inadequate mothers (and hence children at risk) during pregnancy.¹⁴ They showed that women who had been separated from their own parents when they were aged under 11 were more likely than others to have problems with their babies or marriages, and were thus more in need of support.

We acknowledge the help of many people not mentioned in the article who have worked hard with us over many of these cases: family doctors, radiologists, registrars, house physicians, casualty officers, casualty sisters, ward sisters, and others.

We are grateful to the Chief Constable of Derbyshire for giving his approval for publication.

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Measurement of cardiac muscle relaxation in hypothyroidism

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British Medical Journal, 1976, **1**, 1366-1368

Summary

The isovolumetric relaxation time of the left ventricle (IRT) in 20 hypothyroid patients ($133 \pm (\text{SE of mean}) 4 \text{ ms}$) was significantly longer than that in 23 normal subjects ($95 \pm 3 \text{ ms}$). During a trial of thyroxine replacement the IRT in 12 hypothyroid patients fell from $143 \pm 4 \text{ ms}$ to $107 \pm 4 \text{ ms}$. The IRT seems to be a useful index of end-organ function in hypothyroidism.

Introduction

Combined apex cardiography and phonocardiography can reliably measure the isovolumetric relaxation of the left ventricle (IRT).¹⁻³ Since relaxation of skeletal muscle is delayed in hypothyroidism,⁴ relaxation of cardiac muscle might also be delayed. We therefore measured the IRT in hypothyroid patients before and after treatment with thyroxine.

Patients and methods

Apex cardiography was carried out using a hollow bell attached to a piezoelectric transducer.⁵ A phonocardiogram (aortic area) and electrocardiogram (standard lead II) were recorded simultaneously with a multichannel recorder. Ankle reflex time was recorded with a photomograph. IRT was measured from the major deflection of the aortic component of the second heart sound to the 0-point of the apex cardiogram, which coincides with mitral valve opening (fig 1).^{1 3 5 6}

As part of a preliminary assessment of their thyroid status patients were given a clinical hypothyroid diagnostic score.⁷ Protein-bound iodine levels (PBI; normal 315-630 nmol/l 4-8 $\mu\text{g}/100 \text{ ml}$), Thyopac-3 index (radiochemical centre, Amersham; normal 90-110%), serum

FIG 1—Normal apex cardiogram showing how isovolumetric relaxation of left ventricle was measured. ACG = Apex cardiogram. PCG = Phonocardiogram. ECG = Electrocardiogram.

cholesterol concentrations (normal 3.89-7.77 mmol/l 150-300 mg/100 ml), 48-hour ¹³¹I uptake (normal range > 15% of dose), and Achilles tendon reflex half-relaxation time (normal range 250-380 msec)⁴ were also measured, and the thyrotrophin stimulation test (10 units of thyrotrophin for 3 days) was performed.

Hypothyroidism was diagnosed when two or more indices were abnormal, at least one of the abnormal indices being the thyroid score, PBI concentration, or radioiodine uptake.

Twenty patients diagnosed as hypothyroid according to these criteria were studied (table I). Fifteen of the hypothyroid patients consented to undergo a therapeutic trial of thyroxine. The trial consisted of monthly increments of thyroxine 50 $\mu\text{g}/\text{day}$, to a total daily dose of 300 μg or until the patient became clinically and biochemically euthyroid. Before each monthly increment every patient was assessed clinically, and 12-lead electrocardiography, ankle jerk tests, apex cardiography, phonocardiography, and standard lead II electrocardiography were performed as described above.

Twenty-three normal subjects were also studied. All were clinically euthyroid with a normal PBI value and Thyopac-3 index and were either ambulant hospital patients with conditions not referable to the thyroid gland or hospital staff (table II). The normal subjects were matched for age, but not sex, with the patients.

