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Left ventricular function and hyperthyroidism

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SUMMARY Cardiac output, aortic pressure, and left ventricular pressure (using a catheter tip micromanometer), angiographic end-diastolic volume and end-systolic volume were measured in seven thyrotoxic patients in sinus rhythm without heart failure. The following indices were calculated: dP/dt max, [(dP/dt)/TP] max, ejection fraction, mean velocity of fibre shortening, left ventricular mass, and the end-systolic pressure: end-systolic volume ratio (LVESP/LVESV). All measurements were made in the basal state and 20 minutes after 15 mg intravenous propranolol. After hyperthyroidism had been corrected with carbimazole, the same set of measurements was made in four now euthyroid patients in a basal state and while being atrially paced at the same heart rate as that found when they were hyperthyroid. The results were compared with those obtained in 11 normal patients of the same age studied in the basal state and during atrial pacing at the same heart rate as the thyrotoxic patients. After propranolol and when euthyroid, cardiac output, dP/dt max, [(dP/dt)/TP] max, ejection fraction, and mean velocity of fibre shortening decreased, and left ventricular mass decreased with euthyroidism. Reduction of cardiac output was related to a decrease in heart rate and stroke volume. After propranolol, stroke volume decreased because there was a greater increase in LV end-systolic volume than in LV end-diastolic volume. In the euthyroid state stroke volume decreased because of a decrease in LV end-diastolic volume without a change in systolic volume. Comparison of thyrotoxic, euthyroid atrially paced, and normal atrially paced patients disclosed that the increase in cardiac output during hyperthyroidism was related to an increase in LV end-diastolic volume, ejection fraction, mean velocity of fibre shortening, and dP/dt max, and that LVESP/LVESV did not differ between thyrotoxic and normal atrially paced patients. These data suggest that the reduction in cardiac output is mediated by different mechanisms after intravenous propranolol and carbimazole treatment; and that the haemodynamics of hyperthyroidism are related to the interaction of peripheral factors (a decrease in systemic arterial resistance and an increase in blood volume) and cardiac factors (an increase in heart rate).

The hyperdynamic cardiovascular state associated with thyrotoxicosis is well recognised[1–3] though the mechanisms responsible are poorly understood. Increased heart rate, reduction in peripheral arterial resistance,[3] and increased myocardial contractility[4] are likely to be major factors. The relative roles of thyroid hormones[4 5] and catecholamines[6] have not been clearly determined. The relation between the two is likely to be complex since high levels of circulating thyroid hormones result in an increase in the number and activity of beta-adrenergic receptors.[7]

In man the effect of hyperthyroidism on left ventricular function has not been extensively studied. Indirect measurements such as systolic time intervals[8–11] or the estimation of left ventricular dimensions using echocardiography[12] give an incomplete picture of left ventricular function. Left ventricular catheterisation gives a more direct approach; Ueda *et al.*[13] have studied left ventricular volumes and Pietras *et al.*[14] have measured isovolumic indices of left ventricular performance and their modification by the chronic administration of beta-blockers.

Our study was designed to assess left ventricular function in seven hyperthyroid subjects and its modification by intravenous propranolol administration. Four patients were re-examined 30 to 60 days after thyroid function had returned to normal. The second examination was performed both during spontaneous rhythm

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Table 1 *Thyroxine (T4) and triiodothyronine (T3) values in thyrotoxic patients before (H) and after carbimazole treatment (E).*

Case no.	*Sex*	*Age (y)*	*T4 (μg/100 ml)*		*T3 (ng/100 ml)*	
			H	*E*	*H*	*E*
1	M	58	16·5	8·3	338	146
2	M	42	30	5·2	800	65
3	M	46	24	5·7	442	92
4	F	51	22	6	—	—
5	M	24	16·8	—	483	—
6	F	45	10·5	—	155	—
7	M	47	17·1	—	350	—

and with the patients being atrially paced at the same heart rate as when they were thyrotoxic. The results were compared with those of a group of normal euthyroid subjects studied before and during atrial pacing.

Subjects and methods

(1) THYROTOXIC PATIENTS

Five men and two women (range 24 to 58 years) were studied. All had the typical clinical features of thyrotoxicosis, which was confirmed by estimation of thyroxine (T4) (normal range 5 to 12 μg/100 ml) and triiodothyronine (T3) (normal range 90 to 140 ng/100 ml). The principal clinical and biological findings are summarised in Table 1. All patients were in sinus rhythm and showed no clinical evidence of cardiac failure.

