Cardiovascular and Metabolic Sequelae of Inducing Anesthesia with Ketamine or Thiopental in Hypovolemic Swine

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If further sympathetic stimulation is neither possible nor desirable during moderate hypovolemia, anesthetic agents capable of sympathetic stimulation would not be advantageous for induction of anesthesia during hypovolemia. To test this hypothesis, 21 swine were studied during normovolemia and after 30% of their estimated blood volume was removed. Swine were divided randomly into three equal groups to receive no anesthetic or the minimal anesthetic dose of ketamine (6.65 ± 0.38 mg/kg, iv) or thiopental (5.77 ± 0.21 mg/kg, iv). After the initial response to hypovolemia, animals given no drug did not exhibit further changes during the hypovolemic period. Five minutes after induction of anesthesia in the hypovolemic state, ketamine, but not thiopental, caused large increases in plasma epinephrine, norepinephrine, and renin activity. Despite these differences, both anesthetics equally depressed systemic vascular resistance, mean systemic arterial blood pressure, heart rate, and cardiac output. Ketamine, but not thiopental, decreased stroke volume. Neither anesthetic affected oxygen consumption. Both anesthetics caused similar increases in blood lactate concentration. Thirty minutes after induction of anesthesia, plasma epinephrine, norepinephrine, and renin activity remained higher in animals given ketamine than in those given thiopental. Stroke volume, systemic vascular resistance, cardiac output, and oxygen consumption did not differ among groups; however, only the animals given ketamine showed further increase in blood lactate concentration and base-deficit. Thirty minutes after infusion of shed blood, cardiac output and blood lactate concentration were greater in the animals given ketamine than in those given thiopental or no anesthetic. Ninety minutes after infusion of shed blood, no differences existed among groups. The authors conclude that after moderate hemorrhage, further increase in circulating catecholamines is possible but that the levels achieved either exceed the maximal effective concentration at site(s) of action or their effects are overwhelmed by the depressant effects of ketamine. This study failed to document any advantage of ketamine over thiopental when used in the minimal anesthetic dosage for induction of anesthesia during hypovolemia. (Key words: Anesthetics, intravenous: ketamine; thiopental. Blood: loss; volume. Blood pressure: drug effects; measurement; peripheral vascular resistance. Heart: cardiac output; vascular pressures; ventricles. Hemorrhage.)

ALTHOUGH HYPOVOLEMIA usually is corrected before induction of anesthesia, some conditions may not permit restoration of blood volume before surgical intervention. Thus, it is occasionally necessary to induce anesthesia in a hypovolemic patient.

Compensation for hemorrhage is complex; important mechanisms include stimulation of baroreceptors and sympathetic and renin–angiotensin systems and increases in heart rate and systemic vascular resistance. It is not known to what extent anesthetics modify these mechanisms during a stimulated state of compensation for blood loss. Because of its pressor action, cyclopropane was once the recommended anesthetic agent for hypovolemic patients. However, laboratory studies subsequently demonstrated poorer survival rates for animals bled while anesthetized with cyclopropane than while anesthetized with other drugs.[1] Ketamine, like cyclopropane, has been advocated for use during hypovolemia[2–4] because of the hypertension and tachycardia produced in normovolemic animals[5] and humans.[6,7] Studies of animals bled during ketamine anesthesia produced differing interpretations as to the usefulness of this drug during hypovolemia.[8–11] Likewise, the use of thiopental for induction of anesthesia during hypovolemia is controversial.[12]

Neither ketamine nor thiopental has been studied in a controlled fashion for induction of anesthesia during hypovolemia. The single laboratory reports of administration of ketamine[13] or thiopental[14] to hypovolemic dogs are described insufficiently and without adequate controls. We conducted this study to examine the influence of anesthetic agents on compensatory mechanisms to hemorrhage in awake animals and to test our previously stated hypothesis[8] that sympathetic stimulation may be neither possible nor beneficial during induction of anesthesia in hypovolemic subjects.