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TABLE I—Clinical and biochemical details of 20 patients

Case No	Age (years)	Sex	Diagnosis	Thyroid score	PBI (nmol/l)	T3 index	Cholesterol (mmol/l)	4-hour uptake of ¹³¹ I (%)	48-hour uptake of ¹³¹ I (%)	TSH stimulation	ECG
1	71	F	Primary hypothyroidism	+56	<158	111					T-wave inversion
2	68	F	"		221	118	6.48	10.9	22.75	—	Flat T wave
3	65	F	"		252	114		2.6	7.1	—	T-wave inversion
4	64	F	"	+43	<158	114		5.4	10.5	—	Flat T wave
5	64	M	"	+62		117	5.85	2	3.2	—	
6	64	M	"	+43	181	117	7.02	4.0	3.0	—	Flat T wave
7	57	F	"	+59	<258	123	13.0	1.8	4.0	—	Flat T wave
8	54	M	"	+65	<258	117	12.4	4.3	9.8	—	Flat T wave
9	52	M	"		<258	115	9.82	4.0	4.0	—	Flat T wave
10	41	F	"	+37	<258	116	7.87	3.17	7.36	—	Flat T wave
11	17	F	Congenital goitre, dysmorphogenesis		<258	114	4.66			—	Flat T wave
12	76	F	Primary hypopituitarism	+2	189	117	4.87	6.6	19.3	+	Sinus bradycardia, right bundle branch block
13	68	F	After radioiodine	+45	299	114	7.12	14.7	35.0	—	Flat S-T segment
14	60	M	"	—14	268	114	6.37	3.8	11.6	—	T-wave inversion
15	58	F	"	—34	221	115	8.26			—	Flat T wave
16	56	F	"	—42	307	110	6.86	10.14	23.27	—	Flat T wave
17	51	F	"	+10	173	111	7.90	3.2	7.4	—	T-wave inversion
18	48	F	"	+10	315	112	9.40	1.26	4.74	—	Flat T wave
19	41	F	"	—22	260	116	9.66	13.2	21.6	—	Flat T wave
20	54	F	After thyroidectomy	+20	<158	112		1.33	0.79	—	Flat T wave

Conversion: SI to traditional units—PBI: 1 nmol/l $\approx$ 0.0126 μ g/100 ml. Cholesterol: 1 mmol/l $\approx$ 38.6 mg/100 ml.

TABLE II—Details of control group

Case No	Age (years)	Sex	Diagnosis	IRT (ms)	Ankle reflex time (ms)
21	78	F	Carcinoma of lung	112	
22	69	M	Glaucoma	95	87
23	65	F	Thrombophlebitis	91	125
24	61	M	Glaucoma	64	83
25	50	M	Haematemesis	73	85
26	45	M	Septic hand	107	124
27	45	F	Chronic renal failure	127	107
28	38	F	Valium overdose	112	137
29	36	M	Acute coronary insufficiency	105	113
30	25	F	Myopathy	62	110
31	66	M	Healthy	83	93
32	65	F	Healthy	93	96
33	65	M	Healthy	104	105
34	52	M	Healthy	98	120
35	48	F	Healthy	94	113
36	46	F	Healthy	104	118
37	32	M	Healthy	100	87
38	25	M	Healthy	87	
39	25	M	Healthy	87	116
40	61	M	Healthy	105	100
41	58	F	Healthy	87	200
42	49	F	Healthy	92	
43	35	M	Healthy	76	99

Results

The mean IRT ($\pm$ SE of mean) of the control group was 95 ± 3 ms, whereas that of the hypothyroid patients was 133 ± 4 ms (fig 2). The difference between the mean values of these two groups was highly significant ($P < 0.001$). In only two hypothyroid patients was the initial IRT within the normal range, both were clinically euthyroid.

Therapeutic replacement trial—Three of the 15 patients failed to complete the trial, two because they developed angina pectoris and one because she developed congestive cardiac failure when the dose of thyroxine was increased to 200 μ g/day. Before treatment the IRT of the 12 patients who completed the trial was 143 ± 4 ms, and this fell to 107 ± 4 ms after the trial. This change was also highly significant ($P < 0.01$). Nine patients progressed to a thyroxine dose of 300 μ g/day (table III). Fig 3 shows that the reduction in the IRT in these nine patients became significant at the 5% level after the patients had received 100 μ g thyroxine a day for one month and that there was no further fall in the IRT above a dose of 150 μ g thyroxine a day. The half relaxation time of the ankle jerk in the hypothyroid group was 204 ± 25 ms and in the control group 111 ± 6 ms ($P < 0.01$).

Discussion

There are few useful methods for measuring end-organ function in thyroid disease; the only reliable method generally used is measurement of ankle jerk relaxation time,⁴ although this has limited diagnostic value in many cases.⁸

Apex cardiography is the most direct non-invasive method of measuring isovolumetric ventricular relaxation readily available,

FIG 2—Isovolumetric relaxation times in controls (mean 95 ± 3 ms) and hypothyroid patients (mean 133 ± 4 ms).

