Acute Hypokalemia and Inducibility of Ventricular Tachyarrhythmia in a Nonischemic Canine Model

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Inducibility of sustained ventricular tachycardia (VT) and ventricular fibrillation (VF) by programmed ventricular stimulation following acute hypokalemia was studied in 21 anesthetized dogs free of inducible ventricular tachyarrhythmias at baseline. The control mean serum potassium concentration of 3.65 mEq/L was decreased to 2.14 mEq/L by insulin and furosemide administration. Inducibility of arrhythmias was also assessed following isoproterenol infusion before and after induction of hypokalemia. None of the animals developed sustained VT. Only one animal developed VF following hypokalemia (p>0.05). Two normokalemic animals and five hypokalemic animals developed VF following isoproterenol infusion; this difference was not significant (p>0.05). In this study, hypokalemia did not predispose to the development of a substrate necessary for the genesis and maintenance of VT. The inducibility of VF following hypokalemia was not significantly enhanced and appears to be related to the “aggressive” stimulation protocol.

(Chest 1991; 100:1414-20)

PVS = programmed ventricular stimulation; RPM = resting membrane potential; VERP = ventricular effective refractory potential; VF = ventricular fibrillation; VT = ventricular tachycardia

There are several reports incriminating hypokalemia in an increased incidence of ventricular arrhythmias.1-5 Hypokalemia generally develops in patients undergoing treatment with diuretics for systemic hypertension. Many of these patients have underlying ventricular hypertrophy, ischemic heart disease, or other organic heart disease and would be considered at higher risk for malignant or lethal ventricular arrhythmias. The problem was underscored by the unexpected finding of an apparent excess of coronary artery disease mortality, manifested chiefly as sudden death within 1 h,6 in a subgroup of patients with baseline electrocardiographic (ECG) abnormalities treated with diuretics in two large trials.6,7 However, another multicenter trial of treatment of hypertension with thiazide diuretics, the Hypertension Detection and Follow-up Program, did not document an increased risk of sudden death associated with diuretic use.8 Sudden death is considered to result from the development of ventricular fibrillation (VF).9 Severe hypokalemia (serum potassium, <3.0 mEq/L) has been implicated as a cause of sudden cardiac arrest.10,11

The value of electrophysiologic studies using programmed ventricular stimulation (PVS) has been established in the diagnostic and prognostic assessment of patients resuscitated from out-of-hospital sudden cardiac death12 and of patients with syncope of undetermined origin.13 The risk of sustained ventricular tachycardia (VT) and VF in hypokalemia has not been adequately defined by PVS in the normal human or animal heart. We induced hypokalemia in an anesthetized nonischemic closed-chest canine model by insulin and intravenous (IV) furosemide administration and studied the inducibility of VT and VF by PVS. The study was in compliance with the National Institutes of Health guide for the care and use of laboratory animals and was approved by our institution’s board for animal research. The study was designed to answer the primary question: Does acute hypokalemia predispose to development of sustained VT or increase the risk of VF in a normal heart?

Methods

Animals

Twenty-one mongrel dogs of both sexes, weighing 25 to 30 kg, were fasted overnight and anesthetized with IV sodium pentobarbital, 30 mg/kg, and ventilated on room air with use of a dual-phase Harvard respirator. Arterial blood gases and pH were monitored and maintained within normal physiologic range. In addition, serum electrolytes (including serum magnesium), arterial blood pressure, urine output, and a surface ECG lead were monitored. The blood pressure and ECG were displayed on a multichannel recorder (Electronics for Medicine VR-8; PPG Biomedical Systems, Lenexa, Kan). A bipolar 4F pacing catheter was advanced percutaneously via the femoral vein to the right ventricle under ECG monitoring and used for ventricular stimulation. A multiprogrammable stimulator (model ERA-S-HIS; Biotronik Pacemakers, Lake Oswego, Ore) was used for pacing and electrophysiologic assessment. Serum potassium concentration was determined by flame photometry (normal, 4.0 to 5.6 mEq/L). Data were stored on magnetic tape for later retrieval and review.

