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The Effects of dihydroergocornine upon the exercise electrocardiogram of the aged

Clarence H. Swanson Jr
University of Nebraska Medical Center

THE EFFECTS OF DIHYDROERGOCORNINE UPON THE EXERCISE ELECTROCARDIOGRAM OF THE AGED

METHOD OF MASTER, ET AL.

C. H. Swanson, Jr.

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INTRODUCTION

Heart disease is now the leading cause of death in the United States (, 2). This is undoubtedly the result of inadequate means of early diagnosis and inadequate means of treating this disease, as well as a result of the ever increasing mean age of our population. The increased use of tobacco and high cholesterol diets have also been considered as contributory to the increasing incidence of cardiovascular deaths (2, 3, 4).

The majority of all heart disease is considered to be the resultant sequel of coronary artery disease. Estimates state that from 65 t 75 per cent of the diseased hearts are the result of diseased myocardial vessels (1, 5). This fact was well demonstrated by Williams and Smith (6) in their report of 381 autopsys on persons between 70 and 99 years of age. They found a degree of coronary artery sclerosis in all the cases and this was moderate to advanced in 72.5 per cent of the series. Master, Chesky and Pordy (7) found in examining 200 practicing physicians over the age of 40 years, that 42 per cent had evidence of coronary artery disease.

On the other hand Dock (8) has introduced the term "presbycardia" and Harrison and Resnik (9) the term "senile heart disease", on the supposition that the congestive failure

seen in elderly individuals without definite evidence of coronary insufficiency (as angina pectoris and/or previous myocardial infarction) is the result of an aging myocardium rather than the result of an inadequate cardiac blood supply.

Whatever the primary pathology may be, the methods of early diagnosis and treatment are poor.

TESTS FOR THE DETERMINATION OF CORONARY ARTERY INSUFFICIENCY

The presence of coronary artery disease is often not suspected until it causes precardial pain. At this stage it is often difficult or impossible to obtain objective evidence of the disease. Different series point out that from 25 to 60 per cent of the people with angina pectoris have negative resting electrocardiograms, physical examinations and roentgenographic studies of the heart (4, 10, 16). Due to the inadequacy of these tests, other means have been proposed for the determination of the adequacy of the myocardial blood supply.

Symptoms of relative coronary insufficiency arise during periods of effort or stress, when it is believed that a local asphyxia and anoxia of the heart muscle resulting from the increased cardiac demand for oxygen and nourishment exists. Because of this most of the tests for the detection of coronary insufficiency have been designed to put the heart under a similar condition of anoxemia or stress.

Various methods have been used to induce this. Levine Ernstein and Jacobson (17) and others (18) first suggested the use of adrenalin. This was soon abandoned because of the lack of control, the unpleasant subjective reactions and the danger of producing a severe anginal attack. Greene and Gilbert (19) first studied the effects of re-breathing on

the electrocardiogram. Rothchild and Kissen (20) were the first to apply this test to patients with angina pectoris. They noted that RS-T depressions occurred in the controls and in the cardiac patients with or without the onset of angina. The degree of deviation was related to the degree of anoxemia. As a result of these findings they concluded that some factor in addition to anoxemia is concerned in the production of anginal pain, and that this variable makes it impossible to predict accurately whether or not induced anoxemia will cause pai . They discouraged the use of anoxemia because of its variable results and hazards.

Levy, Bruenn and Russell (21) and Biorck (23) studied the effects of inhaling 10 per cent oxygen and 90 per cent nitrogen. Levy, et were unable to obtain significant electrocardiographic findings in 55 per cent of 73 patients with coronary sclerosis. Biorck only got positive results in 20 to 30 per cent of the patients.

Evans and Bourne (24) in comparing exercise tests with anoxemic tests on the same patients, concluded that the exercise test was the better of the two.

Various types of exercise tests have been introduced by Wood, Wolforth anc Livezey (25), Whitten and Herndon (26), and Master, et al (5, 14, 21, 27, 33). Some of these tests have been poor because they caused apprehension through performance of unusual exercise and lacked reliability through non-standardization.

White, Paul L. (34) stated:

> "A simple test is necessary in that it is less apt to strain unaccustomed muscles of the subject, less apt to exhaust prematurely a person not in good physical training, and is more convenient and practical to execute. In fact, such exertion as enters into daily life is best of all."

The exercise test which most nearly fits these criteria is the two step exercise tolerance test devised by Master, et al. This step is simple, safe and standardized. It offers complete freedom of the thoracic movements, gives an accurate measure of work performed, uses ordinary everyday muscle activity and is simple enough for use in the hospital, clinic of office (35).

MASTER'S TWO STEP TEST

In 1929 the "two step" exercise procedure was devised by Oppenheimer and Master (29) as a practical test of circulatory fitness. After thousands of trials, tables were formulated that prescribed the standard number of trips patients should make depending on their age, sex and weight. The tables were first based on the response of the blood pressure and pulse to exercise. Later Master, Freedman and Dock (36) adapted the test for detection of electrocardiographic changes as an index of coronary artery adequacy.