TABLE III—Isovolumetric relaxation times (ms) in hypothyroid patients in thyroxine trial

Case No	Dose of thyroxine (μ g/day)						
	0	50	100	150	200	250	300
2	142				106	119	110
4*	133	107	170	150			
5†	155		133		99		
6*	114		57	93			
7	154			131	90	144	114
8†	132	100		110	81		
9†	138				115		
10	115		117			108	125
12	153		107	98	94	109	111
13	139	148	108	120	127	106	114
14	161	175	152	101	147	143	119
16*	129	72	102	105			
17	150	160	130	91	113	100	116
18	131	117		105	122	85	95
20	146				118	118	82

*Cardiac embarrassment on thyroxine 200 μ g/day.

†Euthyroid on thyroxine 200 μ g/day.

and it reliably reflects the timing of intracardiac events.^{1-3 5 6} Heart rate and intravenous ouabain⁶ influence IRT. In our patients heart rate did not change significantly throughout the study and our results were unchanged when corrected with a rate correction formula.⁹ Only one of our patients was taking digoxin and she continued to take it throughout the study. Increasing age has also been said to prolong IRT,¹⁰ although other work has not confirmed this.⁶ There was no significant difference related to age in the IRT values of the control group.

FIG 3—Mean isovolumetric relaxation times ($\pm$ SE of mean) in nine patients with hypothyroidism who progressed to dose of 300 μ g/day during trial.

Benchimol and Dimond *et al* in their study of the apex cardiogram in ischaemic heart disease made no reference to abnormalities of the IRT.¹¹

Our results show that the IRT is prolonged in hypothyroid patients and reverts to normal after thyroxine replacement treatment. Since there was no radiographic or clinical evidence of pericardial effusion in any of our patients, we may have been measuring the effect of myxoedematous infiltration of the muscle fibres (a finding first reported in 1880¹²), and possibly this infiltration no longer causes detectable change in the IRT when the patient is rendered euthyroid.

It is particularly interesting that there was no reduction in the IRT when the dose of thyroxine was increased above 150 μ g/day, as this finding correlates well with work showing that most hypothyroid patients became euthyroid, using the serum thyrotrophin level as a criterion, on 100-200 μ g/day of thyroxine and

may be hyperthyroid when on the accepted full replacement regimen of 300 μ g/day of thyroxine.¹³

There is at present no readily available clinical or biochemical test that indicates the gradual return to normal body metabolism with increasing doses of thyroxine and, in particular, none that show normal end-organ function on less than the full replacement dose of 300 μ g/day. The IRT as an index of end-organ function in hypothyroidism therefore seems to have great potential as both a research and a diagnostic tool in thyroid disease.

We are grateful to the department of cardiology for their technical help and for use of their equipment.

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Relation between blood pressure, weight, and plasma sugar and serum insulin levels in schoolchildren aged 9-12 years in Westland, Holland

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British Medical Journal, 1976, **1**, 1368-1371

Summary

In 2388 schoolchildren aged 9-12 years who took part in a study of cardiovascular risk factors in Westland, Holland, plasma sugar concentrations were found to be positively correlated with systolic and diastolic blood pressure, independently of weight. Serum cholesterol levels were also related to systolic blood pressure in boys, but much less strongly than plasma sugar levels. The relation between serum insulin and blood pressure, independent of plasma sugar, was weak. The relation between plasma

sugar and systolic pressure existed for both sexes and regardless of whether measurements were made in the morning or afternoon; its association with diastolic pressure was weaker, and was not so consistent over all groups. These findings suggest that the relations between risk factors for coronary heart disease that exist in adults are already evident in childhood.

Introduction

The epidemiology of coronary heart disease (CHD) has been studied extensively in adults. People with raised serum cholesterol levels, blood pressure, and probably body weight are more likely than those with normal levels to have evidence of myocardial ischaemia at the time of the measurement or to suffer overt clinical CHD in the future. Raised blood sugar concentrations (measured after an oral glucose challenge) have also been strongly suggested as a risk factor for CHD but have attracted far less attention than the factors already mentioned.

Reasons for considering raised blood sugar as a precursor of CHD have been well reviewed by Epstein.¹ Necropsy, clinical, and laboratory studies over the past 50 years have mostly

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