Materials and Methods

We briefly anesthetized 21 young swine (Chester-White-Yorkshire crossbreed; weight 20.0 ± 0.25 kg, mean ± SE) with halothane in oxygen and nitrogen, which was adjusted to maintain arterial oxygen tension at 150–200 mmHg). The animals were paralyzed with succinylcholine, 2 mg/kg iv (later followed by administration of metocurine, 0.2 mg/kg iv, which was supplemented as required). The trachea was intubated and the animal ven-

tilated (tidal volume, 20 ml/kg; frequency was adjusted to maintain Pa_{CO_2} at 39.9 ± 0.2 mmHg). After local infiltration with 0.25% bupivacaine, catheters were placed through the superficial femoral artery into the abdominal aorta and percutaneously through the innominate vein into the pulmonary artery.

Halothane then was discontinued and eliminated by ventilation until its end-tidal concentration, as measured by mass spectroscopy (Perkin Elmer Model MGA 1100AB), fell to less than 0.5 mmHg (0.05 MAC). We waited an additional 30 min before beginning our studies. The animals remained intubated and mechanically ventilated.

Systemic arterial, pulmonary arterial, and right atrial pressures were transduced (Statham 23Db) and mean pressures derived electrically by a Gould preamplifier. Cardiac output was estimated using a thermodilution technique (3 ml, 0° C, 0.9% NaCl), a thermistor-tipped 5-Fr pulmonary arterial catheter (Edwards Laboratories) and an analog computer (Edwards Model 9520A). The temperature of the injectate was measured continuously. Cardiac output was measured until two successive values produced satisfactory logarithmic washout curves and differed by no more than 0.2 l/min. We continuously measured partial pressures of oxygen, carbon dioxide, and halothane at the orifice of the endotracheal tube using mass spectroscopy. These physiologic variables were recorded by a Gould polygraph (Model 2800). Temperature, measured in pulmonary arterial blood, was maintained within 0.5° C of its initial value using circulating water heating pads.

We calculated systemic vascular resistance (SVR) as the difference between mean systemic arterial (BPa) and right atrial pressures, divided by cardiac output. Pulmonary vascular resistance was calculated as the difference between mean pulmonary arterial and pulmonary arterial wedge pressures, divided by cardiac output.

During each experimental condition, we used Radiometer electrodes in steel-and-glass cuvets to determine partial pressures of oxygen and carbon dioxide and a Severinghaus-UC electrode to measure pH in both systemic and pulmonary arterial blood. All electrodes were maintained at 37° C. Calibrating gases and buffers were measured before and after each blood sample reading; the measurements were corrected for electrode drift, liquid-gas factor, and body temperature. Oxygen concentrations in systemic and pulmonary arterial blood were measured in duplicate by a galvanic cell instrument (Lex-O_2-Con-TL, Lexington Instruments). We calculated oxygen consumption as the product of cardiac output and the difference between arterial and mixed venous oxygen concentrations. Base-excess was estimated using a nomogram for swine blood.[15]

During each experimental condition, arterial blood samples were obtained for enzymatic measurement of whole-blood lactate concentrations[16] and plasma epinephrine and norepinephrine concentrations,[17] and for radioimmunoassay of plasma renin activity.[18]

All of these measurements and calculations were made while animals were normovolemic. Then 30% of each animal's blood volume (estimated using equations developed by Engelhardt[19]) was removed through the arterial cannula during a 30-min period. An additional 30 min was allowed before measurements were made for this hypovolemic state. Each animal was assigned randomly to receive ketamine (Group K), thiopental (Group T), or no anesthetic (Group C). In all other respects, animals were treated similarly.

We determined the appropriate dose of drug for each animal as follows. Forty-eight to 72 h before the day of experiment, a cannula was inserted into an ear vein of each (unmedicated) swine. Thiopental or ketamine, 6 mg/kg iv, was given rapidly, followed by repeated iv injections of 2 mg/kg every 15–20 s until the animal no longer responded to a painful ear stimulus. On the day of experiment, one-half this dosage was administered as a single bolus. In a separate set of subsequent experiments on swine, using eight littermates, we established that 30% hypovolemia reduces the anesthetic requirement by approximately 33% for thiopental and approximately 40% for ketamine. (Weiskopf RB and Bogetz MS, unpublished data). These reductions did not differ significantly from each other. Group K received ketamine, 6.65 ± 0.38 mg/kg; and Group T, thiopental, 5.77 ± 0.21 mg/kg.

