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CORTICOADRENAL AND ADRENERGIC OVERACTIVITY IN MALE PATIENTS WITH CHRONIC MYOCARDIAL INFARCTION

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SUMMARY

In a group of 22 patients with chronic myocardial infarction, plasma 11-OH corticoids and urinary free 11-OH corticoids, 17-oxo steroids, dehydroepiandrosterone, epinephrine and norepinephrine were studied in resting conditions.

Plasma and urinary 11-OH corticoids as well as catecholamines were significantly higher than normal but the opposite was found for dehydroepiandrosterone excretion. Mean cortisol secretion rate was not significantly elevated.

The recovered myocardial infarct survivors showed markedly increased epinephrine responses to an audiogenic stress. Many of these patients, although fully recovered after long convalescences, seem to have a glucocorticoid and adrenergic overactivity.

INTRODUCTION

IT HAS been shown that in acute myocardial infarction an enhanced secretion of glucocorticoids [1, 2, 3] and catecholamines [4] is almost always present. The pattern of hormonal reactions in these conditions is very intense in some of these patients and the clinical course is frequently complicated or fatal. The acute infarction is regularly followed by several days of marked overactivity of the adrenocortical system, as evidenced by increased plasma cortisol [5, 6].

We report here a study of the cortisol secretion rate, plasma 11-OH corticoids and urinary excretion of dehydroepiandrosterone, 17-oxo steroids and 11-OH corticoids as well as catecholamines in ambulatory, fully-recovered male survivors of myocardial infarction, at least 6 months after the myocardial infarction episode.

MATERIAL AND METHODS

A group of 22 male patients, survivors of myocardial infarction was studied. Their ages were between 40 and 69 yr at the time of this investigation.

Most of them held part time jobs while others did not work at all. They were examined from 6 months to 3 yr after their myocardial infarctions. The diagnosis of myocardial infarction has been supported by the clinical history, the electrocardiographic changes and a rise in serum-enzyme levels.

A thorough clinical and electrocardiographic examination was performed, in basal conditions and after exercise. The patients were taken off treatment at least 1 week before investigation.

Patients who suffered from liver, kidney or thyroid gland diseases were excluded from the present study.

Blood samples were obtained between 8 and 9 a.m. Control groups of equivalent ages that had a complete clinical examination were studied with the same methods.

Twenty-four-hour urine collections were obtained for dehydroepiandrosterone and 11-OH corticoid determinations.

Twelve patients with myocardial infarction as well as 5 normal subjects, were subjected to an auditory stimulation. This sound stimulation consisted of a continuous 2,000 cycles/sec, 90 db sound, as previously reported using controls [7] and psychotics [8].

In this test the subjects were placed under basal conditions and a blood sample was taken. A second sample was taken at the end of a 30 min sound exposure: at 45 min a third blood sample was taken and the blood pressure registered.

Before all the studies, the subjects were instructed to refrain from smoking, drinking coffee, tea, alcoholic beverages or any other stimulants.

In a group of 15 of these patients the cortisol secretion rate was studied.

METHODS

The biochemical studies were performed according to the following methods:

(a) Total Lipids, by Postma *et al.* [9].

(b) Blood Cholesterol by Abells' method [10].

(c) Beta Lipoproteines by Burstein *et al.* [11].

(d) Triglycerides by Carlsson *et al.* method [12].

(e) Total Urinary 17-Hydroxycorticoids by Appleby *et al.* [13].

(f) Total Urinary 17-Oxo steroids by Ricca's technique [14].

(g) Plasma 11-Hydroxycorticoids by Mattingly *et al.* [15]. With this technique cortisol and corticosterone were measured; the amount of the latter is normally negligible in man.

(h) Urinary Dehydroepiandrosterone by Fotherby *et al.* [16]. In this method the DHA sulfate is hydrolysed by heating urine without acidification at 100° for 6 h. Urine is extracted with benzene and transferred to a column of alumina. Dehydroepiandrosterone is eluted with 0·1% (v/v) ethanol in benzene and, together with the standards, subjected to the Pettenkofer reaction.

(i) Urinary Epinephrine and Norepinephrine, by Crout's method [17].

