

Arterial Oxygenation During Hypothermia

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The aims of this study were: to investigate a possible significant relation between the size of the tidal volume during constant volume ventilation and the rate of change of the alveolar-arterial oxygen tension gradient (AaD_{O_2}); to determine whether hypothermia significantly affects this relationship; and to test the accuracy of correction factors previously proposed for the effect of temperature on the oxygen tension of fully saturated blood. Ten patients were surface cooled to 30° C. for over 24 hours. Anesthesia consisted of pentobarbital sodium and *d*-tubocurarine. Constant volume pulmonary ventilation with 100 per cent oxygen was provided by a piston pump. A significant relationship ($P < 0.01$) was found between the size of the constant tidal volume and the rate of increase or decrease of the AaD_{O_2} . This relation showed little evidence of being affected by hypothermia *per se*. The accuracy of previously determined temperature correction factors for oxygen tension was confirmed.

A RECENT study on the effects of accidental hypothermia reported greatly increased alveolar-arterial oxygen tension gradients (AaD_{O_2}) in every patient.¹ This report prompted the present investigation of the effects of hypothermia on AaD_{O_2} in man. We have previously shown that at normal temperature the size of the AaD_{O_2} is dependent upon the past and present pattern of ventilation.^{2, 3, 4} This work suggested a possible significant relationship between the size of the tidal volume during constant volume ventilation and the rate of increase or decrease in the AaD_{O_2} .

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The first aim of the present study was to investigate the significance of the relationship between the size of the tidal volume and the rate of change of the AaD_{O_2} . The second aim was to determine whether hypothermia significantly affects this relationship. By this approach it should prove possible to assess the effect of hypothermia *per se* on AaD_{O_2} .

Measurement of the AaD_{O_2} during hypothermia is complicated by the fact that accurate measurement of blood oxygen tension (P_{O_2}) requires either that the oxygen electrode always be kept at the same temperature as the patient or that the effect of temperature on P_{O_2} be known. At oxygen tensions where hemoglobin is not fully saturated temperature correction for P_{O_2} is complicated by the effect of temperature on the shift of the hemoglobin dissociation curve.⁵ At high arterial oxygen tensions hemoglobin is fully saturated, and the correct arterial oxygen tension of blood can be obtained by an oxygen electrode kept at 38° C. and applying corrections^{6, 7} for the reading given.

Our third aim is to confirm the accuracy of the temperature correction factors previously reported.⁶

Methods

To allow neurological investigation and treatment of cerebral edema 10 patients (average age 33.6 years) weighing an average of 61 kg. (range 45.5 to 83.2) were anesthetized with pentobarbital sodium (initial dose 3–5 mg./kg. body weight). Anesthesia was maintained with pentobarbital sodium given intravenously in intermittent doses of 50–100 mg. A radial artery was cannulated with a polyethylene catheter for sampling and measurement of pressures. Both brachial veins were cannulated to permit injections. All patients were supine during the studies.

d-Tubocurarine was given in intermittent doses of 9–12 mg. for muscle paralysis and to prevent shivering. A cuffed endotracheal tube was introduced in each patient, the cuff being inflated to ensure an airtight fit. Controlled constant volume ventilation was started at a frequency of 20/minute with a tidal volume of 4 ml./kg. body weight delivered by a constant volume sinusoid flow generator (piston pump). All patients were ventilated with 100 per cent oxygen during study periods. Body temperature was measured continuously with an esophageal electrode. A K-thermia unit, model R.K. 101* was used for surface cooling.

Because constant volume ventilation is dependent upon a gas tight system between the oxygen inlet to the piston pump and the patient's lungs, the constancy of ventilation was continually checked by means of a Wright⁸ ventilation meter placed on the expiratory exhaust of the pump. The accuracy of this meter was a known quantity.⁹ Following placement of the intra-arterial catheter, the lungs were ventilated with 100 per cent oxygen and tidal volumes of 4 ml./kg. body weight. After allowing approximately thirty minutes for denitrogenation samples were drawn to determine the AaD_{O_2} . In order to assess the influence of the pattern of ventilation on the AaD_{O_2} , the tidal volumes were changed immediately after the first sample, some patients now receiving larger tidal volumes, others smaller tidal volumes; all were ventilated at a frequency of 20 per minute. The pattern of ventilation was then kept constant for at least 60 minutes, at which time measurement of the AaD_{O_2} was repeated.

