Effect of Cyclopropane Anesthesia on Glucose Assimilation Coefficient of Man

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Cyclopropane anesthesia in man produces a mild, early and transient elevation of blood glucose levels averaging 16 mg./100 ml. Peak elevation of blood glucose levels occurs 20 minutes following induction of anesthesia, blood glucose levels then falling towards normal control values. Cyclopropane anesthesia is also associated with decreased rates of glucose utilization as determined by calculation of the coefficient of glucose assimilation following the rapid intravenous injection of glucose. The decrease in blood glucose levels at a time when glucose utilization is decreased indicates depression of rates of glucose production during cyclopropane anesthesia.

Cyclopropane anesthesia under clinical conditions has variously been reported as being associated with either little significant hyperglycemia 1 or with the development of moderate levels of hyperglycemia. 2-4 Such hyperglycemia as has been found during anesthesia has been ascribed, at least in part, to a decrease in glucose tolerance as indicated by abnormally elevated blood levels following the intravenous administration of glucose. 5,5 The interpretation and significance of glucose tolerance tests during anesthesia are, however, often difficult and uncertain. 6 The present study was designed to evaluate in detail the effect of cyclopropane on blood glucose levels under controlled conditions and to measure changes, if any, in the glucose assimilation coefficient. The glucose assimilation coefficient, expressed as the rate of disappearance of glucose from blood per minute measured at a time when vascular redistribution is no longer occurring, has limitations of interpretation but, unlike the usual intravenous glucose tolerance test, is independent of factors such as estimation of lean body weight, control blood levels, and extra-cellular glucose redistribution. 7-9

Methods

The glucose assimilation coefficient, K, was calculated from the slope of the curve obtained by plotting blood glucose levels on a semi-logarithmic scale against time, after the intravenous injection of a standard amount of glucose. K is expressed as

$$K = \frac{\log_{e} C_1 - \log_{e} C_2}{t_2 - t_1}$$

where $C_1$ and $C_2$ are blood glucose levels (mg./100 ml.) at times $t_1$ and $t_2$, respectively, following the rapid intravenous injection of glucose. Peak blood levels are normally reached within 5 minutes of rapid injection, following which they progressively decline to pre-injection levels over the next 120 minutes. 7,10,11 During the first 25 minutes, the rate of disappearance of glucose from blood is influenced by the rate of equilibration between the intravascular and interstitial fluid compartments; and, since blood levels of glucose are above renal threshold levels, by renal excretion. 12 Accordingly, in the present study K was calculated with $t_1$ and $t_2$ at 45 and 60 minutes following completion of the injection. 7,12 Thus, before anesthesia in a typical patient (fig. 1) K was

$$\frac{\log_{e} 122 - \log_{e} 98}{15} = 1.457$$

and during anesthesia

$$\frac{\log_{e} 154 - \log_{e} 133}{15} = 0.973.$$
Glucose utilization is defined either as the rate of entry of glucose into the intracellular compartment or as the rate of removal from the extracellular compartment by tissues. K values are reproducible in the same individual under the same conditions and are independent of the amount of glucose injected. 13 K values increase in pregnancy 9 and decrease in old age 14 and in patients with diabetes mellitus. 8, 9 Obesity has no effect. 15 Since justification for use of K values depends upon the assumption 13 that the disappearance of glucose from blood is a logarithmic function, the advantages gained in the present study by selecting the very end of the curve could have been offset if anesthetized patients failed to maintain a flat curve for the entire period. To prove whether this assumption regarding K applies during anesthesia, all data taken at each 15 minute interval were plotted on semilogarithmic paper. The resulting points fell on a straight line. K values at the time determined during anesthesia represent, therefore, glucose utilization and not a shift in the time of the normal flattening of the curve.

Thirty-four patients were studied. All were scheduled for elective surgery, most frequently D&Cs, inguinal herniorrhaphies, or hysterectomies, but 3 patients were studied who had cholecystectomies. If the duration of operation was shorter than the duration of the study, anesthesia was prolonged to allow completion of the study. Patients ranged in age from 23 to 66 years, were classified as physical status I or 2, and were free of any metabolic disorder, familial history of diabetes, and abnormal liver function. All patients were unpremedicated except for 10 who received 0.4 to 0.6 mg. atropine intra-muscularly 45-60 minutes before induction of anesthesia. All subjects had fasted for at least 8 hours. Anesthesia was induced with cyclopropane-oxygen and maintained using a circle system with carbon dioxide absorption with endotracheal intubation as required. Manual hyperventilation was produced to avoid carbon dioxide retention. Muscle relaxants (succinylcholine or d-tubocurarine) were administered intravenously as operating conditions indicated. Blood for glucose determinations was obtained from an arm vein, the needle kept patent by a slow infusion of normal saline. The maximum amount of saline administered during the test period of 80 minutes was 150 ml. No other parenteral fluids were administered. Prior to sampling, the infusion was stopped for approximately 10 sec. to wash away the saline in the vein, following which a venous tourniquet was applied, 3-5 ml. of blood withdrawn and discarded, and then 5 ml. of blood withdrawn into a tube containing citrate fluoride. Glucose was injected within 4 minutes as a 50 per cent solution in a dose of 25 g. per 70 kg. body weight. Operation had usually been in process for approximately 40-50 of the 80-minute test period.

