CLINICAL SIGNIFICANCE OF METABOLIC DISTURBANCES INDUCED BY THE USE OF DIURETICS

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Orally effective diuretic agents first became available in 1956, with the parent compound being chlorothiazide. Soon thereafter Freis, Hollander and Wilkins found that chlorothiazide was effective in controlling hypertension and was well tolerated by the patients. In addition to lowering blood pressure, chlorothiazide greatly enhanced the hypotensive effect of other antihypertensive agents. Soon after, it was established for the first time that thiazide diuretics alone or in combination with other, then available agents, could result in a sustained control of hypertension in the majority of patients. In 1963 the Veterans Administration Cooperative Study Group initiated a controlled trial to assess the effectiveness of antihypertensive agents on the prevention of morbity and mortality in patients with essential hypertension. Diuretic based regimens were selected. Thiazide diuretics, reserpine, and hydralazine were used in patients receiving active treatment. As is well known, the results of these VA cooperative studies demonstrated indisputable evidence of benefit from hypertension control (1, 2). Diuretics were popularized and have remained the cornerstone in the management of essential hypertension since then. Through the years a variety of other antihypertensive agents have been developed with different mechanisms of action. Diuretics, however, used as monotherapy have proven to be as effective as any other agent used in hypertension. Their unique mode of action makes them an essential part of any combination regimen and diuretics are the only a agents which cause volume contraction and prevent fluid retention. For these and many other reasons they always have been recommended as the first line agents by most opinion forming bodies and they always have been the first choice of therapy in the step-care approach [3].

Diuretics, like many other therapeutic agents, have side effects. Occasionally these side effects are severe enough to necessitate discontinuation , of treatment or change to another agent. The most frequent and important side effects are: hypokalemia, hyperuricemia, alterations in lipid profiles and glucose metabolism.

Although these metabolic abnormalities of diuretics have been known for a long time, they were viewed with unconcern, since rarely caused symptoms to patients with essential hypertension. It was only the rare patient that would develop frank hyperglycemia or gout due to diuretic therapy.

In recent years however, some of these metabolic abnormalities especially hypokalemia and changes in lipids became a major issue and a subject of continuing controversy. Today then we'll discuss the clinical significance of some of these abnormalities.

Diuretic-induced hypokalemia and cardiac arrhythmias

Following the introduction and widespread use of diuretics, it was noted that plasma potassium was reduced below the normal range in a substantial number of treated patients. Depending on the type and dose of diuretic used, the incidence of hypokalemia is 20 to 40%. Hypokalemia is usually mild, with levels of potassium < 3.0 mEq/L encountered only infrequently.

The initial observations associating hypokalemia with cardiac arrhythmias were made in the early 1950's in digitalized patients. These observations were later confirmed and there is today a consensus that hypokalemia may aggravate digitalis induced arrhythmias. At that time it was primarily this concern that led to attempts to prevent the hypertensive patient from becoming hypokalemic. A variety of potassium supplements and potassium sparing diuretics have been used indiscriminately in hypertensive patients, the annual cost of which in the U. S. exceeded 300 million dollars in recent years.

A variety of reports, mostly retrospective or uncontrolled observations, appeared in the literature associating hypokalemia with cardiac arrhythmias. In 1982 Harrington et al [4] summarized the published reports on the subject in an editorial entitled "Our national obsession with potassium". They pointed out the shortcomings and limitation of most studies, and they concluded that critical review of the literature disclo-

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ses no evidence that fatal ventricular ectopy results from hypokalemia per se.

One of the quoted studies was conducted by Holland and co-workers [5]. This study was the first prospective study conducted in patients with benign uncomplicated hypertension. Holter monitoring was performed in 21 patients before diuretic therapy, after 4 weeks of treatment with hydrochlorothiazide, and after correction of plasma potassium. Holland's study showed some increase in ventricular ectopy in 7 of the 21 patients and it has been quoted since then an evidence that diuretics are arrhythmogenic. The study can be criticized, however for a number of reasons: 1. Patients with any significant ectopy at baseline were excluded. However, because of the large spontaneous variability from day to day, increased arrhythmia in the second or hypokalemic recording should be expected. 2. Hypokalemia cannot be implicated as a cause of arrhythmias because both groups of patients, those who developed arrhythmia and those who did not, had similar changes in their plasma potassium. 3. Correction of hypokalemia and repeat monitoring was performed only in the 7 patients with increased arrhythmias during hypokalemia. This again introduces a selection bias.

TABLE 1 - Ventricular ectopy before and after diuretic therapy all patients (n = 44).