Electrophysiologic Studies

After stabilization of the preparation, a baseline serum potassium sample was drawn. Electrophysiologic study was undertaken in the control normokalemic state and following production of hypokalemia. Although several animals had subnormal serum potassium levels in the control state (Table 1), they will be referred to as normokalemic in this communication. The stimulus current strength was twice the diastolic threshold for capture, with a pulse width of 2 ms. The electrophysiologic study was repeated after isoproterenol infusion in both the normokalemic and the hypokalemic state. The electrophysiologic study sequence was as follows:

1414

Hypokalemia and Ventricular Tachyarrhythmias in Canine Model (Vera, Janzen, Desai)

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Table 1—Potassium Values before and after Hypokalemia Induction and Incidence of PVS-induced VT

<table>
<thead>
<tr>
<th>Animal</th>
<th>Control Serum Potassium, mEq/L</th>
<th>Control PVS*</th>
<th>Isoproterenol PVS*</th>
<th>Posthypokalemia Serum Potassium, mEq/L</th>
<th>Hypokalemia PVS*</th>
<th>Hypokalemia + Isoproterenol PVS*</th>
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<td>1</td>
<td>3.65</td>
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<tr>
<td>2</td>
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<td>2.60</td>
<td>VF (S₄)</td>
<td>x</td>
</tr>
<tr>
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</tr>
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<td>7</td>
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</table>

*0 = no VT or VF; VB = burst ventricular pacing (accompanying value represents number of beats per minute); S₄ = fourth extra stimulus.

1. Rapid ventricular burst pacing of 3- to 5-s duration, starting at a rate of 200 beats per minute with increments of 20 beats per minute up to loss of ventricular capture, usually a 2:1 block, or onset of VT or VF (Fig 1). Two normokalemia animals (serum potassium, 3.5 and 3.9 mEq/L, respectively) developed VF; they were not counted with the 21 dogs qualifying for hypokalemia induction.

2. Programmed ventricular stimulation at a single right ventricular site with a ventricular drive-cycle length (S₁-S₂) of 300 ms was undertaken in all animals. Premature stimuli were delivered at progressively shorter cycle lengths, in 10-ms decrements from drive cycle length to development of ventricular tachyarrhythmias or ventricular refractoriness, as measured by the ventricular effective refractory period (VERP). In the case of the latter, the S₄-S₃ interval was increased 50 ms beyond the value at which ventricular refractoriness was noted, and S₄ was introduced at an S₃-S₄ interval equal to the S₄-S₃ interval. Next, the S₃-S₂ interval was progressively shortened in 10-ms decrements until ventricular tachyarrhythmias or ventricular refractoriness was encountered. In the latter case, S₄ and later S₄ (fourth extra stimulus) were introduced. The end point was development of sustained monomorphic VT (defined as ≥15 ventricular beats in a row at a rate of ≥120 beats per minute), precipitation of VF (Fig 2), or completion of four extra ventricular stimuli (S₄-S₃) until ventricular refractoriness was evidenced.

3. Stimulation protocol steps 1 and 2 were repeated during IV isoproterenol infusion (0.6 µg/min for at least 10 min), which increased heart rate by ≥10 percent. Animals developing VF following isoproterenol infusion in the normokalemic state were

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21636/ on 04/03/2017)

**Figure 1.** Example of postisoproterenol burst ventricular pacing-induced VF. Marker channel (top), ECG (middle), and blood pressure (BP) (bottom) values are shown. There is 1:1 capture by the ventricular pacing rate of 410 beats per minute prior to VF. This animal demonstrated a 2:1 block in capture at a similar rate without isoproterenol.
promptly defibrillated and further studied after production of hypokalemia. A blood sample for serum potassium determination was drawn 10 min into the infusion and prior to the stimulation protocol.

4. A glucose and insulin solution containing 100 ml of 15 percent dextrose with 100 units of regular insulin was infused over 1 h. In addition, the animals received 150 mg of IV furosemide. This was given as two or three boluses over 15 to 30 min prior to the glucose-insulin infusion. Serum potassium was measured at the end of the infusion. Urine was collected for determination of potassium level in eight animals, starting with bladder catheterization before normokalemic PVS and continuing to the termination of the study.

5. Electrophysiologic studies were repeated immediately after the insulin-furosemide infusion. Animal 2 could not be successfully defibrillated following hypokalemic VF and thus was not studied with isoproterenol challenge.

6. A repeat infusion of isoproterenol, 0.6 µg/min for 10 min, was administered, and PVS was repeated. In each case the study was terminated whether or not VT or VF developed, and the animal was killed.

Statistical analysis to assess the probability of VT or VF in normokalemic versus hypokalemic animals was undertaken by using the nonparametric Sign test. Serum potassium values and VERPs in the control and hypokalemic states were evaluated by Student's t test for paired values. Differences were considered statistically significant at a level of p≤0.05. Data are reported as mean ± 1 SD.