Following the first study period the patient was again ventilated with tidal volumes of 4 ml./kg. body weight and cooled to $30^\circ\text{C} \pm 2^\circ\text{C}$. After the temperature had stabilized at this level the AaD_{O_2} was again measured and the piston pump again adjusted to deliver a larger or smaller tidal volume—frequency still 20 per minute. Following one hour of constant volume ventilation the AaD_{O_2} was again measured.

During periods when measurements of AaD_{O_2} were not being made the patient re-

ceived our standard respiratory care¹⁰ including tracheal aspiration followed by intermittent passive hyperinflation of the lungs. The temperature was maintained at $30^\circ\text{C} \pm 2^\circ\text{C}$. for an average of 24.2 hours (range 24–26 hours). The patient was then rewarmed to 37°C ., and a portable chest roentgenogram was taken.

Arterial carbon dioxide tension (P_{aCO_2}) was measured with the Severinghaus electrode¹¹ and the arterial oxygen tension (P_{aO_2}) with a modified Clark electrode † (0.001 inch platinum cathode)¹² using a Sanborn polarization cell (model 350–416). Great care was taken to perform the polarographic measurements at 3 minutes after sampling. The accuracy of the Severinghaus¹¹ and Clark¹² electrodes were repeatedly checked against water and blood equilibrated with known percentages of oxygen and carbon dioxide.

In order to confirm the accuracy of previously proposed^{6,7} temperature correction factors for P_{O_2} of fully saturated blood, the following technique was used. Paired consecutive samples of arterial blood were drawn over a period of at least three respiratory cycles into syringes whose dead space was filled with heparin. The P_{O_2} of one of the paired samples was measured at 38°C .—that of the other was measured at the temperature of the patient. Oxygen electrodes were maintained both at 38°C . and at the temperature of the patient. The sample measured at 38°C . was warmed for one minute at 38°C . in the water bath in which the electrode was immersed. The P_{O_2} of this sample at 38°C . was multiplied by the appropriate correction factors^{6,7} and the result compared with the P_{O_2} of the other sample obtained from the electrode kept at the patient's temperature.

Because 100 per cent oxygen was used, the alveolar oxygen tension (P_{AO_2}) was calculated from the following equation:

$$P_{AO_2} = P_B - (P_{H_2O} + P_{aCO_2}), \quad (1)$$

thus

$$AaD_{O_2} = P_B - (P_{H_2O} + P_{aCO_2} + P_{aO_2}), \quad (2)$$

where P_B is the barometric pressure¹³ and P_{H_2O} is the water vapor pressure in the patient's alveoli.¹⁴

* Manufactured by Gorman Rupp Industries, Inc. Belville, Ohio.

† Obtained from Beckman Instruments, Inc., Fullerton, California.

Calculations

The change in AaD_{O_2} in millimeters of mercury per hour was obtained by subtracting the value for the AaD_{O_2} at the end of the hour of constant volume ventilation from the AaD_{O_2} at the beginning of the hour. This method was chosen to express the rate of increase or decrease in the AaD_{O_2} , although it is realized that the rate of change of AaD_{O_2} may not be constant over a given time period.

After the change in AaD_{O_2} per hour at normothermia had been plotted against the size of the tidal volume we decided arbitrarily to relate these variables by means of a linear regression, whose slope or regression coefficient (b_1) was estimated by the formula:

$$b = \frac{\sum xy - [(\sum x)(\sum y)/N]}{\sum x^2 - [(\sum x)^2/N]}, \quad (3)$$

where the x axis represents the independent variable, *i.e.*, the tidal volume in milliliters per kg. body weight, and the y axis represents the dependent variable, *i.e.*, the change in AaD_{O_2} (in mm. of mercury per hour).

Another regression coefficient (b_2) was calculated to assess the dependence of the same variables during hypothermia. The specific effect of hypothermia on the slope relative to the base line provided by normothermia could then be assessed by comparing the two regression coefficients, b_1 and b_2 . Finally we also fitted a regression line for the data pooled from these two groups. For further methods, including tests for the significance of the difference between the regression coefficients b_1 and b_2 , see appendix.