Variable	Baseline	Diuretic
SBP	154 ± 16	136 + 12 *
DBP	98 ± 8	89 ± 6 *
BW	87.6 ± 16.9	85.9 ± 16 9 *
PK	4.07 ± 0.26	3.36 ± 0.44 *
PVC/hour	11.3 ± 40.2	7.5 ± 18.8
Total Couplets	129	18
Total VT Episodes	7	8

SBP = sistolic blood pressure
DBP = diastolic blood pressure
BW = body weight
PK = plasma potassium
PVC = premature ventricular beats
VT = ventricular tachicardia

TABLE 2 - Ventricular ectopy in patients with or without hypokalemia on diuretic therapy.

	Hypokalemia (n = 27)		No/Hypokalemia (n = 17)	
	Baseline	Diuretic	Baseline	Diuretic
BW	92.2 ± 17.5	90.1 ± 17.6 *	81.1 ± 14.4	79.8 ± 14.1 *
PK	4.00 ± 0.22	3.08 ± 0.24 *	4.20 ± 0.28	3.81 ± 0.28 *
PVC/hour	16.8 ± 7	9.1 ± 22.0	2.6 ± 5.9	5.1 ± 9.2
Total Couplets	124	12	5	6
Total VT episodes	2	2	5	1

* P < 0.001; Statistics compare values before and after diuretic therapy. Abbreviations as in Table 1.

Other well designed, controlled prospective studies-conducted in the last 4 years failed to confirm Holland's results. In our laboratory 44 patients with benign essential hypertension were monitored for 48 hours before and after diuretic therapy. As shown on table 1 there was no change in the number of PVC,S, couplets or episodes of ventricular tachycardia with diuretic therapy. Of the 44 patients, 27 developed plasma potassium -<3.4 mEq with diuretic therapy. Ventricular ectopy remained unchanged (table 2).

It has been suggested from previous studies that patients with left ventricular hypertrophy (LVH) have more arrhythmias and thus they may be more susceptible to hypokalemia. We therefore separated out those patients who had hypertrophy proven by echocardiography (table 3). Patients with LVH had more arrhythmias at baseline but those arrhythmias were not adversely affected by diuretic therapy. Table 4 summarizes all the recently published studies on the subject. Most studies showed no increase in arrhythmias following diuretic therapy.

TABLE 3 - Ventricular ectopy in patients with or without left ventricular hypertrophy before and after hydrochlorothiazide.

	LVH (n = 28)		No LVH(n = 16)	
Variable	Baseline	Diuretic	Baseline	Diuretic
LVPWT	1.39 ± 0.14	–		
VW	86.3 ± 14.7	85.4 ± 14.7 *	90.0 ± 20.8	88.1 ± 20.6*
PK	4.06 ± 0.23	3.39 ± 0.45 *	4.10 ± 0.32	3.33 ± 0.43
PVC/hour	16.6 ± 49.8	10.1 ± 22.9	2.1 ± 5.0	3.0 ± 5.9
Total Couplets	123	15	6	3
Total VT Episodes	5	3	2	0

* = P < 0.001; t = P < 0.05; * = compare values before and after diuretic; t = compare values between groups at baseline; LVPWT = left ventricular posterior wall thickness; Other abbreviations as in Table 1.

TABLE 4 - Hypokalemia and ventricular ectopy in patient with uncomplicated hypertension

Report	Nº. of patients	Plasma K Basel	Plasma K Diuretic	Hours of ECG Monit.	Arrhythmic Change
Holland et al	7	4.0	3.0	24	increase
	14	3.9	3.0	24	no change
Papademetriou	27	4.0	3.0	48	no change
	17	4.2	3.8	48	no change
Leif et al	13	4.0	3.0	48	no change
Madias et al	20	4.4	3.0	24	no change
	16	4.2	3.6	24	no change
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If hypokalemia was a cause of arrhythmia in patients with uncomplicated hypertension, correction of hypokalemia should result in disappearance or decrease of arrhythmias. Information on this aspect of the problem is limited. In Holland's study, 7 patients

who demonstrated increased ventricular ectopy during hypokalemia improved after potassium repletion. We studied 16 patients with overt hypokalemia, but we could not demonstrate any improvement in their arrhythmias following correction of their potassium [7]. in the Medical Research Council Trial [8] 8 patients were monitored before and after correction of their hypokalemia, but no change in arrhythmias was noted either.

The interest in ventricular arrhythmias is based on the assumption that frequent or complex ectopy serves as a predictor of sudden death. If mild hypokalemia was a risk for sudden death, one would expect increased mortality in hypokalemic patients. This question was addressed in a recent from the Glaskow report blood pressure clinic entitled "Mild hypokalemia is not a risk factor in treated hypertensives"[9]. In that study 3783 patients were followed for an average of 6.5 years. Diuretic therapy did not appear to adversely affect mortality. The age-adjusted mortality was similar for all quartiles of serum K. That was true for all cause mortality and for ischemic heart disease 4 mortality, for both men and women. The group with the highest serum K tended to have higher mortality but the difference was not statistically significant. Even patients with serum K less than 3.0 mEq/L had similar mortality to the group as a whole.

