Cardiac and Skeletal Myopathy Associated with Cardiac Dysrhythmias

ANN DUNNIGAN, MD, MARY ELLA PIERPONT, MD, PhD, STEPHEN A. SMITH, MD, GALEN BRENINGSTALL, MD, DAVID G. BENDITT, MD, and D. WOODROW BENSON, Jr., MD, PhD

Electrophysiologic studies, echocardiograms, cardiac catheterizations and histologic and biochemical analyses of skeletal muscle biopsies were performed in 10 patients (aged 10 to 37 years, mean 21) who had dysrhythmias as the initial manifestation of cardiomyopathy. Presenting symptoms and signs attributable to dysrhythmias included sudden cardiac arrest in 2 patients, syncope in 3, presyncope in 3 and palpitations in 2. There was no clinical evidence of skeletal muscle weakness in any patient. Multicatheter electrophysiologic evaluation established diagnoses of ventricular tachycardia in 6 patients, primary atrial tachycardia in 2 and third degree infra-Hisian heart block in 1 patient. One patient presenting with palpitations had no inducible arrhythmia or conduction disturbance. Echocardiographic, angiographic and hemodynamic studies demonstrated previously unsuspected dilated cardiomyopathy in 7 patients and restrictive cardiomyopathy in 3. Skeletal muscle histologic characteristics were abnormal in all 10 patients; increases in lipid droplets and endomysial fibrosis were the characterstic findings. Serum free carnitine and short- and long-chain acylcarnitine were normal in 9 patients. However, skeletal muscle long-chain acylcarnitine was reduced in 9 patients. These findings support the concept that in certain patients presenting with dysrhythmias, the dysrhythmia may be a manifestation of cardiac and skeletal (that is, generalized) myopathy.

(Am J Cardiol 1984;53:731-737)

The spectrum of initial clinical manifestations of cardiomyopathy is not limited to symptoms of heart failure, but includes dysrhythmias that may result in symptoms of palpitations, syncope or sudden cardiac arrest.[1-3] In patients with cardiomyopathy and dysrhythmias, functional limitation or symptoms of congestive heart failure are often absent.[1-3] The precise cause of cardiomyopathy is unknown in most cases.[4] However, more than 10 years ago, Meerschwam and Hootsman[5] speculated, on the basis of abnormal electromyography, that hypertrophic cardiomyopathy could be viewed as "a generalized myopathy with early and serious cardiac manifestations." Subsequent studies have demonstrated functional and microscopic abnormalities of skeletal muscle in patients with cardiomyopathy,[6-8] supporting the idea that a disorder of both cardiac and skeletal muscle, that is, a generalized myopathy, is present in these patients. Better understanding of the pathophysiology of cardiomyopathy is important, because this may permit definitive treatment in some patients, as has been possible, for example, in patients with systemic carnitine deficiency.[9]

This study presents results of noninvasive and invasive cardiac hemodynamic and electrophysiologic evaluation and histologic and biochemical skeletal muscle evaluation in 10 patients with symptomatic dysrhythmias.

Methods

Four males and 6 females, aged 10 to 37 years (mean 21), form the basis of this report. All patients came to medical attention because of a symptomatic dysrhythmia.

Clinical and hemodynamic evaluation: A complete history was obtained, with attention also to the family history,

From the Departments of Pediatrics and Medicine, University of Minnesota Hospital, and the Department of Pediatric Neurology, Hennepin County Medical Center, Minneapolis, Minnesota. Manuscript received August 29, 1983; revised manuscript received November 3, 1983, accepted November 11, 1983.

Address for reprints: Ann Dunnigan, MD, Pediatric Cardiology, Box 34, Mayo Building, University of Minnesota, Minneapolis, Minnesota 55455.

and a physical examination was performed. The cardiac evaluation included a standard 12-lead ECG, chest roentgenogram, at least 48 hours of ambulatory or bedside electrocardiographic monitoring, and M-mode and 2-dimensional echocardiography. Additionally, all patients underwent hemodynamic cardiac catheterization. The results of these studies were used to characterize the type of cardiomyopathy using criteria modified from Goodwin.[10] *Dilated cardiomyopathy* was defined as the presence of decreased left ventricular ejection fraction or shortening fraction, with ventricular dilation. *Restrictive cardiomyopathy* was defined as the presence of normal ventricular size and normal ejection fraction, but elevated ventricular end-diastolic pressures.