Results

There was a significant overall relation ($P < 0.01$) between the size of the tidal volume during constant volume ventilation and the rate of change of the AaD_{O_2} (fig. 1). Indeed, the regression coefficient for the pooled data, obtained both at normothermia and hypothermia, was $-14.98 \ddagger$ with the fitted regression line intercepting the line representing zero change in AaD_{O_2} at a tidal volume of 7.2 ml./

\ddagger All regression coefficients in this study represent change in AaD_{O_2} in mm. of mercury on time in hours versus constant tidal volume in milliliters per kilogram body weight.

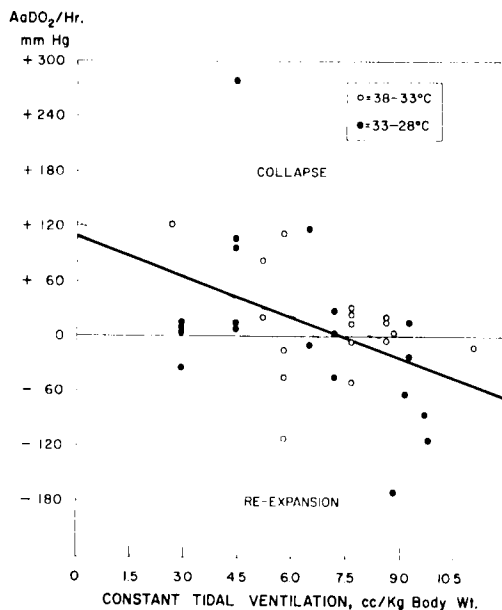


FIG. 1. The overall relation between the size of the tidal volume during constant volume ventilation and the rate of increase or decrease of the alveolar-arterial oxygen tension gradient (AaD_{O_2}) is significant ($r = -0.44$, $P < 0.01$). The fitted regression line for the pooled data obtained at both normothermia and hypothermia (continuous diagonal —) intercepts the line representing zero change in AaD_{O_2} at a tidal volume of 7.2 ml./kg. body weight. The slope of the linear regression line (---) fitted to the measurements made at normothermia was not significantly different from the slope of the line fitted to the measurements made at hypothermia (—). (See text for statistical analysis.)

kg. body weight. At a frequency of 20 per minute, this tidal volume caused neither increase nor decrease of AaD_{O_2} , in the average patient, suggesting that this particular pattern of ventilation led neither to collapse nor re-expansion of the lungs. At 37° C. this pattern of ventilation led to a Pa_{CO_2} of approximately 25 mm. of mercury. For each milliliter increase in constant tidal ventilation above 7.2 ml./kg. body weight the rate of *fall* of the AaD_{O_2} increased an average of 14.98 mm. of mercury per hour. For every milliliter that the tidal volume was below 7.2 ml./kg. body weight the rate of *increase* of the AaD_{O_2} rose an average of 14.98 mm. of mercury per hour.

During hypothermia the regression coefficient of this relationship was $-18.42, \ddagger$ while during normothermia it was $-9.77 \ddagger$ (fig. 1).

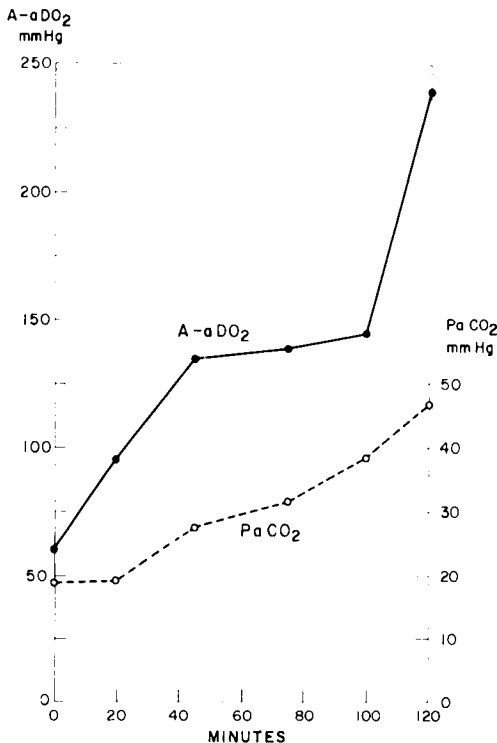


FIG. 2. Arterial carbon dioxide tension (P_{aCO_2}), and alveolar-arterial oxygen tension differences ($A-aDO_2$) in a 45 year old 44.5-kg. female patient ventilated at $30^\circ C$. with a constant tidal volume of 200 ml. 100 per cent oxygen, frequency 20 per minute.

