Effect of Treatment on Morbidity in Hypertension. Veterans Administration Cooperative Study on Antihypertensive Agents

Effect on the Electrocardiogram

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SUMMARY

Electrocardiographic (ECG) data are presented from the Veterans Administration Cooperative Study of 143 nontreated and 137 treated male patients with initial diastolic blood pressures averaging 90-114 mm Hg. Average follow-up was 2.9 years and longest follow-up was 5 years. Significant differences were observed with respect to the ECG signs of left ventricular hypertrophy (LVH). In the patients not meeting criteria for LVH prior to randomization, the incidence of abnormal QRS voltage, ST-segment depression or T wave flattening or inversion developing in the treated patients was approximately one-fourth that found in the control group. In the patients with ECG evidence of LVH prior to randomization, the reversion to normal of QRS voltage or ST-segment depression was approximately 2.5 times greater in the treated than in the control patients. Although no significant effect of treatment was observed on other ECG changes such as Q and QS patterns, A-V or ventricular conduction defects or arrhythmias, the incidence of such events was too low to make valid comparisons. However, the present results indicate that antihypertensive drug treatment markedly improved the ECG changes specifically related to hypertension.

Additional Indexing Words:

Systolic blood pressure — Diastolic blood pressure — Antihypertensive treatment
Electrocardiogram — ST segment changes and hypertension — T wave changes and hypertension

PREVIOUS REPORTS of serial electrocardiograms taken during the course of antihypertensive drug treatment have indicated that certain electrocardiographic abnormalities associated with hypertension may revert toward normal following treatment.[1-5] All of these studies, however, were retrospective and did not include untreated controls. Helmcke, Schneckloth and Corcoran, in their study of 78 hypertensive patients, found that although ECG improvement was more common in those classified as blood pressure responders as compared to the nonresponders the relationship was

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Classification of Patients According to Number of Post-randomization Annual Electrocardiograms

No. of annual exams	Control group No.	Treated group No.
1	143	137
2	116	112
3	83	81
4	47	50
5	20	20

not consistent.[3] Dern et al. found improvement in the electrocardiograms of 44 treated patients.[4] However, a valid estimation of benefit of antihypertensive drug treatment based on such studies must be limited because of the absence of an untreated control group with which to compare results. Considerable electrocardiographic variability can occur over time in both normal individuals[6] and in patients with heart disease.[7] Without a control group it is not possible to differentiate between therapeutic effect and the effect of such spontaneous variability.

The present report describes the electrocardiographic changes occurring during the course of the Veterans Administration Cooperative Study on antihypertensive agents.[8] The patients were randomly assigned, double blind to either active drugs or placebos. Follow-up averaged 2.9 years and in some cases was longer than 5 years. This study, therefore, permitted a quantitative assessment of the benefits of antihypertensive medications, if any, on the electrocardiographic abnormalities associated with hypertension.

Methods and Materials

The design of the cooperative study and an analysis of morbid events which occurred other than electrocardiographic changes have been described previously.[8, 9] All patients were males who exhibited an average diastolic blood pressure of 90 mm Hg or higher from the fourth through the sixth day of hospitalization. Also, the average diastolic blood pressure of the last two posthospitalization clinic visits prior to randomization was in the range of 90–114 mm Hg. The patients were then randomly assigned, double-blind to either active drugs (hydrochlorothiazide 50 mg plus reserpine 0.1 mg combined in a single tablet given twice daily, and hydralazine 25 or 50 mg three times daily) or to placebos of these agents.

Copies of the prerandomization and one year postrandomization 12 lead electrocardiograms were obtained in 143 of 194 patients randomized into the control or placebo treated group and in 137 of 186 treated patients. In addition, some of these patients' electrocardiograms were obtained for 2, 3, 4 and 5 years postrandomization (table 1), the average being 2.9 years.

