Electrolytes and pH Changes in Relation to Hypothermic Ventricular Fibrillation

By BENJAMIN G. COVINO AND A. H. HEGNAUER

Coronary arteriovenous electrolyte differences were studied in normo- and hypercapnic dogs at normal temperature and at 24 C. The ions measured were sodium, potassium, calcium, magnesium, chloride and hydrogen. Coronary arteriovenous electrolyte differences did not change during cooling in 16 dogs which did not suffer ventricular fibrillation. Ten hypercapnic hypothermic dogs exhibited characteristic Ca, K, and H ion changes at 24 C. before succumbing to ventricular fibrillation. The data suggest that ventricular fibrillation at low body temperatures is related to a gain of Ca and a loss of K and H ions by the hypothermic hypercapnic myocardium.

It has become common observation that 50 to 70 per cent of pentobarbitalized hypothermic dogs succumb to ventricular fibrillation between the temperatures of 25 and 19 C., unless pulmonary ventilation is maintained at a rate sufficient to keep the systemic blood pH near normal. The progressive hypercapnia which otherwise accompanies the fall in body temperature apparently acts in most instances as a cardiac excitant. In a systematic study of the ventricular excitability cycle in hypothermic dogs it was revealed that a significant rise in excitability occurs at all points in the cycle except at its very beginning (i.e., during the inscription of the electrocardiographic QRS) when hypercapnia develops, as in spontaneous respiration.

It remained to be determined whether the augmented ventricular excitability and consequent high incidence of ventricular fibrillation were due to the low pH per se or to some process which was triggered by the low pH. In this regard it is known that the potassium balance of the cell may be altered by the pH of the surrounding medium. Although no similar studies have been carried out with calcium, Van Slyke and McLean and Hastings have reported that a fall in pH will slightly increase the plasma level of ionized calcium.

Thus, pH probably does alter the cellular equilibrium state for calcium also. That such changes in the membrane equilibria for potassium and calcium may augment myocardial excitability and so provoke ventricular arrhythmias has been demonstrated experimentally and clinically.

Electrolyte studies made on hypothermic animals thus far do not afford much information about the ionic balance of the myocardium itself. Hence the present study, in which the concentrations of a number of electrolytes in arterial and coronary venous blood were measured in groups of normocapnic and hypercapnic dogs at normal and low temperatures. The data, presented herein, are concerned with sodium, potassium, calcium, magnesium, chloride and hydrogen ions as affected by temperature and pH.

Methods

Twenty-six apparently healthy mongrel dogs, ranging in weight from 7.3 to 17.4 Kg., were anesthetized with intraperitoneal pentobarbital sodium (30 mg./Kg.). The following procedures were carried out in all dogs prior to immersion in an iced bath: insertion of an endotracheal tube; placement of standard limb leads for electrocardiographic recording; exposure of both external jugular veins and the right common carotid artery; insertion of a catheter, bearing a thermocouple at its tip, into the right atrium via the jugular vein to yield an approximation of heart temperature. Temperature was continuously recorded on a Leeds and Northrup Speedomax.

By Cambridge pH recorder, pH measurements were made on heparinized systemic whole blood at normal temperature, 35 and 30 C. and every two degrees thereafter to terminus. Coronary venous pH was measured only at normal temperature and at

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24 C. Arterial samples were from the exposed carotid artery. Coronary venous sampling was performed as follows: Left thoracotomy was performed at the fifth intercostal space, the ribs retracted, and the pericardium incised longitudinally. The great circumflex vein was punctured with a 20 gage needle bent into a right angle, and the blood was withdrawn into a heparinized syringe. This simple but direct method obviated the need for coronary sinus catheterization with its attendant arrhythmia-producing hazards. Following arterial and coronary venous sampling, the pericardium was sutured, the ribs approximated, and the incision closed after reduction of the pneumothorax. The above procedure was then repeated after induction of hypothermia, at 24 C.

