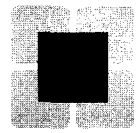

Potassium loading as adjunct treatment of repetitive ventricular arrhythmias

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■ To evaluate potassium supplementation as adjunct therapy for ventricular arrhythmias, consecutive normokalemic patients undergoing in-hospital antiarrhythmic therapy for ventricular tachycardia were randomly assigned to one of four groups: intravenous potassium chloride (Group I, 44 patients) *v* intravenous saline (Group II, 48 patients); and oral potassium chloride capsules (Group III, 50 patients) *v* no additional treatment (Group IV, 47 patients). All groups underwent serial serum potassium determinations and 24-hour electrocardiographic monitoring. Analysis revealed no significant differences in ventricular ectopic activity among groups, and there was no significant association between serum potassium level and incidence of ventricular arrhythmias. We conclude that normokalemic patients undergoing antiarrhythmic therapy for ventricular tachycardia benefit little from concomitant short-term potassium supplementation.

□ INDEX TERMS: ARRHYTHMIA; POTASSIUM □ CLEVE CLIN J MED 1990; 57:223–231

PATIENTS suffering from structural heart disease and repetitive ventricular ectopy are at increased risk of sudden death.[1,2] Therapeutic maneuvers that reduce the incidence of this ectopy may prolong lives and are therefore of interest.

Bettinger and associates[3] and Fisch and associates[4] proposed intravenous potassium loading as an effective therapy for ventricular arrhythmias. Recent interest has focused on the hypertensive patient who is taking diuretics and sustains a myocardial infarction. This patient profile has been identified as prone to ventricular ectopic activity and vulnerable to arrhythmic death directly resulting from myocardial infarction in conjunction with potassium depletion. However, little attention has been paid to the role of potassium augmentation for normokalemic subjects with heart disease and known ventricular tachycardia. This investigation was undertaken to determine the possible beneficial effect of adding acute potassium loading to the in-hospital treatment of normokalemic patients with recently documented ventricular tachycardia.

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METHODS

Study sample

During a 17-month period, adults admitted to the Cleveland Clinic arrhythmia monitoring unit with documented ventricular tachycardia (at least three repetitive ventricular ectopic beats) were candidates for this study except for the following: patients with serum

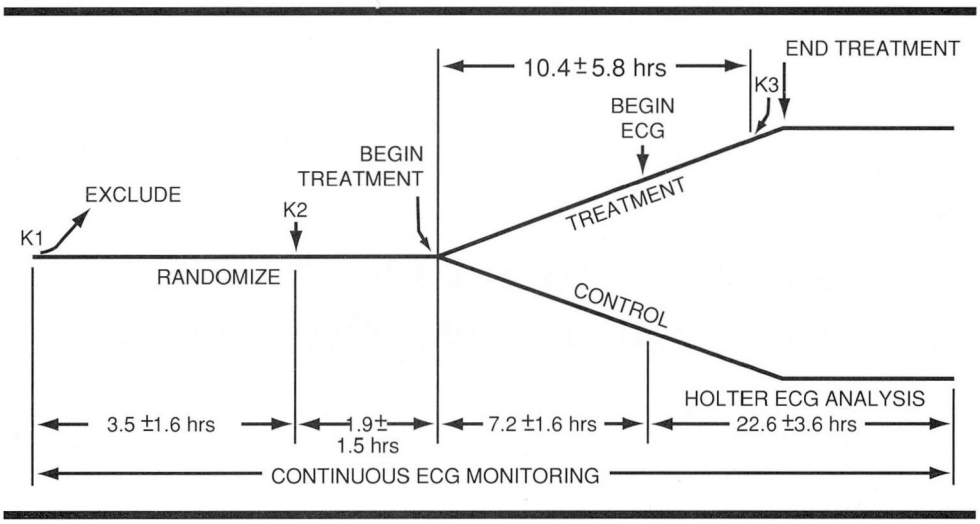

FIGURE 1. Diagram of the potassium-loading protocol. K1, K2, K3 = serum potassium determinations. Time intervals are means ± SD (hours).