The background characteristics of the patients are presented in tables 2 and 3. Approximately 42% of the patients were black in both the control and treated groups. Those showing cardiac enlargement by X-ray were 22% in the control patients and 28% of the treated patients (table 2). The average age at entrance in both groups of patients was approximately 51 years (table 3). Average heights and weights were not significantly different. The known duration of hypertension averaged 4.5 years in both groups of patients. The average prerandomization blood pressure in the control group was 164/104 and in the treated patients was 164/105 mm Hg. There were no significant differences in the two groups of patients with respect to serum creatinine or blood urea nitrogen levels, serum potassium concentration, fasting blood sugar or serum cholesterol values.

The changes in blood pressure following randomization are shown in table 4. The average blood pressure of the control patients changed little from the prerandomization values except for a slight rise in systolic blood pressure. In the treated patients the average blood pressure fell from a prerandomization value of 164/105 mm Hg to a four month post-randomization average of 137/87 mm Hg and remained at essentially that level or slightly lower for the duration of the study.

All of the collected electrocardiograms were read and classified by one of the authors (P.P.) without his knowledge of any other clinical features of the patients including type of therapeutic regimen or changes in blood pressure. The electrocardiographic characteristics were classified according to the Minnesota code as revised by Rose and Blackburn.[10] This classification eliminates some of the ambiguities present in the original code[11] and includes a more comprehensive set of procedural rules.

Table 2

Background of Randomized Patients: Numeration Data

Characteristic	Control group No.	%	Treated group No.	%	Total
Number randomized	143		137		280
Black	59	41	57	42	116
Other	84	59	80	58	164
Heart size by roentgenogram					
Ungerleider enlarged	31	22	39	28	70

Table 3

Measurement Data Prior to Randomization

Characteristic	Control group Mean	Treated group Mean
Age (yrs)	51.6	50.3
Height (in)	69.1	68.4
Weight (lb)	181.8	176.6
Duration of known hypertension (yrs)	4.4	4.5
Average clinic systolic BP (mm Hg)	164.1	163.5
Average clinic diastolic BP (mmHg)	103.9	104.7
Serum creatinine (mg/100 ml)	1.27	1.24
Blood urea nitrogen (mg/100 ml)	16.0	16.4
Serum potassium (mEq/liter)	4.5	4.4
Fasting blood sugar (mg/100 ml)	96.1	100.2
Cholesterol (mg/100 ml)	245.5	247.6

In the analysis of Category 4 of the revised Minnesota code (ST-junction and segment depression) only items 4-1 to 4-3 were included. These items require ST-segment depressions that are horizontal or downward sloping which are considered to be more representative of "ischemia" than is item 4-4 which includes upward sloping or U-shaped ST-segments.[12] Also excluded were optional code 5-4 of category 5 (T wave items) and category 9 (miscellaneous items). In addition to the above analyses the sum of the magnitudes of the S wave in V_1 and the largest R wave in either V_5 or V_6 was calculated. A sum exceeding 35 mm was considered to be indicative of left ventricular hypertrophy in accordance with Sokolow and Lyon's criteria.[13]

As shown in table 5 the prerandomization electrocardiograms were similar in the control and treated groups of patients except that a higher percentage of the treated group exhibited high amplitude R waves in the left side leads and deep S waves in V_1. Evidence of left ventricular hypertrophy using Sokolow's criteria was present in 32.1% of the treated group as compared to only 18.2% of the control patients prior to randomization. The prevalence of T wave flattening or inversion, however, was not significantly different in the two groups of patients nor were there any significant differences with respect to any of the other electrocardiographic characteristics that were analyzed.

Results

Incidence of Abnormalities

The incidence of electrocardiographic abnormalities developing over an average follow-up of 2.9 years after randomization is shown in table 6 and figure 1. Marked differences in voltage, T wave and ST-segment changes were found in the control as compared to the treated patients. Thus, of the patients not meeting criteria for LVH prior to randomization, 25% of the control and only 6.6% of the treated group developed abnormal voltage. In addition, 25.5% of the control patients as compared to 7.5% of the treated group developed T wave flattening or inversion. The incidence of ST-segment depression was 19.3% in the placebo group and 3.8% in the treated patients. All of these differences were significant ($P < .005$). There were no significant differences between the two groups of patients in the incidence of Q and QS patterns, left axis deviation, A-V or ventricular conduction defects or arrhythmias.