Since it has been demonstrated that exercise, even in the absence of coronary artery disease, will produce electrocardiographic changes (4), the criteria designated for electrocardiographic changes following exercise significant of coronary artery disease, must, of necessity, not include the changes following moderate exercise.

Master (28) has stated that the electrocardiographic alterations following the exercise exerted following a controlled two step test significant of coronary artery disease are seen most frequently in the RS-T segment and in T wave changes. His criteria of ECG changes characteristic of coronary insufficiency are listed in Table 1.

TABLE 1

MASTER'S CRITERIA OF ELECTROCARDIOGRAPHIC CHANGES CHARACTERISTIC OF CORONARY INSUFFICIENCY

1. Depression of the RS-T segment by more than 0.5 mm. below the medium isoelectic line as determined with reference to P-R segment.
2. Flattening or inversion of a positive T wave.
3. Conversion of a negative T wave into a flat or positive one.
4. Increased frequency of extra systoles or other types of arrhythmias.
5. Lengthening of the QRS complex.
6. Flattening of the wave or development of large Q waves.
7. Lengthening of the P-R interval.
8. Block.

Other authors have proposed different exercise ECG changes as being significant of coronary artery insufficiency (37, 40). The difference in their criteria from that of Master consists mainly in the amount or RS-T depression and degree of T wave changes that are indicative of coronary insufficiency.

In order to maintain consistency throughout this paper, I have used Master's criteria for a positive exercise electrocardiogram.

It is worthy of note that Seusenbach (4) has produced ECG changes following strenuous exercise of normal individuals, that would be classified as significant of coronary artery disease according to Master's criteria. With this in mind, the necessity of controlled exercise can be appreciated.

It is often important to make a distinction between functional and organic heart disease. Unfortunately the exercise tolerance tests do not always make this differentiation. Master et al (11, 15 have observed RS-T and T wave patterns that are indistinguishable from those changes produced by coronary artery disease in 6 per cent of normal subjects. They have suggested hat these changes, which are usually found in anxiety states, may be the result of an induced coronary insufficiency resulting from psychic impulses acting through the autonomic nervous system causing coronary vasoconstriction (13, 16, 28, 41).

The assumption that cardiac function and ECG changes can result from autonomic nerve fiber induced coronary artery spasm has been substantiated by Manning, Caudwell, and others (42) in work upon dogs. In their experiments they were able to reduce the incidence of fatal ventricular fibrillation following sudden occlusion of a coronary artery from 75 per cent to 10 per cent by sympathetic denervation of the heart. They were also able to demonstrate that coronary dilator and anti-spasmotic drugs are effective, but to a lesser degree, in reducing this mortality.

Master et al (11, 13, 15, 16, 28, 41) have been able to revert positive two step tests to negative by administering sympatholytic drugs. These changes were usually noticed in patients with anxiety states or with neuro-circulatory asthenia.

Pordy, Chesky and Master (11, 12, 15, 41) have reported the results of a one to five year follow up on 200 cases, 100 with abnormal and 100 with normal exercise electrocardiograms. In the group with normal tests, no deaths have occured subsequent to testing. In only one instance did a coronary episode occur after the exercise test had been found normal. This was in a woman in whom an acute coronary occlusion developed three years after the test.

All the 100 cases with abnormal exercise electrocardiograms had normal resting ECG's at the time of the two step test. However several displayed Q waves of previous

myocardial infarction. No RS-T deviations, or T wave inversions were present. The follow-up investigation revealed evidence of organic coronary artery disease in 71 of this group. In seven of these cases the patient has died as a result of a coronary episode. The 29 cases of as yet unconfirmed coronary disease include only a few cases in which the clinical diagnosis was neurogenic or functional coronary insufficiency.

These favorable reports, however, have not been repeated by other men. Grossman, Weinstein and Katz (39) using the same methods, found positive tests in 24 of 43 patients with symptoms of coronary insufficiency and in 5 of 108 patients with a negative cardiac history. Unterman and DeGaff (40) were able to demonstrate positive exercise electrocardiographic changes in one-half the cases with coronary insufficiency.

ALKALOIDS OF ERGOT

AND THEIR DIHYDROGENATED DERIVITIVES

It would seem that the effects on the exercise tolerance ECG caused by psychic disturbances could be eliminated by the use of direct antispasmodic and coronary dilator drugs, or by the use of sympatholytic drugs.

Various investigators have used drugs which act on the autonomic nervous system to eradicate these electrocardiographic abnormalities, and through their results it seems these changes are especially related to the sympathetic nervous system. The alkaloids of ergot were found to be a series of related drugs with a powerful effect on the sympathetic nervous system.

In 1908, Dale (43) recognized the two active principles in the ergot alkaloids - the direct pharmacologic effect of constricting smooth muscle and the inhibition of sympathetic activity. On animals, ergotamine tartrate appears to be both sympatholytic and adrenolytic. However, its peripheral vasoconstrictive action masks these properties. If ergotamine tartrate is sympatholytic then according to older physiologic concepts of coronary innervation it would favor constriction and resultant decrease of coronary blood flow. But when used, there is a disappearance of the electrocardiographic abnormalities with the appearance of a bradycardia and decreased blood

pressure. There must be, then, other factors with independent effect on cardiac action potentials which can compensate in healthy hearts for all factors leading to cardiac anoxemia. Its pharmacological effects suggest either a vagotonic action, sympathicolysis, a direct effect on the S-A node, or a combination of these factors. However, ergotamine tartrate is contraindicated as a routine for this diagnostic purpose because of its angina provoking properties through its direct vasoconstrictive action (27).