The study contruibuted the most to the concepet thatdiuretics may increase the risk of sudden death is the MRFIT [10]. This study was a primary prevention trial designed to assess the effect of a multiple risk factor reduction on the coronary artery disease mortality. When the study failed to demonstrate the expected benefit in the intensively treated group, a retrospective search was carried out between a number of subgroups. An unfavorable trend was found among hypertensive men with baseline ECG abnormalities treated intensively with diuretics. However. it is possible that these unexpected findings are simply due to retrospective subgroup analysis. Equally surprising is the fact that patients in the usual care group with abnormal ECG's had lower mortality than those with normal ECG's. It is not surprising, therefore, that subsequent analysis of the HDFP data [11] in a similar manner to MRFIT failed to confirm the MRFIT findings.

Further evidence that diuretics are safe is seen in the many large scale-long term trials that have been conducted in the last 2 decades. A major study that tested the efficacy and safety of diuretics was the MRC trial [12]. In that study over 17.000 patients were randomized to placebo, propranolol or bendrofluazide; and they were followed for an average of 7 years. Results of this study further demonstrate the safety of diuretics. Bendrofluazide reduced stroke rates more than propranolol, whereas propranolol was somewhat more effective in preventing coronary events in nonsmokers, but overall cardiovascular events and mortality were similar between the two drugs. If diuretics were arrhythmogenic they should have resulted in an increased rate of sudden deaths and increased mortality. When compared to propranolol however, which has antiarrhythmic properties, the mortality rates were the same. A frequently asked question is whether diuretic therapy represents an increased risk for malignant arrhythmias in patients with acute myocardial infarction. An inverse relationship between potassium level and incidence of ventricular tachycardia/fibrillation (VT/VF) has been indicated in many studies. However, it should be emphasized that several methodologic problems undermine the reliability of those observations. Most of those studies were retrospective and included patients with cardiomyopathies or treated with digitalis. Most of them had inadequate monitoring systems and temporal association between low K and arrhythmias had not been established. In many patients potassium was measured after resuscitation and after administration of epinephrine or bicarbonate. With all of these limitations in mind let us then examine the role of diuretics.

In one study by Johanson [13] more than 5300 patients with acute MI were examined. It was found that the incidence of VT/VF was higher in patients with low K. Hypokalemia was present in 22% of the patients treated with diuretics. However, it was present also in 13% of patients with no prior diuretic therapy. The incidence of VT/VF was higher in patients with low K in both groups, but more so in the non diuretic treated patients. Overall the incidence of VT/VF was similar between diuretic-treated patients, non diuretic treated and patients receiving beta-blocker. If diuretic-induced hypokalemia were the cause of these arrhythmias, diuretic treated patients should have had twice as many episodes of tachyarrhythmias than non diuretic treated patients, and probably many times that of patients receiving beta-blocker. Of all the published studies on the incidence of VT/VF in acute MI patients, none has shown any relationship between prior diuretic therapy and these arrhythmias (table 5). This raises the question as to why there should be a correlation between low K and VT/VF? Ischemia is a well known cause of catecholamine elevation. Catecholamines may cause both low K and arrhythmias. This suggests that low K could have been only a marker of high catecholamines and not related causally to tachyarrhythmias. Finally, it has been shown that in the ischemic area, the area of infarction, there is marked increase in extracellular K soon after the occlusion of a vessel. Local hyperkalemia then is present in the ischemic/ arrhythmogenic area in contrast to systemic hypokalemia.

Diuretic therapy and plasma lipids

An increase in plasma cholesterol secondary to thiazide diuretics, in patients with essential hypertension has become a major concern in recent years.

A variety of reports attempted to associate lipid changes induced by diuretic therapy with the recognized failure of hypertension control to prevent coronary artery disease and myocardial infarctions.

TABLE 5 - Relationship between diuretic therapy and arrhythimias

	No. of Patients %	Hypokalemic PTS with prior diuretic RX %	Relationship of VT/VF and diuretics	Use of digitalis
Hulting	537	50	?	YES
Solomon	141	71	NONE	YES
Nordrehaug	1047	55	NONE	YES
Cooper	586	26.6	NONE	YES
Nordrehaug	60	?	NONE	NO
Johansson	5342	43	NONE	?