creatinine level above 2.0 mg/dL; patients who were hypokalemic (serum potassium level below 3.5 mEq/L) or hyperkalemic (serum potassium level above 5.0 mEq/L); patients undergoing cardiac surgery in the 5 days before the study began; patients scheduled for major surgical procedures or invasive cardiac procedures (such as cardiac catheterization) during the period of the study; patients with severe acute illness such as acute myocardial infarction, pulmonary edema, or pulmonary embolus; and patients who preferred not to participate. Informed written consent was obtained from all participants.

Trials

The study consisted of two potassium augmentation trials: an intravenous trial (9 months) followed by an oral trial (8 months). *Figure 1* outlines the protocol for both trials. An initial serum potassium determination (K1) ensured that the patients were normokalemic. All patients included in the trials were randomly assigned to treatment and control groups. Approximately 2 hours before treatment was to begin, serum potassium level was measured again (K2). Treatment lasted from 10 to 12 hours, and 10 hours after it began, a third serum potassium determination (K3) was made. Continuous electrocardiographic recording began 7 hours after treatment was initiated and continued for approximately 24 hours.

During the intravenous trial, treatment patients (Group I) received a continuous infusion of 250 mL of one-half normal saline with potassium chloride added. Intravenous control patients (Group II) received an infusion of 250 mL of one-half normal saline. During the oral trial, treatment patients (Group III) received potassium chloride capsules (8 mEq) divided into two to five approximately equal doses. Oral control patients (Group IV) did not receive any treatment.

Intravenous and oral treatment patients (Groups I and III) received potassium chloride based on initial serum potassium measurement, using the following scale: Serum potassium 3.5 to 3.9 received 1.0 mEq/kg; 4.0 to 4.5 received 0.5 mEq/kg, and 4.6 to 5.0 received 0.25 mEq/kg. These doses conformed with the recommendation of Scribner and Burnell.[5]

During the trial period, patients continued treatment for their arrhythmias and other medical conditions as deemed appropriate by their physicians. Since the purpose of the trials was to determine the utility of potassium loading as an adjunct to antiarrhythmic therapy, other antiarrhythmic medications were not discontinued.

Data collection

Variables recorded to assess the adequacy of randomization included age; sex; type of heart disease; presence or absence of clinical congestive heart failure; presence or absence of systemic hypertension; administration of digitalis or amiodarone in the week prior to the date of the trial; administration of beta-blocking medications, calcium-blocking medications, procainamide, quinidine, tocainide, mexiletine, disopyramide, and diuretics during the day before the trial; administration of oral or intravenous potassium supplements and nitrates during the trial period; and administration of lidocaine during electrocardiographic monitoring.

Continuous electrocardiographic recordings were analyzed by an experienced technician interacting with a computer scanner (Delmar Avionics). The number of runs of ventricular tachycardia (at least three consecutive ventricular ectopic beats), the number of ventricu-

TABLE 1
DISTRIBUTION OF AGE, SEX, AND OTHER CARDIOVASCULAR DISEASES

	Intravenous trial		Oral trial		Significance
	Group I (n=44) (Saline with KCl)	Group II (n=48) (Saline)	Group III (n=50) (KCl capsules)	Group IV (n=47) (No supplement)	(t-test, χ^2, or Fischer's exact)
Age (mean)	59	61	60	63	NS
Number of men	40	34	43	35	NS
Coronary disease	31	37	36	35	NS
Previous infarction	25	21	22	24	NS
Rheumatic valvular disease	4	2	2	2	–
Mitral valve prolapse	5	4	3	4	–
Cardiomyopathy	10	12	9	6	NS
Myocarditis	1	0	1	0	–
Pericarditis	0	0	0	2	–
Systemic hypertension	12	17	18	21	NS
Congestive heart failure	9	10	10	10	NS