In 1943, Stoll and Hofmann (44) demonstrated that well defined compounds of the ergot alkaloids could be obtained by hydrogenating the readily reducible bond of their lysergic acid, resulting in the formation of the compounds dihydroergotamine, dihydroergocornine, dihydroergocristine and dihydroergokyptine. They found these compounds to be less toxic, less emetic with an increased sympathicolytic effect and decreased or absent direct vasoconstrictive action on smooth muscle.

Rothlin, E. (45) states that the more toxic the natural alkaloid, the less toxic the hydrogenated form.

The most potent dihydrogenated alkaloid of ergot is dihydroergocornine, which possesses the sympatholytic effects of ergotamine tartrate but appears to possess minimal smooth muscle constrictor effects of the latter. This particular form, though, is also the most toxic of the dihydrogenated

ergot derivitives. Consequently two of these forms, dihydroergocristine and dihydroergokryptine, which have the same pharmacological action have been added to the former. The resultant product, DHC-180 (Hydergine-Sandoz) produces pharmacologic effects approximately equal to dihydroergocornine, but is less toxic (45). The direct pharmacology of dihydroergocornine is mainly that of sympathicolysis and possibly adrenolysis. Its action appears to be mainly central (i.e. medulla and/or hypothalamus). It is as follows(42, 46, 52):

In animals it lowers the blood pressure, decreases the heart rate and reduces or reverses the pressor effects of sympatheticomimetic amines without affecting their cardiac or vasodilator properties. It appears also to have a very weak peripheral vasoconstrictor action. However, if it is given following ganglionic blocking with tetraethyl ammonium, it produces an elevation of the blood pressure. It also produces a similar result in the anesthetized, decerebrate and spinal cat. Thus, it is concluded that the vasomotor centers, are its main site of action, and when the vasomotor centers or the autonomic efferent fibers are put out of action the normally latent vasoconstrictor effect of these alkaloids may predominate and produce an elevation in the blood pressure.

In man the findings are, in general, similar. The drug however often does not lower the blood pressure in normotensive subjects, and it also does not appear to have the

marked adrenolytic action it shows in animals. Due to its inconstant action in different human subjects, some observers feel that its effect is actually the net result of two opposing actions.

It is of interest that Manning and Caudwell (42) found that in dogs, the previous administration of dihydroergocornine reduces the incidence of sudden death (death in 24 hours) after ligation of a coronary artery from 75 per cent to 30 per cent.

APPLICATION OF DHO-180 TO THE ELECTROCARDIOGRAM

Pordy, Chesky and Master (11, 12, 15, 41) have found that the two step exercise electrocardiogram is abnormal in 6-8 per cent of normal persons, mainly in patients with anxiety states or neurocirculatory asthenias. Thus, they concluded that a purely functional, rather than organic coronary insufficiency existed In the hope of finding a means of differentiating between the two they tried preliminary injection of sympatholytic drugs as a means of blocking functional ECG changes. They found that ergotamine tartrate was effective for this purpose, but, due to its angina provoking properties, its use was discontinued. In most patients with functional heart disturbances dihydroergocornine (DHO-180) was also found to prevent the appearance of ECG abnormalities after the two step test. This drug did not predispose to angina and was found to have few side effects.* Moreover, most patients in whom the two step test remained abnormal after the use of dihydrocornine, follow up studies revealed definite evidence of the presence of coronary disease.

Pordy, Arai and Master (53) found that intravenous injections of DHO-180 (0.25-1.0 mgm) caused resting ECG

*Side effects of DHO-180 are nasal stuffiness (adrenergic blockade). Occasional nausea and vomiting, headache, flushing of the head and orthostatic hypotension have been reported.

changes in half of the cases they studied. The changes seen were heightening of the T waves and rarely, slight RS-T elevation. They considered these changes insignificant and felt that they, per se, had no effect on the exercise electrocardiogram.

METHOD

For this study patients between the ages of 60 and 80 years were chosen. Each of these patients was originally questioned as to cardiac symptomatology. Patients who had a history of any cardiac disease, excessive exertional dyspnea, orthopnea, angina pectoris, cardiac ankle edema, or previous treatment for cardiac disease, were excluded from the test. A physical examination emphasizing the cardiovascular system was then done. Patients with any signs of myocardial decompensation, cardiomegaly or a blood pressure over 160/90 were likewise excluded from the test. Roentgenograms of the chest to rule out cardiac hypertrophy and dilatation were also observed.

If the above criteria were met, a resting electrocardiogram was made at least one hour following the subject's last meal, one hour after smoking and after sufficient rest for blood pressure and pulse stabilization. The two step test was then performed only if the resting ECG was normal. The subject was instructed to climb the two step stairs (each 9 inches high) with the four electrodes left in place. Standard leads 1, 2, 3 and CF_4 had been taken previous to the test. In the standard test the required number of ascents for every patient was determined from Table 2 and 3. These tables were derived from a graphic extension of the plotted

curves of Master's standard figures for the age groups over 69 years. The figures for the age groups 60-69 years are from Master's charts.