The difference between these two regression coefficients has a t value of 0.732, which has a probability level using a two-tailed t table for 33 degrees of freedom of 0.45;¹⁵ this implies close agreement. A sampling error complicated comparison of the measurements made during hypothermia and normothermia. The variance ratio between the groups (F) equalled 2.42. With 19 degrees of freedom in the numerator and 16 in the denominator, using a two-tailed test, the probability that the observed value of the variance ratio would be this extreme or more, if the populations were alike, is between 2 and 10 per cent.¹⁵ Taking into account this possible disparity in sampling error we have not detected a significant difference between hypothermia and normothermia in the slopes of the lines relating the rate of change of the $A-aDO_2$ and the size of the tidal volume.

We analyzed the distribution of the plots of measurements of hypothermia and normothermia about their common regression line; using a 2×2 contingency table this gave a value for chi square of 2.166. This value of chi square is approximately at the 14 per cent level¹⁵ and thus is not significant at the usual levels. We concluded that this study produced little evidence of a distinction between the effect of hypothermia and normothermia on the relationship between the size of the tidal volume during constant volume ventilation and the rate of increase or decrease in the $A-aDO_2$.

With a small $A-aDO_2$ at the start of the period of constant volume ventilation, and a small tidal volume, the rate of increase in $A-aDO_2$ may be large (figs. 2 and 3). If large tidal volumes are employed the existing small gradients will be diminished (fig. 3). If a large $A-aDO_2$ is present at the start, then large tidal volumes will most probably lead to a greater diminution in $A-aDO_2$. If the tidal volume is small and the $A-aDO_2$ is already large the rate of increase in $A-aDO_2$ is variable, but usually small (fig. 1).

The *in vivo* accuracy of correction factors for the effect of temperature on the P_{O_2} of

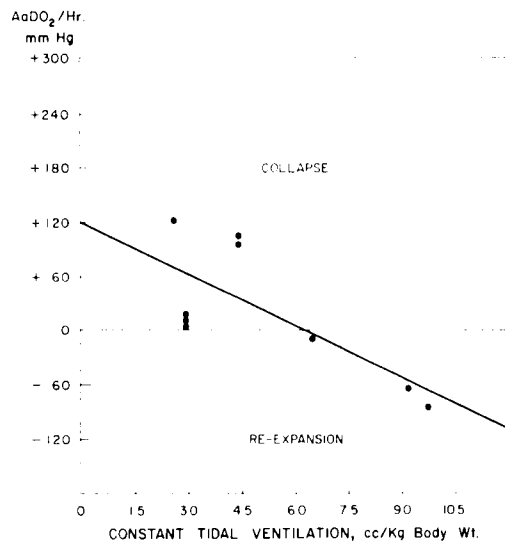


FIG. 3. Data obtained when the alveolar-arterial oxygen tension difference ($A-aDO_2$) was 50-100 mm. of mercury at the start of the period of constant volume ventilation. The relation between the size of the tidal volume and rate of increase or decrease of the $A-aDO_2$ is significant ($r = -0.746$, $P < 0.05$).

fully saturated blood was determined. The correlation between the results of paired consecutively drawn arterial blood samples is shown in figure 4. For paired samples with oxygen tensions between 190 and 350 mm. of mercury the standard deviation of the distribution of differences (S.D.) is 8.3, for samples with P_{O_2} 350–550 mm. of mercury S.D. is 34.6, for samples of oxygen tension 550–710 mm. of mercury the S.D. is 27.1. These standard deviations show that oxygen tensions above 350 mm. of mercury were measured less accurately. No systematic error in measurement was found at any temperature. Variances were evenly distributed about the mean, except that at oxygen tensions between 190 and 220 mm. of mercury previously proposed^{6,7} correction factors appeared to give 2–3 per cent undercorrection for the effect of temperature on the oxygen tension of samples measured at 38° C. The slight undercorrection at these relatively low tensions may indicate incomplete saturation of hemoglobin in the samples. At higher tensions (above 250 mm. of mercury) this effect was not observed, and temperature correction factors gave satisfactory correction.

