Quebec Cooperative Study
of Friedreich's Ataxia

Increased Plasma Catecholamines in Patients with Friedreich's Ataxia

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SUMMARY: *We studied free plasma catecholamines in 23 patients with Friedreich's ataxia, having a mean age of 22 ± 9.6 (SD) years. Conjugated catecholamines were also studied in 10 patients. Mean plasma norepinephrine and epinephrine were significantly higher than controls both in the supine and standing positions. In total 15 out of 23 patients (65%) had increased free and/or conjugated plasma catecholamines. The increase in plasma catecholamines was more marked in patients with severe neuromotor impairment. Among the patients with left ventricular concentric hypertrophy (wall thickness >12 mm), only 3 had no demonstrable sympathetic hyperfunction.*

Since the high local concentrations of norepinephrine at the site of release from sympathetic nerve terminals may serve as a trigger for the hypertrophic response of the myocardial cell, it is suggested that early pharmacological intervention could prevent or limit the cardiomyopathic process or its clinical consequences.

RÉSUMÉ: *Nous avons étudié le niveau des catécholamines plasmatiques libres chez 23 patients porteurs d'ataxie de Friedreich dont l'âge moyen était de 22 ± 9.6 (DS) années. Le niveau des catécholamines conjugées a aussi été étudié chez 10 patients. Les taux de norépinéphrine et d'épinéphrine plasmatiques étaient significativement plus élevés chez les patients que chez les sujets contrôles, en position couchée et debout. En tout, 15 sur 23 patients (65%) avaient des catécholamines plasmatiques libres et/ou conjugées élevées. L'élévation des catécholamines plasmatiques était plus marquée chez les patients porteurs d'une atteinte neuro-motrice plus sévère. Parmi les patients porteurs d'une hypertrophie ventriculaire concentrique (épaisseur de la paroi >12 mm), seulement trois ne présentaient pas d'hyperfonctionnement sympathique.*

Puisque les fortes concentrations locales de norépinéphrine au niveau des terminaisons nerveuses sympathiques peuvent servir de facteur déclenchant pour la réponse hypertrophique de la cellule myocardique, il est suggéré qu'une intervention pharmacologique précoce pourrait prévenir ou limiter le processus cardiomyopathique ou ses conséquences cliniques.

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Reprint requests for the entire supplement on Friedreich's Ataxia (Phase Three, Part Two) to: Prof. André Barbeau, Clinical Research Institute of Montreal, 110 West Pine Avenue, Montreal, Quebec, Canada, H2W 1R7.

INTRODUCTION

Increased sympathetic stimulation has been held responsible for inappropriate sinus tachycardia in Friedreich's ataxia since early observations by Loiseau (1938) and then by Thorén (1964) and by Côté et al (1976), but has never been fully documented.

The primary purpose of this study was therefore to measure plasma catecholamine levels (Micalizzi and Pals, 1979; Kopin et al, 1980) and thus documents the hyperfunction of the adrenergic system in patients with Friedreich's ataxia.

In addition, since involvement of the heart in Friedreich's ataxia consists most often of concentric hypertrophy (Gottdiener et al, 1979; Pasternac et al, 1980; St-John Sutton et al, 1980), we explored the possible relationship between the degree of ventricular hypertrophy and the dysfunction of the adrenergic nervous system which might provide the connection with the neurologic disorder (Perloff, 1981; Hartman and Booth, 1960). The documentation of a hyperadrenergic state in Friedreich's ataxia would provide support to the "Catecholamine Hypothesis" proposed by Goodwin (1974) as a pathogenesis of hypertrophic cardiomyopathies in general.

METHODS

We studied 23 patients (14 males, 9 females) with documented Friedreich's ataxia, having a mean age of 21.5±8.9 (SD) years (range 13-41).

The patients consisted of two groups: there were 9 adult patients (5 males, 4 females) (mean age 30.6±7.1 years) and 14 children (10 males, 4

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females) (less than 20 years of age) (mean age 15.7±2.8 years). The severity of Friedreich's ataxia was assessed independently at the Montreal Neurological Institute (by Dr. Andermann) for adult patients and at Ste-Justine Hospital (by Dr. Mélançon) for the pediatric group. Patients were classified into 4 stages of severity (from 0 to 4) according to Pourcher and Barbeau (1980) classification. None had clinical evidence of heart failure.

These patients were compared to 35 adult control subjects (22 males, 13 females) (mean age 29.4±11.2 years) and to 9 young control subjects (7 males, 2 females) (mean age 15.8±2.2 years).

