EXPERIMENTAL APPROACHES

Acid-Base Relationships and the Cardiac Response to Aerosol Inhalation*

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In a study of 30 dogs exposed to fluoroalkane-propelled aerosol preparations it was found that half survived while the other half succumbed to a very similar pattern of rhythm disturbance which resulted in asystole. In an analysis of blood-gas data, it was found that the survivors had in common a lower pH, a higher Pco₂ and, at certain points in the experiment, a greater base deficit. These data suggest that one factor in determining the likelihood of survival or death in young people who sniff aerosols deliberately may relate to the acid-base response of the host to the inhalant.

Reports of sudden deaths in persons who deliberately inhale fluoroalkane propelled commercial products prompted our studies.1,2

Because human exposure characteristically has been in the form of repeated deep inhalations from a balloon filled with the gas, or from a plastic bag repeatedly sprayed with the gas, the presumption was made that hypoxemia, hypercapnia, or both were necessary to sensitize the human myocardium. Fluoroalkane gases subsequently were shown to sensitize mice to asphyxia-induced rhythm disturbances.3 However, when arterial oxygen tension (Po₂), carbon dioxide tension (Pco₂), and oxygen saturation (O₂ sat) were rigidly controlled, sudden death due to rhythm disturbances still occurred.4,6

Having established that careful control of parameters reflecting ventilation and oxygenation did not protect against lethal arrhythmias, we proposed a larger study in order to further analyze variables which might predict the life or death outcome in the human experience. We concentrated on arterial blood gas differences in survivors as compared to nonsurvivors at many stages during the experiments.

METHODS

Thirty heartworm-free mongrel dogs, weighing between 10 and 23 kg, were anesthetized with intravenous pentobarbital, 30 mg/kg. The animals were intubated and artificially ventilated between 1 and 14 times per minute with a volume of room air and oxygen controlled by nomogram, taking into consideration the dead space of the apparatus, the dead space of the animal, and the animal's size. The determination of Po₂, Pco₂, oxygen saturation, pH, base excess and bicarbonate was made from blood samples obtained from an indwelling cannula in the right femoral artery, or from a percutaneously introduced catheter advanced to the central aorta. In order that no animal enter the experiment with drastically altered acid-base relationships, corrections were made if necessary to assure that the Po₂ was above 60 and Pco₂ below 50. Oxygen saturations were all above 95 percent. The remainder of the blood gas data were made available to us only after the experiments were completed.

A No. 5 bipolar electrode catheter was placed via the right jugular vein high in the right atrium for recording a high atrial electrical signal. A tripolar electrode recording catheter was introduced via the left femoral vein and passed retrograde to the atrium and across the tricuspid valve. The catheter was withdrawn until a sharp deflection was noted between the A wave and the V wave of the intracardiac electrogams and was validated as likely originating from the bundle of His.4-7 High-frequency standard leads II and V₁-V₅ were

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recorded from needle electrodes along with the intracardiac electrograms. Respiration was also monitored constantly. The signals were recorded onto Ampex FR1300 magnetic tape for permanent storage. Constant oscillographic monitoring occurred during the experiments. Final recording in permanent form was accomplished with a Grass kymograph oscillographic camera at film speeds of 500, 250, and 100 mm per second. In all instances recording was without a hand pass filter or other means of limiting the frequency spectrum which was between 0.2 and 40,000 Hz.

\[ P_{CO_2}, \ P_{CO_2}, \ \text{pH}, \ \text{oxygen saturation}, \ \text{calculated base excess,} \]
and bicarbonate levels were checked at the beginning of the experiment, at least at five-minute intervals during the experiment, at every change in rhythm, and at the termination of the experiment. Measurements were made to the nearest one-half millisecond of the R-R intervals, the total and fractionated P-R intervals. Included were measurements of the approximate intra-atrial conduction times as estimated by the time lapse between the high atrial signal and the low atrial signal recorded from the catheter placed across the tricuspid valve (P-A interval), the time lapse for the impulse to travel from the region of the low atrium through the atrioventricular node to the region of the bundle of His (A-H interval), and the time lapse for the impulse to travel from the bundle of His through the bundle branches and the Purkinje-myocardial junction (H-V interval).