(j) Cortisol secretion rate was performed basically as described by Cope and Black [18]. It was done as follows: 0·5 μCi of [^{14}C]-Cortisol was administered orally to the patient after he emptied his bladder. Urine was collected for 24 h.

A 200 ml urine aliquot was adjusted to pH. 4·7 after adding acetic acid and incubated for 48 h with β-glucuronidase. Urine was then extracted three times with 1/3 volume of purified methylene chloride the extract was washed once with 1/3 volume of 0·1N NaOH and once with 1/3 volume of distilled water and evaporated to dryness. The residue was transferred with fresh chloroform to the line of origin of a paper chromatogram (Whatman No. 1) and run for 18 h with the benzene–methanol–water system with 20 μg THE and THF standards in separate lanes. The standard strips and a 5 mm strip which was cut along the length of the chromatogram were tested with blue tetrazolium. Both zones were eluted with methanol: ethyl acetate, aliquots from the eluate were taken for determination of radioactivity and similarly suitable aliquots in duplicate were taken for estimation of reducing steroids by blue tetrazolium regaent with the use of tetramethyl ammonium hydroxide as the alkali. For the chemical analysis, a

paper blank of the same area from a part of the paper free of reduction steroid is also eluted and treated similarly.

From the results the specific activity of the THE and THF were calculated and expressed as counts per min per μg of reducing steroid.

RESULTS

1. *Blood lipids*

In 13 out of 22 patients the cholesterol levels were above the upper normal limit with a mean of 261 mg/100 ml. S.D. 44, ($P < 0{\cdot}01$) (Table 4).

Mean control values were 298 mg/100 ml ± 17.

Beta lipoprotein values paralleled those of chlosterol with a mean of 5·77 ± 1·73 g/l. The values were significantly elevated ($P < 0{\cdot}01$) when compared to control whose mean value was 3·76 ± 0·5 g/l.

In some cases total blood lipids were above the upper normal limit with mean 847 ± 272 mg/100 ml but it was not statistically significant.

The triglyceride values were above the upper normal limits in 50% of the cases (Table 4). Their mean value was 186 ± 65 mg/100 ml for the infarct patients and 79 ± 17 mg/100 ml for the control group ($P < 0{\cdot}01$).

Table 1. Steroid and Catecholamine values in chronic cardiac infarction patients

	Urine					Plasma		
Patients	DHA (mg/24h)	17-oxo steroids (mg/24h)	17-OH-corti-coids (mg/24h)	11-OH-corti-coids (μg/24h)	Epinerine (μg/100ml)	Nor-epinerine (μg/100ml)	11-OH-corti-coids (μg/100ml)	Cortisol secretion (mg/24h)
V R	—	5·7	7·0	70	12·7	52·9	36·0	19·7
G J	0·25	7·5	8·6	240	4·3	23·0	12·0	17·5
G M	—	7·6	5·7	272	12·6	25·0	27·0	—
G O	—	7·2	7·2	285	10·8	27·4	18·0	20·5
G A	1·2	10·0	13·0	168	5·1	32·2	22·0	—
L C	2·0	14·7	19·0	269	10·5	27·6	23·0	19·0
P H	0·2	5·0	9·0	480	9·8	19·5	24·0	30·0
O A	0·9	5·1	10·2	530	10·4	21·6	18·0	15·1
D E	0·22	6·7	5·8	185	6·2	46·4	21·0	15·9
G A	0·02	1·3	2·2	210	16·7	60·4	30·0	17·0
G M	0·3	4·3	6·7	260	15·0	30·2	34·0	—
M C	0·3	5·6	5·2	98	7·2	16·2	24·0	19·0
F P	0·7	6·0	5·5	260	6·5	28·2	20·0	21·8
T R	0·8	9·9	6·5	180	4·1	42·0	10·0	—
M T	0·2	4·0	7·0	150	6·9	52·8	20·0	—
T L	—	3·4	6·0	—	25·0	46·4	23·0	—
M L	0·003	4·5	2·5	189	12·0	12·6	30·0	18·0
M R	0·5	7·0	13·0	243	5·09	18·3	32·0	19·8
M G	0·9	7·7	8·6	153	3·1	27·6	15·0	18·0
G R	0·7	6·0	6·0	120	—	—	18·0	17·2
R C	0·2	3·5	8·0	104	14·4	23·1	15·0	—
M H	1·5	10·8	11·3	180	27·1	108·0	18·5	16·9
X	0·60	6·5	7·9	221	10·7	37·8	22·2	19·0
S D	0·2	2·9	3·6	113	6·4	16·2	7·0	6·4

DHA: dehydroepiandrosterone.