Chest roentgenograms taken after rewarming showed no radiological abnormalities according to the separate reports of two radiologists. One patient developed bronchopneumonia six days after rewarming. Chest roentgenograms of this patient were normal for the first four days after hypothermia.

Discussion

In patients receiving constant volume ventilation, and breathing 100 per cent oxygen, the rate of increase or decrease in the AaD_{O_2} is dependent on the size of the constant tidal volume. Hypothermia has no specifically detectable effect on this relationship. We therefore cannot agree with McNicol and Smith's¹ postulate that cold injury to lung specifically caused the large AaD_{O_2} found in their patients and was the precursor of bronchopneumonia.

Bronchopneumonia, however, can be a problem during and after hypothermia, especially when the patients do not have the benefit of a pattern of ventilation appropriate for maintaining adequate alveolar expansion.^{2, 3, 4, 16}

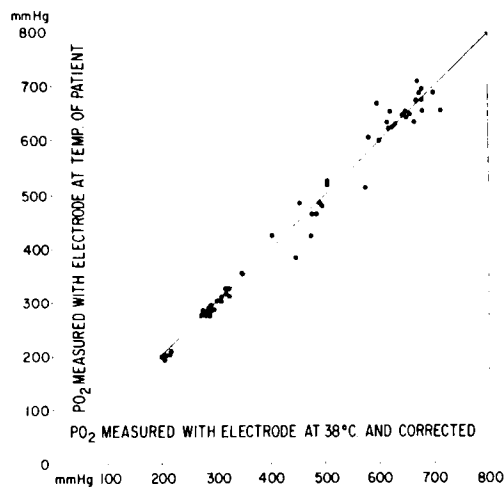


FIG. 4. Pairs of arterial blood samples were drawn, one after the other, from patients at 29° C.–33° C. The oxygen tension (P_{O_2}) of one of the paired samples was measured at 38° C. and multiplied by our correction factors.⁶ The P_{O_2} of the other sample was measured at the temperature of the patient. At oxygen tensions between 190 and 350 mm. of mercury the standard deviation of the distribution of the differences (S.D.) is 8.3, for samples with P_{O_2} 350–550 mm. of mercury S.D. is 34.6, for samples of P_{O_2} 550–710 mm. of mercury S.D. is 27.1. The correlation coefficient (r) was 0.976. The 2–3 per cent undercorrection at oxygen tensions between 190 and 220 mm. of mercury may indicate incomplete saturation of hemoglobin in the blood samples.

In recent years our techniques of managing therapeutic hypothermia have changed. We used to allow hypothermic patients to breathe spontaneously, but found that approximately 30 per cent of patients developed bronchopneumonia within the first 24–36 hours after the start of cooling (unpublished data). A similar experience has been reported by other groups.^{1, 17} In this investigation we imitated a normal pattern of ventilation¹⁶ by giving passive hyperinflation 3–6 times an hour between study periods.² By paying scrupulous attention to respiratory care¹⁰ we prevented respiratory complications, although one out of 10 patients did develop bronchopneumonia six days after the termination of hypothermia.

Arterial carbon dioxide tension (P_{aCO_2}) is used as an index of ventilatory adequacy. According to Radford's nomogram,¹⁸ at normothermia and at a rate of 20 breaths per minute, the tidal volume, required to maintain a P_{aCO_2} of 40 mm. of mercury is 4.7–5.6 ml./kg. body

weight. In spite of adequate ventilation (in terms of carbon dioxide elimination) such tidal volumes can lead to an increasing AaD_{O₂} (figs. 1 and 3); thus in some patients Pa_{CO₂} measurements cannot predict the onset of impaired oxygenation. Without oxygen tension measurements the significance of this impairment of oxygenation is often unrecognizable since an AaD_{O₂} of less than 500 mm. of mercury does not cause arterial desaturation when 100 per cent oxygen is inspired. A gradient of 500 mm. of mercury does, however, reflect a right to left shunt of approximately 35 per cent of the cardiac output.³ If air is inspired instead of oxygen such a shunt will cause profound hypoxemia. Even when smaller AaD_{O₂} are present on 100 per cent oxygen hypoxemia may result if the inspired oxygen tension is lowered.¹⁹ An additional reason for this is that the physiological shunt which caused the AaD_{O₂} when 100 per cent oxygen was inspired may now be augmented by the effects of a nitrogen build-up in underventilated alveoli. In a denitrogenated patient breathing 100 per cent oxygen these underventilated alveoli contribute insignificantly to the AaD_{O₂}, but as the inspired oxygen tension is lowered their effect on AaD_{O₂} increases.²⁰