RESULTS

Serum Potassium Levels

The mean baseline serum potassium value of 3.65 ± 0.28 mEq/L (range, 2.9 to 4.40 mEq/L) decreased to 2.14 ± 0.29 mEq/L (range, 1.4 to 2.6 mEq/L) following insulin and furosemide infusion (p<0.05) (Fig 3). All animals developed severe hypokalemia (serum potassium, 2.6 mEq/L or less). Eight of 21 animals demonstrated even more severe hypokalemia (serum potassium, 2 mEq/L or less) (Table 1). The low serum potassium values in the control state could be related to diet, overnight fasting, anesthesia, stress, or other undetermined factors. Serum magnesium levels were unchanged.

Urine Potassium

The urine potassium losses for the duration of the study were measured in eight animals. The mean loss was 92 ± 86 mEq/L.

Control (Normokalemic) Ventricular Stimulation

The study was designed to exclude animals that developed VT or VF in the normokalemic state. Thus, two animals that developed VF, both with S1-S5 stimulation, were excluded from further study. One other dog with severe acidosis due to an endotracheal tube leak was excluded and is not included in the study group of 21 dogs.

Post-Isoproterenol Ventricular Stimulation

This was carried out in all 21 normokalemic animals.

![Figure 3](image-url)
Animals 11 and 14 developed VF, both during burst ventricular pacing at rates of 450 and 410 beats per minute, respectively (Table 1). Both animals were promptly defibrillated. Following hypokalemia, animal 11 developed VF only after the addition of isoproterenol. Animal 14 subsequently did not demonstrate VF after hypokalemia or with the addition of isoproterenol.

**Posthypokalemia PVS**

Animal 2 developed VF with the fourth extra stimulus (S4) with a serum potassium level of 2.60 mEq/L (Table 1). This animal could not be successfully defibrillated. None of the animals developed sustained VT.

**Posthypokalemia/Postisoproterenol PVS**

Five of the 20 hypokalemic animals studied developed VF with ventricular stimulation during isoproterenol administration (animals 1, 7, 11, 12, and 15). This result, although showing a trend, was not significant compared with the findings in normokalemic controls (p>0.05). In all 21 animals, VF had been noninducible in the absence of isoproterenol (Fig 4). In animal 11, VF had been inducible in the normokalemic state in the presence of isoproterenol. No animal demonstrated sustained VT.

**Induction of VF and Severity of Hypokalemia**

We analyzed the results to ascertain whether the animals that developed VF posthypokalemia had a lower serum potassium level or a higher percentage of decrease in serum potassium concentration compared with those that did not demonstrate inducible VF. A number of logistic regressions were done in which the incidence of VF under various interventions was regressed on postfurosemide potassium levels, change in potassium levels (the difference between initial and postfurosemide potassium levels), and percentage of change in potassium levels. In only one case did any regressor prove marginally useful in modeling the probability of VF. Under the intervention of hypokalemia and isoproterenol, percentage of change in potassium levels entered the model with a p value of 0.0961.

**Determination of VERPs**

The VERPs were determined in the normokalemic state (156.3 ± 17.1 ms) and after isoproterenol administration (148.4 ± 16.4 ms). In the hypokalemic state, the VERP was 165.8 ± 23.4 ms. After hypokalemia plus isoproterenol infusion, the VERP was 160.5 ± 23.4 ms. There was no significant difference between normokalemic and hypokalemic values (p>0.05). The VERP for normokalemia plus isoproterenol administration was significantly shorter than both the VERP for hypokalemia and the VERP for hypokalemia plus isoproterenol administration (p<0.05).

**Discussion**

There is controversy about the role of hypokalemia in the genesis of ventricular arrhythmias and the risk of increased mortality due to sudden cardiac death. Hirsch and co-workers undertook intraoperative arrhythmia monitoring in 447 patients undergoing major cardiovascular operations. The frequency and severity of arrhythmias were analyzed in relation to the degree of preoperative hypokalemia. The authors concluded that the incidence and complexity of ventricular arrhythmias was not related to either hypokalemia or diuretic therapy but to the presence of congestive heart failure, left ventricular aneurysm, and digoxin therapy. Although it is possible that hypokalemia could enhance the arrhythmogenic potential of an ischemic, or perhaps a normal, ventricle, a prognostically important question is whether hypokalemia can induce lethal arrhythmias or predispose to the genesis of VT or fibrillation. The present study was designed to address the latter question.

