Quebec Cooperative Study of
Friedreich's Ataxia

Hemodynamic Findings in Friedreich's Ataxia

M. COTE, A. DAVIGNON, G. ELIAS, A. SOLIGNAC,
G. GEOFFROY, B. LEMIEUX, AND A. BARBEAU

SUMMARY: *Thirteen patients with classical Friedreich's ataxia underwent cardiac catheterization with recordings of retrograde cardiac pressures, measurements of cardiac output and calculation of the left ventricular volumes and mass. The cardiomyopathy in Friedreich's ataxia falls into the hypertrophic group of cardiomyopathies with decreased compliance of ventricular myocardium, varying degrees of concentric and asymmetric hypertrophy and outflow tract obstruction. Although there is no clear parallel between the degree of abnormal hemodynamic findings and the degree of neurological impairment, severely handicapped patients may present a diffusely hypertrophied and hypokinetic left ventricular myocardium.*

RÉSUMÉ: *Une cathétérisation cardiaque fut faite chez 13 patients souffrant d'ataxie de Friedreich "typique". On mesura les pressions cardiaques rétrogrades ainsi que le débit cardiaque et on fit le calcul du volume ventriculaire et de la masse gauche. La cardiomyopathie de l'ataxie de Friedreich appartient au groupe des cardiomyopathies hypertrophiques avec diminution de l'accommodation du myocarde ventriculaire, avec divers degrés d'hypertrophie concentrique et asymétrique. Même s'il ne semble pas exister de parallélisme entre le degré d'anormalité des résultats hémodynamiques et le degré d'atteinte neurologique, il est certain que les patients fortement handicapés peuvent présenter un myocarde ventriculaire gauche hypertrophié de façon diffuse, et hypocinétique.*

From the Centre Hospitalier de l'Université de Sherbrooke; the Hôpital Ste-Justine, Montreal; the Hôpital Maisonneuve-Rosemont, the Hôpital Hôtel-Dieu de Montreal; and the Clinical Research Institute of Montreal.

Reprint requests for the complete supplement on Friedreich's ataxia to: Dr. André Barbeau, Clinical Research Institute of Montreal, 110 Pine Avenue West, Montreal, H2W 1R7 Quebec, Canada.

INTRODUCTION

In recent years, hemodynamic studies of the cardiomyopathy in Friedreich's ataxia have contributed important information as to the type, severity and variation of this heart disease. Right heart catheterization in one patient reported by Boyer et al. (1962) revealed normal findings. Thoren (1964), in the most exhaustive study of cardiopulmonary function in Friedreich's ataxia, reported the hemodynamic findings in seventeen cases with right heart catheterization. No systolic pressure gradient was demonstrated. The right ventricular end-diastolic pressures (RVEDP) were elevated (>9 mm. Hg) in 6 cases. The cardiac index was at the upper limit of normal or high in 4 cases but often low, with a definite small stroke volume in most cases. Angiography in 2 cases revealed a distinct right infundibular systolic contraction and left ventricular free wall hypertrophy and small end-diastolic volume. The elevated right and/or capillary wedge pressures in more than 15% of the cases with evidence of left ventricular hypertrophy and small end-diastolic volumes in the 2 cases studied, were compatible with an hypertrophic type of cardiomyopathy with decreased ventricular elasticity, explaining the frequently elevated ventricular filling pressures.

A study of 7 patients (Soulié et al., 1966) reported the findings of 7 right and 5 left heart catheterizations. All had elevated RVEDP and/or LVEDP in basal conditions with moderate right ventricular outflow tract obstruction in 2 and a left systolic gradient was present, at rest, in 1 (40 mm. Hg), appearing in an additional 3 cases during post ectopic beats or isoproterenol infusion. These were the first documented cases of Friedreich's ataxia associated with an idiopathic hypertrophic subaortic stenosis (IHSS) type of cardiomyopathy.