The test is performed in one and one-half minutes. After the exercise is completed the patient is returned to his original recumbent position and the immediate four lead ECG taken, another after four minutes and a third after ten minutes. Each electrocardiogram taken consisted of the four previously mentioned leads. Blood pressure and pulse were taken at two minutes after exercise. Dizziness was avoided by having the patient turn toward the examiner after every trip over the steps. For this paper, only single two-step tests were performed.

All leads were standardized so that one milli-volt produced a deflection of one cm.

If the recordings were found to be abnormal* then a repeat two step exercise test was performed in not less than 24 hours after the first exercise**. After the patient was in the supine position and he blood pressure and pulse were stabilized 0.6 mgm. of DHO-180 was injected intravenously. In approximately 10 minutes, but not before, or until the blood pressure and pulse were again stabilized, another resting

*Master's criteria.

**Five patients with negative initial exercise electrocardiograms were also given repeat tests following DHO-180 injection.

TABLE 2

Males - Standard Number Of Ascents

Wt. in Lbs.	Age in Yrs.							
	60 to 64	65 to 69	70 to 74	75 to 79	80 to 84	85 to 89	90 to 94	95 to 100
80-89	24	23	22	21	20	20	19	18
90-99	23	22	21	21	20	19	18	17
100-109	22	22	21	20	19	19	18	17
110-119	22	21	20	20	19	18	18	17
120-129	21	20	19	18	17	17	16	15
130-139	20	20	19	18	18	17	16	15
140-149	20	19	18	17	16	16	15	14
150-159	19	18	17	16	15	14	14	13
160-169	18	18	17	16	15	14	13	12
170-179	18	17	16	15	15	14	13	12
180-189	17	16	15	14	13	13	12	11
190-199	16	15	14	13	13	12	11	10
200-209	16	15	14	13	12	12	11	10
210-219	15	14	13	12	11	10	10	9
220-229	14	13	12	11	10	9	8	7

TABLE 3

Females - Standard Number Of Ascents

Wt. in Lbs.	Age in Yrs.							
	60 to 64	65 to 69	70 to 74	75 to 79	80 to 84	85 to 89	90 to 94	95 to 100
80-89	21	20	19	18	17	16	15	15
90-99	20	19	18	17	16	15	14	13
100-109	19	18	17	16	15	14	13	12
110-110	18	18	17	16	15	13	12	11
120-129	18	17	16	15	14	13	12	11
130-139	17	16	16	14	13	12	11	10
140-149	16	16	15	13	13	11	11	9
150-159	16	15	14	13	12	11	10	9
160-169	15	14	13	12	11	10	9	8
170-179	14	13	13	11	11	9	9	8
180-189	14	13	12	11	10	9	8	7
190-199	13	12	11	10	9	8	7	7
200-209	12	11	11	10	9	8	7	7
210-219	11	11	10	9	8	8	7	7
220-229	11	10	9	9	8	8	7	6

ECG was taken. The remainder of the test then followed exactly the routine of the original test.

Four patients with positive and two with negative exercise electrocardiograms were given daily intramuscular injections of 0.3 mgm. DHO-180 for 30 days. One month later and four to eight hours after the last injection of DHO-180 a third resting and exercise ECG was taken according to the above method.

RESULTS

Tests were run on 17 male and 3 female patients between the ages of 60 and 80 years of age. Each of these patients was carefully selected from the standpoint of having an essentially normal cardiovascular system according to the previously mentioned criteria.

Table 4 summerizes the results of this experiment.

The resultant tests indicate that six of the twenty patients tested had coronary insufficiency. Two of these had negative exercise electrocardiograms after intravenous injection of 0.6 mgm. DHO-180, indicating that the relative coronary insufficiency was functional.

Table 5 lists the positive electrocardiographic findings, the lead in which they occurred, and the measurements of the same lead in the other tests run on that particular patient.

TABLE 4

Exercise Electrocardiograms And Interpretation
(Master's Criteria)

Patient	Initial Exercise ECG	Exercise ECG after 0.6 mgm. DHO-180	Exercise ECG after 30 Daily Injections of DHO-180
1	+	0	+
2	+	+	0
3	+	+	0
4	+	+	0
5	0	0	+
6	0	0	0
7	0	0	
8	0	0	
9	0	0	
10	+	0	
11	0		
12	0		
13	0		
14	0		
15	+		
16	0		
17	0		
18	0		
19	0		
20	0		
Total +	6	3	2

TABLE 5

Positive ECG Findings (Master's Criteria)

Readings are from ECG taken immediately after exercise unless otherwise indicated. (Measurement of Millimeters deviation from base line.)