At the time of the first catheterisation, patients received no treatment. Cases 1 to 4 were receiving 10 to 20 mg carbimazole daily during the second examination.

(2) NORMAL EUTHYROID PATIENTS

This group consisted of 11 men (range 24 to 56 years) who were in sinus rhythm. Six were catheterised because of atypical chest pain and were subsequently found to have normal coronary angiograms, and five because of cardiac systolic murmurs which proved to be innocent.

(3) TECHNIQUES AND MEASUREMENTS

Each cardiac catheterisation study was performed after the patient's consent had been given. The following measurements were made: heart rate per min; cardiac output (l/min) by the dye dilution technique (mean of two successive measurements); aortic and left ventricular pressures (mmHg) using a Millar 5 F tip-micromanometer. Ventricular volumes were measured using cineangiography (50 frames/s) filmed in the frontal projection in forced inspiration. Calculation of ventricular volumes was made using the method of Dodge *et al.*[15] Corrections for enlargement and distortion were made by a grid calibration technique. The first three to five cardiac contractions were used to calculate ventricular volumes. Any post-extrasystolic beat was excluded. The following were calculated: stroke volume (SV ml), total systemic arterial resistance ($\overline{TSAR}=\overline{MAP}\times 80$/cardiac output (dyne s cm^{-5}), ($\overline{MAP}$ is the mean aortic pressure (mmHg)); the isovolumic indices of left ventricular performance: the maximum value of the first derivative of left ventricular pressure dP/dt max and the ratio [(dP/dt)/TP] max, where TP is total pressure; the ejection phase indices of left ventricular performance: the ejection fraction (EF)=LVEDV–LVESV/LVEDV per cent (LVEDV=left ventricular end-diastolic volume, LVESV=left ventricular end-systolic volume); the mean velocity of fibre shortening ($\overline{VCF}$)=EDD–ESD/EDD×Ejt (per s) (EDD: maximum end-diastolic diameter, ESD: end-systolic diameter in same plane, Ejt: ejection time (s) measured from the aortic pressure recorded simultaneously with left ventricular angiogram): the systolic pressure-volume

Table 2 *Mean value (m) and standard deviation (SD) in hyperthyroid subjects (H), normal euthyroid patients (N), and normal euthyroid paced patients (N.AP) of heart rate, ventricular end-diastolic pressure, mean arterial pressure, cardiac output, stroke volume, total systemic arterial resistance, dP/dt max, [(dP/dt)/TP] max, left ventricular end-diastolic volume, left ventricular end-systolic volume, ejection fraction, mean velocity of fibre shortening, and of the end systolic pressure-end systolic volume ratio (LVESP/LVESV)*

	Heart rate/min			*LV end-diastolic pressure (mmHg)*			*Mean arterial pressure (mmHg)*			*Cardiac output (l/min)*			*Stroke volume (ml)*			*Total systemic arterial resistance (dyne s cm^{-5})*		
	H	*N*	*N.AP*	*H*	*N*	*N.AP*	*H*	*N*	*N.AP*	*H*	*N*	*N.AP*	*H*	*N*	*N.AP*	*H*	*N*	*N.AP*
m	110	78††	117	8·4	8·0	5·0*	8·4	101†	106**	13·1	7·1††	7·9**	119	93	68**	590	1150††	1084**
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
SD	12	12	3	2·6	3·0	2·0	11	17	17	4·6	0·9	1·2	34	17	10	266	211	209

p values between H and N
†p<0·05
††p<0·01

p values between H and N.AP
*p<0·05
**p<0·01

relation of the left ventricle and the end-systolic pressure (LVESP)–end-systolic volume (LVESV) ratio=LVESP/LVESV (mmHg/ml) using a previously described method[16]; the left ventricular mass (m) using the method Rackley *et al.*[17]

(4) CARDIAC CATHETERISATION PERFORMED UNDER FOLLOWING CONDITIONS

(a) Seven hyperthyroid patients in a basal state (H) and 20 minutes after an intravenous injection of 15 mg of propranolol (P).