Artificial respiration with room air was instituted during open chest procedures, and throughout the cooling process in those dogs whose blood pH was to be maintained near normal. The remaining dogs were allowed to respire spontaneously during cooling to 25 C., at which time artificial respiration with a 5 per cent CO2-O2 mixture was started in order to insure adequate oxygenation without a concomitant rise in pH.

Arterial and coronary venous blood samples were centrifuged immediately at 3000 r.p.m. for 15 to 20 minutes and the plasma taken for electrolyte and protein measurements. Sodium and potassium were determined by means of a Baird flame photometer; chlorides by the method of Volhard;21 total calcium by the Tisdall method;19 and magnesium by the method of Simonson and associates.14 Plasma protein concentration was obtained by the copper sulfate technic,19 and the ionized calcium concentration was calculated from the total calcium level and the plasma protein concentration by means of the nomograms of McLean and Hastings,14 which according to them is valid at all temperatures in the range of the present study.

RESULTS

The data reported are from two series of experiments. Series A consisted of 8 dogs in which arterial pH was maintained between 7.35 and 7.55 via controlled respiration throughout the period of cold water immersion. All animals in this series survived to heart temperatures of 16 to 18 C., at which time the heart passed into asystole. Series B was composed of 18 dogs in which a state of acidosis was allowed to develop through spontaneous respiration during induction of hypothermia. As had been noted previously,6,8 two subgroups could be distinguished here on the basis of the terminal cardiac event. Ventricular fibrillation occurred in 10 dogs between the temperatures 18 and 23 C. The remaining eight dogs suffered asystolic deaths at 16 to 18 C. One may, therefore, discuss the ionic balance of the heart in three distinct groups of animals: group 1, comprised of normocapnic hypothermic dogs; group 2, hypercapnic hypothermic fibrillators; group 3, hypercapnic hypothermic non-fibrillators.

Sodium, Chloride, Magnesium. Coronary arterial and venous electrolyte determinations were made in all dogs at normal temperature and at heart temperatures of 24 C. The mean coronary A-V differences and their standard deviations are given in tables 1 and 2. Since, apart from K, the mean arterial levels of the several ions were unaffected by the experimental procedures, omission of those figures was deemed warranted and advisable.

A comparison of the data for Na, Cl and Mg at 24 C. (table 2) with those at normal temperature (table 1) indicates that these ions, whether considered in terms of levels or coronary A-V differences, are unaffected by acute hypothermia, regardless of systemic pH. The mean arterial pH for all groups at normal temperature was 7.42. This was also the mean for the hypothermic normocapnic dogs. For the hypothermic acidic fibrillators and nonfibrillators the mean pH values at 24 C. were 7.16 and 7.14 respectively. Since neither levels nor A-V differences of these ions are affected by this pH range at low temperature one may reasonably conclude that the balance between blood and myocardium is also stable. One observation regarding the coronary A-V difference in Na is worthy of mention. Of 26 dogs, 25 showed a higher level of Na in the venous blood than in the arterial, suggesting a negative cardiac Na balance at both normal and low temperatures. This cannot actually represent a negative Na balance, for a steady loss at this rate could last at most for a few moments. Another explanation must obtain, but does not readily suggest itself. The A-V Na-difference is real in all groups at both temperatures studied (p = <0.01).

Potassium, Calcium and Hydrogen Ions. Determination of the K, Ca and H ion concentrations in arterial and coronary venous blood did reveal certain basic differences at 24 C. between those animals which succumbed to
ventricular fibrillation, and those which died in asystole at lower temperatures. These are revealed in table 2. In regard to plasma K concentrations the most conspicuous features are (1) The concentrations are lower in both arterial and coronary venous blood at 24 C. in all three groups (p = <0.01 in every instance). The mean values at 24 C. are 0.6 mEq. per L. less than at normal temperature. Since the difference is of the same magnitude in all groups it would appear to be totally unrelated to pH; (2) nine of the 10 hypothermic dogs exhibited a negative coronary A-V difference at 24 C. Elimination from the series, (for analytic purposes) of the only dog in this group that failed to demonstrate such a difference but rather deviated widely in the other direction, yields the mean difference for the remaining 9 dogs of —0.30, a value which is significant at the 5 per cent level. Among the 16 dogs of groups 1 and 3 (all asystolic deaths) only 4 had negative coronary A-V differences at 24 C., the mean value for the 4 being —0.13.