Patient	Initial Exercise ECG	Exercise ECG after 0.6 mgm. DHO-180	Exercise ECG after 30 days DHO-180
1	RS-T_{II} -0.8 RS-T_{IV}-0.2	RS-T_{II}-0.1 RS-T_{IV}-0.4	RS-T_{II}-0.3 RS-T_{IV}-0.6
2	RS-T_{II}-0.7 RS-T_{III}-0.8	RS-T_{II} -0.6 RS-T_{III}-0.4	RS-T_{II}-0.5 RS-T_{III}-0.3
3	T_{I} -0.0 RS-T_{II}-0.3 RS-T_{III}-0.6 RS-T_{III}-0.1*	T_{II}-0.8 RS-T_{II}-0.7 RS-T_{III}-0.7 RS-T_{III}-0.9*	T_{I}-0.3 RS-T_{II}-0.3 RS-T_{III}-0.4 RS-T_{III}-0.1*
4	RS-T_{II}-0.8	RS-T_{II}-0.6	RS-T_{II}-0.1
5	RS-T_{II}-0.5	RS-T_{II}-0.1	RS-T_{II}-0.7
10	RS-T_{II}-0.6	RS-T_{II}-0.4	
15	RS-T_{IV}-0.2 RS-T_{IV}-0.6* RS-T_{IV}-0.6**		

*Four minutes after exercise.

**Ten minutes after exercise.

(Note) - All positive readings are underlined.

All but one of the positive findings indicative of coronary artery disease were seen as an RS-T depression. The inconsistancy of positive findings to occur in the same lead in patient #1 should be noted.

P waves were found to increase in some cases with exercise and in others, the waves became smaller. This also occured following the administration of DHO-180, but these changes were not consistent or predictable.

QRS complexes, likewise were noted to increase in size in some cases following exercise and decrease in others. These changes were also not consistent or predictable and did not appear to be affected by the administration of DHO-180.

On the other hand both RS-T segment changes and T wave changes were more consistent. Tables 6 and 7 list the averages of these changes.

TABLE 6

Average Deviation From Base Line or RS-T Segment
Immediately After Exercise

Initial 20 Cases	1 Injection DHO-180 10 Cases	Initial on Same Subjects	30 Days DHO-180 6 Cases	Initial on Same Subject
RS-T_I-0.5	-0.10	-0.13	-0.10	-0.19
RS-T_{II}-0.18	-0.27	-0.42	-0.32	-0.52
RS-T_{III}-0.06	-0.11	-0.27	-0.15	-0.37
RS-T_{IV}+0.15	+0.10	+0.30	0.00	+0.03

TABLE 7

Average Deviations From The Size of Resting T-Waves
As Measured In ECG
Taken Immediately After Exercise

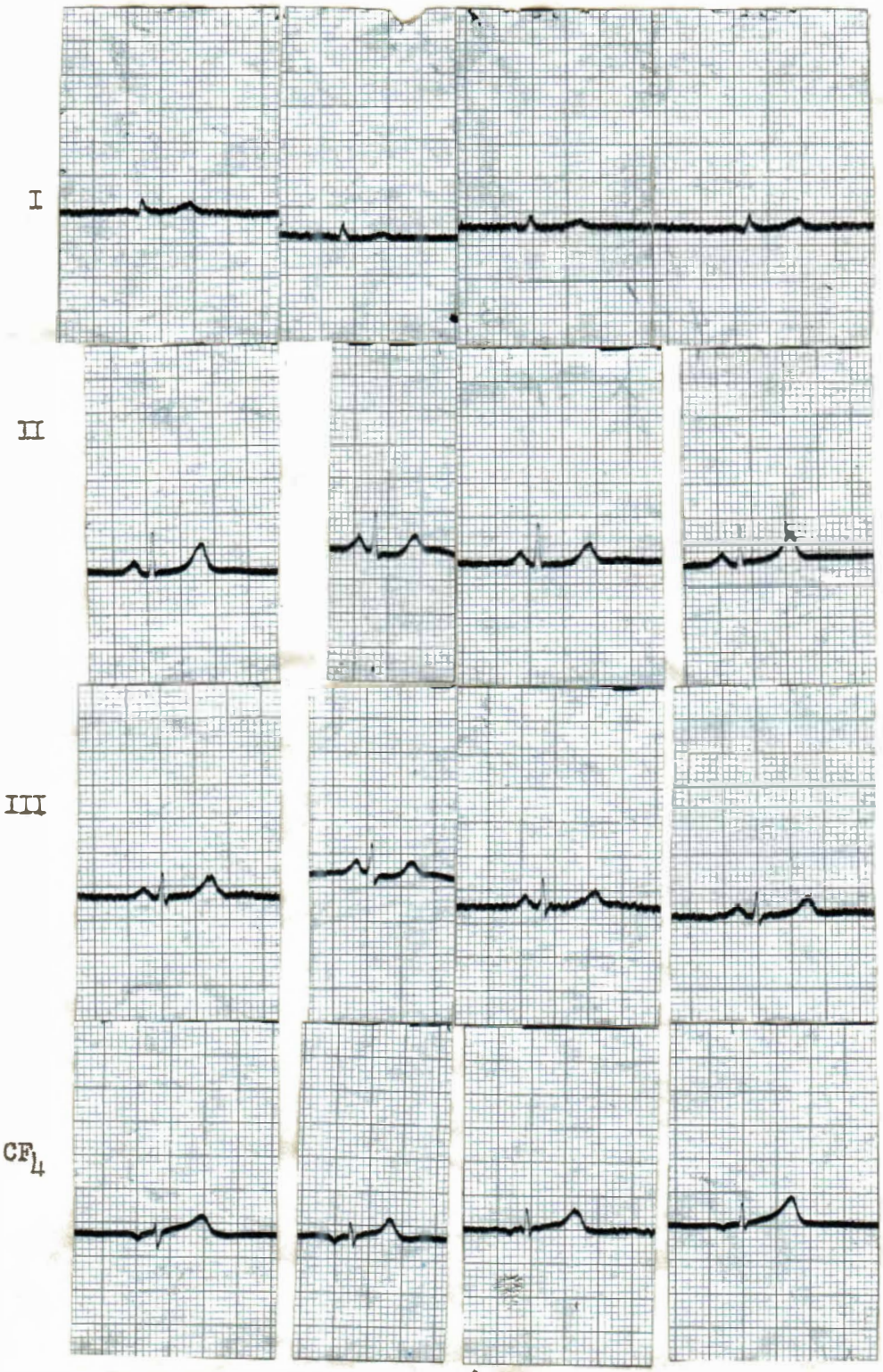
Initial 20 Cases	1 Injection DHO-180 10 Cases	Initial on Same Subjects	30 Days DHO-180 6 Cases	Initial on Same Subject
T_I-.21	-.74	-.28	-.30	-.33
T_{II}-.21	-.72	+.31	-.13	-.43
T_{III}-.11	-.34	-.09	+.04	-.04
T_{IV}+.14	-.51	-.11	-.60	-.35