Ruschhaupt et al. (1972) described the hemodynamic findings in 6 patients. No significant right or left ventricular systolic gradients were present at rest. During isoproterenol infusion, an important left gradient was present in 1, a moderate one in another case and a discrete right gradient in another. The RVEDP was slightly elevated in 3 cases and the LVEDP in 1. The angiograms demonstrated increased left ventricular wall thickness in each patient.

Four additional reports of IHSS associated with Friedreich's ataxia are reported. Two cases had a significant left peak systolic left intraventricular pressure gradient at rest (Moore and Lambert, 1968; Boehm et al., 1970), another a 160 mm. Hg left gradient only during isoproterenol infusion (Gach et al., 1971) and finally a case of typical IHSS left ventricular angiogram, but no gradient (Gabriel, 1974). The case reported by Coté and Elias (1972) is included in our study group.

CASE MATERIAL AND METHODS

Thirteen patients with classical Friedreich's ataxia were studied. Twelve underwent both right and left cardiac catheterization and 1, only right-heart catheterization. Eight were males and 5, females. Their age ranged from 11 to 27. Nine were neurologically moderately handicapped, 4 severely. Eight had no cardiac symptoms and in the remainder, the chief complaint was dyspnea. Seven presented systolic

https://doi.org/10.1017/S0317167100025555 Published online by Cambridge University Press

TABLE 1

Hemodynamic Data

No.	PATIENT	HEART RATE (Beats/Min)	RIGHT ATRIUM (mm. Hg)	RIGHT VENTRICLE mm. Hg)	PULMONARY ARTERY (mm. Hg)	LEFT VENTRICLE (mm. Hg)	AORTA (mm Hg)	CARDIAC INDEX (L/min./M²)
1- MAB 4	C.S.	92	8	26/8	24/6	108/14	108/72	3.11
4- MGG 6	S.S.	80	8	35/12 28/12	28/15	190/25 112/25	112/80	—
7- MAB 9	P.R.	110	7	36/14 30/12	32/12	96/14	100/74	3.40
13- MAB 23	R.B.	140	6	26/4	26/10	107/12	108/92	1.35
19- MGG 1	S.T.	100	5	30/2	30/12	112/10	125/85	3.93
20- MGG 2	C.D.	80	5	20/6	20/9	100/15	90/56	4.81
21- MGG 3	D.D.	70	3	20/5	20/9	130/16	120/90	5.06
22- MGG 4	A.B.	100	2	21/2	21/6	106/5	115/80	6.60
23- MGG 5	G.L.	115	4	19/3	21/8	100/8	110/78	5.23
25- SBL 6	G.H.	130	13	40/11 27/16	30/23	-/18	—	—
27- SBL 3	L.F.	80	12	38/16	38/22	76/20	74/43	3.50
28- SBL 4	D.F.	90	10	20/11	29/14	86/22	79/49	—
35- SBL 15	G.M.	80	9	25/5	22/9	160/20 100/15	100/65	3.00

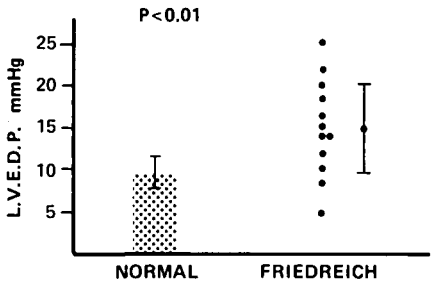

Figure 1 — Left ventricular end-diastolic pressures (mm. Hg).

murmurs on auscultation and 8 either a third or fourth heart sound.

Retrograde cardiac pressures were recorded with fluid filled catheters, the cardiac output was measured by the dye dilution technique and left ventricular volumes and mass were calculated from the right anterior oblique or antero-posterior single plane left ventricular angiograms by the method of Kennedy et al. (1970).

RESULTS

Mean right atrial pressures were elevated (>9 mm. Hg) in 3 patients with elevated right ventricular end-diastolic filling pressures in 5 (Table 1). Mean wedge pressure or left ventricular end-diastolic pressures were increased (>12 mm. Hg) in 10 of 13 cases (mean of 14 mm. Hg) significantly different from a group of normal controls (Table 1 and Figure 1).