Figure 2 shows the incidence of ST-T and voltage changes by the life table method of analysis. This method adjusts for the variable length of follow-up of different patients. It also adjusts for any differences in losses to observation between the control and treated groups and it determines whether the benefit of treatment occurs early or late

Table 4

Trends of Blood Pressure

	Control group			Treated group		
Time of observation	No. observed	Average systolic blood pressure (mm Hg)	Average diastolic blood pressure (mm Hg)	No. observed	Average systolic blood pressure (mm Hg)	Average diastolic blood pressure (mm Hg)
Prerandomization	143	164	104	137	164	105
Postrandomization						
4 months	142	168	105	137	137	87
8 months	141	170	107	137	137	88
12 months	143	168	105	137	136	86
16 months	116	171	106	112	135	86
20 months	116	173	106	112	133	86
24 months	113	173	107	109	134	86
28 months	83	175	107	81	134	86
32 months	83	172	104	80	135	85
36 months	82	170	103	79	134	86

Table 5

Electrocardiographic Data Prior to Randomization

Electrocardiographic item	Control group No. tracings read*	Control group No. with codable items	Control group %	Treated group No. tracings read	Treated group No. with codable items	Treated group %
Total randomized	143			137		
Q & Q-S patterns	143	12	8.4	136	10	7.4
Left axis deviation	137	10	7.3	133	8	6.0
High amplitude R waves (left)	140	29	20.7	134	47	35.1
ST-segment depression	132	18	13.6	126	21	16.7
T wave flattening or inversion	132	30	22.7	126	33	26.2
A-V conduction defect	143	4	2.8	137	2	1.5
Ventricular conduction defect	143	5	3.5	137	3	2.2
Arrhythmias	143	10	7.0	137	6	4.4
Increased voltage (S in V_1 + R in V_5 or V_6 > 35 mm)	137	25	18.2	134	43	32.1

*Numbers vary because of exclusions for evaluating some of the codable items as described in Minnesota code.[8]

or is continuous throughout the period of observation.

It is evident from figure 2 that a lower incidence of ST-T and voltage changes was manifested early in the treated group and that the difference in incidence of such ECG changes between the control and the treated group increased with the passage of time. Thus, for ST-segment depression the 5 year cumulative incidence rate for the control group was 29% as compared to 5% in the treated group. With respect to T wave flattening or inversion at 5 years the cumulative incidence rate was 38% for the control group and 10% for the treated patients. Finally, abnormal voltage change was 34% at 5 years in the control group as compared to 9% in the treated group.

Only a small proportion of patients developed both voltage and ST-segment or T wave abnormalities. Such a change occurred in 10 control patients and in 2 treated patients. Four of these 10 control patients exhibited neither voltage nor ST-T abnormalities prior to randomization while 6 showed one or the other of these abnormalities in the prerandomization period. The latter prerandomization finding also was present in the two treated patients

Table 6

Patients with Normal Prerandomization Electrocardiograms Which Developed Abnormality (Codable Item) Postrandomization

Electrocardiographic item	Control group No. randomized without item	Control group No. developing abnormality	Control group %	Treated group No. randomized without item	Treated group No. developing abnormality	Treated group %	Significance of difference (P-value)*
Q & Q-S patterns	131	10	7.6	126	5	4.0	NS
Left axis deviation	127	3	2.4	125	1	0.8	NS
High amplitude R waves (left)	111	32	28.8	87	5	5.7	<0.005
ST-segment depression	114	22	19.3	105	4	3.8	<0.005
T wave flattening or inversion	102	26	25.5	93	7	7.5	<0.005
A-V conduction defect	139	9	6.5	135	2	1.5	NS
Ventricular conduction defect	138	4	2.9	134	3	2.2	NS
Arrhythmias	133	15	11.3	131	17	13.0	NS
Increased voltage (S in V_1 + R in V_5 or V_6 >35 mm)	112	28	25.0	91	6	6.6	<0.005

*Either the χ^2 test or the Fisher exact probability test was used depending on sample size according to criteria given in reference 15.