(b) Four of the seven thyrotoxic patients who had been made euthyroid (E) with carbimazole were studied in a basal state and during atrial pacing to the same heart rate found before antithyroid treatment (E.AP).

(c) 11 normal control subjects in a basal state (N) and during atrial pacing (N.AP) to an approximate rate of 120/min.

(5) STATISTICS

Results in the hyperthyroid patients before and after propranolol injection were compared using the Wilcoxon T test for paired data. The comparison of the results obtained in the hyperthyroid group with those in the normal euthyroid subjects (before and after atrial pacing) was made using the Mann and Whitney U test.

Results

HYPERTHYROIDISM

(1) *Comparison with normal euthyroid patients in sinus rhythm (Table 2)*

In thyrotoxic patients cardiac output and heart rate were increased ($p<0·01$). dP/dt max and [(dP/dt)/TP] max were increased ($p<0·01$). Mean arterial pressure ($p<0·05$) and total systemic arterial resistance ($p<0·01$) were lower. Left ventricular end-diastolic pressure, stroke volume, left ventricular end-diastolic and end-systolic volumes, ejection fraction, mean velocity of fibre shortening, and LVESP/LVESV were not significantly different.

(2) *Comparison with normal euthyroid patients during atrial pacing (Table 2)*

Heart rate was not significantly different in thyrotoxic patients. Cardiac output appeared to be augmented ($p<0·01$) by an increase in stroke volume ($p<0·01$) in conjunction with an increase in left ventricular end-diastolic volume ($p<0·01$). Left ventricular end-systolic volume was similar. dP/dt max was raised ($p<0·05$). Left ventricular end-diastolic pressure was higher ($p<0·05$). Mean arterial pressure ($p<0·01$) and total systemic arterial resistance ($p<0·01$) were lower. [(dP/dt)/TP] max, ejection fraction, mean velocity of fibre shortening, and LVESP/LVESV were not significantly different.

(3) *After intravenous injection of propranolol (Table 3)*

Heart rate, cardiac output, and stroke volume were reduced ($p<0·05$). The reduction of stroke volume was in relation to a more pronounced increase in left ventricular end-systolic volume ($p<0·05$) compared with end-diastolic volume ($p<0·05$). dP/dt max, [(dP/dt)/TP] max, ejection fraction, mean velocity of fibre shortening, and LVESP/LVESV were reduced ($p<0·05$).

EUTHYROID STATE (Table 4)

(1) *Basal values*

Compared with the hyperthyroid state, heart rate, cardiac output, and stroke volume were constantly reduced, with an increase in mean arterial pressure in three out of four patients, and in all four an increase in total systemic arterial resistance. dP/dt max, [(dP/dt)/TP] max, ejection fraction, mean velocity of fibre shortening, and mass were reduced. Though left ventricular end-diastolic volume was always reduced,

(dP/dt) max (mmHg/s)			*[(dP/dt)/TP] max (s)*			*LV end-diastolic volume (ml)*			*LV end-systolic volume (ml)*			*Ejection fraction (%)*			*Mean velocity of fibre shortening (s)*			*LVESP/LVESV (mmHg/ml)*		
H	*N*	*N.AP*	*H*	*N*	*N.AP*	*H*	*N*	*N.AP*	*H*	*N*	*N.AP*	*H*	*N*	*N.AP*	*H*	*N*	*N.AP*	*H*	*N*	*N.AP*
2843	1780††	2190*	78	52††	73	149	146	111**	45	52	44	70	64	61	1·6	1·3	1·4	2·2	2·4	2·7
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
533	410	400	20	13	16	35	33	27	14	18	14	7	7	9	0·3	0·2	0·3	0·8	0·8	0·9

Table 3 *Effects of intravenous injection of propranolol (P) in hyperthyroid patients (H)*