A left ventricular peak systolic pressure gradient was documented in 2 cases (78 and 60 mm. Hg) under basal conditions and in 5 of 8 cases during isoproterenol infusion. No significant right outflow tract obstruction was evident at rest although 1 of 4 patients did develop a 22 mm. Hg gradient with isoproterenol (Table 2). Seven of twelve patients therefore had evidence of spontaneous or inducable obstructive cardiomyopathy. All but one suffered a moderate neurological handicap. A systolic murmur was audible in 6, but in only 1 of 3 patients with no obstruction at rest or with isoproterenol. The pulmonary artery pressure was slightly elevated in 2 patients.

TABLE 2

Intraventricular Systolic Pressure Gradients (mm. Hg) at Rest and During Isoproterenol Infusion

No.	RIGHT		LEFT	
	Rest	Isoproterenol	Rest	Isoproterenol
1	0	22	0	22
4	0	—	78	—
7	0	12	0	0
13	0	—	0	0
19	0	—	0	0
20	0	0	0	38
21	0	0	0	24
22	0	—	0	33
23	0	—	0	68
25	13	—	—	—
27	0	—	—	—
28	0	—	—	—
35	0	—	60	—

The cardiac index was normal in the majority of cases, but was clearly low in 1 patient with atrial flutter, a markedly hypertrophied and hypokinetic left ventricle associated with severe neurological impairment. He died of renal failure 18 months after this study. In 3 cases, the cardiac output was above 5.0 l./min./m². All 3 were in their late teens. Thoren (1964) also found evidence of a hyperkinetic circulation in 5 of his 17 cases.

The ejection fraction derived from the left ventricular cineangiogram (Figure 2) was normal in 10 of 12 patients (range 55 to 83%) and depressed in 2 (39 and 44%) (Figure 3). End-diastolic volumes were normal or even small (range 24 - 120 ml./m²) in most patients (Figure 4). The left ventricular mass index, derived from the left ventricular free wall thickness, showed a wide range (64 - 240 gm/m²) of values, half the cases compatible with moderate to severe hypertrophy (Figure 5). The majority of patients, although statistically not significantly different when compared to normals, had an elevated mass-volume ratio (range 1.2 - 3.6) reflecting the frequent finding of a normal or moderately hypertrophied left ventricle associated with a normal or small end-diastolic volume (Figure 6).

The hemodynamic data coupled

https://doi.org/10.1017/S0317167100025555 Published online by Cambridge University Press