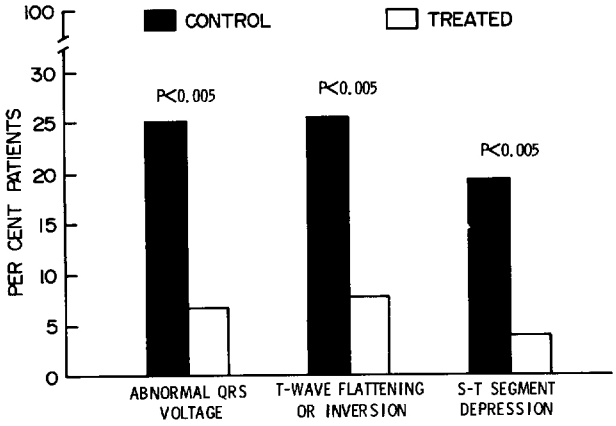

Figure 1

Percent of patients developing either voltage or ST-T abnormalities following randomization who did not exhibit such change prior to randomization.

who developed both voltage and ST-T changes during the postrandomization period.

Reversions to Normal

Of the patients exhibiting voltage criteria for left ventricular hypertrophy prior to randomization 74.4% of the treated patients as compared to 24.0% of the control group reverted to normal voltage ($P < .005$) (table 7, fig. 3). A favorable trend also was evident with respect to flattened or inverted T waves with 51.5% of the treated and 33.3% of the control group reverting to normal, although this difference was not statistically significant. A significant difference was observed, however, with respect to normalization of ST-segment depression. Such reversion was seen in 57.1% of the treated patients and 22.2% of the control group ($P < .05$). No

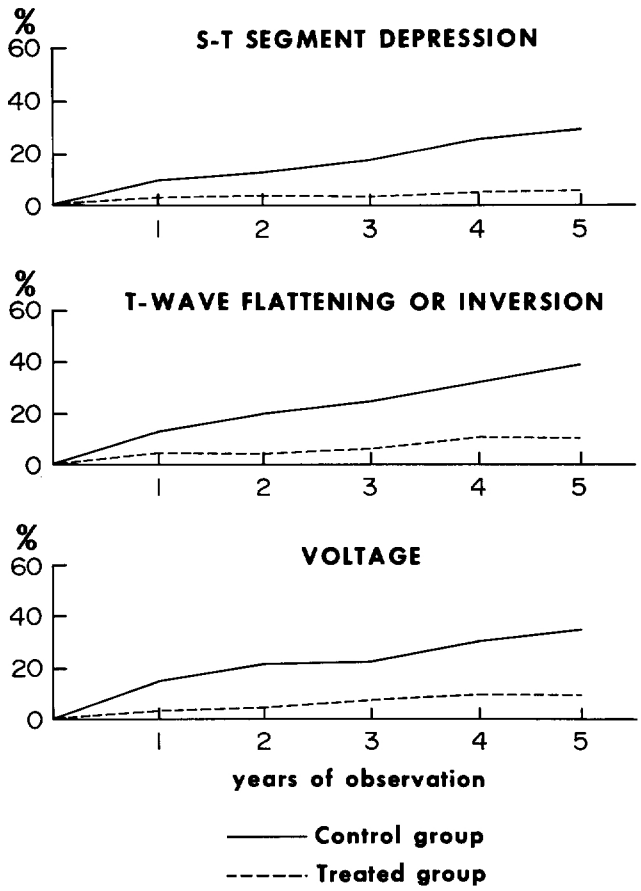

Figure 2

Estimated cumulative incidence of either ST-T or voltage abnormalities over a five-year period as calculated by the life-table method.

significant differences were found with respect to reversion to normal of other electrocardiographic

Table 7

Patients with Prerandomization Electrocardiograms Showing Abnormality (Codable Item) which Reverted to Normal Postrandomization