Owing to advances in the technique of polarography²¹ and increased understanding of the solubility of oxygen in blood,⁶ previous difficulties with the measurement²² of high oxygen tensions during hypothermia appear to have been overcome. Factors previously proposed by us⁶ give accurate correction for the effect of temperature on P_{O₂} when hemoglobin is fully saturated.

Bradley, Stupfel, and Severinghaus²³ and Severinghaus^{24, 25} proposed other temperature correction factors for P_{O₂}. These factors ignore the change in O₂ solubility of blood with temperature and take into account only shifts in the position of the dissociation curve; they are thus intended for use only when hemoglobin is not fully saturated. Unfortunately, the use of the Severinghaus factors^{23, 24, 25} for practical purposes is limited by the fact that for the "same pH the oxygen dissociation curve of a blood sample with metabolic acidosis will be to the left of that of a 'normal' curve such as that published by Severinghaus^{23, 24, 25} and vice versa for metabolic baseosis."²⁶ This dif-

ficulty is compounded by the fact that Severinghaus' correction factors for tensions between 100 and 300 mm. of mercury are based on dissociation curves²⁷ that are probably incorrect.⁶ We thus believe that, to measure arterial oxygen tension when hemoglobin is not fully saturated (*i.e.*, below P_{O₂} 200 mm. of mercury), the oxygen electrode must be kept at the temperature of the patient.

The practical importance of assessing AaD_{O₂} during controlled ventilation with 99-100 per cent oxygen is to estimate the probable physiologic shunt. Shunts under 30 per cent of the cardiac output are not immediately dangerous while almost pure oxygen is being inspired. Their importance lies primarily in the catastrophic effects they may have when air is breathed;¹⁹ and secondarily in the decreased compliance and atelectasis implied by the presence of such shunts.^{3, 28} Atelectasis may be succeeded by pneumonia. Thus, we can be certain that the patient receives a pattern of ventilation, optimal for prevention of post-operative complications, *only* if the AaD_{O₂} does not increase. This applies equally at hypothermia and at normothermia.

Summary

A significant relation was found in 10 patients between the size of the tidal volume during constant volume ventilation with 100 per cent oxygen and the rate of increase or decrease of the alveolar-arterial oxygen tension gradient (AaD_{O₂}). Tidal ventilation of 7.2 ml./kg. body weight, frequency 20 per minute, gave, on average, a stable AaD_{O₂}. This pattern of constant volume ventilation, therefore, apparently prevents increasing atelectasis.

For every milliliter that tidal ventilation was below 7.2 ml./kg. body weight the rate of increase of the AaD_{O₂} rose an average of 15 mm. of mercury per hour. For every milliliter that tidal ventilation was above 7.2 ml./kg. body weight the rate of fall of the AaD_{O₂} increased an average of 15 mm. of mercury per hour.

This relation between the size of the tidal volume during constant volume ventilation and the rate of change of the AaD_{O₂} was not demonstrably affected by hypothermia *per se*. This study confirmed the accuracy of factors we had previously proposed, to correct for the effect of temperature on the oxygen tension of fully saturated blood.

APPENDIX

Linear regression coefficients for the effect of size of tidal volume on rate of change of A-a)O₂ during normothermia (*b*₁) and during hypothermia (*b*₂) were calculated using equation 3 (see calculations). Since the variance of the difference (*d*) between the two regression coefficients *b*₁ and *b*₂ is the sum of the individual variances,²⁰ we compute the deviate

$$d = \frac{b_1 - b_2}{\sqrt{\frac{s_1^2}{\sum_1(x - \bar{x}_1)^2} + \frac{s_2^2}{\sum_2(x - \bar{x}_2)^2}}}, \quad (\text{A-1})$$

where *s*₁² and *s*₂² are residual variances about the regression line for normothermia and hypothermia, respectively.