Case no.	*HR/min*		*LV end-diastolic pressure (mmHg)*		*Mean aterial pressure (mmHg)*		*Cardiac output (l/min)*		*Stroke volume (ml)*		*Total systemic arterial resistance (dyne s cm^{-5})*	
	H	*P*	*H*	*P*	*H*	*P*	*H*	*P*	*H*	*P*	*H*	*P*
1	110	97	7·5	8·0	84	110	13·0	9·0	118	93	516	977
2	100	90	4·0	12·0	70	76	15·0	14·0	150	156	373	434
3	115	95	10·0	14·0	80	82	18·0	14·5	157	153	355	452
4	115	100	12·0	20·0	100	108	9·5	7·3	83	73	842	1183
5	130	95	10·0	17·5	80	94	19·5	12·8	150	133	328	587
6	105	82	7·5	9·0	80	94	8·9	6·4	85	78	719	1175
7	92	88	8·0	12·0	100	102	8·0	6·6	87	75	1000	1236
m±SD	110± 12	92*± 6	8·4± 2·6	13·2*± 4·3	85± 11	95*± 13	13·1± 4·6	10·1*± 3·6	119± 34	109*± 37	590± 266	863*± 360

Same legends as Table 2. *p<0·05 (Wilcoxon T test).

changes in left ventricular end-systolic volume, left ventricular end-diastolic pressure, and the ratio LVESP/LVESV were variable.

The results obtained in the patients after treatment of hyperthyroidism resembled normal euthyroid subjects in sinus rhythm.

(2) *Atrial pacing*

During atrial pacing the results closely resembled those observed in the normal paced controls: stroke volume was constantly diminished and mean arterial pressure was slightly increased. Changes in cardiac output and total systemic arterial resistance were not uniform. The reduction of stroke volume corresponded to a more pronounced reduction in left ventricular end-diastolic volume than in left ventricular end-systolic volume. Left ventricular end-diastolic pressure fell. dP/dt max and [(dP/dt)/TP] max increased. Ejection fraction and mean velocity of fibre shortening were not modified. The ratio LVESP/LVESV increased.

Discussion

Our observations were made on a comparatively small number of subjects. None the less there appears to be sufficient information in this study to permit a discussion of the different mechanisms involved in the hyperdynamic cardiovascular state in thyrotoxicosis and certain aspects of the acute action of beta-blockers.

Variations in stroke volumes observed in the same individual may be explained by the fact that measurement of stroke volume by the dye dilution method was performed during spontaneous respiration, whereas determination of ventricular volume during angiography was made in forced inspiration.

MECHANISMS OF HYPERDYNAMIC CIRCULATORY STATE IN THYROTOXICOSIS

This syndrome is characterised by an increase in cardiac output without an increase in aortic pressure,

Table 4 *Effects of propranolol (P) and carbimazole treatment (E) in hyperthyroid patients (H), and effects of atrial pacing in hyperthyroid treated patients (E.AP). Comparison with the values obtained in normal euthyroid patients (N) and during atrial pacing of normal euthyroid patients (N.AP)*

Case no.	*Heart rate/min*				*LV end-diastolic pressure (mmHg)*				*Mean arterial pressure (mmHg)*				*Cardiac output (l/min)*				*Stroke volume (ml)*				*Total systemic arterial pressure (dyne s cm^{-5})*				*dP/dt max (mmHg/s)*			
	H	P	E	E.AP	H	P	E	E.AP	H	P	E	E.AP	H	P	E	E.AP	H	P	E	E.AP	H	P	E	E.AP	H	P	E	E.AP
1	110	97	90	110	7·5	8·0	6·0	5·0	84	110	140	148	13·0	9·0	6·3	7·0	118	93	70	64	516	977	1777	1691	2200	1900	2000	2500
2	100	90	70	100	4·0	12·0	8·0	4·0	70	76	82	90	15·0	14·0	9·0	9·0	150	156	129	90	373	434	728	800	2600	2500	2200	2800
3	115	95	90	115	10·0	14·0	10·0	8·0	80	82	80	90	18·0	14·5	9·8	10·9	157	153	108	95	355	452	653	660	2800	2400	1500	2200
4	115	100	76	115	12·0	20·0	8·0	2·0	100	108	120	128	9·5	7·3	5·7	5·4	83	73	75	47	842	1183	1684	1896	3200	2800	2200	2500
	110	95	81	110	8·4	13	8·0	4·7	83	94	105	114	13·9	11·2	7·7	8·1	127	119	95	74	521	761	1210	1262	2700	2400	1975	2500
m±SD	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±
	7	4	10	7	3·4	5	1·6	2·5	12	18	29	29	3·5	3·6	2·0	2·4	34	42	28	23	225	377	602	622	416	374	330	245
N			N	N.AP			N	N.AP			N	N.AP			N	N.AP			N	N.AP			N	N.AP			N	N.AP
			78	117			8·0	5·0			101	106			7·1	7·9			93	68			1150	1084			1780	2190
m±SD			±	±			±	±			±	±			±	±			±	±			±	±			±	±
			12	3			3·0	2·0			17	17			0·9	1·2			17	10			211	209			410	400

Same legends as Table 2.