After the baseline data were obtained, the animal was allowed to spontaneously breathe from a bag of volatileized substances. In 28 out of the 30 cases there was a concentration of 65 percent trichloromonofluoromethane and 35 percent dichlorodifluoromethane. In two instances the concentrations of these two products were reversed. At the first onset of rate or rhythm change, which included detectable slowing from the baseline sinus rhythm on the oscilloscope, a blood gas sample was obtained, the bag removed, and the animal placed back on controlled ventilation. Monitoring was continued throughout a series of developing rhythm disturbances with a blood gas determination at each detectable change, at a maximum of five-minute intervals, and terminally. The bag was sprayed by a short blast at approximately two-minute intervals to simulate the manner of deliberate human autoexposure.

RESULTS

Four animals were eliminated due to laboratory accidents. Thirteen of the 26 remaining animals developed a remarkably similar sequence of rhythm disturbances, including sinus bradycardia, junctional or ventricular escape rhythms with ultimate electrical asystole in nine, and ventricular fibrillation in four. The other 13 animals all developed sinus slowing but in nine, no other disturbances of mechanism occurred. In the case of two animals, ventricular tachycardia developed and in two others, only ventricular premature beats were seen. These animals were observed for one hour and were killed at the end of that time in sinus rhythm. Details of the delays that occurred in intra-atrial transmission, atrioventricular nodal transmission and His-ventricular conduction times will be reported elsewhere. H-V intervals generally remained quite constant until H-V dissociation occurred, and such dissociation occurred only in animals which died.

Figure 1 (and all figures) show the means and standard deviations of the survivors (open circles) as compared to the nonsurvivors (opaque circles). The standard deviations and the statistical differences of the two groups are shown. There was a baseline difference in the level of base excess in the survivors compared to the nonsurvivors. There was a greater base deficit at the beginning of the experiment and the lower pH is associated with ultimate survival after exposure to fluorolalkane-propelled aerosols.

![Figure 1](image-url)

Figure 1. In this and in all subsequent figures arterial blood-gas and acid-base data are illustrated for animals which lived (open circles) and animals which died (opaque circles). Means and standard deviations are illustrated for oxygen tension \(P_{O_2}\), carbon dioxide tension \(P_{CO_2}\), oxygen saturation \(S_{sat}\), pH, base excess \(BE\), and bicarbonate \(HCO_3^-\). When the differences between the means were significant, the \(p\) value is indicated. In each instance, both hydrogen ion concentration and pH values were checked for statistical significance though only pH level is plotted. In Figure 1 we see that there is a significant difference between the mean pH value and base excess value of the survivors as compared with the nonsurvivors. The greater base deficit at the beginning of the experiment and the lower pH is associated with ultimate survival after exposure to fluorolalkane-propelled aerosols.

![Figure 2](image-url)

Figure 2. Arterial blood-gas data at the time of discontinuation of exposure is illustrated showing a higher \(P_{CO_2}\), lower pH, and greater negative base excess (base deficit) associated with survival. The differences in the \(P_{O_2}\), oxygen saturation, and bicarbonate were not significant.
a base excess of about −4 mEq/L in the survivors compared to −2 in the nonsurvivors (P<.05). This was reflected in the pH with a mean level slightly above 7.3 in the survivors and slightly below 7.4 in the nonsurvivors. The significance of the difference based on hydrogen ion concentration as well as pH was determined and both were significant (P<.025). The other parameters, however, were not significantly different.

Figure 2 shows comparisons of the blood gas analysis at the time of discontinuation of exposure. The survivors had a higher mean PCO₂, as well as a lower pH and a greater base deficit. Again, oxygen tension, saturation, and bicarbonate level demonstrated no significant differences.