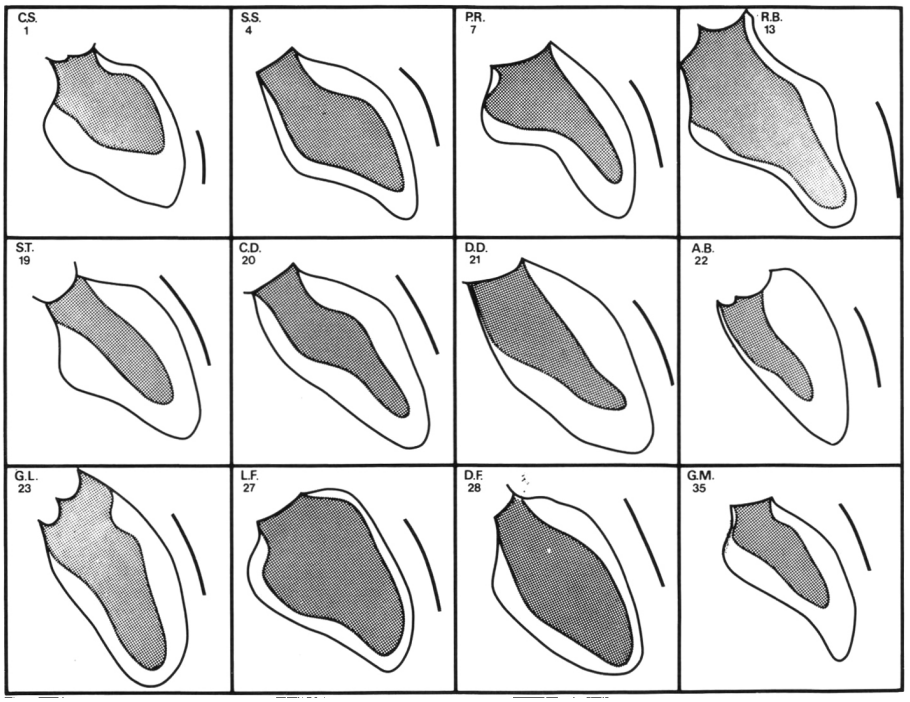

Figure 2 — Left ventricular end-systolic and end-diastolic outlines with left ventricular free wall thickness.

with the angiographic studies are compatible with a hypertrophic type of cardiomyopathy with varying degrees of dynamic ventricular outflow tract obstruction.

DISCUSSION

Previous reports (Boyer et al., 1962; Ivemark and Thoren, 1964) of necropsy studies have universally observed evidence of severe myocardial damage, with diffuse myocardial fibrosis and varying degrees of small and medium size coronary artery obstruction.

The pathophysiology of this cardiomyopathy remains unexplained. There is no evidence of increased mechanical pressure after load (hypertension, valvular stenosis) or other congenital heart defects (tetralogy of Fallot, abnormal papillary muscle attachment). Thoren (1964) suggested a poor utilization or transporting capacity of oxygen as a possible metabolic abnormality based on a high mixed-venous blood oxygen saturation in relation to heart rate even during work tests. In another group of patients with Friedreich's ataxia, we also observed evidence of high coronary sinus oxygen concentration suggesting, even though coronary flow was not measured, the same conclusion. Furthermore, evidence of myocardial anaerobic metabolism and increased hemoglobin affinity for oxygen was evident in some patients.

Although diabetes mellitus is not associated with IHSS, the frequent finding of overt diabetes mellitus or glucose intolerance in patients with Friedreich's ataxia might explain in part the varying degree of small vessel disease in this cardiomyopathy.

Recently, abnormalities in the main pathways of carbohydrate oxidation associated with slow pyruvate oxidation and low activities of pyruvate and oxoglutarate dehydrogenase complexes have been described (Blass et al., 1976). It is possible that such biochemical disorders may help elucidate the pathophysiology, not only of the cardiomyopathy associated with Friedreich's ataxia, but of other hypertrophic cardiomyopathies. These measurable metabolic abnormalities may also provide a useful test in identifying carrier states and help reduce the incidence of this fatal neurological disorder.

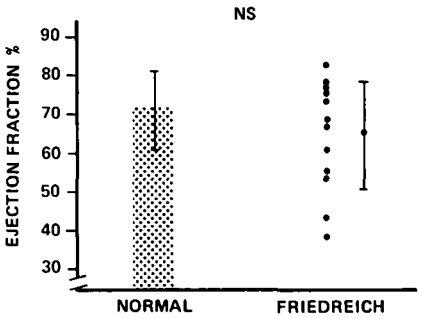

Figure 3 — Ejection fraction of normal and patients with Friedreich's ataxia. N. S.: no significant statistical difference.

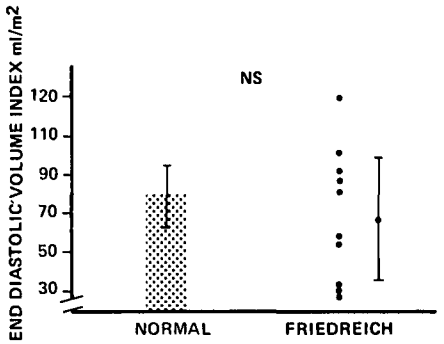

Figure 4 — End-diastolic volumes (ml./m²). N. S.: statistically not significant.