All measurements were repeated 5 and 30 min after induction of anesthesia. Shed blood was then returned to the animal and measurements were repeated 30 and 90 min later.

For each experimental condition, results among groups were compared using analysis of variance with repeated measures and the Newman–Keuls method of multiple comparisons.[20] Statistical significance was accepted when $P < 0.05$.

Results

HEMORRHAGE (TABLE 1)

Right- and left-sided cardiac filling pressures decreased. Plasma renin activity, plasma concentrations of epinephrine and norepinephrine, heart rate, and systemic vascular resistance increased. However, these responses did not sustain stroke volume, cardiac output, or mean systemic arterial blood pressure. Oxygen consumption increased; and a decrease in base-excess and an increase in whole blood lactate concentration indicated the development of systemic acidosis.

and T to values less than that for Group C. As a result, mean systemic blood pressures did not differ between Groups K and T; however, both groups had pressures that were less than those for Group C. Oxygen consumption did not differ among the groups, but whole blood lactate concentrations increased similarly in Groups K and T.

Thirty Minutes after Induction: Thirty minutes after induction, most values had recovered towards preanesthetic levels during hypovolemia; however, significant differences remained. Plasma epinephrine concentration was still greater in Group K than in Groups C and T (which were not different from each other). Although plasma norepinephrine concentration was greater in Group K than in Group T, these two groups did not differ from Group C. Plasma renin activity was greater in Group K than in Group T, but the activity in these groups was not different from Group C. For Groups K and T, SVR did not differ from each other but was less than that for Group C.

Right- and left-sided cardiac filling pressures and heart rate remained similar, and cardiac output no longer differed among groups. Also, the resultant mean systemic arterial pressure was similar for Groups T and K; both were less than that for Group C.

Oxygen consumption did not differ among groups, but whole blood lactate concentration continued to increase and base-excess continued to decrease significantly only in Group K ($P < 0.05$).

Return of Shed Blood: Thirty minutes after return of shed blood, cardiac output was greater in Group K than in Groups C or T. Blood lactate was still greater in Group K than in either Group T or C. There were no other significant differences among groups.

Ninety minutes after return of shed blood, there were no significant differences among groups for any variable.

All animals survived 24 h, at which time they were killed.

Discussion

The cardiovascular effects produced by induction of anesthesia with ketamine during hypovolemia differ from those seen during normovolemia. Heart rate, mean systemic blood pressure, and cardiac output increase when ketamine is administered to normovolemic animals[5] or humans.[6,7] In contrast, these variables decrease during hypovolemia. In our study, ketamine and thiopental produced identical cardiovascular changes initially. Although these two anesthetics affected plasma catecholamine concentrations and renin activity differently, both caused similar deterioration of the animal's compensation for hemorrhage, and decreased SVR, cardiac output, and BPa. Thirty minutes after induction, hypovolemic animals who had received ketamine for induction became pro-

gressively more acidotic, while those who had received thiopental or no anesthetic did not.

Administration of ketamine further increased circulating catecholamine concentrations above the already elevated levels caused by the sympathetic response to hypovolemia. Thus, one portion of our hypothesis was not supported. In swine, the sympathetic response to 30% hemorrhage was not maximal; further sympathetic response was possible. The concomitant increase in plasma renin activity after administration of ketamine may be a function of increased sympathetic activity,[21,22] other circulating substances,[21] or a separate action of ketamine. The progressive lactic acidosis 30 min after induction, seen only in the ketamine group, may be a result of increased oxygen demand caused by increased sympathetic activity without concomitantly increased blood flow or decreased hepatic uptake of lactate, or both.

In intact experimental animals, it is not certain which measure best reflects inadequacy of tissue perfusion. Huckabee proposed blood "excess lactate" as a measure,[23] but later Cain demonstrated blood lactate concentration to be at least as good,[24] if not a better measure[25] of oxygen deficit. Previously, we have shown in asplenic dogs, bled while anesthetized, that blood lactate concentration and base-deficit developed to a greater extent when they were anesthetized with ketamine than with halothane, enflurane, or isoflurane.[8] Conversely, Longnecker *et al.* have reported higher excess lactate in rats bled while anesthetized with halothane than similar rats anesthetized with ketamine.[11] However, we have calculated that those rats anesthetized with ketamine had a greater base-deficit (approximately 11 mmol/l) than those anesthetized with halothane (approximately 2.5 mmol/l).