FIGURE I

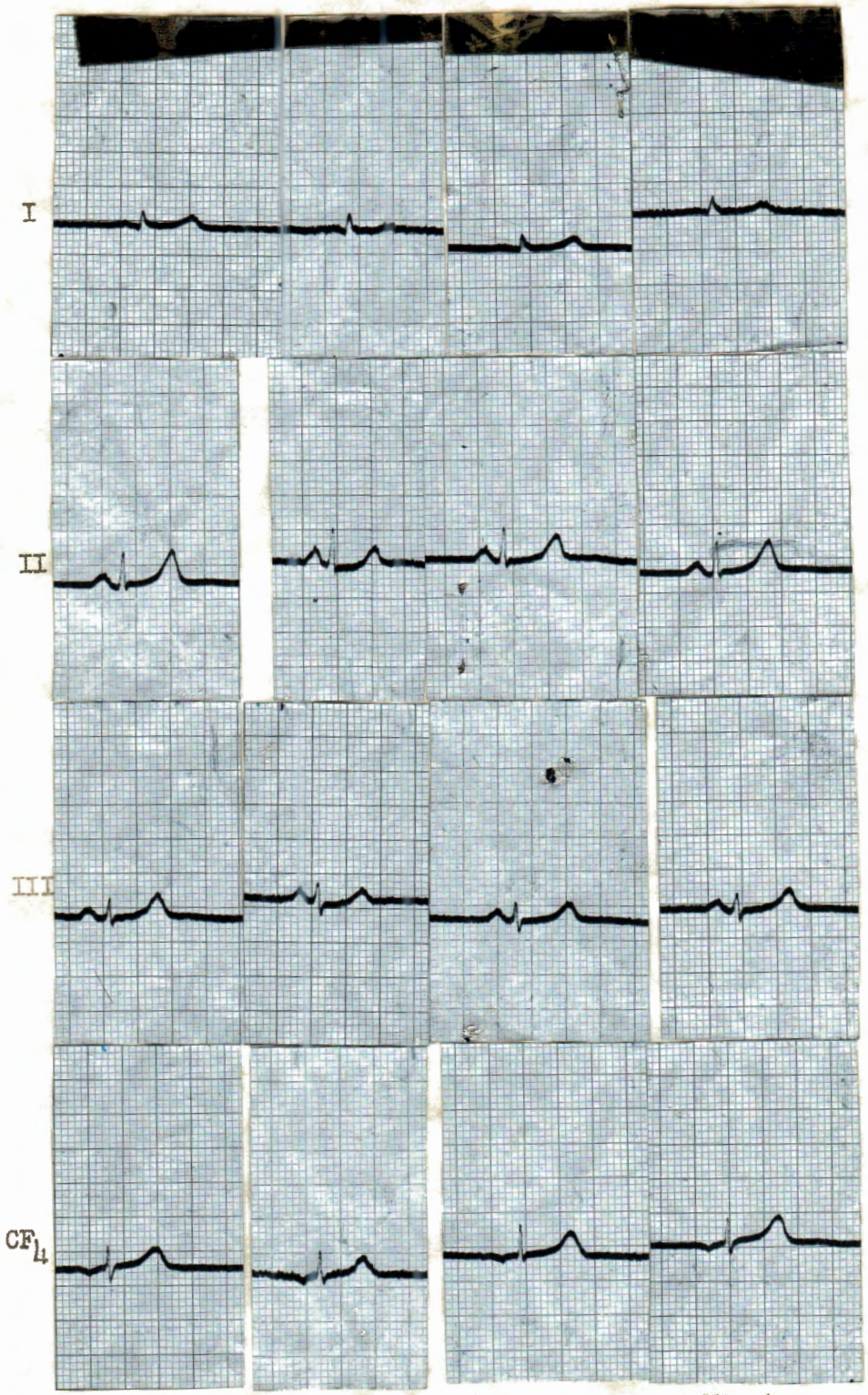
A healthy negro male (#3), 73 years of age, weight 115 pounds. Patient was hospitalized for treatment of a small arteriosclerotic ulcer on is left leg. Resting control electrocardiogram was within normal limits. Electrocardiogram after 20 trips over the two steps was abnormal, demonstrating a RS-T_{II} depression of 0.7 mm. and a RS-T_{III} depression of 0.8 mm. This depression was trancient, not being demonstrated in the ECG taken 4 minutes after exercise.