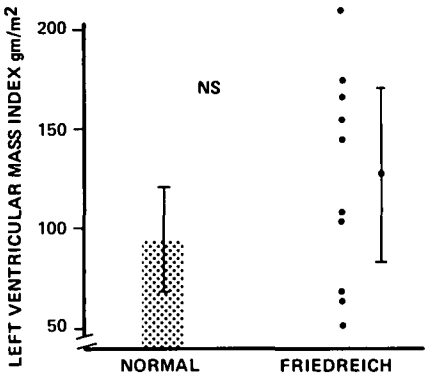

Figure 5 — Left ventricular mass index (gm./m²). N. S.: statistically not significant.

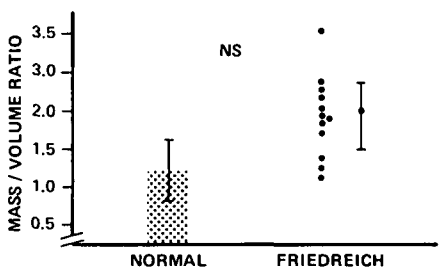

Figure 6 — Left ventricular mass-volume ratio. N. S.: Not statistically significant.

https://doi.org/10.1017/S0317167100025555 Published online by Cambridge University Press

ACKNOWLEDGMENTS

We express our gratitude to Dr. André David and Dr. Guy Dumont (Hôpital Notre-Dame, Montreal) and to Dr. A. G. Tsakiris (Centre Hospitalier de l'Université de Sherbrooke) for some of the hemodynamic data. These studies were supported by l'Association Canadienne de l'Ataxie de Friedreich and the Medical Research Council of Canada.

REFERENCES

BLASS, J. P., KARK, R. A. P., and MENON, N. K. (1976). Low activities of the pyruvate and oxoglutarate dehydrogenase complexes in five patients with Friedreich's ataxia. N.E.J.M., 295, 62-67.

BOEHM, T. M., DICKERSON, R. B., and GLASSER, S. P. (1970). Hypertrophic subaortic stenosis occurring in a patient with Friedreich's ataxia. Amer. J. Med. Sci., 260, 279-284.

BOYER, S. H., CHISHOLM, A. W., and McKUSICK, V. A. (1962). Cardiac aspects of Friedreich's ataxia. Circulation, 25, 493-505.

COTE, M., and ELIAS, G. (1972). Hemodynamic and myocardial metabolism abnormalities in Friedreich's ataxia. Amer. J. Cardiol., 33, 132 (Abstract).

GABRIEL, B., PINSARD, N., GERARD, R., and LOUCHET, E. (1974). Association d'une cardiomyopathie et d'une dégénérescence spino-cérébelleuse (maladie de Friedreich). A propos d'une observation. Pédiatrie, 29, 367-377.

GACH, J. V., ANDRIANGE, M., and FRANCK, G. (1971). Hypertrophic obstructive cardiomyopathy and Friedreich's ataxia. Report of a case and review of literature. Amer. J. Cardiol., 27, 436-441.

IVEMARK, B., and THOREN, C. (1964). The pathology of the heart in Friedreich's ataxia — Changes in coronary arteries and myocardium. Acta Med. Scand., 175, 227-237.

KENNEDY, J. W., TRENHOLME, S. E., and KASSER, I. S. (1970). Left ventricular volume and mass from single plane cineangiogram. A comparison of anteroposterior and right anterior oblique methods. Amer. Heart J., 80, 343-352.

MOORE, A. A. D. and LAMBERT, E. C. (1968). Cardiomyopathy associated with musuclar and neuromuscular disease. In: Paediatric Cardiology, The C. V. Mosby Co.

RUSCHHAUPT, D. G., THILENIUS, O. G., and CASSELS, D. E. (1972). Friedreich's ataxia with idiopathic hypertrophic subaortic stenosis. Amer. Heart J., 84, 95-102.

SOULIE, P., VERNANT, P., GAUDEAU, S., CALESTO, G., JOLY, F., BOUCHARD, F., and FORMAN, I. (1966). Le coeur dans la maladie de Friedreich. Etude hémodynamique droite et gauche. Malattie Cardiovascolari, 7, 369-386.

THOREN, C. (1964). Cardiomyopathy in Friedreich's ataxia with studies of cardiovascular and respiratory functions. Acta Paediat. (Stockholm), 53 (Suppl.), 153.