2. *Steroid studies*

(1) *11-Hydroxycorticoids.* Mean plasma 11-OH corticoids of the infarct survivors was $22{\cdot}2 \pm 7{\cdot}0$ μg/100 ml significantly higher than the mean value of the control group that was $17{\cdot}6 \pm 3{\cdot}4$ μg/100 ml ($P < 0{\cdot}01$).

The group of 12 patients that were subjected to an audiogenic stress showed an even higher mean basal level ($24{\cdot}2 \pm 7{\cdot}74$ μg/100 ml) but the response to the noise exposure was not significant since in some of the cases a reduction of very high pre-noise plasma corticoids were registered after the test (Table 2).

Mean urinary 11-OH-corticoids was 221 μg/24 h and also showed a significant increase compared with controls ($P < 0{\cdot}001$).

(2) *Cortisol secretion rate (Table 1).* The mean value was $91 \pm 6{\cdot}4$ mg/24 h, higher than that of the controls, ($15{\cdot}6 \pm 3{\cdot}6$ mg/24 h) but the difference was not significant ($P < 0{\cdot}2$).

(3) *17-Oxo steroids and dehydroepiandrosterone excretion.* The urinary 17 oxo-steroids were significantly lower than control ($P < 0{\cdot}001$) with mean 6·5 mg/24 h $\pm 2{\cdot}9$).

The urinary dehydroepiandrosterone values were generally low, reaching 1 mg/24 h or more in only 3 patients (Table 1).

Urinary DHA mean value was of $0{\cdot}60 \pm 0{\cdot}2$ mg/24 h significantly lower ($P < 0{\cdot}001$) than mean control values ($\bar{X}$ 1·3 mg/24 h $\pm 0{\cdot}6$) (Table 3).

(4) *Epinephrine and norepinephrine (Table 3).* The mean adrenalin excretion was $10{\cdot}7 \pm 6{\cdot}4$ μg/24 h significantly higher than the normal mean value (Table 3) of $5{\cdot}40 \pm 2{\cdot}6$ μg/24 h ($P < 0{\cdot}001$).

Mean Nor-Epinephrine was also increased with a mean value of $37{\cdot}8 \pm 16{\cdot}2$ μg/24 h. Seven of the patients showed in half of the cases, levels above 40 μg/24 h. Mean control value (Table 3) was $21{\cdot}5 \mp 7{\cdot}4$ μg/24 h ($P < 0{\cdot}001$).

Table 2. Chronic cardiac infarction patients. Response of plasma cortisol and cholesterol and urinary catecholamines to sound

Patient	Plasma cortisol (μg/100ml)		Plasma cholesterol (mg/100ml)		Urinary epinephrine (μg/h)		Urinary norepinephrine (μg/h)	
	b	s	b	s	b	s	b	s
1 PH	24	7·6	217	230	0·36	0·58	1·3	1·2
2 FP	32	31	290	290	0·46	0·68	0·86	1·11
3 OA	18	22	209	240	0·43	0·54	0·9	2·53
4 VR	36	44	365	320	0·39	0·42	1·27	2·29
5 DE	21	60	260	260	0·5	0·59	1·6	2·42
6 MC	24	—	295	340	0·14	0·18	0·88	1·79
7 GO	18	15·5	268	285	0·45	0·78	1·12	1·42
8 GM	34	22	245	250	0·41	0·67	1·24	2·01
9 GJ	12	—	260	255	0·33	0·73	0·82	1·4
10 GA	29	22	215	290	0·43	0·74	1·5	1·8
11 LC	19	19	270	300	0·41	0·46	1·08	4·16
12 GE	—	18·4	—	250	0·68	0·34	2·20	5·03
Mean	24·2	26·1	263	275	0·41	0·55	1·23	2·26
SD	7·74	15·2	44	37	0·1	0·17	0·3	1·1
p	—	—	0·40		0·001		0·001	
% Change					+34 %		+83 %	

b = baseline; s = stimulated by sound.