M-mode and 2-dimensional echocardiograms were obtained with a Picker Echoview 80C. For the M-mode study, we used a 3.5 megaHertz transducer, and for the cross-sectional study, we used a mechanical transducer with a variable angle of 30 to 45^0. Images were recorded and stored on videotape for subsequent analysis. End-diastolic septal and posterior wall thickness and left ventricular end-diastolic dimension were measured at the peak of the R wave of the ECG.

In all patients and control subjects, heart rate, systolic and diastolic blood pressures were measured first in the basal state, after resting in a comfortable supine position for 20 minutes and secondly 10 minutes after assuming a standing position. Serial measurements were performed every minute and the values obtained for each state resulted from the mean of all those values obtained after stabilization was established.

Catecholamine measurements

In each state, 10 ml blood samples were drawn from a brachial vein for measurements of catecholamine levels. These samples were taken between 9 and 10 in the morning, following a 10 hour fast, all patients having abstained from drinking coffee or tea and from smoking for the last 24 hours. All patients were allowed to eat their usual diet without attempt to control their sodium intake. None were taking any medication. Serum electrolytes were normal.

For the determination of free norepinephrine, epinephrine and dopamine, we used the radioenzymatic assay developed by Peuler and Johnson (1977) and adapted by de Champlain. This catechol-o-methyl transferase catalyzed assay is sensitive to 1-2 pg for norepinephrine and epinephrine and less than 10 pg for dopamine.

In 9 pediatric patients and in the pediatric control subjects, norepinephrine, epinephrine and dopamine conjugates were also measured on the same sample by the sulfatase technique of Johnson et al (1980).

To make sure that the age difference between controls and young patients had no influence on the catecholamine comparisons, free and conjugated catecholamine levels were obtained in a group of nine pediatric controls of similar age. However, since the pediatric control catecholamine levels were almost identical to the adult control group, the 35 adult controls will be used for comparison, but an independent comparison of the pediatric groups will also be presented.

An increase in adrenergic function was considered present when one of the free catecholamines was elevated beyond 2 standard deviations of the controls for the corresponding age group.

Statistical analysis

A statistical comparison of results was performed by means of Student's t test for paired and unpaired data. Differences were considered significant for p values less than 0.05. Results are expressed as mean ± standard error of the mean.

RESULTS

Tables 1 and 2 show the clinical, hemodynamic and metabolic data of individual patients with Friedreich's ataxia. Table 3 shows the mean values of the data obtained in the control subjects.

TABLE 1: *CLINICAL, HEMODYNAMIC AND METABOLIC DATA OF ADULT PATIENTS WITH FRIEDREICH'S ATAXIA*

Patient	Age	Sex	Systolic BP (mmHg)		Diastolic BP (mmHg)		Heart rate (beats/min)		TPC (NE + E) (pg/ml)		FREE CATECHOLAMINES NE (pg/ml)		E (pg/ml)		DA (pg/ml)		ADR Hyperf.	Wall Thickness		Friedreich's ataxia severity
			S	St	S	St	S	St	S	St	S	St	S	St	S	St		SEPT.	PW	
1. JP	21	M	124	110	60	70	64	94	442	676	393	572	119	104	20	0	+	10	10	2
2. LP	36	M	128	143	80	98	78	80	268	437	218	366	50	71	15	33	0	11	11	2
3. GG	41	F	110	108	80	80	70	76	592	624	537	513	55	109	189	555	+	11	11	4
4. GJ	36	M	110	105	80	80	98	130	837	755	759	661	78	94	13	14	+	12	12	3
5. HP	34	F	114	108	80	78	86	88	429	589	366	484	63	105	36	62	+	13	13	3
6. CG	31	F	114	136	72	100	70	88	669	799	601	705	68	94	37	30	+	14	14	3
7. MO	23	M	115	123	85	90	68	92	365	709	312	608	53	101	24	50	+	10	10	2
8. MR	31	M	100	102	85	90	120	128	457	753	387	607	70	146	56	101	+	12	12	4 (†)
9. JV	22	F	96	96	68	80	66	74	345	635	323	576	22	59	67	72	+	7	7	0
Mean	30.56	4F/5M	112.33	114.56	76.67	85.11	80	94.44	489.33	664.11	425.11	565.78	64.22	98.11	50.78	101.89	8/9	11.11	11.11	
SD	7.09		10.15	15.97	8.35	9.96	18.57	20.76	178.85	109.65	171.91	100.91	26.07	24.50	54.97	172.67		2.03	2.03	
SE	2.36		3.38	5.32	2.78	3.32	6.19	6.92	59.62	36.55	57.3	33.69	8.69	8.17	18.32	57.56		0.68	0.68	

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TABLE 2: *CLINICAL, HEMODYNAMIC AND METABOLIC DATA OF YOUNG PATIENTS WITH FRIEDREICH'S ATAXIA.*