Electrocardiographic item	Control group: No. randomized with item	Control group: No. reverting to normal	Control group: %	Treated group: No. randomized with item	Treated group: No. reverting to normal	Treated group: %	Significance of difference (P-value)*
Q & Q-S patterns	12	3	25.0	10	2	20.0	NS
Left axis deviation	10	2	20.0	8	4	50.0	NS
High amplitude R waves (left)	29	8	27.6	47	35	74.5	<0.005
ST-segment depression	18	4	22.2	21	12	57.1	0.029
T wave flattening or inversion	30	10	33.3	33	17	51.5	NS
A-V conduction defect	4	3	75.0	2	0	0.0	NS
Ventricular conduction defect	5	1	20.0	3	0	0.0	NS
Arrhythmias	10	8	80.0	6	5	83.3	NS
Increased voltage (S in V_1 + R in V_5 or V_6 > 35 mm)	25	6	24.0	43	32	74.4	<0.005

*Same notation as in table 6.

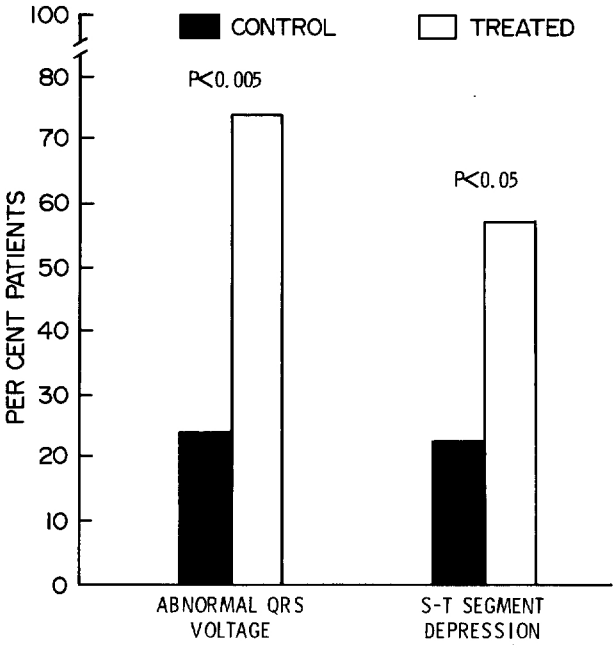

Figure 3

Percent of patients reverting from abnormal to normal ST-T or voltage change during the postrandomization period.

characteristics. The prevalence of some of these characteristics was too low, however, to permit a reliable estimate (table 7).

Figure 4 shows the incidence of reversions to normal of ST-T and voltage changes during the postrandomization period as indicated by the life-table method of analysis. The figure indicates a relatively high incidence of reversion to normal in the first year of follow-up as compared to subsequent years. Few reversions occurred after the third year of follow-up. With respect to ST-segment depression the 5 year cumulative reversion rate to normal was 63% in the treated group as compared to 22% in the control group (fig. 4). The reversion rate of T wave changes for the cumulative 5 year period was 56% in the treated patients and 36% in the control patients. With respect to voltage the 5 year cumulative reversion rate was 87% of the treated group and 26% of the control group.

Nine patients in the control and 15 in the treated group exhibited abnormal voltage plus T wave or ST-segment criteria for left ventricular hypertrophy prior to randomization. Disappearance of all of these evidences of left ventricular hypertrophy was noted following randomization in 9 or 60% of the treated group as compared to none of the control patients ($P < 0.005$).

