Section 3
Electrolyte Changes and the Myocardium: Defining the Risk

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Potassium Loss, Ventricular Irritability, and the Risk of Sudden Death in Hypertensive Patients

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Summary

In the past, potassium depletion in both non-digitalised patients and in patients without cardiac disease was thought to cause no adverse cardiac effects. However, several studies have now demonstrated a significant incidence of ventricular ectopic activity (VEA) with diuretic-induced hypokalaemia, even in hypertensive patients without overt heart disease. Additional evidence suggests that sudden death may occasionally result from this VEA. Potassium repletion with potassium-sparing diuretics or with potassium chloride supplementation has generally demonstrated a beneficial therapeutic effect in reducing VEA. However, after diuretic therapy occasional patients may have persistent VEA which may result from focal myocardial lesions associated with potassium depletion. In contrast, diuretic therapy in which normokalaemia is maintained has only been associated with a very low occurrence of VEA. Thus, with the preservation of normokalaemia, diuretic therapy for hypertension does not appear to be associated with the significant hazards of VEA.

An increase in sudden death was noted in the Multiple Risk Factor Intervention Trial (MRFIT) in a subgroup of patients with baseline electrocardiographic (ECG) abnormalities (left ventricular hypertrophy, nonspecific ST-T changes, and minor conduction defects) [Sherwin 1984]. These patients were part of the special intervention group which received a higher dose of diuretics, with the subsequent development of a greater hypokalaemia. In addition, these patients remained somewhat more hypokalaemic during long term therapy. Hypokalaemia was not uniformly corrected in these patients because, at the time this study was initiated, hypokalaemia secondary to diuretic therapy was not felt to lead to ventricular ectopic activity (VEA) in hypertensive patients without overt cardiac disease. However, this previous opinion was based more on clinical impression than scientific study. Hence, several clinical studies utilising accurate techniques such as 24-hour ambulatory ECG monitoring and ECG monitoring during exercise testing have since provided good evidence that diuretic-induced hypokalaemia may be associated with a significant incidence of VEA, even in patients without overt cardiac disease.

1. Evidence That Diuretics Increase VEA

1.1 Potassium Repletion with Spironolactone

One such study (Holland et al. 1981) assessed VEA during diuretic-induced hypokalaemia in patients with mild to moderate uncomplicated es-
esential hypertension and a history of diuretic-induced hypokalaemia. These patients were taken off previous antihypertensive medications and given supplemental potassium chloride for a period of 2 to 3 weeks during an initial 4-week placebo phase. Near the end of the placebo phase, baseline 24-hour ambulatory ECG monitoring was done to document that less than 6 unifocal ventricular premature beats (VPBs) per hour and no other types of ventricular ectopic activity (VEA) were present. In addition, an exercise test was done to evaluate the patients for occult coronary artery disease. Those patients who qualified for the study were then treated with hydrochlorothiazide (100 mg/day) for a period of 4 weeks to induce hypokalaemia. At the end of this time, ambulatory ECG monitoring, plasma potassium determination and exercise testing were repeated. Seven of 21 hydrochlorothiazide-treated patients developed an increase in the number of unifocal VPBs to greater than 30 per hour or developed complex VEA (ventricular tachycardia, ventricular couplets, multifocal ventricular premature beats), which was seen in 4 of the 7 patients. At the end of the hydrochlorothiazide treatment phase only 2 of these 7 patients had VEA provoked by exercise testing, demonstrating a greater sensitivity of ambulatory ECG monitoring in identifying VEA. Those patients who developed VEA were then potassium repleted with spironolactone, and the effect of potassium repletion was assessed by periodic additional 24-hour ambulatory ECG monitoring.

Spironolactone therapy significantly reduced VEA in all patients. However, 1 patient had persistent unifocal VPBs after potassium repletion varying from 31 to 220 unifocal VPBs per hour during 4 ambulatory ECG monitorings performed during 13 weeks. It thus appeared that this patient may have undergone some kind of cardiac change as a result of hydrochlorothiazide-induced hypokalaemia that led to permanent ventricular irritability in spite of potassium repletion. This change might have been explained by focal cardiac lesions which have previously been observed with potassium depletion (Holland 1984a; Perkins et al. 1950; Welt et al. 1960). However, patients in the study by Holland et al. (1981) who exhibited VEA with ambulatory ECG monitoring could not be identified by clinical criteria and did not complain of symptoms compatible with VEA. Patients with and without VEA had essentially the same average age and severity of hydrochlorothiazide-induced hypokalaemia, and they were not more likely to have left ventricular hypertrophy. Thus, diuretic-induced hypokalaemia was associated with VEA, even in patients without apparent underlying cardiac disease.

1.2 Potassium Repletion with Amiloride

A subsequent study (Holland et al. 1984) was initiated to evaluate the genesis of diuretic-induced VEA. Two 24-hour ambulatory ECG monitorings were done to document more accurately the baseline ambulatory ECG pattern, and an exercise test was also done to help exclude occult coronary artery disease. Patients were divided into groups treated with either hydrochlorothiazide 100 mg/day or a combination of hydrochlorothiazide and amiloride, in an attempt to maintain normokalaemia during diuretic therapy. As with the previous study of Holland et al. (1981), it was noted that an increase in VEA occurred in patients allowed to become hypokalaemic with hydrochlorothiazide treatment alone. In patients receiving amiloride with hydrochlorothiazide to maintain normokalaemia, only a very low incidence of VEA without ventricular tachycardia was noted. Hypomagnesaemia was not observed during the 4 weeks of hydrochlorothiazide therapy.

Unfortunately, 1 patient died suddenly 2 days before ambulatory ECG monitoring, which had been scheduled 2 weeks after the initiation of the hydrochlorothiazide treatment. Even though this patient did not have ambulatory ECG monitoring at the time of death, the autopsy was highly suggestive of an arrhythmic death.

When patients with VEA were potassium-repleted with amiloride or with supplemental potassium chloride, VEA frequency decreased. Amiloride was more effective than supplemental potassium chloride, perhaps because it provided more effec-