This study indicates that the normal animal heart does not develop inducible sustained VT in the presence of acute hypokalemia. The frequency of PVS-induced VF in 21 animals was 0/21 in the normokalemic state, 2/21 with normokalemia and isoproterenol infusion, 1/21 in the hypokalemic state, and 5/20 in the hypokalemic animals after the addition of isoproterenol (Fig 4). These differences were not significant (p>0.05). Thus, the frequency of VF with hypokalemia was not significantly increased. These results differ from the observations of Hohnloser et al, who found...
that hemodialysis-induced hypokalemia enhanced the propensity for VF in the normal as well as in the ischemic canine heart. These authors assessed the VF threshold by delivering a train of pulses in the ST-T segment. The intensity of this train was increased in 2-mA steps until VF ensued. While we assessed for the inducibility of VF in the normokalemic vs hypokalemic model, Hohnloser et al determined the intensity of the stimulus required for precipitating VF. Thus, the two techniques are not directly comparable. Furthermore, Hohnloser et al instituted acute intravascular hypokalemia by removing whole-body potassium by hemodialysis. Our hypokalemic model used insulin to drive the potassium intracellularly while producing some body potassium depletion. In a canine study of glucose- and insulin-induced hypokalemia, Hall and his co-workers14 demonstrated earlier onset of VT (four ventricular premature contractions in a row) in response to a constant infusion of digoxin. However, Garan et al17 studied a chronic potassium-depleted acute myocardial infarction model and found that negative total-body potassium balance, rather than serum potassium level, was a better predictor of electrical instability (ie, risk of developing VT or VF in response to PVS). Our preparation had normal hearts. It therefore appears that an arrhythmogenic substrate, such as myocardial infarction, is necessary for hypokalemia to act on. The mechanism of arrhythmias in hypokalemia, the type of ventricular stimulation technique, the presence or absence of organic heart disease, and the role of isoproterenol are important variables in assessing the response to PVS in this study.

Electrophysiologic Effects of Hypokalemia

In the isolated cardiac cell, according to the Nernst equation, the resting membrane potential (RMP), or maximal diastolic potential, is a function of the ratio of the intracellular and extracellular potassium concentrations.18,19 The extracellular potassium level is the single most important determinant of RMP (phase 4). With decreasing extracellular potassium concentrations, the phase 4 of the cardiac monophasic action potential becomes more negative or hyperpolarized (Fig 5). At levels below 2.5 mEq/L, this hyperpolarization can be present in different types of cardiac fibers.18 Below approximately 2 mEq/L, the RMP stabilizes; with severe extracellular potassium deficiency, depolarization can be seen.19 The magnitude of the depolarization sodium current (phase 0) is related to the RMP. Hypokalemia, by hyperpolarizing cells, increases the upstroke of the action potential.18,19 With progressive hypokalemia, repolarization becomes slower and the action potential duration increases. The slope of phase 2 becomes steeper and the slope of phase 3 slower, causing a prolonged "tail" of the action potential (Fig 5). The period of incomplete repolarization tends to be longer in the Purkinje fibers than in the ventricular fibers. Thus, the difference between the Purkinje and ventricular action potential durations is increased, which may lead to an increased dispersion of repolarization and refractoriness.20 There is a progressive change in the repolarization slope, because of which the cell may not be fully repolarized at the time of depolarization by the subsequent impulse. The study of isolated hearts has demonstrated VF when the perfusate had a low potassium content. Addition of potassium reversed this fibrillatory effect.21,22 Sustained VT in these studies has not been described, and it can be inferred that hypokalemia alone may not be sufficient to promote and maintain VT.

Ventricular Effective Refractory Period

The increase in the total duration of the action potential due to hypokalemia may not be associated with a concomitant increase in VERP; the latter may shorten.18 Gettes and Surawicz19 suggest that the shortening of the VERP is probably related to the rapid initial rate of repolarization. The transmembrane potential may reach the threshold potential earlier during phase 3 repolarization than if the potassium concentration were normal. In our study, the control VERP (156.3 ± 17.1 ms) was not significantly different from the posthypokalemia VERP (165.88 ± 21.9 ms). A short refractory period allows a narrower coupling interval for ectopic beats. The arrhythmogenic effects of hypokalemia may result from reentrant arrhythmias due to slowed conduction, unidirectional block, increased dispersion of refractoriness, and shortening of the VERP. Increase in automaticity may lead to automatic ectopic beats and rhythms.18

Figure 5. Diagrammatic representation of changes in the Purkinje fiber action potential (AP) induced by severe hypokalemia (dotted line) compared with normokalemic control (solid line). Note the increased duration of hypokalemia AP change in the repolarization slope, increase in phase 4 slope, and decrease of RMP. (Modified from Lloyd and Surawicz. Reproduced by permission.)
**Programmed Ventricular Stimulation**