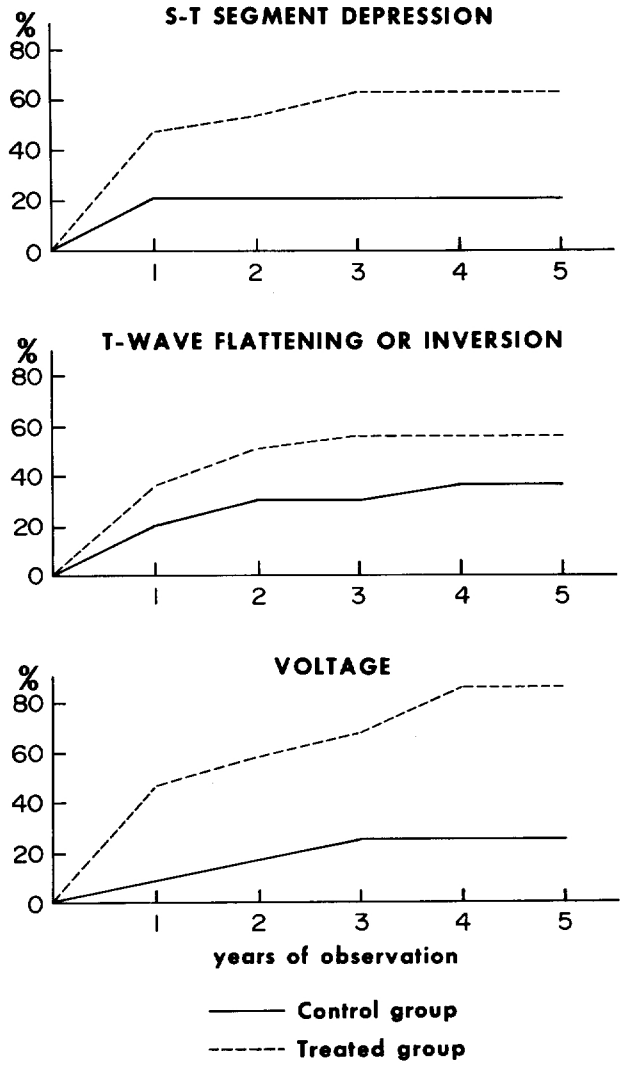

Figure 4

Estimated cumulative incidence of either ST-T or voltage reversion from abnormal to normal over a five-year period as calculated by the life-table method.

Relationship of Effectiveness of Treatment to Level of Prerandomization Blood Pressure and to Age

Approximately one-fourth of the control group developed voltage criteria for left ventricular hypertrophy during the postrandomization period. However, in the treated group a smaller percentage of patients with blood pressures of 165 systolic and above or diastolic pressures of 105-114 mm Hg developed increased voltage than did those with lower blood pressures (table 8). For this reason the percent "effectiveness of treatment" (difference between percent incidences in control and treated groups divided by percent incidence in control

Table 8

Development of Major QRS Voltage Change with Respect to Prerandomization Blood Pressure

Subgroup	Control group No. randomized	Control group No. showing change	Control group %	Treated group No. randomized	Treated group No. showing change	Treated group %	% Effectiveness*
I. Normal initial voltage becoming abnormal. Prerandomization BP							
Systolic < 165 mm Hg	63	17	27	57	5	9	67
Systolic 165+ mm Hg	49	11	22	34	1	3	86
Total	112	28	25	91	6	7	72
Diastolic 90-104 mm Hg	51	13	25	42	4	10	60
Diastolic 105-114 mm Hg	61	15	25	49	2	4	84
Total	112	28	25	91	6	7	72
II. Abnormal initial voltage reverting to normal. Prerandomization BP							
Systolic <165 mm Hg	9	3	33	21	12	57	42
Systolic 165+ mm Hg	16	3	19	22	20	91	79
Total	25	6	24	43	32	74	68
Diastolic 90-104 mm Hg	10	1	10	16	14	88	89
Diastolic 105-114 mm Hg	15	5	33	27	18	67	51
Total	25	6	24	43	32	74	68

*% Effectiveness

$$\text{for subgroup I} = \frac{\text{Incidence \% control} - \text{\% treated}}{\text{\% control}}$$

$$\text{for subgroup II} = \frac{\text{Reversion \% treated} - \text{\% control}}{\text{\% treated}}$$

group) was greater in the patients with the higher levels of blood pressure.