P/dt max *mmHg/s)*		*[(dP/dt)/TP]* *max (s)*		*LV end-diastolic volume (ml)*		*LV end-systolic volume (ml)*		*Ejection fraction (%)*		*VCF (s)*		*LVESP/LVESV (mmHg/ml)*		*LV mass (g)*
	P	*H*	*P*	*H*	*P*	*H*	*P*	*H*	*P*	*H*	*P*	*H*	*P*	
00	1900	60	60	130	138	32	78	75	43	1·42	0·8	3·0	1·4	207
00	2500	80	68	167	192	40	60	76	62	1·7	1·1	1·8	1·3	188
00	2400	70	54	206	217	69	91	67	58	2·0	1·3	1·1	0·9	222
00	2800	68	60	113	135	45	56	60	58	1·3	0·8	2·3	2·0	150
00	2700	80	52	176	198	60	90	66	54	1·1	1·0	1·4	1·1	181
00	1700	120	65	110	130	38	61	65	53	1·9	1·6	2·3	1·8	136
00	1900	70	60	142	152	31	52	78	66	1·7	1·2	3·4	2·1	146
43±	2271*±	78±	60*±	149±	166*±	45±	70*±	70±	56*±	1·6±	1·1*±	2·2±	1·5*±	176*±
53	435	20	6	35	35	14	16	7	7	0·3	0·3	0·8	0·4	32

corresponding to a net decrease in peripheral arterial resistance.

The reduction in peripheral arterial resistance could not be explained by an increased metabolic requirement of the tissues, since the arteriovenous oxygen difference is reduced in hyperthyroidism.

It is possible that the reduced arterial resistance is mediated by the alpha-adrenergic system, as has been recently suggested by Williams and Lefkowitz.[18]

An increase in cardiac output can be caused by: (1) at constant stroke volume, an acceleration of heart rate; (2) at constant heart rate, an increased end-diastolic volume or a decreased end-systolic volume. End-diastolic volume depends on left ventricular distensibility and on the transmural end-diastolic pressure, which in this study may be reasonably represented by the intraventricular pressure. End-systolic volume depends on end-systolic pressure and on the performance of the left ventricular pump. Suga and Sagawa[19] have shown experimentally that left ventricular end-systolic pressure-E (LVESV–Vd), where Vd was shown to be negligible in comparison with left ventricular end-systolic volume. The ratio LVESP/LVESV therefore provides an index of performance of the left ventricular pump.

The comparison between thyrotoxic, treated thyrotoxic paced patients, and normal paced controls suggests that the increase in stroke volume caused by an increase in left ventricular end-diastolic pressure and volume may be explained by the increased circulatory blood volume which is known to occur in thyrotoxicosis.[20] The existence of an increased inotropic state, independent of the tachycardia, seems more doubtful. Comparison of thyrotoxic patients and normal paced controls shows the similarity of [(dP/dt)/TP] max at an identical heart rate, of ejection fraction, mean velocity of fibre shortening, and the ratio LVESP/LVESV. It is true that dP/dt max was higher in the thyrotoxic patients, but it has been shown that this index increases at the same time as the end-