TABLE 2
DISTRIBUTION OF CARDIAC MEDICATIONS

	Intravenous trial		Oral trial		Significance
	Group I (n=44) (Saline with KCl)	Group II (n=48) (Saline)	Group III (n=50) (KCl capsules)	Group IV (n=47) (No supplement)	(χ^2, or Fischer's exact)
Other K supplements	11	12	15	10	NS
Diuretics	16	21	24	22	NS
Digoxin	28	29	31	26	NS
Lidocaine	2	9	1	5	–
Procainamide	18	13	15	21	NS
Quinidine	5	9	5	4	NS
Tocainide	0	1	5	5	–
Mexiletine	4	4	3	1	–
Disopyramide	0	0	2	0	–
Beta blockers	10	7	12	10	NS
Amiodarone	14	5	16	11	NS

lar couplets, and the number of premature ventricular contractions (PVCs), as well as the length (number of beats) of ventricular tachycardia were reported. For quality control, electrocardiographic tapes (25%) were reanalyzed and compared by paired t-tests and Wilcoxon signed rank tests; significant differences were not found.

Statistical analysis

Chi square, Fischer's Exact Test, and Student t-tests (significance defined as $p<0.05$) were used to compare age, sex, type of heart disease, presence or absence of congestive heart failure or systemic hypertension, and use of medications among the four groups. The Wilcoxon rank sum test was used to compare the incidence of ventricular tachycardia, the length of the average run of ventricular tachycardia, the number of ventricular couplets per hour, and the number of PVCs per hour in the four groups. Serum potassium levels before treatment (K2) and after treatment (K3) were compared by Student t-tests. All 189 subjects in both trials were divided according to whether or not they had experienced ventricular tachycardia and again according to whether or not they had ventricular couplets. The median serum potassium levels (K3) in the patients with either of these arrhythmias were compared by the Wilcoxon rank sum test with the median potassium levels (K3) in patients without these arrhythmias. Since PVC distribution was less skewed than runs of ventricular tachycardia or ventricular couplets, the Spearman rank correlation was used to uncover any association between potassium level and PVCs.

The incidence of ventricular tachycardia, ventricular couplets, and more than 30 PVCs per hour was charted on histograms and 95% confidence intervals were con-

TABLE 3
CONTINUOUS ECG RESULTS (MEAN ± SD)

	Intravenous trial		Oral trial	
	Group I (n=44) (Saline with KCl)	Group II (n=48) (Saline)	Group III (n=50) (KCl capsules)	Group IV (n=47) (No supplement)
Runs of ventricular tachycardia/h	4.5 ± 23.4	3.2 ± 18.9	3.9 ± 21.4	1.9 ± 8.3
Runs of ventricular tachycardia/h in first 12 h	4.7 ± 24.9	2.9 ± 16.0	4.3 ± 25.4	1.9 ± 8.5
Length of average run (beats)	41.7 ± 166.1	5.0 ± 6.0	3.4 ± 1.3	9.9 ± 29.7
Couplets/h	20.2 ± 67.6	11.4 ± 30.4	11.7 ± 52.6	9.0 ± 27.0
PVCs/h	120 ± 177	190 ± 323	104 ± 167	203 ± 378

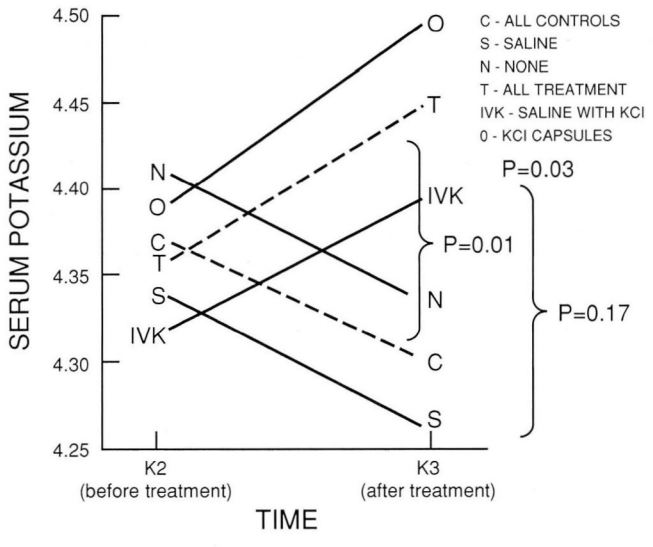

FIGURE 2. Changes in serum potassium level induced by potassium loading.