The situation was reversed with respect to ST-segment depression. In the prevention of this abnormality treatment was 100% effective in the patients with systolic levels below 165 mm Hg and 69% effective in those with systolic blood pressures above this level (table 9); and was 91% effective in the patients with diastolic levels below 105 mm Hg as compared to 69% in the 105-114 diastolic subgroup. Similar differences were observed with regard to T wave flattening or inversion. However, these differences in the effectiveness of treatment at different levels of blood pressure between voltage changes on the one hand and ST-T changes on the other may have been due to chance. Nonrepresentative trends can occur as a result of subdividing the patients into such small sample sizes.

As would be expected, a greater percentage of patients with average blood pressures above 164 systolic or 104 diastolic exhibited abnormal voltage prior to randomization than did those with initial blood pressures below these levels (table 8). However, no consistent pattern of change with relation to blood pressure was evident in the postrandomization period. Treatment was effective in both groups. The same was true with respect to reversion of ST-segment depression to normal (table 9). Treatment had approximately the same effectiveness irrespective of the level of initial blood pressure.

Twenty-five patients in the control group exhibited abnormal voltage prior to randomization. Six of these patients reverted to normal during the postrandomization period (table 8). This improvement was unrelated to changes in blood pressure. For example, at one year following randomization the average blood pressure of the six patients who reverted was 7/0 mm Hg higher than their average blood pressure prior to randomization. This was not significantly different from the blood pressure change observed in the control patients who did not revert to normal. The latter exhibited an increase of 4/3 mm Hg at one year after randomization. The reversion to normal seen in six of the control patients probably reflects spontaneous variation that may occur over time with respect to electrocardiographic changes.[6, 7] However, its occurrence in the control group was considerably lower ($P < .005$) than the 74% reversion to normal observed in the treated patients (table 8).

Table 9

Development of ST-Segment Change with Respect to Prerandomization Blood Pressure

Subgroup	Control group No. randomized	Control group No. showing change	Control group %	Treated group No. randomized	Treated group No. showing change	Treated group %	% Effectiveness*
I. Normal base line ST-segment becoming abnormal. Prerandomization BP							
Systolic < 165 mm Hg	70	8	11	64	0	0	100
Systolic 165+ mm Hg	44	14	32	41	4	10	69
Total	114	22	19	105	4	4	79
Diastolic 90-104 mm Hg	53	12	23	48	1	2	91
Diastolic 105-114 mm Hg	61	10	16	57	3	5	69
Total	114	22	19	105	4	4	79
II. Abnormal base line ST-segment reverting to normal. Prerandomization BP							
Systolic < 165 mm Hg	5	1	20	12	5	42	52
Systolic 165+ mm Hg	13	3	23	9	7	78	71
Total	18	4	22	21	12	57	61
Diastolic 90-104 mm Hg	8	2	25	7	4	57	56
Diastolic 105-114 mm Hg	10	2	20	14	8	57	65
Total	18	4	22	21	12	57	61

*Same notations as in table 8.

The relation between blood pressure and voltage changes was also examined in the treated group of patients. In the treated patients who exhibited reversion to normal voltage the average blood pressure at one year postrandomization was 31/19 mm Hg lower than during the prerandomization period. In the patients with abnormal voltage which did not revert, the one year average blood pressure was 21/16 mm Hg lower than the prerandomization blood pressure. This difference in the extent of average blood pressure reduction between the two groups was not significant.

Patients aged 50 and above responded to treatment as well as or better than the patients below 50 years of age. The percent effectiveness of treatment in the prevention of abnormal QRS voltage was 68 for the patients below age 50 and 77 for the older patients (table 10). Reversion of abnormal voltage to normal also was greater in the older subjects, the percent effectiveness of treatment being 79 in the patients age 50 and above as compared to 56 for those below 50 years of age.