The significance of *d* (equation A-1) was determined by treating it as a Student's *t* with *f* degrees of freedom given by:

$$f = \frac{1}{\frac{n^2}{n_1 - 2} + \frac{(1 - n)^2}{n_2 - 2}}, \quad (\text{A-2})$$

where

$$n = \frac{s_1^2/\sum_1(x - \bar{x}_1)^2}{s_1^2/\sum_1(x - \bar{x}_1)^2 + s_2^2/\sum_2(x - \bar{x}_2)^2}. \quad (\text{A-3})$$

These variances *s*₁² and *s*₂² were obtained from the equation,

$$s^2 = \frac{1}{n-2} \left\{ \sum (y - \bar{y})^2 - \frac{[\sum(x - \bar{x})(y - \bar{y})]^2}{\sum(x - \bar{x})^2} \right\}, \quad (\text{A-4})$$

where the subscripts identifying the two groups have been dropped.

The regression lines shown in figures 1 and 3 were obtained from the equation:

$$y = a + bx, \quad (\text{A-5})$$

where

$$a = \bar{y} - b\bar{x}. \quad (\text{A-6})$$

The equality of the residual variances of each group *s*₁² and *s*₂² about their respective regression lines was tested by the variance ratio test,

$$F = \frac{s_1^2}{s_2^2}. \quad (\text{A-7})$$

The appropriate value of *F* using a two-tailed test was read from the tables of Fisher and Yates¹⁵ for (*n*₁ - 1) degrees of freedom in the numerator and (*n*₂ - 1) in the denominator.

To help test the Null Hypothesis that hypothermia has no effect on the relationship between the change in A-a)O₂ per hour and the size of the tidal volume, a 2 × 2 contingency table was constructed. This table showed the distribution of plots obtained from measurements made at hypothermia and normothermia above and below the regression line obtained from the pooled data.

The formula for chi square with Yates' correction was used:

$$\chi^2 = \frac{n \{ |ad - bc| - \frac{1}{2}n \}^2}{(a + b)(c + d)(a + c)(b + d)}, \quad (\text{A-8})$$

where *a* is the number of plots from hypothermic measurements above the pooled regression line, *b* is the number of plots from hypothermic measurements below this regression line, *c* is the number of plots derived from normothermic measurements above the pooled regression line, and *d* is the number of plots from normothermic measurements below this regression line. The tables of Fisher and Yates on the distribution of χ^2 ¹⁵ were examined for one degree of freedom to see whether the observed value of χ^2 was larger than would be expected by chance on the Null Hypothesis that postulated no effect of hypothermia on the relationship between the change in A-a)O₂ per hour and the size of the tidal volume.

Correlation coefficients (*r*) were obtained by using the formula:

$$r = \frac{\sum(x - \bar{x})(y - \bar{y})}{\sqrt{\sum(x - \bar{x})^2 \sum(y - \bar{y})^2}}. \quad (\text{A-9})$$

The probability value (*P*) for *r* was then read from the tables of Fisher and Yates¹⁵ for *n* - 2 degrees of freedom.

The standard deviation (*sd*) of the oxygen tensions of the paired blood samples was calculated from the formula:

$$sd = \sqrt{\frac{D^2}{n - 1}}, \quad (\text{A-10})$$

where *D* is the difference between the oxygen tensions of each paired sample.

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DRUG-INDUCED LIVER DISEASE One hundred and fifty-five cases of drug-induced hepatic injury were studied and were divided into six histopathologic groups: (1) zonal injury; (2) uncomplicated cholestasis; (3) nonspecific drug-induced hepatitis; (4) reactions simulating viral hepatitis; (5) nonspecific reactive hepatitis; and (6) drug-induced steatosis. In ten instances, within the viral hepatitis type, halothane had been employed as an anesthetic agent. In eight of these the anesthesia had been repeatedly used. In an additional case, methoxyflurane had been employed shortly before the outbreak of jaundice. Nonspecific drug hepatitis and the hepatic reaction resembling viral hepatitis both possibly represent immunologic injuries. The difference between these two reactions may be only quantitative, and they should be considered as variants of the same group. (*Popper, H., and others: Drug-Induced Liver Disease, Arch. Intern. Med.* **115**: 128 (Feb.) 1965.)