Electrophysiologic evaluation: In addition to ambulatory or bedside monitoring, all patients underwent 1 or more multicatheter electrophysiologic studies. Cardioactive medications were withheld for 48 hours before electrophysiologic studies, which were performed in the fasting state. Using the percutaneous technique, 3 quadripolar electrode catheters were inserted through the femoral vein and positioned in the high right atrium, the His bundle region and the right ventricular apex under fluoroscopic guidance. Stimulation was performed from either the high right atrium or right ventricular apex using square-wave stimuli of 2 ms duration at twice diastolic current threshold from a custom-made programmable stimulator. All patients were evaluated with standard methods for assessing atrioventricular and ventriculoatrial conduction.[11]

In 7 patients with previously documented ventricular tachycardia or in whom ventricular tachycardia was suspected from the presenting symptoms, the following programmed ventricular stimulation protocol was performed[12]: the introduction of 1 to 4 premature ventricular stimuli after an 8-beat ventricular paced train at cycle lengths of 600, 500, and 400 ms, and ventricular burst pacing from cycle lengths 400 to 250 ms.

Laboratory evaluation: As part of routine hematologic testing, complete blood counts and serum electrolyte levels were determined in all patients. Additionally, tests for hepatic function (alkaline phosphatase, serum aspartate aminotransferase and lactate dehydrogenase), renal function (urea nitrogen and creatinine) and thyroid function (T_3 and T_4) were performed. Serum aldolase was determined in 8 of 10 and CK in 9 of 10 patients.

Fasting serum free carnitine and acylcarnitine (short-chain and long-chain) were measured by modification of the radioisotopic methods of Pearson et al[13] and McGarry and Foster.[14] In these methods, long-chain acylcarnitine is separated from free- and short-chain acylcarnitine by acid precipitation followed by alkaline extraction. Free- and short-chain acylcarnitine are acid soluble; alkaline hydrolysis liberates the short-chain fatty acids to free carnitine. Aliquots of each fraction are added to a reaction mixture containing 50 m*M* HEPES-KOH buffer pH 7.6, 0.25 m*M* N-ethylmaleimide, 0.01 μCi (1-^{14}C) acetyl coenzyme A and 0.5U carnitine acetyl transferase. After incubation at 25°C, the reaction is terminated by addition of charcoal in acidified alcohol. An aliquot of centrifuged reaction mixture is added to scintillation fluid and radioactivity determined. Results are compard with L-carnitine standard solutions.

Skeletal muscle evaluation: After electrophysiologic study, a skeletal muscle biopsy was obtained in all 10 patients. Chronic pharmacologic therapy had been initiated in 3 patients before the skeletal muscle biopsy: Patient 1 was treated with prednisone and theophylline for asthma; Patient 4 received digoxin and furosemide for congestive heart failure; and Patient 7 received procainamide for ventricular tachycardia treatment.

TABLE I Clinical Characteristics

Case	Age (yr) & Sex	Past Illness	Initial Cardiac Sign/Symptom
1	37F	Asthma	Palpitations
2	10F	ASD repair (8 mo)	Bradycardia, syncope
3	15F	0	Palpitations, syncope
4	27F	Recent pregnancy	Palpitations, dyspnea
5	21M	0	Cardiac arrest
6	10F	0	Syncope
7	28M	0	Tachycardia, presyncope
8	24M	0	Tachycardia, presyncope
9	24F	AVC repair (8 yr)	Presyncope
10	11M	0	Cardiac arrest

ASD = atrial septal defect; AVC = complete atrioventricular canal.