Table 3. Mean values of steroids and catecholamines in chronic myocardial infarction and controls

	Urine						Plasma	
	Dehydro epi-An-droster (mg/24h)	17-oxo steroids (mg.24h)	17-OH Cortic. (mg/24h)	11-OH Cortic. (mg/24h)	Epineph-rine (μg/24h)	Nor E-pinephr. (μg/24h)	11-OH Cortic. (μg/100ml)	Cortisol secretion rate (mg/24h)
$\bar{X}$ Infarct	0·6	6·5	7·90	221	10·7	37·8	22·2	19·0
$\bar{X}$ Controls	1·3	9·1	8·44	89·6	5·4	21·5	17·6	15·6
P	0·001	0·001	0·60	0·001	0·001	0·001	0·01	0·2

Table 4. Mean values of lipids

	Cholesterol (mg 100ml)	Total Lipid (mg/100ml)	Beta Lipoprot. (g/L)	Triglycerides (mg/100ml)
$\bar{X}$ Infarct	261	847	5·77	186
$\bar{X}$ Controls	208	583	3·76	79
p	0·001	0·2	0·001	0·001

Before the audiogenic stimulation the mean value for epinephrine hourly excretion was $0{\cdot}41 \pm 0{\cdot}1$ μg/h and for norepinephrine $1{\cdot}23 \pm 0{\cdot}3$ μg/h. With sound stimulation these values rose to a mean of $0{\cdot}55 \pm 0{\cdot}26$ μg/h for epinephrine.

DISCUSSION

A striking difference between the low levels of some androgen indexes and the signs of a permanent increase of glucocorticoid activity have been found in the subjects of this study.

The total urinary 17-oxo steroids were significantly lower than normal.

The patients of this study showed a dehydroepiandrosterone excretion also significantly lower than the controls and a hypercholesterolemia which agrees with Adlercreutz's findings [19]. It is believed that a reduced secretion of dehydroepiandrosterone might counteract the inhibitory effect of this steroid on the glucose-6-phosphate dehydrogenase (G-6-PD) and so an increased synthesis of NADPH results with an augmented synthesis of cholesterol and fatty acids [19]. Fatty acids increased by this mechanism could account for the augmented triglycerids frequently found in cases of coronary disease.

As approximately one-third of the total urinary 17-oxo steroids represents the metabolites of testosterone secreted by testes, future studies of testosterone secretion rate in these patients would be of great interest.

Cook [20] and Marshall [21] have also discussed the effect of certain 17-oxo steroid fractions on lipid metabolism.

Many authors [22–24], have studied adrenergic function in myocardial infarction, but they have reported its overactivity only in the acute state.

In our subjects plasmatic and urinary free 11-OH corticoids under basal conditions were found to be significantly elevated. Under the conditions in which the patients were studied the 11-OH-corticoids are practically entirely cortisol.

An unexpected finding was that the audiogenic stress in some of these patients did not cause a glucocorticoid elevation although highly significant responses of

catecholamines were observed. As the remaining basal plasma corticoid levels were very high this fact would indicate that patients with coronary heart disease are emotionally stressed people who arrived at the hospital with exaggerated pituitary-corticoadrenal activity and who were reassured and relaxed during a study that did not cause them pain or discomfort.

The cortisol secretion rate was not significantly increased although its mean value was considerably higher than that of the control group and in one third of the cases this index was abnormally high.

We have found that patients having completely recovered after convalescence from cardiac infarction showed marked responses to stressful stimuli. It is considered that in contrast to the circulating basal cortisol which is more than 90 % protein-bound, the ratio of stress-released unbound cortisol to the bound moiety is increased, and consequently its biological activity is also higher than in less stressed subjects showing equivalent total plasma cortisol levels [24].

Selye [25], has demonstrated that gluco and mineralocorticoids experimentally administered to rats could cause myocardial necrosis particularly when the animals were subjected to stress (cold bath or restraint). According to the results obtained in this study, the myocardial infarct patients, after long convalescing periods and with apparently healed lesions still reveal signs of an elevated concentration of blood glucocorticoids. This might be characteristic of a predisposition to overreact to stressful stimuli, a fact also demonstrated in our patients by the marked rise of catecholamine excretion induced by noise. This characteristic could be one of the most important factors of myocardial infarction in modern urban life.

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