The site of stimulation in the normal heart does not appear to be an important factor for inducing VF with a critically timed stimulus. Therefore, we used a single right ventricular endocardial site for our stimulation protocol. In the normal canine heart, only VF, not VT, is inducible. The frequency of VF induction appears to be directly related to the number of extra stimuli used. Employing three ventricular extra stimuli, Wetstein et al. observed VF in all ten normal dogs. The authors utilized several subepicardial, intramycocardial, and subendocardial locations along the left anterior descending coronary artery for plunge electrode pacing. Ninety percent of the animals with chronic myocardial infarction developed VT and 10 percent developed VF with the three extra stimuli technique. Likewise, in a human study assessing the significance of ventricular arrhythmias initiated by PVS, the authors concluded that nonsustained polymorphic VT and VF were nonspecific responses to aggressive stimulation protocols. Thus, if our data are analyzed at the three extra stimuli cutoff and burst ventricular pacing is excluded, none of the animals in either category developed VF.

**Isoproterenol Induction of Ventricular Tachyarrhythmia**

Several studies have documented the efficacy of isoproterenol infusion in facilitating the induction of clinically documented VT, which was otherwise nonducible. These studies were confined to patients with clinically documented VT. We hypothesized that if hypokalemia alone does not increase the frequency of VT inducibility, then hypokalemia in the presence of isoproterenol may bring about the electrophysiology derangement necessary to induce a sustained VT. None of the animals in either category developed sustained VT. There were two episodes of VF with normokalemia and isoproterenol (none with S1–S3) and five with hypokalemia and isoproterenol (three with S3 and two with ventricular burst pacing). This difference was not significant (p > 0.05). Isoproterenol and other beta-agonists can induce hypokalemia by facilitating K+ entry into the cell via generation of cAMP and activation Na+ K+ adenosine triphosphatase. Ajioka et al. evaluated the mechanisms of cardiac arrhythmias induced by another catecholamine, epinephrine, in dogs with hypokalemia. Following 5 min of epinephrine infusion in normokalemic controls and hypokalemic animals, mitochondrial calcium content and phospholipase activity of plasma membrane fraction were determined. Both of these were significantly increased in dogs with hypokalemia and a high arrhythmia ratio. These results suggested that hypokalemia enhances the calcium influx induced by epinephrine, resulting in activation of phospholipase.

The latter was considered responsible for the development of ventricular arrhythmias. In the present study, episodes of VF induced by burst pacing during isoproterenol infusion appeared to be due to 1:1 ventricular capture at rates over 400 beats per minute. Similar rates without isoproterenol effect resulted in 2:1 capture. It can be suggested that shortening of ventricular refractory period due to isoproterenol and perhaps further decrease in serum potassium promoted 1:1 capture. Serum levels were determined in the last six hypokalemic animals after isoproterenol infusion. The hypokalemic serum potassium level (2.15 ± 0.12 mEq/L; range, 2.0 to 2.3 mEq/L) was not significantly decreased (p > 0.05) after isoproterenol infusion (2.18 ± 0.21 mEq/L; range, 1.8 to 2.4 mEq/L). This could probably be explained on the basis of preexisting severe hypokalemia; previous studies have investigated the fall in serum K+ value following catecholamine infusion from normal or near normal control values.

**Limitations of the Study**

Induced VF in a normal heart is a nonspecific end point and is considered to be a manifestation of aggressive stimulation protocols. Thus, the question arose whether changes in VF inducibility could be used as an end point in this study. Our goal was to assess whether hypokalemia in the normal heart could predispose to stimulation-induced sustained VT (≥15 consecutive ventricular complexes). This was not observed in any of the animals studied. A secondary goal was to assess whether the nonspecific VF inducible in a normal heart could be induced with fewer extra stimuli in the presence of hypokalemia. It should be noted that all episodes of VF were precipitated by either four extra stimuli (S1–S4) or burst pacing. Interestingly, VF induced by burst ventricular pacing was observed only after isoproterenol. Thus, if the more commonly used and less aggressive protocol utilizing three extra stimuli (S1–S3) and no burst ventricular pacing had been employed, no instance of VT or VF would have been observed in any of the categories studied.

**Conclusions**

We conclude that in the normal heart, presence of acute severe hypokalemia does not predispose to the risk of sustained VT as determined by PVS. The production of VF is probably a nonspecific, stimulation protocol-related arrhythmia and does not necessarily imply high risk for VF in the normal heart in the presence of hypokalemia.

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