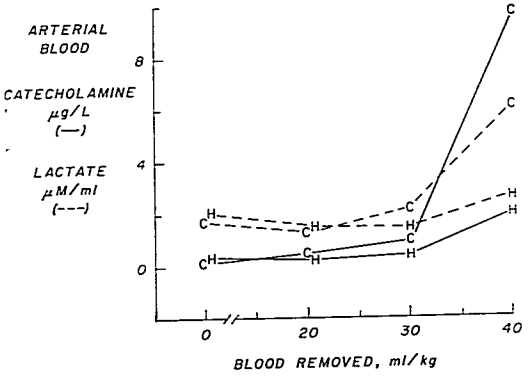


FIG. 3. Arterial plasma catecholamine (——) and blood lactate (– – –) levels before and after progressive removal of blood during halothane (H) and cyclopropane (C) anesthesia.

rather than from hypoxia itself." Robinson,[15] while agreeing with this view, has stressed in addition the role of interference with lactate removal and metabolism occurring primarily in the liver. This point was well illustrated in the present studies wherein, terminally, the liver ceased to consume and began to produce lactic acid and arterial blood lactate levels increased sharply.

These findings cannot be used to answer unequivocally the classic question of whether to use an anesthetic like halothane or one such as cyclopropane in circumstances of actual or potential hemorrhagic hypotension. They can, however, be used to re-emphasize much that is germane to the discussion. In the presence of cyclopropane, the response to unreplaced blood loss includes vigorous stimulation of the sympathetic nervous system with release of catecholamines, and initially there is better maintenance of arterial pressure and, presumably, cardiac output. To some extent, the actual reduction in blood volume is concealed by the various responses initiated via the sympathetic nervous system. To us, this seems an appropriate initial response to an acute threat. However, after further unreplaced blood loss, profound metabolic acidosis ensues and the circulation deteriorates, presumably, to a greater extent than would have occurred in the absence of the previous compensatory responses mediated by the release of catecholamines. In this regard the comments of Walter B. Cannon,[16] a pioneer investigator of the interrelationships among acidosis, shock, and the sympathetic nervous system, seem particularly appropriate. Dr. Cannon, in reviewing his experiences with the wounded in World War I, concluded by commenting:

> Operation on men suffering from shock and acidosis results in serious and rapid sinking of arterial pressure when it is already low, and in marked and sudden decrease of the alkali reserve of the blood when that reserve likewise is already low. This change may not occur if nitrous oxide–oxygen anesthesia, instead of ether, is employed, but that anesthetic affords no guarantee against the ominous decline.

## References


1. Theye RA: Effects of halothane, anoxia, and hemorrhage upon canine whole-body, skeletal muscle, and splanchnic excess lactate production. ANESTHESIOLOGY 35:394–400, 1971
2. Deutsch S, Linde HW, Price HL: Circulatory and sympathoadrenal responses to cyclopropane in the dog. J Pharmacol Exp Ther 135:354–357, 1962
3. Eger EI II, Brandstater B, Saidman LJ, et al: Equipotent alveolar concentrations of methoxyflurane, halothane, diethyl ether, fluroxene, cyclopropane, xenon and nitrous oxide in the dog. ANESTHESIOLOGY 26:771–777, 1965
4. Theye RA, Brown AL Jr, Van Dyke RA: The effects of halothane and succinylcholine on oxygen uptake of the canine gracilis muscle. ANESTHESIOLOGY 35:304–308, 1971
5. Theye RA: Calculation of blood $O_2$ content from optically determined Hb and $HbO_2$. ANESTHESIOLOGY 33:653–657, 1970
6. Huckabee WE: Relationships of pyruvate and lactate during anaerobic metabolism. I. Effects of infusion of pyruvate or glucose and of hyperventilation. J Clin Invest 37:244–254, 1958
7. Miller AT Jr: Energy Metabolism. Philadelphia, F. A. Davis Company, 1968
8. Renzini V, Brunori CA, Valori C: A sensitive and specific fluorimetric method for the determination of noradrenalin and adrenalin in human plasma. Clin Chim Acta 30:587–594, 1970
9. Walker WF, Zileli MS, Reutter FW, et al: Adrenal medullary secretion in hemorrhagic shock. Am J Physiol 197:773–780, 1959
10. Bagwell EE, Woods EF, Durst GG Jr: Influence of reserpine on cardiovascular and sympatho-adrenal responses to cyclopropane anesthesia in the dog. ANESTHESIOLOGY 25: 148–155, 1964
11. Goodman LS, Gilman A: The Pharmacological Basis of Therapeutics. Fourth edition. New York: The Macmillan Company, 1970
12. Price HL, Deutsch S, Davidson IA, et al: Can general anesthetics produce splanchnic visceral hypoxia by reducing regional blood flow? ANESTHESIOLOGY 27:24–32, 1966
13. Drucker WR, Davis HS, Burget D, et al: Effect of halothane and cyclopropane anesthesia on energy metabolism in hypovolemic animals. J Trauma 5:503–512, 1965
14. Irving MH: The sympatho-adrenal factor in haemorrhagic shock. Ann R Coll Surg Engl 42:367–386, 1968
15. Robinson JS: Acidosis in low flow states. Int Anesthesiol Clin 7:895–903, 1969
16. Cannon WB: Acidosis in cases of shock, hemorrhage and gas infection. JAMA 70: 531–535, 1918