Patients were divided into 3 groups. In Group 1, 10 patients, the effect of cyclopropane in blood glucose levels was studied. A venous blood sample was taken within 15 minutes prior to induction and subsequent samples were taken 20 minutes after start of induction and then every 15 minutes for 4 additional samples. In Group 2, 10 anesthetized patients, after fasting blood samples, rapid intravenous glucose injections were performed. Venous blood glucose samples were taken 4 minutes later and then every 15 minutes for 4 samples. In Group 3, 14 anesthetized patients, rapid intravenous glucose injections were performed during anesthesia. Samples were taken within 15 minutes prior to induction of anesthesia and 20 minutes after start of induction of anesthesia, immediately fol-
lowing which the rapid intravenous glucose injections were performed and blood glucose samples taken at 4 minutes and every 15 minutes for 4 samples. In Groups 2 and 3, 7 patients served as their own controls, having intravenous glucose injections without anesthesia and again during cyclopropane anesthesia with an interval of at least 3 hours between the tests.

Determinations of blood glucose were made in replicate by the Somogyi-Nelson macro-techniques.

Statistical significance was determined by calculating standard error of the means, comparing the difference between the means of observed results and calculating t values. Significance was assumed if corresponding P values were 0.01, or less.

Results

The effect of cyclopropane anesthesia on blood glucose and the effect of the intravenous injection of glucose are shown in figure 2. In Group 1 all patients except one had a rise in blood glucose during anesthesia. The levels rose significantly from pre-induction values (mean ± S.E.) of 79.5 ± 3.9 mg./100 ml. to a peak mean value of 96.3 ± 4.0 mg./100 ml. 20 minutes later. Over the course of the next 60 minutes levels decreased slightly reaching 90.6 ± 4.6 mg./100 ml. 80 minutes following induction, a level not significantly different from that prior to induction of anesthesia. Operation had started in most instances about 25 minutes after induction of anesthesia, but that it was not responsible for the hyperglycemia is indicated by the fact that blood glucose levels decreased after operation had started.

In Groups 2 and 3, the intravenous injection of glucose during anesthesia resulted in blood levels higher than those observed following the injection of the same amount of glucose without anesthesia. The glucose assimilation coefficients, K, for the two groups shown in table 1. Without anesthesia the mean glucose assimilation coefficient was 1.390; during anesthesia the mean value was 0.905, statistically significant, indicating decrease in glucose utilization during anesthesia. Each of the 7 patients who served as their own controls had lower K values during anesthesia, the mean values being 1.411 and 0.912, respectively a statistically significant decrease in glucose utilization during anesthesia. The relatively
short period of time between the two tests in these 7 patients was not the explanation for the observed results. Glucose loading will either increase glucose disappearance or have no effect, but it will not decrease it. In this study K was always lower after glucose loading than in the control state.

Discussion

The present results demonstrate that cyclopropane is associated with a transient hyperglycemia which reaches a peak 20 minutes after induction of anesthesia following which there is a gradual decrease in glucose levels towards pre-anesthetic values. Eighty minutes following the induction of anesthesia hyperglycemia had decreased to the point where it was no longer significant. The changes in glucose levels were associated with a significant decrease in glucose utilization. The present results differ in several respects from studies previously reported, primarily in animals, in patients premedicated with narcotics or barbiturates, in patients with metabolic disorders, or in poor risk patients exposed to anesthesia of variable length. The present findings confirm the conclusion of Hennehan and Bunker in 1961 that cyclopropane is associated with decreased rates of glucose utilization, the reservations held by one of the present investigators (N. M. C.) regarding this conclusion proving to be unfounded.