Comparisons of the various parameters at the times of lowest pH occurring at any time during the experiment demonstrated a higher PCO₂ (P<.025), a lower pH (P<.005) and greater base deficit (P<.01). There was an insignificant difference in the other parameters.

Differences in the degree of change from baseline to final analysis during exposure in survivors versus nonsurvivors (Fig 3) were significant, although the levels themselves are not extreme. The PCO₂ went up in the survivors and dropped slightly in the nonsurvivors (P<.05). The pH followed with a decrease from the before to the after determinations in the survivors, and went up slightly in the nonsurvivors with a significant difference (P<.025). The group differences in degrees of change in the levels of oxygen saturation, tension, base excess, and bicarbonate were not significant.

The comparative changes from baseline determinations to the maximum alteration followed the same pattern of significance as did the before to after analysis. There was a change upward when the baseline PCO₂ was compared with the maximum, with the significantly greater degree of change in the survivors (P<.025). Oxygen saturation and PO₂ dropped in both survivors and nonsurvivors, but the differences in the degree of drop was insignificant, as was the difference in bicarbonate and base excess levels. The pH again was seen to drop in the survivors, to slightly rise in the nonsurvivors with a statistically significant difference in the degree of change between the two groups (P<.025).

Finally, every sample for each animal regardless of how many were taken was considered (Fig 4). From these values, a single mean was entered for each animal representing the average for that animal for the entire experimental period. Survivors versus nonsurvivors means showed significant differences in the carbon dioxide tension, the base excess, and the pH. The higher PCO₂ and lower pH and base excess (greater base deficit) were apparent in the survivors. Oxygen tension, saturation, and bicarbonate levels did not differ significantly.

**DISCUSSION**

In 1968, Bass² called attention to the lethal aura surrounding inhalation of substances intended for rapid frosting of cocktail glasses. At that time he suggested that death might be associated with anoxia due to gradual displacement of air or to freezing injury of the lungs, or possibly laryngeal spasm. Later, upon review of 110 collected cases, the same investigator appreciated the unlikeliness of death from hypoxia because of the suddenness of collapse as repeatedly verified by eyewitness re-
ports. Because other sniffers were found dead with their head encased in plastic bags used for administration of the aerosol, it was suggested that death might be due to medullary depression and consequent respiratory failure. This, too, was probably an erroneous assumption in the case of sudden death.2

Taylor and Harris9 suggested that the propellant may have sensitized animals to asphyxia-induced rhythm disturbances while Reinhardt and coworkers4 reported that sensitization to epinephrine occurred upon inhalation of high concentrations of aerosols. While the foregoing investigations were quite valid, in our previous studies, we demonstrated that the careful maintenance of blood gases at absolutely normal levels did not prevent a rapid progression to ultimate fatality.46

With the present extension of the studies to further mimic human exposure, it appears that the survivors have in common at any sampling point in the experiment a somewhat lower pH level. The basis for the reduction appears to be both respiratory and metabolic (Fig 1-4). Significant group differences do not occur in bicarbonate, oxygen tension or saturation at any sampling point.

When consideration is given to the magnitude of change during total exposure (Fig 3) or from onset of exposure to maximum pH drop, the respiratory component (PCO2) emerges as the significant factor in pH drop. Base excess as well as bicarbonate, oxygen tension and saturation do not show meaningful differences between survivors and nonsurvivors when viewed in terms of comparative degree of change during the experiments. There was, however, a significant change in oxygen saturation from before to after exposure, and before to maximum pH drop within the group of survivors (P<.005), and the group of nonsurvivors (P<.01). Even so, the absolute levels were usually above 85 percent and in only four instances dropped below 77 percent.