structed around the differences between treatment and control for the oral trial, intravenous trial, and for both trials combined.

RESULTS

Of the 189 patients participating in the trials, 152 were men. The mean age was 61 years (range 25 to 84). Fifty-eight patients (31%) had documented monomorphic ventricular tachycardia (at least 13 beats). One hundred thirty-six patients (72%) had nonsustained ventricular tachycardia (three to 13 beats). Eight patients (4%) had previously documented spontaneous ventricular fibrillation.

Of the 92 patients participating in the intravenous trial, 44 patients were assigned to the potassium chloride subgroup (Group I) and 48 to the one-half normal saline subgroup (Group II). The protocol had to be discontinued in six of the former because of intolerable pain caused by the intravenous infusion of the concentrated solution of potassium chloride. Of the 97 patients participating in the oral trial, 50 were assigned to the potassium chloride subgroup (Group III) and 47 to the control group (Group IV).

There were no significant differences between the groups in age; sex; type of cardiac disease; presence or absence of systemic hypertension or congestive heart failure; or other medications, including diuretics, antiarrhythmics, and other potassium supplements. *Tables 1* and *2* show the distribution of most of these variables among the four groups.

No significant differences in serum potassium at the initiation of therapy (K2 in *Figure 1*) were found between groups. When comparing serum potassium near the end of therapy (K3 in *Figure 1*), control patients in both trials (oral and intravenous) had decreased serum potassium while treatment patients demonstrated an increase. However, near the end of therapy the difference between oral and control was significant only for patients receiving oral potassium ($p = 0.03$). *Figure 2* demonstrates these relationships. *Table 3* shows the results of continuous electrocardiographic monitoring.

There were no significant differences between groups by the Wilcoxon rank sum test for the number of runs of ventricular tachycardia per hour, the number of ventricular tachycardia episodes per hour in the first 12 hours of monitoring, the length of the average run of ventricular tachycardia, the number of couplets per hour, or the number of PVCs per hour. When both treatment groups were combined and compared with both control groups, there were no significant differences between any of these variables by the Wilcoxon rank sum test. *Figures 3*,

4, and 5 are histograms showing the incidence of ventricular tachycardia, ventricular couplets, and PVCs in treatment and control groups for the intravenous trial, the oral trial, and both trials combined, respectively. The incidence of ventricular tachycardia, couplets, and premature contractions was actually slightly higher in the intravenous treatment group than in the intravenous control group. *Figure 3* demonstrates that the likelihood of a large decrease in the incidence of these arrhythmias following intravenous potassium loading is small. *Figure 4* shows a small, insignificant decrease in the incidence of ventricular tachycardia, couplets, and PVCs in patients receiving potassium chloride capsules as opposed to control patients receiving no treatment.

When all 189 patients were divided between those with and without ventricular tachycardia and with and without ventricular couplets, the Wilcoxon tests showed no significant difference in their serum potassium levels. The relationship between the number of PVCs and serum potassium level (K3) in the 189 patients was also examined and the Spearman rank test showed no significant correlation (r = –0.08).