In these experiments, despite the increase in catecholamine concentrations and renin activity, SVR, BPa, and cardiac output decreased. This failure of massively increased levels of circulating catecholamines to maintain BPa, SVR, and cardiac output implies that ketamine has a powerful opposing depressant effect, or that the maximal response to stimulation had been achieved. Ketamine has been shown to be a direct myocardial depressant,[5,26–28] not to cause contraction of rabbit aortic strips,[29] and to relax phenylephrine-induced contracted rabbit aortic strips.[29] Similarly, thiopental depresses the myocardium[30] and peripheral vasculature.[31] In our experiments, both anesthetics decreased SVR. The fall in stroke volume index, at a time when left ventricular preload increased, seen after administration of ketamine, tends to indicate myocardial depression. However, since heart rate, afterload, and myocardial compliance were not controlled, no conclusion can be drawn.

Alternatively, the increase in circulating catecholamines in the animals given ketamine could have been a response

to the hypotension produced by the drug. This would imply that thiopental blocked a similar response. Our experimental data can not differentiate between these proposed mechanisms. Nevertheless, our data do support the second part of our hypothesis, that further sympathetic stimulation during induction of anesthesia during hypovolemia is not beneficial.

Several aspects of our methods should be discussed. Our animals were not "trained"; therefore, data obtained in the absence of anesthesia, with the animals' tracheas intubated and the animals mechanically ventilated, may not be equivalent to data for "resting" animals. Nevertheless, cardiovascular data we obtained for the unmedicated, normovolemic state fall within the range of values reported by other investigators.[19,32-39] Furthermore, hypovolemic and/or traumatized humans are not in a "resting" state. The few limited reports of hemorrhage in unmedicated swine have shown an arterial blood pressure response similar to that of our animals.[32,34,¶] Because detailed cardiovascular response of unmedicated swine to hemorrhage has not been reported, we cannot compare some of our results with those of other investigators.

Hemorrhage produced changes similar to those we have observed in a larger group of similar swine (Weiskopf RB, Bogetz MS: unpublished data). All cardiovascular and metabolic responses to hemorrhage in our swine are consistent with what is known for humans. Although the dog has been the species most frequently used to study hemorrhage, its response and that of the rat differ in important ways from that of humans.[40,41] In these species, contraction of the hepatic sphincter causes splanchnic engorgement and a number of sequelae not seen in humans.[40,41] The response of the gastrointestinal tract of swine in shock resembles that of humans.[42]

Because we did not conduct a dose–response study, we cannot address the question of whether other doses of ketamine or thiopental could have produced different effects during hypovolemia. However, the minimal anesthetic dose required during normovolemia was determined for both agents and individually for each animal. This dose then was reduced by half, which is in close agreement with our subsequent findings that hypovolemia similarly reduces the anesthetic requirement for thiopental and ketamine. Smaller doses would not have been anesthetic, and other cardiovascular responses could have occurred.

Our data do not demonstrate a beneficial effect from using ketamine during hypovolemia. Studies reporting

satisfactory use of ketamine for patients in "hemorrhagic shock" have had some shortcomings: the concomitant use of other drugs, and/or the failure to substantiate major blood volume deficit, to indicate the dose of ketamine administered, or to document cardiovascular responses at specific time intervals.[2-4] The literature concerning the use of thiopental for induction of anesthesia during hypovolemia is also anecdotal.[12]

Our data indicate that moderate hypovolemia does not produce a maximal increase in circulating catecholamines. Administration of ketamine, but not thiopental, causes a further increase. However, the increased plasma concentrations do not further stimulate the circulation, either because they are above the maximal possible effective concentrations or because their effect is overwhelmed by the depressant qualities of ketamine, or both. Administering ketamine for induction of anesthesia during hypovolemia did not offer any advantages over thiopental when both were used at the minimal anesthetic dose. The clinician should note that an anesthetic agent is not a substitute for adequate restoration of blood volume and venous return; and when an anesthetic must be administered during significant hypovolemia, cardiovascular depression should be expected.

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