Although excellent work has been reported from the early part of this century to the present, there still is conflicting evidence as to the effect of the various blood-gas parameters on cardiac rhythm. It has been reported that the ventricular fibrillation threshold was unaltered in alkalosis whether of metabolic or respiratory origin while metabolic and respiratory acidosis reduced the ventricular fibrillation threshold.9 On the other hand, respiratory alkalosis has been associated clinically with an increased incidence of both supraventricular and ventricular rhythm disturbances.10 Other investigators11 report that metabolic alkalosis raised the threshold of ventricular fibrillation, while metabolic acidosis had the reverse effect. In their experience pH changes resulting from respiratory causes had no effect on the fibrillation threshold.

Efforts have been made to set up an experimental situation for studying the shift of potassium under conditions of various pH levels. A decrease in extracellular buffer has been shown to occur in respiratory alkalosis because of an increasing lactate concentration, and by the shift of potassium as well as sodium into cells.12 With extracellular alkalization, intracellular pH levels underwent similar elevations in an almost linear fashion. Contrarily, with extracellular acidification, intracellular response to the changes appears to lag.13 This would suggest that alkalemia produces an intracellular alteration with considerably greater ease than does acidemia and might be extrapolated to suggest the cause-and-effect relationship in our own observations through extreme levels of alkalemia or acidemia were not present in our animals. However, if the fluoroalkane itself renders cardiac pacemaker cells even more sensitive to small upward shifts in pH and to changes in electrolyte gradient, part of the explanation may be approximated.

There seems to be an increased effect of adrenalin on heart rate and blood pressure in an alkaline medium, and a decreased effect in the presence of acidemia.14 Ventricular irritability which also may be an effect of adrenalin, was not a prominent feature of our observations, but in the few animals that developed ventricular premature beats or tachycardia, the pH was above the mean.

Brown and Miller,15 concluded that ventricular fibrillation may follow the sudden reduction of high levels of carbon dioxide tension, while other investigators were either unable to duplicate these results, or their results were to the contrary.16-19 Many studies have associated cardiac sequelae with severe blood gas derangement.11,20-24 Information derived from such extreme shifts, however, is difficult to apply to our study where the shifts are more subtle, but a variable, which is possibly metabolic poison, has been introduced.

An acid solution raises the level of threshold potential in Purkinje fibers, reduces the level of diastolic depolarization, and, thus, suppresses spontaneous activity. In alkaline solution, spontaneous activity is induced or enhanced.25 This may relate to the rarity of rhythm disturbances arising from increased automaticity or increased excitability in our animals, and is especially applicable to the surviving group with lower pHs. Pertinent also is a study showing an increased tendency to develop ectopic tachycardias in alkalotic dogs treated with acetylstrophanthidin.26
It has been well demonstrated that cells with diastolic depolarization consistent with present or potential automaticity tend to constantly leak ion and thus "leak current." When the firing point is reached, these cells spontaneously depolarize.\(^2\) Such spontaneous depolarization can be increased by catecholamines and hypoxemia. Because the mode of death in most of our animals was asystole, as opposed to the development of ectopic tachycardias and ventricular fibrillation, we would suggest that sensitization of the myocardium to catecholamines probably was not the pertinent mechanism. Furthermore, in a previous study we explored the role of even minimal hypoxemia in the experimental set-up reported here. We found essentially no difference in incidence and types of rhythm disturbances in the clearly nonhypoxemic animals and the ones with some degree of hypoxemia, when both groups were similarly exposed to fluoroalkane propellants.\(^4\)

Further elucidation of the biochemical abnormalities responsible for the electrophysiologic sequelae of aerosol inhalation is needed. Until we are able to correlate our present findings with actual alterations in the action potential of cardiac pacemaker and nonpacemaker cells exposed to the fluoroalkane, we can only speculate regarding the apparently protective role that a slightly lowered pH with a slightly elevated \(\text{PCO}_2\) seems to offer.

There appears to be a wide variation of host response to aerosol inhalation. A young person may expose himself on one occasion, sniff over several hours and experience only a feeling of intoxication. On another occasion, the first exposure may result in sudden death. These data suggest that one factor determining the likelihood of survival or death may be the acid-base response of the host to the intoxicant.

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