The cause of the increase in blood glucose levels early in cyclopropane anesthesia is best explained as the result of a combination of simultaneously acting factors rather than any single factor. Possible contributory factors can be divided into those which increase glucose production and those which decrease glucose utilization, hyperglycemia being the end result of the balance between rate of production and rate of utilization. There are two major factors which might increase glucose production during cyclopropane anesthesia; first, increased sympathetic nervous activity. Sympathetic activity is associated with increased blood glucose levels primarily because of hepatic glycogenolysis. That increased rates of hepatic glycogenolysis secondary to changes in sympathetic activity are a cause of cyclopropane hyperglycemia is, however, not likely in view of the observation by Price et al. that hepatic glucose production is decreased in man during cyclopropane anesthesia. Two patients were studied by these investigators. Both had increased arterial blood glucose levels and marked increases in splanchnic vascular resistance during anesthesia. In one, however, the rate of glucose liberation from the splanchnic area decreased from control levels of 120 down to zero mg./minute, while in the second corresponding values went from 300 to 165 mg./minute.

Secondly, increased blood levels of adrenocorticosteroids could contribute to the hyperglycemia by increasing glucose production. Increased steroid levels occur during cyclopropane administration, and they could contribute to hyperglycemia much as in patients with Cushing’s syndrome.

Decreases in renal blood flow occur during cyclopropane anesthesia and might contribute to hyperglycemia by decreasing urinary excretion of glucose. However, such an explanation could not explain the origin of a hyperglycemic state, although it could explain the duration and degree of a hyperglycemia initiated by other factors. Decreases in renal blood flow only contribute to hyperglycemia after other causes have elevated blood glucose levels above the renal threshold but cannot by themselves cause hyperglycemia in patients whose blood glucose concentrations remain below renal threshold levels. In the present series, increased blood glucose levels during anesthesia alone were probably unaffected by changes in renal blood flow since blood glucose levels never rose high enough to exceed the renal threshold.

The early and transient hyperglycemia of cyclopropane anesthesia could also in part be due to decreased rates of glucose utilization. Hyperglycemia will be associated with decreased glucose utilization if glucose production remains normal or if glucose production is decreased but not decreased more than utilization. The present data indicate that cyclopropane anesthesia is indeed associated with decreased rates of glucose utilization as shown by lower K values (table 1). What is surprising, however, is that blood glucose levels were decreasing at the time K values were
determined. Decreasing blood glucose levels in the presence of decreased rates of glucose utilization can only mean that the rate of production is decreasing more than the rate of utilization. The decrease in glucose production during cyclopropane anesthesia is unexplained. Perhaps cyclopropane alters or partially blocks the glycogenolysis normally associated with increased sympathetic system activity. The cause of the decrease in glucose utilization during cyclopropane anesthesia is also unknown. Perhaps cyclopropane inhibits insulin and so decreases glucose utilization much in the same manner as ether has been hypothesized as having an inhibitory effect and so contributing to the hyperglycemia of ether anesthesia.25

The relation of changes in rates of glucose production and glucose utilization to altered blood levels of carbohydrate metabolites such as lactate and pyruvate28 also remains undefined. If excess lactate production during anesthesia is the result of decreases in tissue oxygen tension large enough to impair glycolysis, it could be hypothesized that impaired metabolism along the glycolytic pathway would result in decreased rates of glucose consumption. But unexplained remains the decreased rate of glucose production.

**Summary**

Glucose metabolism during cyclopropane anesthesia was studied in 34 elective surgical patients by measuring blood glucose levels and glucose utilization rates. Glucose utilization rates were calculated from glucose assimilation coefficients following the rapid intravenous injection of glucose. Cyclopropane anesthesia was associated with an early, transient and mild hyperglycemia. The average increase in venous blood glucose was 16 mg./100 ml. This increase was attained 20 minutes following induction of anesthesia, after which time there was a progressive and gradual decrease in blood glucose levels towards pre-anesthetic control levels. Glucose utilization was significantly decreased by cyclopropane anesthesia. The decrease in utilization occurring at a time when blood glucose levels were falling suggests a decrease in rate of glucose production. The reason(s) for the decreased glucose production remain undefined.

**References**


Drugs

ALLOGERIN AND GALANTHAMINE The chemistry and pharmacology of dialyl-lor-toxiferine (Allogerin), a nondepolarizing relaxant, and galanthaminum hydrobromicum (Galanthamine) a true anticholinesterase are described. Allogerin has a rapid action, has a reliable reproducible effect, is easily antagonized by anticholinesterases, provides good abdominal relaxation after respiration has returned to normal, and causes no adverse side reactions. Galanthamine is an anticholinesterase which shows a distinct antagonistic effect on the nondepolarizing relaxants. It has a large therapeutic margin, good tolerance, reliable action, and a long lasting effect. Ten to 20 mg. of Galanthamine gives a reliable anticholinester effect. Since the muscarinic effect of the drug is small, no atropine need be given prior to the decurarization. Galanthamine has a distinct stimulating action on bowel peristalsis. (Mayerhoefer, O. Clinical Experiences with Dialyl-Nor-Toxiferine and the Curare Antidote Galanthamine, South. Med. J. 59: 1384 (Nov.) 1966.)