One week later the test was repeated following an intravenous injection of 0.6 mgm. DHO-180. This test demonstrated a RS-T depression of 0.6 mm in lead II. RS-T_{III} depression at this time was 0.4 mm.

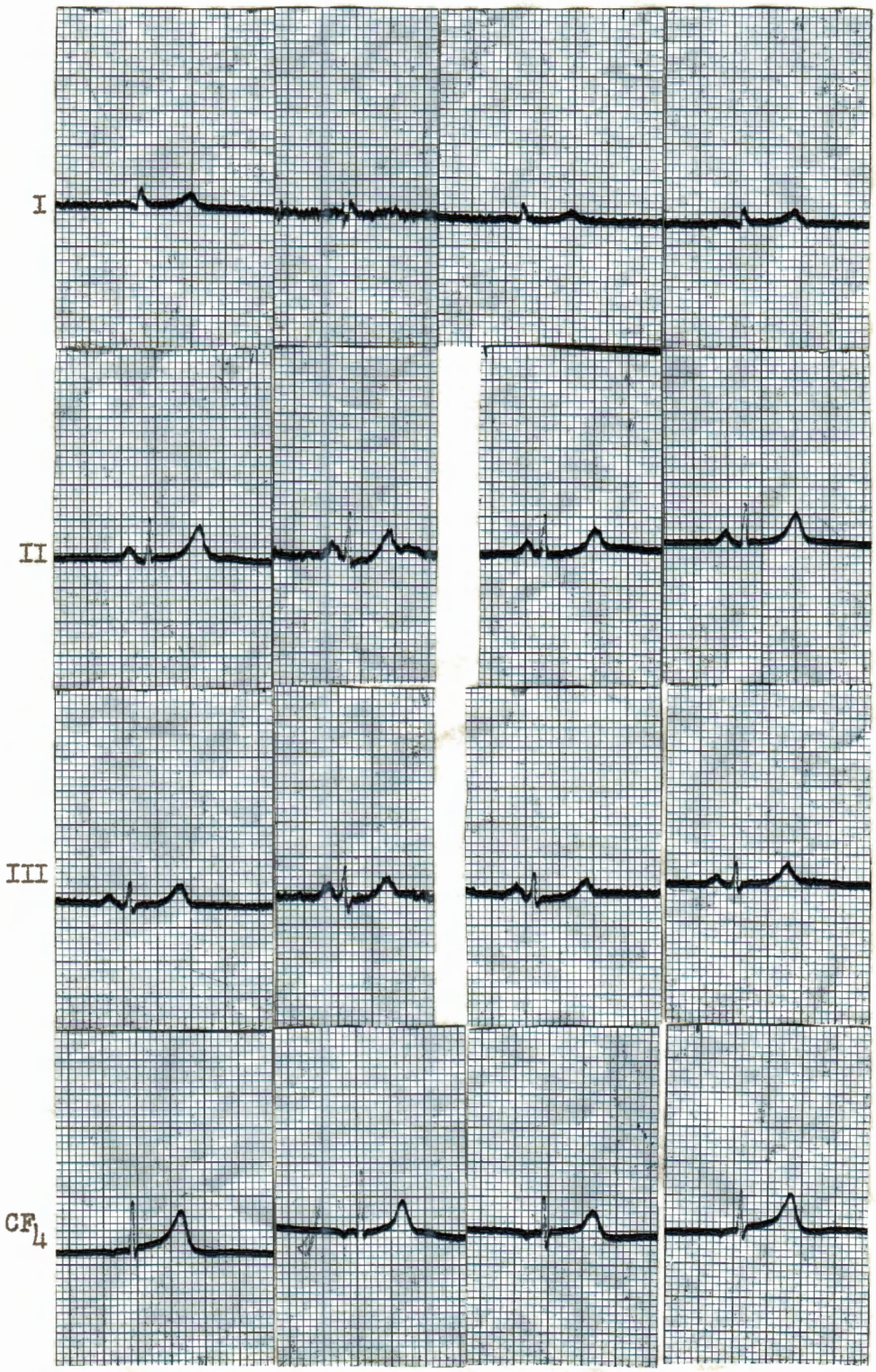
After 30 daily intramuscular injections of DHO-180 and 5 hours following the last injection, a third exercise ECG was run. This was negative according to Master's Criteria, demonstrating a RS-T_{II} depression of 0.5 mm. RS-T_{III} was depressed of 0.3 mm.