A rise in cholesterol was reported shortly after the introduction of diuretics by Schoenfield and Goldberger [14] in five of six cardiac patients treated with thiazide diuretics. In 1976 Ames and Hill [15] reported increases of serum cholesterol by 11 in g/dl and serum triglycerides of 34 mg/dl in patients treated with chlorthalidone or hydrochlorothiazide. In a recent article Weinberger [16], reviewing studies, concluded that there is evidence of short and long-term increase of cholesterol induced by diuretic therapy. However, a closer look at the studies reviewed demonstrates that the follow-up period was rather short, ranging from only a few weeks to almost one year. Several problems with these trials have been previously pointed out [17] The majority of truly long-term, large scale trials, have almost uniformly shown no significant change in serum cholesterol or triglyceride levels with diuretic therapy. The European Working Party Hypertension [19] provided data showing an average decrease of 6.2 mg/dl in serum cholesterol in diuretic-treated patients.

The Hypertension Detection and Follow-up Program trial presented the annual changes in serum cholesterol over 5 years for thiazide treated step care participants [20] These data demonstrated an average increase in cholesterol of 4 mg/dl at one year followed by a continuous decline amounting to 9 mg/dl by the fourth and fifth years. Similarly Alcazar et al [21] and the Oslo trial [22] reported no significant changes in cholesterol or triglycerides after the first year of therapy with diuretics. Finally in a Veterans Administration controlled trial [23] hydrochlorothiazide alone was given to 343 patients with uncomplicated hypertension. The serum cholesterol rose by 8.8 mg dl during the initial 4 to 10 weeks of treatment, but fell to 3.0 mg/dl below the pretreatment average by 12 months.

In summary then, most long-term large scale trials demonstrate either no increase or below baseline decline of serum cholesterol in thiazide treated patients. The increase in cholesterol noted in some short-term studies is short-lived and probably does not increase the risk of atherosclerosis.

Effect of diuretic therapy on plasma uric acid and glucose

Hypertensive patients have been shown to have higher incidence of hiperuricemia. It has been hypothesized that elevated uric acid in primary hypertension could lead to deposition of uric acid in the renal parenchyma and result in renal damage. Moreover uric acid is presumably a causal part of the gout syndrome, and some studies suggested an association with increased mortality. Since thiazide therapy regularly produces a modest increase in uric acid levels. the possibility that thiazide induced hiperuricemia could worsen the patient's status is of considerable importance.

A recent publication from the Hypertension Detection and Follow-up Program [24] examined each one of those concerns. The interaction of thiazide diuretics, serum uric acid and creatinine level was studied in 3693 stepped care participants. Therapy with thiazide diuretics tended to increase levels of uric acid and creatinine, but the increase was less in patients with higher uric acid. Patients who received uric-acid lowering agents had the same increase in creatinine as those who didn't, suggesting the lack of causal association between uric-acid and creatinine elevation. Changes in uric acid at one year of treatment were inversely correlated with mortality in men. Only 15 episodes of gout were reported among the 3692 participants in 5 years. The authors concluded that uric acid changes caused by diuretics are benign and there is no reason to lower uric acid levels pharmacologically in the treated hypertensives unless they present with gout.

Thiazide diuretics have been said to induce glucose intolerance, and occasionally frank diabetes mellitus in susceptible individuals. Although some reports [25, 26] indicated that long-term treatment with diuretics have a diabetogenic effect others found opposing results [27, 28]. In a recent report the European Working Party reported a modest increase in fasting blood glucose of 2.5 mg/dl in 371 patients treated hydrochlorothiazide for one year. The change in blood glucose did not differ further placebo treated patients in the subsequent 2 years.

Berglund et al [30] reported results on 106 hypertensive patients treated with either thiazide diuretics or propranolol for 10 years. They found no evidence that diuretics induced diabetes or glucose intolerance.

To summarize, although diuretics may have metabolic consequences, they rarely cause symptoms necessitating discontinuation of treatment. These metabolic changes are usually mild and do not appear to adversely affect prognosis. Diuretics have served us well for many years. They are safe, effective, easy to titrate and inexpensive. All prospective large scale trials conducted in hypertensive patients utilized diu-

retic based regimens. Almost in all trials a dramatic decrease in strokes and congestive heart failure was evident. Although it has been difficult to demonstrate decrease in coronary heart disease in individual studies, mortality from heart attacks has been steadily declining. Since 1972 the adjusted death rate from coronary artery disease decreased by 35% and from stroke by 48%. Although this decrease can be attributed to a number of factors, control of hypertension has been an important contributor. Diuretics were the first drugs to make the control of hypertension possible. They have remained of proven effectiveness over the years. Other agents need to be carefully tested and proven superior before they can be used to replace diuretics.

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