The distinction between "fibrillators" and "nonfibrillators" becomes more conspicuous when one considers the Ca balances. Groups 1 and 3 showed a slight but insignificant negative coronary A-V difference at both normal temperature and 24 C. Group 2, the fibrillators, did not differ in this regard at normal temperature, but showed a significant positive balance at 24 C., i.e., the coronary venous Ca level was less than the arterial. Despite the fact that in 2 of the 10 dogs no difference in total Ca was observed the mean difference was significant (p = <0.02). Moreover, if one considers only the ionized Ca, which increases at the expense of the nonionized fraction at low pH and temperature,16 then all of the fibrillators showed a positive coronary A-V difference; whereas the nonfibrillators regardless of pH and temperature showed either no difference or a slight negative balance. The fact that in 10 of 10 fibrillators a positive Ca balance occurred concomitantly with a negative K balance in 9 of the 10, whereas under the same conditions of pH and temperature a normal Ca and K pattern obtained in the 8 nonfibrillators of group 3, suggests strongly that one is dealing with a basic, perhaps causative, mechanism in regard to hypothermic ventricular arrhythmias. The explanation for the resistance to Ca penetration into the myocardium of the non fibrillators at low systemic pH is a problem unto itself, solution of which has not been attempted.

Coincident with the above measurements were those of pH on both the systemic arterial

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<th>Table 1.—Coronary A-V Electrolyte Differences in mEq. per Liter in 86 Dogs Prior to Subjection to Immersion Hypothermia</th>
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<tr>
<td>Group 1. 8 normocapnic non-fibrillators</td>
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<tr>
<td>pH</td>
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<td>Group 2. 10 hypercapnic fibrillators</td>
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<td>Group 3. 8 hypercapnic non-fibrillators</td>
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<th>Table 2.—Coronary A-V Electrolyte Differences in mEq. per Liter, Measured in Three Groups of Hypothermic Dogs at 24 C.</th>
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<td>pH</td>
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<td>Group 3. 8 hypercapnic non-fibrillators</td>
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<td>+0.06 (±0.16)</td>
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and coronary venous blood. The mean coronary A-V pH differences are given for all groups at both normal and low temperatures. It very soon became obvious that one could predict with absolute accuracy at 24°C, which dogs would succumb to ventricular fibrillation as opposed to death in asystole at lower temperatures. In every instance the coronary venous pH of the group 2 dogs at 2-4°C was more than 0.05 pH units lower than the arterial, the mean being 0.08 units. In no instance was there a difference as great as 0.05 units among the non-fibrillators of either group 1 or group 3.

Considering these three ions together it appears that the myocardium of some dogs at low temperature and pH loses its resistance to Ca penetration and such penetration occurs in exchange for K and H ions, with a consequent rise in excitability, the initiation of arrhythmias, and ventricular fibrillation. The character of the failure which thus permits the entrance of excess Ca into the myocardium is at present unknown.

**Discussion**

The etiology of hypothermic ventricular fibrillation has been vigorously pursued for the past five years. Swan and associates' first reported that prevention of acidosis during cooling was capable of controlling these cardiac irregularities. This observation has been confirmed repeatedly since the time of that initial report. The suggestion has also been made that acidosis exerts its deleterious effect via a change in the electrolyte balance of the heart. The data presented herein reveal that sodium, chloride, and magnesium play no observable role in the production of ventricular arrhythmias at low temperature.