Patient	Age	Sex	Systolic BP (mmHg)		Diastolic BP (mmHg)		Heart rate (beats/min)		TPC (pg/ml)		FREE CATECHOLAMINES NE (pg/ml)		E (pg/ml)		DA (pg/ml)	
			S	St	S	St	S	St	S	St	S	St	S	St	S	St
1. PS	19	F	108	110	76	74	80	104	257	320	215	237	42	83	27	104
2. GM	13	F	116	124	60	58	76	92	235	206	190	175	45	31	22	21
3. JSt	13	M	84	92	54	70	76	92	174	390	146	337	28	53	34	26
4. JS	16	M	94	102	74	80	76	84	225	272	205	248	20	24	26	21
5. JF	16	M	102	98	70	74	84	98	594	574	507	438	87	136	36	35
6. GMc	9	F	90	96	52	62	100	132	172	305	144	155	28	150	118	94
7. MM	15	M	118	128	72	84	76	84	369	364	339	324	33	40	11	18
8. LH	15	M	92	92	56	68	84	88	108	172	93	138	15	34	13	48
9. DM	17	F	96	96	58	70	72	80	178	341	165	321	13	20	18	36
10. CG	16	M	110	112	78	86	74	88	239	489	201	405	38	84	76	57
11. GS	19	M	122	108	80	90	78	140	407	1060	360	929	47	131	0	105
12. GM	17	M	122	112	70	90	80	114	553	1277	475	1118	78	148	0	33
13. GL	15	F	110	109	68	66	120	132	1442	2316	1327	2114	115	202	46	68
14. BL	19	M	126	135	74	96	68	80	300	562	234	433	66	129	69	125
MEAN	15.64	5F/9H	106.43	108.14	67.29	76.29	81.71	100.57	375.21	617.7	328.64	526.57	46.79	90.36	35.43	56.50
SD	2.73		13.55	13.47	9.43	11.55	13.31	20.73	338.67	581.97	312.98	537.54	29.72	58.61	32.77	36.46
SEM	0.73		3.62	3.60	2.52	3.9	3.56	5.54	90.51	155.54	83.65	143.66	7.94	15.66	8.76	9.74

CONJUGATED CATECHOLAMINES NE (pg/ml)		E (pg/ml)		DA (pg/ml)		FREE CATECHOLAMINES NE (pg/ml)		E (pg/ml)		DA (pg/ml)		ADR Hyperf.	Wall Thickness (mm) SEPT	PW	Friedreich's ataxia severity
S	St	S	St	S	St	S	St	S	St	S	St				
957	987	930	885	5897	6118	18	19	4.3	8.6	0.5	1.7	+	13	12	4
225	161	95	64	439	345	45.8	52.1	32.1	32.6	4.8	5.7	0	16	12	1
511	548	241	250	1117	1182	22.2	38.1	10.4	17.5	2.9	2.1	+	12.5	13	0
623	725	224	225	1195	1318	24.8	25.5	8.2	9.6	2.1	1.6	+	15.5	14.5	2
474	469	158	193	629	667	50.6	48.3	35.5	41.3	5.4	5.0	+	13	13	1
280	213	177	103	853	592	34.0	42.1	13.6	59.3	12.1	13.7	+	16.5	14.5	0
556	537	357	360	2823	2718	37.9	37.6	8.5	10.0	0.4	0.7	+	17	16.5	1
524	501	224	274	1554	1562	15.1	19.2	6.3	11.0	0.8	3.0	0	13	12	2
447	529	338	331	2102	2621	27.0	37.8	3.7	5.7	0.8	1.3	+	15	15	2
400	327	178	165	1034	1026	33.4	55.3	17.6	33.7	6.8	5.3	+	14	14	2
												+	16	16	2
												+	12	12	1
												+	15	15	3
												0	15	15	2
451.44	454.44	221.33	218.33	1305.11	1336.78	30.88	37.50	14.02	22.93	3.66	4.01	11/14	14.54	13.89	
129.75	184.12	83.84	98.44	752.80	845.25	11.64	12.86	11.25	17.92	3.73	3.85		1.62	1.56	
43.25	61.37	27.95	32.81	250.93	281.75	3.68	4.07	3.56	5.67	1.18	1.22		0.43	0.42	

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TABLE 3: *CLINICAL, HEMODYNAMIC AND METABOLIC DATA OF CONTROL SUBJECTS.*