I
II
III
CF_4
Initial
Immediately After Exercise
4 Minutes After Exercise
10 Minutes After Exercise

0.6 Mgm. DHO-180



30 Days - DHO-180



The blood pressure and pulse of a normal individual returns to within five points of the original reading in two minutes after a single two step exercise (29). This occurred in only one case (#2) in this study and that occurred following 30 daily injections of DHO-180. No corrolation was discernable between the degree of exercise, ECG changes and the degree of blood pressure and pulse deviations from resting levels. However, in most of the cases the resting pulse was found to decrease from 2 to 10 points following the single injection of DHO-180. A definite blood pressure drop of from 2-26/0-8 mm. of mercury was noted in 7 of the 10 cases given single injections of DHO-180. The remaining three cases demonstrated no change following DHO-180.

DISCUSSION

Evidence of coronary artery insufficiency was detected in six of twenty patients between 60 and 80 years of age. This was indicated by an RS-T depression of over 0.5 mm. in all but one case. That case demonstrated the reversion of positive T wave to an isoelectric T wave following exercise. Subsequent exercise electrocardiograms following a single administration of DHO-180 demonstrated a reversal from positive to negative evidence of coronary insufficiency in two of these patients. This indicates that the former positive test on these two patients was on a functional bases.

Six of these patients, four with positive and two with negative electrocardiograms, were then given daily injections of 0.3 mgm. DHO-180. A third exercise electrocardiogram on these 6 patients was then performed. One case, who had reverted from positive to negative after a single dose of DHO-180, again demonstrated evidence of coronary insufficiency, Three patients, who had demonstrated evidence of coronary insufficiency on the two previous testings, failed to reveal it after thirty days administration of DHO-180. It should be noted, that in patient #2 this change from positive to negative was represented by a reduction of only 0.1 mm. in the depression of the RS-T segment from the base line. A fifth patient, who had formerly not demonstrated

evidence of coronary insufficiency, now had an RS-T depression of 0.7 mm. below the base line. The sixth patient had negative exercise electrocardiograms throughout.

Electrocardiographic changes following exercise were also noted in the P waves, in the size of the QRS complexes, and in the size of the T waves. The changes noted in the P waves and in the QRS complexes were inconstant. This inconsistency remained after administration of DHO-180. The average deviation of the RS-T segment in the ECG taken immediately following exercise was decreased in all leads, by both a single and 30 day injection of DHO-180. The average T wave deviation from the size of the T waves in the resting ECG was found to decrease with exercise in the three standard limb leads and to increase in lead CF_4. This average decrease was found to be greater after a single injection of DHO-180*. Thirty day administration of the drug was found to cause an average T wave depression after exercise that was less than the changes seen prior to the administration of the sympathicolytic agent in leads I and II. A greater decrease in size was noted in lead CF_4 after 30 days of DHO-180 and the drug caused an increase in the size of T_{III}.

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*Average value for T_2 changes was greater after exercise for the 10 cases subsequently administered DHO-180.

SUMMARY

Heart disease is now the leading cause of death in the United States. A majority of this disease is thought to be the result of coronary artery disease; however, some investigators believe that aging of the myocardium plays a more important role. Since commonly used diagnostic measures are inadequate for early detection of this disease, tests causing anoxia or stress to the heart have been devised. These tests can be divided into two groups, those using exercise and those utilizing the breathing of low oxygen mixtures.

Master's two step exercise tolerance test is one of these tests and is effective for detecting coronary insufficiency in from 50 to 70 per cent of the cases. False positives, however, occur in this test 6 to 8 per cent of the time. Dihydroergocornine (DHO-180), a sympatholytic agent has proven effective in eliminating many of these false positives. The rationale for this is that it blocks functional coronary spasm, which is mediated by the sympathetic nervous system.

For this paper two step exercise tests were performed on 20 normal patients over the age of 60 years. Ten of these were subsequently re-tested after a single injection of DHO-180, and six were tested for the third time after 30 day administration of the drug.

The results of the electrocardiographic changes after

exercise and of the exercise tolerance both before and after the administration of DHO-180 are listed and discussed.

CONCLUSIONS

1. Thirty per cent of the apparently cardiologically normal aged people tested have coronary insufficiency of such a degree as to be objectively evident electrocardiographically following a single Master's two step exercise. This figure was reduced to 15 per cent by the administration of a single injection of Dihydroergocornine (DHO-180) and to 10 per cent by the administration of the drug for a period of 30 days. This indicates that a degree of the coronary insufficiency could be the result of coronary artery spasm as well as a result of arteriosclerotic changes, or that an organic insufficiency is corrected by coronary vasodilatation.

2. Coronary artery insufficiency exists from a mild to a severe degree. Likewise electrocardiographic indications of this malady can be from minimal to definite evidence of the disease process.

3. DHO-180 (Hydergine) may be of value not only in the detection but in the treatment of coronary artery disease.

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