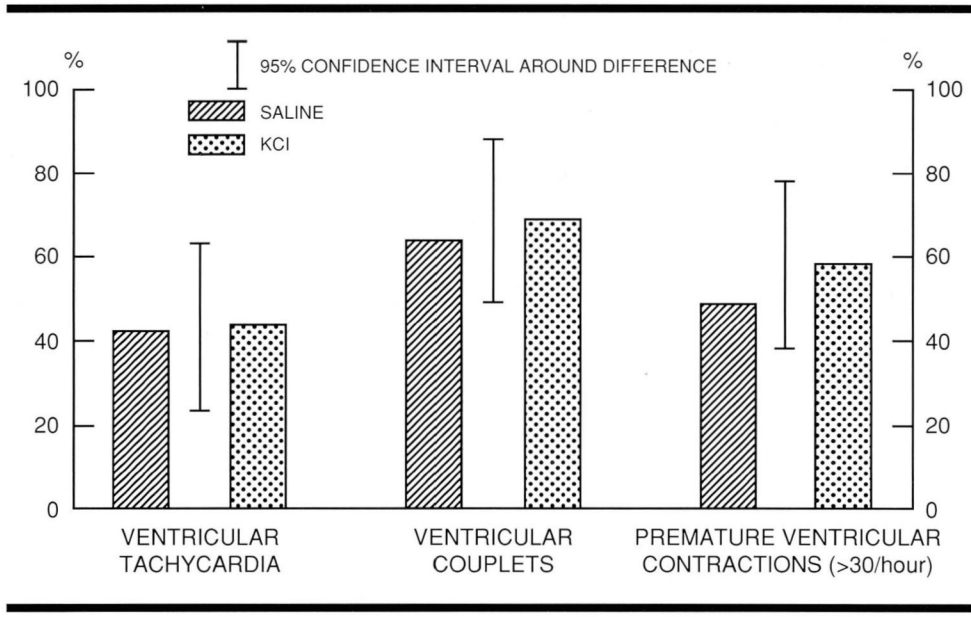

FIGURE 3. Incidence of arrhythmias in groups receiving intravenous saline *v* intravenous saline plus potassium chloride. Ninety-five percent confidence intervals indicate that a beneficial effect is unlikely.

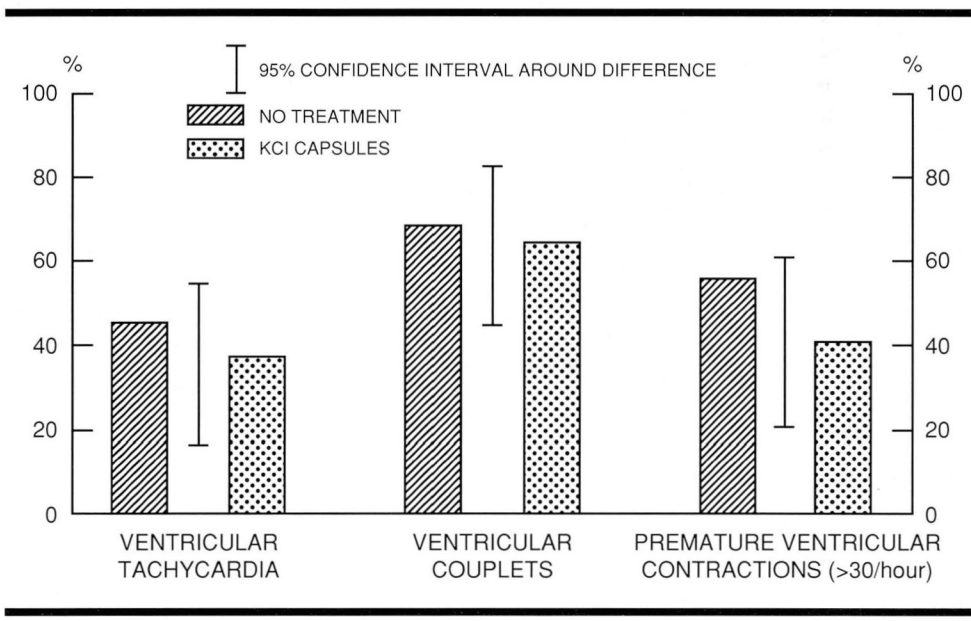

FIGURE 4. Incidence of arrhythmias in control and oral potassium groups.