		Age	Sex	Systolic BP (mmHg)		Diastolic BP (mmHg)		Heart rate (beats/min)		TPC (pg/ml)		FREE CATECHOLAMINES NE (pg/ml)		E (pg/ml)	
				S	St	S	St	S	St	S	St	S	St	S	St
Adults n=35	Mean	29.4	22M/13F	112	108	74.3	80.7	64.3	72.5	201.7	410.8	169.1	360.0	32.6	50.8
	SD	11.2		8.3	8.9	8.3	5.9	7.1	10.1	88.7	153.8	71.0	130.1	23.1	40.8
	SEM	1.9		1.4	1.5	1.4	1.0	1.2	1.7	15.0	26.0	12.0	22.0	3.9	6.9
Children n=9	Mean	15.8	7M/2F	108.7	104.0	68.9	79.1	62.6	80.2	202.3	423.8	157.7	363.0	44.7	
	SD	2.2		13.1	12.3	8.0	8.6	6.7	10.7	25.6	75.1	20.1	79.6	21.5	
	SEM	0.7		4.4	4.1	2.7	2.9	2.2	3.6	8.5	25.0	6.7	26.5	7.1	

CONJUGATED CATECHOLAMINES								% FREE CATECHOLAMINES					
DA (pg/ml) (9 pts)		NE (pg/ml)		E (pg/ml)		DA (pg/ml)		NE (pg/ml)		E (pg/ml)		DA (pg/ml)	
S	St	S	St	S	St	S	St	S	St	S	St	S	St
22.4	25.0												
16.8	15.0												
5.6	5.0												
18.2	15.1	484.6	480.8	198.4	197.6	1871.8	1800.8	24.6	43.9	21.7	25.4	1.0	0.9
18.8	13.2	119.9	110.8	98.1	76.4	1008.7	854.0	4.1	6.1	13.3	13.4	0.9	0.9
6.2	4.4	40.0	36.9	32.7	25.5	336.2	284.7	1.4	2.0	4.4	4.5	0.3	0.3

Figure 1 shows the distribution of patients according to age, severity of disease and left ventricular wall thickness. Thus, 16 patients were in stages 0 to 2 and seven were in stages 3 or 4; 18 patients had left ventricular wall hypertrophy, including one patient with asymmetrical septal hypertrophy.

Resting heart rate (81±6.19) was significantly increased when compared to controls (64.3±1.2) ($p<0.001$), the difference remained significant in the standing position ($p<0.001$) (fig. 2). Mean systolic and diastolic pressures did not change significantly with the upright posture in patients with Friedreich's ataxia; in both positions, they were comparable to control values.

Total plasma catecholamine levels (norepinephrine and epinephrine) were significantly higher in Friedreich's ataxia patients than in controls, both in the supine and standing positions ($p<0.001$). However, the increase in total plasma catecholamines with the upright position was of a lesser magnitude in patients than in controls (fig. 3). Plasma norepinephrine was significantly higher in patients with Friedreich's ataxia than in controls in both positions ($p<0.001$ supine, and $p<0.02$ standing), but the relative increase observed with the standing position was less marked than in controls (fig. 4).

Plasma epinephrine was significantly higher than in controls in both supine ($p<0.01$) and standing ($p<0.001$) positions, but the difference was more marked in the standing position, due to a greater relative increase with the upright posture ($p<0.001$) (fig. 5).

Free dopamine was also higher than in controls in both positions [41.5±8.8 pg/ml vs 22.4±5.6 pg/ml, in the supine position ($p<0.01$) and 74.3±23.0 pg/ml vs 25.0±5.0 pg/ml in the standing position ($p<0.01$)]. The change observed with the standing position was significant only in patients.

Plasma catecholamines were higher in patients with stages 3 and 4 than in those with stages 0, 1, 2; the difference reached significance in the supine position only ($p<0.01$) (fig. 6).

To make sure that age was not a confounding factor, comparisons were also carried out between the young patients with Friedreich's ataxia and the pediatric control group. Total plasma catecholamines in patients were higher in the supine position ($p<0.05$) (fig. 7).

Overall, values in young patients with Friedreich's ataxia were lower than in adult patients. With the excep-

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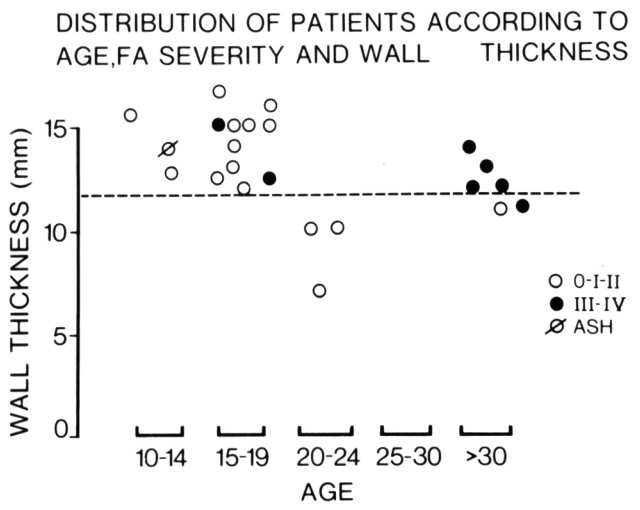

Figure 1 — Distribution of patients according to age (years), neuromotor severity (graded from 0 to 4) and to left ventricular wall thickness (mm). ASH = asymmetrical septal hypertrophy.