Before biopsy, 5 patients underwent electromyography. All patients had open skeletal muscle biopsies performed from the biceps or deltoid muscle. The biopsy tissue was divided for the following studies: (1) light microscopy; (2) histochemical analysis; (3) electron microscopy; and (4) carnitine assay. The muscle samples for light microscopic and histochemical analysis were immediately frozen in liquid methylbutane. Subsequently, the biopsy samples were subjected to the following standard reactions[15]: hematoxylin-eosin, modified Gomori trichrome, phosphorylase A, adenosine triphosphatase at pH 9.4, and after preincubation at pH 4.55 and 4.75, α-glycerol phosphate dehydrogenase, reduced diphosphopyridine nucleotide dehydrogenase, succinic dehydrogenase, periodic acid Schiff, oil red 0 and Sudan black. The muscle samples for electron microscopy were placed immediately in 5% phosphate-buffered gluteraldehyde, and following standard preparation, the grids were stained with uranyl acetate and lead citrate.[15] All histologic and histochemical reactions were reviewed independently by 2 observers, who did not have knowledge of specific clinical data.

The muscle sample for carnitine and acylcarnitine determination was immediately frozen in liquid methylbutane. Homogenates were prepared using a Polytron PT-20® (Brinkman Instruments) to homogenize 20 mg of tissue in distilled water. Aliquots were removed for measurement of noncollagenous protein.[16] Other aliquots were treated with acid followed by alkali to separate free carnitine from the acylcarnitines. Extracts were then assayed for carnitine by the technique described for serum carnitine.

Results

Clinical and hemodynamic characteristics: The clinical features for all 10 patients are summarized in Table I. Patients 2 and 9 had histories of structural congenital cardiac abnormalities. Patient 2 had undergone surgical correction of a secundum atrial septal defect at age 8 months and Patient 9 had surgical correction of a complete atrioventricular canal defect at age 8 years. Both patients had undergone cardiac catheterization 2 or 3 years after surgery and were judged to have excellent operative results (normal intracardiac pressures and no residual shunts), and we believed that the dysrhythmias in these 2 patients were not late complications of surgery. Patient 4 had completed her second uncomplicated term pregnancy 4 months before palpitations and dyspnea developed. Patient 1 had chronic asthma, but no other patient had any recognized medical problems.

TABLE II Cardiac Evaluation

Case	CXR (CT Ratio)	LVEED* (mm)	SF (%)*	LV (mm Hg)	PA (mm Hg)	RA (mm Hg)	PAW (mm Hg)	CI (l/min/m²)	EF (%)
1	0.59	54	20	160/20	20/10	6	12	3.5	27†
2	0.58	45	26	95/6	18/9	4	9	2.7	. . .
3	0.47	44	23	110/16	22/12	2	16	3.2	. . .
4	0.58	86	13	95/30	50/25	11	28	1.3	28†
5	0.48	74	22	100/8	27/12	2	9	3.5	31†
6	0.48	43	47	130/16	30/20	7	14	3.1	81†
7	0.56	70	20	113/30	60/36	7	36	2.4	30†
8	0.39	67	18	116/8	21/9	4	8	4.4	40†
9	0.55	55	30	115/22	32/20	19	20	3.2	64‡
10	0.49	42	40	100/40	44/24	14	28	3.8	69‡

* Normal adult values: LVEDD ≤58 mm; normal SF = 28 to 41%.[17]
† By multigated blood pool scan.
‡ By cineangiography.
CI = cardiac index; CT = cardiothoracic ratio; CXR - chest roentgenogram; EF = ejection fraction; LV = left ventricular pressure; LVEDD = echocardiographic left ventricular end-diastolic dimension; PA = pulmonary artery pressure; PAW = mean pulmonary artery wedge pressure; RA = mean right atrial pressure; SF = echocardiographic shortening fraction.

Three patients had a family history suggestive of cardiomyopathy. The father of Patient 2 died suddenly at age 30 years; no autopsy was performed. Two relatives of Patient 5 died suddenly: his 51-year-old father, in whom an autopsy examination showed no evidence of coronary heart disease but mild cardiomegaly (heart weight, 565 g), and an ostensibly healthy 14-year-old male cousin in whom no autopsy was performed. Nine months after the onset of symptoms in Patient 4, her 22-year-old nulliparous sister developed heart failure, and a diagnosis of idiopathic dilated cardiomyopathy was made.

The initial cardiac signs or symptoms prompting evaluation in these 10 patients are listed in Table I. Two patients had a sudden cardiac arrest, 6 had syncope or presyncope, and 2 had palpitations. Only Patient 4 had signs or symptoms of congestive heart failure at the time of initial presentation. Detailed neurologic examinations, including tests of muscle strength, were normal in all patients.