P/dt)/TP] *ax (s)*				*LV end-diastolic volume (ml)*				*LV end-systolic volume (ml)*				*Ejection fraction (%)*				*VCF (s)*				*LVESP/LVESV (mmHg/ml)*				*LV mass (g)*	
l	*P*	*E*	*E.AP*	*H*	*P*	*E*	*E.AP*	*H*	*P*	*E*	*E.AP*	*H*	*P*	*E*	*E.AP*	*H*	*P*	*E*	*E.AP*	*H*	*P*	*E*	*E.AP*	*H*	*E*
0	60	50	54	130	138	108	80	32	78	46	40	75	43	57	50	1·4	0·8	1·1	1·1	3·0	1·4	3·0	3·2	207	190
0	68	64	80	167	192	155	120	40	60	57	45	76	62	63	62	1·7	1·1	1·2	1·2	1·8	1·3	1·4	2·1	188	160
0	54	56	60	206	217	182	119	69	91	68	48	67	58	63	60	2·0	1·3	1·1	1·1	1·1	0·9	1·1	1·9	222	208
8	60	48	54	113	135	80	62	45	56	35	25	60	58	56	59	1·3	0·8	0·9	1·0	2·3	2·0	3·0	5·3	150	140
9	60	54	62	154	170	131	95	46	71	51	39	69	55	60	58	1·6	1·0	1·1	1·1	2·1	1·4	2·1	3·1	192	174
±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±
8	6	7	12	41	41	46	29	16	16	14	10	7	8	4	5	0·3	0·2	0·1	0·1	0·8	0·4	1·0	1·5	31	30
		N	N.AP			N	N.AP			N	N.AP			N	N.AP			N	N.AP			N	N.AP		
		52	73			146	111			52	44			64	61			1·3	1·4			2·4	2·7		
		±	±			±	±			±	±			±	±			±	±			±	±		
		13	16			33	27			18	14			7	9			0·2	0·3			0·8	0·9		

diastolic volume.[21] The increase in dP/dt max, chiefly related to the increase in heart rate and decrease in aortic pressure, is sufficient to explain the shortening of the pre-ejection period reported in these thyrotoxic patients.[11]

On the other hand, the reduction of ejection fraction and mean velocity of fibre shortening associated with antithyroid treatment should not be interpreted as evidence of a negative inotropic effect since in three out of four patients there was an increase in aortic pressure, and ejection fraction and mean velocity of fibre shortening are strongly dependent on the systolic load of the ventricle.[22] These facts suggest that there is not an increased inotropic effect in hyperthyroidism independent of the tachycardia. Therefore experimental evidence for a positive inotropic effect of hyperthyroidism provided by the works of Buccino *et al.*,[4] Skelton *et al.*,[23] and Taylor[5] appears of doubtful relevance in man. If an increased inotropic effect does exist in thyrotoxicosis, its importance appears relatively modest compared with the increased heart rate and a relative hypervolaemia.

EFFECTS OF PROPRANOLOL

The effects of propranolol administration in this study are similar to those previously reported.[14 24 25] If the effects of the intravenous injection of propranolol in thyrotoxic patients are compared with those in carbimazole-treated patients, certain similarities are seen: a reduction in heart rate, stroke volume, cardiac output, dP/dt max, and [(dP/dt)/TP] max, and an increase in aortic pressure and systemic arterial resistance. For all these variables, the values obtained after propranolol were intermediate between those found in untreated and carbimazole-treated patients. The same did not apply to the left ventricular end-diastolic pressure, left ventricular end-diastolic and end-systolic volumes, and LVESP/LVESV ratio. The reduction of LVESP/ LVESV and the increase in left ventricular end-systolic volume are signs of the pronounced negative inotropic effects of the beta-blocker, which differentiates its action from carbimazole. The increase in left ventricular end-diastolic pressure and volume are obligatory compensatory mechanisms to maintain stroke volume. Thus it appears that stroke volume is reduced by beta-blockers and by antithyroid treatment by quite different mechanisms. Beta-blockers cause an increase in end-systolic volume and antithyroid treatment a reduction in end-diastolic volume. These results were obtained after a single injection of propranolol and require validation by further studies after chronic administration of the drug. Nevertheless, these results suggest that the part played by the noradrenergic system in the cardiovascular manifestations of hyperthyroidism is of questionable significance. On the other hand, some changes in left ventricular performance induced by beta-receptor blockade are completely different from those observed with euthyroidism. This may suggest, at least, that beta-blockade is not, by itself, the best treatment for the haemodynamic changes induced by hyperthyroidism.

In summary, the hyperkinetic circulatory state in thyrotoxicosis is caused by a complex interaction of mechanisms (1) *peripheral:* reduction of the systemic arterial resistance and an increase in circulatory blood volume; (2) *cardiac:* principally caused by an increase of heart rate. Previous workers have allocated a major role to the adrenergic nervous system in the genesis of cardiocirculatory disturbance in thyrotoxicosis. The results reported here do not tend to support this conclusion.

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