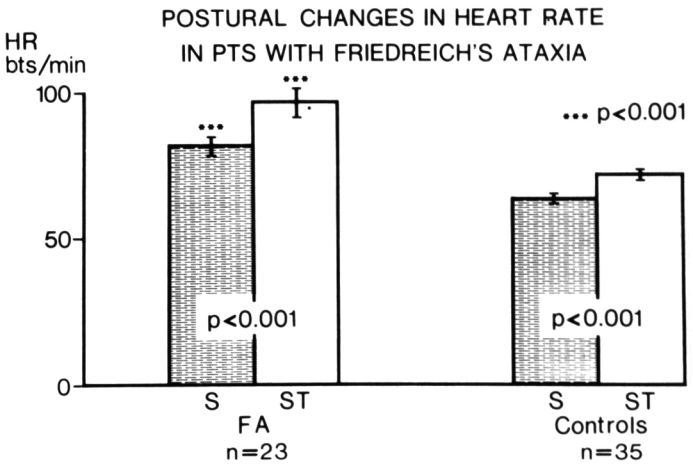

Figure 2 — Heart rate was higher than in controls in both supine (S) and standing (ST) positions ($p<0.001$). FA = Friedreich's ataxia.

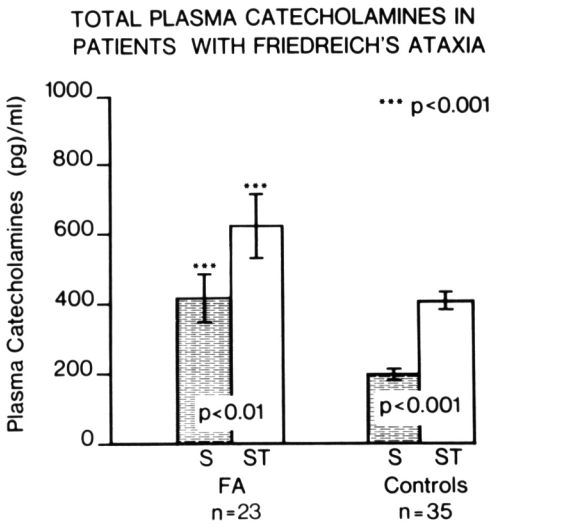

Figure 3 — Total plasma catecholamines were higher than in controls in both supine and standing positions ($p<0.001$). With the upright posture, the catecholamine increase was relatively less marked in patients than in controls ($p<0.01$ vs $p<0.001$).

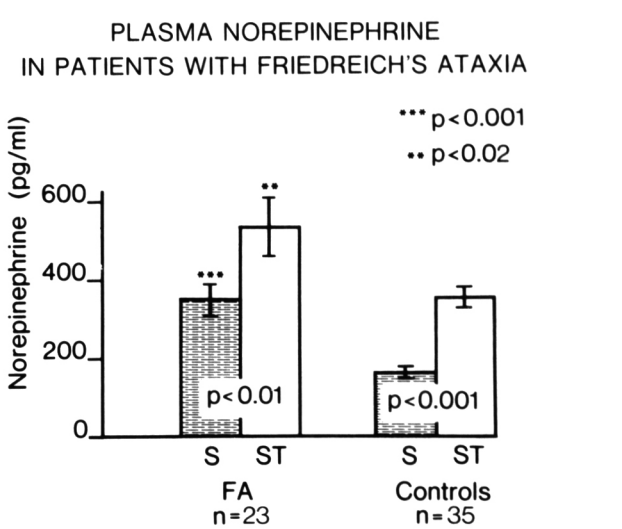

Figure 4 — Plasma norepinephrine was higher than in controls in both supine ($p<0.001$) and standing ($p<0.02$) positions. When standing, the increase in norepinephrine was relatively less important in patients than in controls ($p<0.01$ vs $p<0.001$).

tion of one patient (#1), no abnormalities were detected in conjugated catecholamine levels.

Thus, 15 out of 23 patients had definite increased adrenergic function. In 12 patients (52%), the increase in catecholamines consisted predominantly in an increase in norepinephrine levels (Table 4).