Of the 189 patients, 114 were taking digoxin during the trials. Fifty-five of these fell into one of the control groups and 59 into one of the treatment groups. No significant differences were found among the number of runs of ventricular tachycardia, ventricular couplets, or PVCs. Eighty-three of the 189 patients were taking diuretics (not potassium-sparing). Forty-three of these were in control groups and 40 in treatment groups. No significant differences were found for the incidence of any of the arrhythmias.

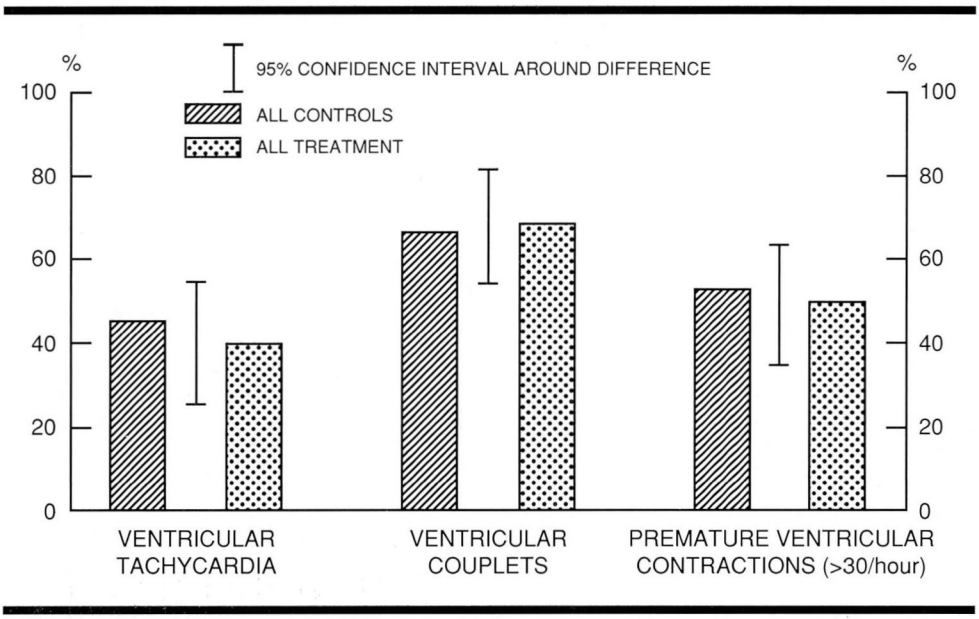

FIGURE 5. Incidence of arrhythmias in combined potassium chloride treatment *v* combined control groups.

DISCUSSION

The results of this investigation suggest that intravenous potassium loading in normokalemic patients is not helpful as an adjunct to therapy directed at decreasing the incidence of ventricular arrhythmias. Though treatment with potassium chloride capsules produced no significant improvement in cardiac rhythm, the rather wide confidence intervals leave open the possibility of a beneficial effect from oral therapy. The sample sizes of this trial are such that only very dramatic differences in ventricular ectopy could be detected with adequate statistical power. Statistical power is best for detecting differences in the incidence of ventricular couplets. Detectable differences for this variable range from 33% to 47%. It is of course possible that larger doses are necessary for acute benefit of cardiac rhythm.

The dose of potassium chloride used in both the intravenous and oral trials was chosen to comply with the estimates of Scribner and Burnell[5] and because the investigators thought that these doses were clinically safe and appropriate. The mean increase in the serum potassium levels of subjects in the treatment groups (0.1 mEq/L) was small, partially because serum potassium tended to decrease in the control groups during the period of the study. Such decreases can be explained by changes in potassium metabolism associated with meals, activity, and medications such as diuretics.