Discussion

The present data indicate that antihypertensive therapy not only protects against the development of increased QRS voltage, ST-segment depression

Table 10

Development of QRS Voltage Change with Respect to Age

	Control group No. randomized	Control group No. showing change	Control group %	Treated group No. randomized	Treated group No. showing change	Treated group %	% Effectiveness*
I. Normal initial QRS voltage becoming abnormal							
Age < 50 yrs	54	15	28	47	4	9	68
Age 50 + yrs	58	13	22	44	2	5	77
Total	112	28	25	91	6	7	72
II. Abnormal initial QRS voltage reverting to normal							
Age < 50 yrs	15	4	27	26	16	62	56
Age 50 + yrs	10	2	20	17	16	94	79
Total	25	6	24	43	32	74	68

*Same notations as in table 8.

and T wave flattening or inversion in hypertensive patients but also causes a significant reversal of these abnormalities when they are present prior to treatment. These manifestations of left ventricular hypertrophy are specifically although not exclusively related to hypertension and are probably the direct consequence of a chronically increased afterload.

In contrast to the marked changes associated with treatment, particularly on QRS voltage and ST-segment depression, there were no statistically significant changes in Q or Q-S patterns or in conduction defects between the placebo and treatment groups. However, the low incidence of these latter events in both the control and treated groups did not permit an accurate assessment of the effectiveness of treatment. Although as shown in table 6 treatment appeared to lower the incidence of Q or Q-S patterns and of A-V conduction defects, the total incidence of these events was too low to achieve statistical significance.

The various electrocardiographic changes observed during the study are consistent with other data from the trial relating to morbid events.[8] Thus, treatment greatly reduced the incidence of "hypertensive" complications such as hemorrhagic stroke, congestive heart failure, progressive renal damage and accelerated hypertension. However, treatment did not appear to favorably influence the atherosclerotic complication of myocardial infarction. This negative result with respect to atherosclerosis may only mean that treatment must be initiated at an earlier stage in the hypertensive process.

The mechanism of the ST-T alterations in left ventricular hypertrophy is uncertain. Traditionally, these changes are considered to reflect a severe load on the left ventricle or "left ventricular strain" causing increased myocardial oxygen demand. The ST-T changes could, therefore, reflect chronic ischemia which may be prevented or reversed by reducing the blood pressure. It has also been suggested that the ST-T changes are secondary to higher voltages in these patients. However, some studies have shown that the ST-T changes are usually greater than would be expected as a consequence of the magnitude of the QRS voltages, suggesting that ST-T changes in patients with left ventricular hypertrophy may represent a primary disturbance in the recovery process of the left ventricular myocardium.

In a recent report Hamer, Shinebourne and Fleming[14] correlated hemodynamic findings with electrocardiographic abnormalities in 17 hypertensive patients. On the basis of the electrocardiogram they were divided into two groups. Nine (Group 1) had either a normal tracing or only QRS voltage changes of LVH with normal T waves and ST-segments. Group 2 (8 patients) had, in addition, ST depression and/or T wave inversion in the left chest leads. The results indicated no significant difference in the two groups with respect to cardiac output, peripheral resistance, and diastolic blood pressure. However, the systolic blood pressure was significantly higher in Group 2 as compared to Group 1. The present data (table 9) also indicate that the control patients with systolic blood pressure levels of 165 mm Hg and above developed ST-segment depression three times more often than the control patients with lower systolic levels. This difference was significant at the $P < .025$ level.

Hamer postulated that because of the higher systolic blood pressure seen in Group 2 patients the myocardium must generate a greater force. This leads to a primary change in the ST-segments and T waves by producing localized subendocardial changes which may alter the direction of repolarization or interfere with the spread of the activation process. However, this author also pointed out that the ST-T changes must represent more than a mechanical effect, as they do not revert to normal immediately when the left ventricular pressure is reduced. However, as indicated in the present study, many do revert with treatment after a period of time. Thus, the pathogenesis of the ST-T changes is still not completely clarified.

The present results, with respect to the effect of antihypertensive drugs on the electrocardiogram, provide further support for the value of treating patients with essential hypertension. It should be emphasized, however, that the blood pressure was reduced to or near normotensive levels in the great majority of the treated group. Less effective reduction of blood pressure may not have resulted in such a salutary effect.

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