The 12 patients who had both increased adrenergic function and left ventricular hypertrophy belonged to all stages of severity of Friedreich's ataxia.

Only one patient had normal adrenergic function and normal wall thickness. Adrenergic hyperfunction did exist without left ventricular hypertrophy in 4 patients, one being a stage 4 Friedreich's ataxia.

Among the 7 patients who had an increased left ventricular wall thickness and normal plasma catecholamines, one had asymmetric septal hypertrophy (ASH).

DISCUSSION

The existence of overstimulation of the sympathetic system in Friedreich's ataxia has been suspected since 1938. Loiseau (1938) had ascribed the myocardial changes to lesions of the medulla which involve the vagal nuclei, thus facilitating sympathetic overstimulation. Thorén (1964) observed the inappropriate sinus tachycardia and Côté et al (1976) noted in addition an increased heart rate response to

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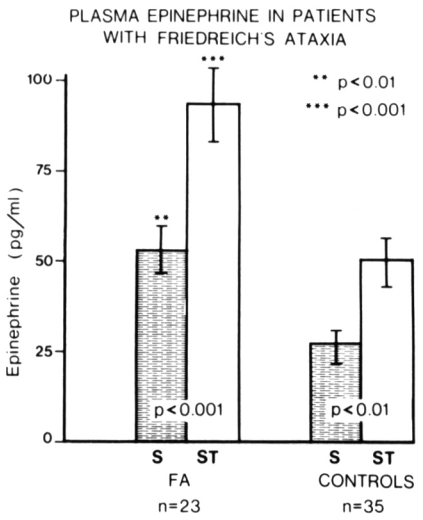

Figure 5 — Plasma epinphrine was higher than in controls in both supine and standing positions; the difference was however more marked in the standing position ($p<0.001$ vs $p<0.01$).

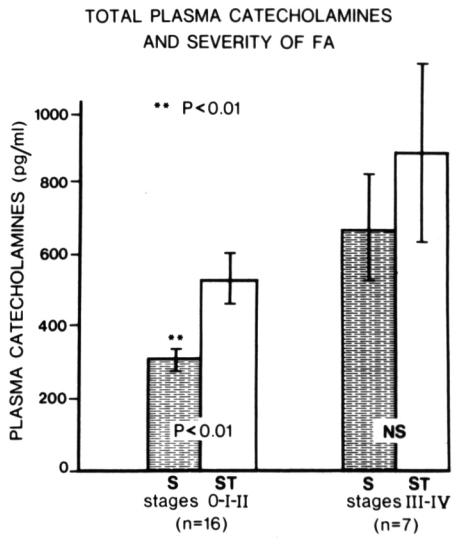

Figure 6 — The level of total plasma catecholamines was lower in patients whose stages of neuromotor involvement were 0 to 2 than in those whose stages were 3 or 4; the difference reached significance only in the supine position ($p<0.01$).

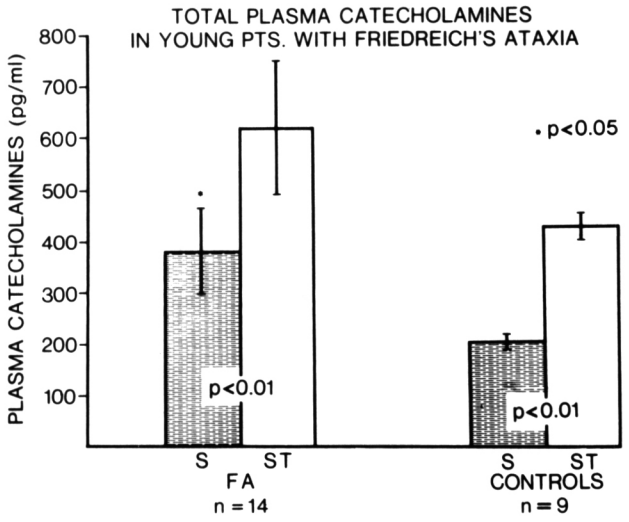

Figure 7 — In young patients with Friedreich's ataxia (<20 years), total plasma catecholamines were lower than in age-matched controls; the difference reached significance ($p<0.05$) only in the supine position.

TABLE 4:
INCREASED ADRENERGIC FUNCTION AND VENTRICULAR HYPERTROPHY IN FA PATIENTS

STAGE FA	↑ FREE CATECHOLAMINES NE	E	NE + E	DA	Total	↑ WT
0 (n = 3)	1	1			2/3	2/3
I (n = 4)	1		2		3/4	4/4
II (n = 9)	2	1		1	4/9	6/9
III (n = 4)	3		1		4/4	4/4
IV (n = 3)	1		1		2/3	2/3
TOTAL (n = 23)	8	2	4	1	15/23 (65%)	18/23 (78%)

stress.