Limitations of trials

Early attempts to demonstrate the efficacy of potassium loading[4] in the treatment of cardiac arrhythmias suffered from the lack of continuous electrocardiographic recording and from the failure to recognize the large spontaneous variability of these arrhythmias.[6,7] With the advent of continuous recording, it soon became apparent that the spontaneous variation in arrhythmia frequency was so great as to require relatively large sample sizes to compare the efficacy of an antiarrhythmic therapy in treatment and control patients.

In order to avoid interpatient variability, several antiarrhythmic trials have used a randomized, crossover pattern.[8] Crossover trials are appropriate in stable clinical situations, such as in the treatment of outpatients with antiarrhythmic therapy, when there is good control over medications and other variables. Perhaps the best examples of nonapplicability of the crossover trial of antiarrhythmic therapy are the trials of various antiarrhythmic medications in the early postmyocardial infarction period.[9–11] Similarly, in the present investigation, changes in medication could produce an instability that would make a crossover comparison inappropriate. Using a separate control group of patients, as we have done, requires a relatively large sample size to demonstrate small effects.

Potassium supplementation controversial

Controversy surrounds the use of potassium supplements in persons receiving diuretic therapy for systemic hypertension. Hollifield and Slaton[12] studied 38 hypertensive patients without other medical disease who took hydrochlorothiazide at progressively increasing dosages. These authors noted a decrease in serum potassium and total body potassium as well as an increase in the incidence of PVCs.

Holland and associates[13] studied 21 patients with a

history of thiazide-induced hypokalemia, all of whom had systemic hypertension and no other cardiovascular disease. The patients were first treated with hydrochlorothiazide (50 mg twice a day) and then those who manifested Grade II or higher ventricular ectopic activity on continuous electrocardiographic monitoring were treated with hydrochlorothiazide and spironolactone. These authors noted an increase in ventricular ectopic activity during the initial phase of their study and a decrease in this activity after spironolactone administration. By repleting potassium stores only in patients who demonstrated ventricular ectopy on continuous electrocardiographic monitoring, these authors may have picked just those patients in whom cycles of ventricular ectopic activity had peaked and in whom premature ventricular beats would have decreased in any case.[14] This would bias the study into showing an efficacy for spironolactone therapy. The magnesium-sparing effect of spironolactone might also have been responsible for its antiarrhythmic efficacy.[15]

Whelton and colleagues[16] studied 91 hypertensive subjects, 43 of whom were randomly assigned to treatment with a thiazide and further randomly assigned to subgroups (22 also received potassium supplements and 21 received only thiazide). After 9 weeks of this therapy, there were no differences in the counts of ventricular ectopic beats in the placebo and thiazide groups. However, there was a significant drop in the ectopic count in the patients who received both potassium and thiazide.

Dyckner and Wester[17] gave oral or intravenous potassium supplements to 54 hypokalemic patients, many of whom had congestive cardiac failure and some of whom were taking diuretics. These patients received potassium supplements for approximately 4 days, after which relative short-term continuous electrocardiographic monitoring (3 hours) showed no difference in the counts of ventricular ectopic beats of various Lown classifications.

Madias and associates[18] were unable to demonstrate the arrhythmogenicity of hypokalemia produced after 1 month of treatment with hydrochlorothiazide in 20 patients with systemic hypertension and no heart disease. Papademetriou and associates[19] studied 21 hypertensive patients who had demonstrated hypokalemia while receiving diuretic treatment. No patient had a history of heart disease. They obtained 24-hour continuous electrocardiographic records both before and after several weeks of treatment with 48 mEq to 96 mEq a day of potassium chloride supplements. No significant reduction in the incidence of ventricular premature beats or ventricular couplets could be demonstrated.

In 1988, Papademetriou and colleagues[20] compared the incidence of ventricular arrhythmias before and after 4 weeks of thiazide therapy in 44 patients with hypertension. There was no significant increase in the incidence of arrhythmias, despite a significant reduction in serum potassium. Furthermore, the subset of patients with echocardiographic or electrocardiographic evidence of left ventricular hypertrophy also did not demonstrate an increase in ventricular arrhythmias. Most of these investigations concerned subjects with systemic hypertension without other cardiovascular disease. Though there are definite discrepancies, many studies show no significant effect on arrhythmia incidence after potassium supplementation.