The ions which apparently do determine the various types of hypothermic deaths are potassium, calcium, and hydrogen. The data suggest that the augmented ventricular excitability and the extrasystolic activity observed in acidic hypothermic dogs is the result of a myocardial exchange between intracellular potassium and hydrogen ions and extracellular calcium ions.

Little attention has been paid to the role of calcium in the genesis of hypothermic ventricular fibrillation, although the arrhythmia-producing effects of calcium in normothermia are well known. Hoff and co-workers and Grumbach and associates have demonstrated experimentally that a gradual increase in the calcium concentration of the blood lowers the threshold of the intact normothermic mammalian ventricle as indicated by the onset of ventricular arrhythmias. However, studies performed on the isolated papillary muscle of the cat by Grenier and associates and Green and co-workers reveal that a rise in the calcium concentration of the perfusing medium produces a decreased excitability. This apparent contradiction between results obtained with in vivo and in vitro preparations may possibly be resolved if one considers the rate at which the intracellular level of calcium is increased and the possible dual effect of calcium on cellular excitability, i.e., a primary excitability increase followed by a secondary depressant effect. There can be little doubt that calcium would penetrate the isolated muscle much more rapidly than the intact heart. Thus, only the depressant effect due to a rapid marked increase in the intracellular level of calcium might be observed in an in vitro preparation whereas the intact heart would exhibit the initial excitatory action of a small calcium rise. Evidence for such a theory is forthcoming from the report of Hoff and associates who observed in the intact dog a primary excitatory stage as the plasma level of calcium was increased. Most dogs suffered ventricular fibrillation during this period. However, those animals which survived this initial phase of increased excitability then entered a secondary stage of depression during which cardiac arrest occurred. Our data tend to support the thesis that a small increase in the intracellular calcium level augments cellular excitability. The perfect correlation, between the small but significant influx of calcium into the hypothermic acidic myocardium and the elevated ventricular excitability, which is the predisposing condition for the observed ventricular fibrillation, definitely suggests a causal relationship between the two phenomena.
The negative coronary A-V potassium difference observed in 90 per cent of our dogs at low temperatures suggests that the hypothermic myocardium loses potassium. This finding is confirmed by the work of Olsen and co-workers who, by the use of radio-active potassium, were able to demonstrate a reduction in the intracellular myocardial potassium concentration of hypothermic dogs. The outflow of potassium from the ventricular musculature may act synergistically with calcium penetration to augment the excitability of the ventricle prior to the onset of fibrillation at low temperatures. In this regard, Harris and associates also observed a potassium exodus from the myocardium just prior to ventricular fibrillation in normothermic dogs, subjected to coronary ligation.

The results obtained in this study differ from those reported by Montgomery and associates. This is probably not surprising in view of the difference in the experimental procedures. In order to obtain coronary venous samples Montgomery and associates utilized the technic of coronary sinus catheterization which necessitated pretreatment of these dogs with acetylcholine, prostigmine or vagal stimulation to prevent ventricular fibrillation, due to the presence of a catheter in the coronary sinus. That vagal stimulation and probably acetylcholine itself may alter the potassium balance of the heart has been demonstrated.

**SUMMARY AND CONCLUSIONS**

Arterial and coronary venous concentrations of sodium, chloride, magnesium, potassium, calcium and hydrogen ions were measured in normo- and hypercapneic dogs subjected to immersion hypothermia.

Neither temperature nor pH had any effect on the arterial or coronary venous levels of sodium, chloride or magnesium.

Myocardial exchange between intracellular potassium and hydrogen ions and extracellular calcium ions was observed only in those hypothermic acidotic dogs which succumbed to ventricular fibrillation. All dogs suffering fibrillary deaths exhibited a positive calcium coronary A-V difference and a negative hydrogen ion difference. Ninety per cent showed a negative potassium coronary A-V difference.

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