In this study, we have shown that increased plasma catecholamines were present in 15 out of 23 patients with Friedreich's ataxia (65%); it was predominately due to norepinephrine elevation in 52% of patients. The increase in plasma catecholamines was more marked in patients with severe neurological impairment. Among the patients with increased wall thickness, 7 had no demonstrable adrenergic hyperfunction.

Significance of increased plasma catecholamines in Friedreich's ataxia

Plasma catecholamine levels reflect sympathetic and adrenal medullary activity. Epinephrine is formed endogenously from norepinephrine in the adrenal medulla and in chromaffin tissues in other areas of the body. This catecholamine is also present in the brain although in small quantities. After removal of the adrenal glands, almost all epinephrine disappears from urine and plasma, indicating that plasma epinephrine is derived almost exclusively from the adrenal medulla (Micalizzi and Pals, 1979). Norepinephrine is the neurotransmitter released from sympathetic nerve endings, but is also present in the adrenal medulla from which it is secreted along with epinephrine. Since adrenalectomy does not result in a significant decrease in urinary excretion of norepinephrine, the adrenal medulla is not usually considered an important source of norepinephrine

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(Micalizzi and Pals, 1979).

Our observations of increased plasma catecholamines in our series of young and adult patients indicate an increase in sympathetic activity but could also suggest some increase in secretion from the adrenals. Resting values were significantly elevated and standing was accompanied by a 50% increase in plasma levels of norepinephrine and an almost twofold increase of epinephrine over those in the basal reclining state. Thus, the elevated levels observed in the upright posture reflected essentially the increased basal levels.

In the human data of Silverberg et al (1978), norepinephrine levels in excess of 1,800 pg/ml were required to produce hemodynamic and/or metabolic effects. It is therefore unlikely that increased levels of plasma norepinephrine of such small magnitude as those reported in our study could be responsible for any hemodynamic change. Rather, the biologic actions of norepinephrine are to be attributed to its sympathetic neurotransmitter function; thus, in this setting, the increased plasma norepinephrine levels would essentially be a reflection of increased norepinephrine release from sympathetic nerves and of increased concentrations of norepinephrine within the symaptic clefts (Goldstein, 1981). However, the possibility must be raised that abnormalities in plasma norepinephrine and epinephrine could be secondary to the patient's neurological condition which may constitute a permanent stress. This is consistent with the observation that catecholamine levels tended to reflect the severity of the neurological dysfunction. Finally the possibility exists that the abnormalities of wall motion observed in hypertrophic cardiomyopathies may stimulate mechanosensitive afferent sympathetic fibers and activate a cardiocardiac sympathetic reflex responsible for increased sympathetic traffic (Malliani et al, 1973).

In addition, although examination of plasma levels of catecholamines provides a valid index of sympathoadrenal medullary discharge, various factors tend to limit the appreciation of the overall function of the sympathetic system, such as emotional or physiological stimuli which may evoke discharge of catecholamines from the adrenal medulla (Micalizzi and Pals, 1979; Kopin et al, 1980). These factors were carefully controlled in our study. In addition, sampling was obtained at a fixed time in both patients and controls to avoid the influence of diurnal variations (Sauebier and Von Mayers Bach, 1977).

The measurement of conjugated catecholamines (Kuchel et al, 1978) did not help uncover a stage of adrenergic hyperfunction in this study. Finally a complete estimation of adrenergic function should also take into account the status of the α- (Kafka et al, 1977) and β-adrenergic receptors (Williams et al, 1976) which may reflect various hormonal or metabolic influences (Davies et al, 1981). The permanent elevation of circulating catecholamines could also alter receptor numbers through the desensitization phenomenon.

Further studies analyzing the effects of various agonists (Kopin et al, 1980; Lake et al, 1980) or antagonists on adrenergic receptors may help define more clearly the abnormalities of sympathetic control suggested by our study in patients with Friedreich's ataxia.

Relationship between increased plasma catecholamines and left ventricular hypertrophy in patients with Friedreich's ataxia

There is some circumstantial evidence in support of the hypothesis that cardiac sympathetic nerves are the final common pathway in the induction of cardiac hypertrophy (Östman-Smith, 1981), and many observations point to norepinephrine as the essential trigger factor for ventricular hypertrophy.