Is hypokalemia an etiologic factor?

The treatment of hypokalemia is often aggressive because approximately half of patients who present with sustained ventricular tachycardia or as survivors of sudden death are found to be hypokalemic.[21] The hypokalemia is then assumed to be an etiologic or contributing factor to the clinical arrhythmias. However, normokalemic patients with induced sustained ventricular tachycardia during cardiac electrophysiologic studies demonstrate spontaneous postcardioversion hypokalemia.[22] This hypokalemia presumably is mediated through stress-induced catecholamine release.

This finding of hypokalemia has important implications for current cardiac electrophysiologic testing. Frequently, after initial induction of sustained ventricular tachycardia, subsequent testing is performed in the presence of anti-arrhythmic medication. These subsequent attempts to induce tachycardia may therefore be performed during unrecognized hypokalemia. Hypokalemia, especially in patients who are taking digoxin, may also decrease the threshold for electrophysiologic induction of ventricular tachycardia.[22] Therefore, hypokalemic patients with clinical ventricular tachycardia or sudden death may not always require antiarrhythmic medication. Instead, potassium supplementation, particularly if electrophysiologic studies fail to induce ventricular tachycardia during normokalemia,[23] may be all that is required. Further studies are necessary, such as prospective serial electrophysiologic testing in normokalemic and hypokalemic patients.

The controversy surrounding the contribution of hypokalemia to clinical arrhythmias can also be extended to several other specific clinical settings. Nordrehaug and von deu Lippe[24] have reported that hypokalemia on admission for acute myocardial infarction portends a worse prognosis and a higher likelihood of ventricular fi-

brillation. Kafka and colleagues[25] reported that hypokalemia during acute myocardial infarction is associated with increased incidence of complex ventricular ectopy. In addition, in the postoperative period after open heart surgery, intravenous potassium supplementation has been empirically advocated by cardiovascular surgeons and is purported to prevent ventricular arrhythmias.[26] From our experience with the automatic implantable cardioverter defibrillator, successful cardioversion also often appears more difficult in the presence of hypokalemia.

Future considerations

Our study did not consider the possible beneficial effects of prolonged potassium therapy or those of combined potassium and magnesium replacement. Either or both of these might benefit cardiac rhythm even though acute potassium-loading therapy does not. The role of magnesium in the genesis of ventricular arrhythmias has recently been explored in greater detail, and continues to remain a source of great interest. There have been several well-documented cases of ventricular arrhythmias secondary to hypomagnesemia.[27,28] Recently, it has been determined that patients with acute myocardial infarction may present with lower serum magnesium levels.[29] Abraham and associates[30] have proposed the use of empiric magnesium supplementation during acute myocardial infarction for the prevention of lethal arrhythmias. Further investigation into the relationship of magnesium to ventricular ectopy is necessary.

We know of no recent trial of potassium supplementation for the treatment of ventricular arrhythmias in normokalemic patients with structural heart disease. We conducted the present investigation to determine whether acute potassium loading could benefit the cardiac rhythm of these high-risk patients. Many patients with heart disease have potassium depletion from diuretic therapy, secondary hyperaldosteronism, or both. When potassium depletion demonstrates itself as hypokalemia, we concur that potassium supplementation is indicated.

Our previous report[31] indicated that while most physicians do not use potassium supplements for normokalemic patients with ventricular arrhythmias, some do. The results of the present study suggest that acute loading doses of potassium, especially when given intravenously to normokalemic patients, do not decrease the frequency of ventricular ectopic activity. This seems to be true also for those taking diuretics or digitalis. Further study is required to determine the possible role of chronic potassium therapy and combination therapy with potassium and magnesium.

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