First, Laks et al (1973) have observed isolated left ventricular hypertrophy following chronic infusions of "subhypertensive" doses of norepinephrine and have postulated that norepinephrine is the "myocardial hypertrophy hormone". Likewise, the regular administration of low-doses of the β-adrenoceptor agonist isoprenaline causes a generalized cardiac hypertrophy (Cohen, 1974; Stanton et al, 1969). Secondly, long-term treatment of rabbits with β-adrenoceptor antagonists reduces the growth of the heart (Vaughan Williams et al, 1975). Lastly, it has been shown that isoprenaline treatment can still induce cardiac hypertrophy in chemically sympathectomized rats, which shows that the sympathetic nerves may not be required for cardiac hypertrophy to take place (Östman-Smith, 1979). The finding that a moderate elevation of the circulating levels of catecholamines is not sufficient to induce cardiac hypertrophy (Östman-Smith, 1976) suggests that high local concentrations of norepinephrine, such as occur at the site of release from sympathetic nerve terminals, are required for the triggering of the hypertrophic response in the myocardial cell.

Previous studies have pointed out the validity of the Syrian hamster cardiomyopathy as a model for the cardiomyopathy observed in Friedreich's ataxia (Azari et al, 1979). If this is indeed true, the recent study of Karliner et al (1981) may be very relevant since these authors have shown that the sensitivity to norepinephrine is apparently increased in tissues derived from cardiomyopathic hamsters. Possible explanations for the raised response to norepinephrine in cardiomyopathic hamsters include an increased concentration of norepinephrine in the synaptic cleft due to defective neuronal uptake and/or stimulation of an augmented population of α_1- (postsynaptic) receptors (Karliner et al, 1981).

In fact, Bajusz et al (1966) had showed that B10 14.6 hamsters were very sensitive to epinephrine during the myolytic stage such that administration of this amine produced rapidly fulminating cardiac necrosis and congestive heart failure.

Available evidence suggests in addition that the cardiomyopathic hamster heart is subjected to increased sympathetic activity since norepinephrine synthesis and turnover is increased during the myolytic and hypertrophic stages of the disease (Sole et al, 1977). Norepinephrine concentration also increases concomitantly with the development of necrosis (Angelakos et

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al, 1973; Angelakos et al, 1972). With the development of myocardial scarring and hypertrophy, however, norepinephrine concentration declines despite increased fluorescence intensity of nerve endings, possibly due to loss of innervation in necrotic tissue (Angelakos et al, 1972; Alousi and Beards, 1972). These results led to the conclusion that the Syrian hamster cardiomyopathy was adrenergic in origin (Angelakos et al, 1973). This speculation has been reinforced by the observation of enhanced activity of norepinephrine by Karliner et al (1981).

New avenues of therapy may therefore become available that might prevent the development of left ventricular hypertrophy in Friedreich's ataxia which is largely responsible for the fatal outcome of this disorder. It is likely that subendocardial ischemia occurs in this setting, like in other cardiomyopathies (Pasternak et al, 1982), possibly contributing to the occurrence of ventricular fibrillation (Goodwin and Krikler, 1976). Adrenergic blockers must be considered first. However, before using them, one must specify the exact nature of the autonomic defect in an individual patient and assess whether the α-, β- or both adrenergic systems are hyperactive. For example, propranolol may cause increased α-adrenergic activity and depending on whether patients with Friedreich's ataxia have increased α or β activity, the drug may alleviate or worsen the symptoms. Although caution is to be exercised before extrapolating Karliner's results to the cardiomyopathy of Friedreich's ataxia, it is interesting to speculate that a similar situation may occur. Even before the development of overt congestive failure, Karliner et al (1981) observed an increase in both β- and α_1- adrenergic receptor density in the hearts of cardiomyopathic hamsters as compared with control values. However, only norepinephrine showed an enhanced response in the cardiomyopathic hamsters. This observation suggests the possibility that the enhanced response could have been due to stimulation of α_1 receptors since the response to the pure β-receptor agonist, isoprenaline, was unchanged between the groups of animals.

Thus, the suggestion by Karliner et al (1981) that norepinephrine largely mediates its effects by stimulation of α-adrenoceptors requires further investigation as it may well apply to the cardiomyopathy of Friedreich's ataxia and lead to useful trials by α-adrenoceptor blocking agents. Alternatively, a possible post-receptor mechanism might involve calcium metabolism. It has been shown that myocardial calcium uptake and content is increased in the myopathic hamster (Lossnitzer et al, 1975) and this might enable an increased response to receptor stimulation in view of the observations of Ledda et al (1975) that myocardial α stimulation is more calcium dependent than in β-receptor stimulation. Thus, slow channel calcium blockers may find here, like in other types of hypertrophic cardiomyopathies (Rosing et al, 1979; Lorell et al, 1982), a possible use in limiting the myopathic process or at least its clinical consequences.

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