TABLE III Electrophysiologic Evaluation

Case	ECG	Monitoring	Electrophysiologic Diagnosis
1	Normal	Normal	VT (Nonsustained)
2	1° HB	Intermittent 3° HB	3° HB, Infra-Hisian block
3	NSSTTWC	Ectopic atrial tachycardia	Ectopic atrial tachycardia
4	LVH with STTWC	PVC	Occasional PVCs
5	Normal	PVC	VT
6	Normal	Normal	VT
7	LBBB	Multimorphic PVC	VT
8	LBBB	Normal	VT
9	1° HB, RBBB, LAD	1° HB	Atrial flutter
10	RAE, NSSTTWC	Normal	VT

HB = heart block; LAD = left-axis deviation; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; NSSTTWC = nonspecific ST-T-wave changes; PVC = ventricular extrasystoles; RAE = right atrial enlargement; RBBB = right bundle branch block; STTWC = ST-T wave changes; VT = ventricular tachycardia.

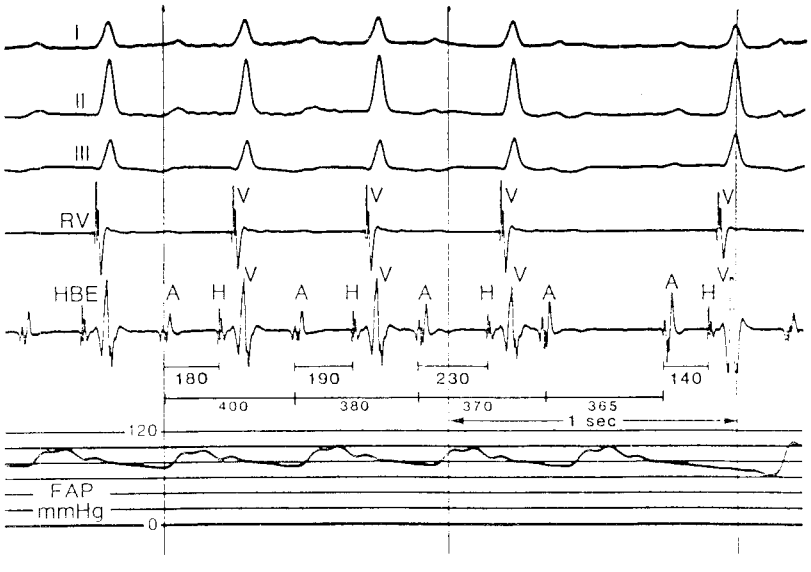

FIGURE 1. Ectopic, automatic atrial tachycardia in Patient 3. This sequence demonstrates atrioventricular nodal second-degree heart block (Wenckebach) associated with shortening of the tachycardia cycle length. The absence of atrioventricular conduction does not affect the atrial tachycardia; thus, it represents a primary atrial tachycardia. During electrophysiologic study, the tachycardia could not be initiated or terminated with programmed stimulation, therefore defining an ectopic, automatic atrial tachycardia.[18] A = low septal atrial electrogram; FAP = femoral artery pressure; H = His bundle potential; HBE = His bundle electrogram; RV = right ventricular electrogram; V = ventricular electrogram.

TABLE IV Carnitine

Case	Serum Carnitine (nmol/ml)			Muscle Carnitine (nmol/mg NCP)		
	FC	SCAC	LCAC	FC	SCAC	LCAC
1	31.5	7.1	1.47	17.58	2.73	0.04
2	25.7	11.9	1.57	13.64	4.96	0.05
3	35.0	4.6	0.70	12.74	6.96	0.10
4	68.9	19.7	3.63	21.74	4.28	0.11
5	44.4	4.2	1.27	23.26	3.19	0.03
6	43.9	4.0	1.27	21.39	2.76	0.16
7	43.3	7.2	1.06	22.66	1.16	0.11
8	38.7	5.2	1.17	17.98	3.51	0.12
9	44.7	5.5	1.57	19.47	3.05	0.07
10	28.5	7.1	1.80	28.33	2.74	0.26
Controls*	38.5	5.1	0.93	15.85	2.77	0.73
	±12.1	±2.0	±0.31	±5.03	±1.01	±0.37

* n = 20 for serum controls, n = 7 for muscle controls; values are mean ± standard deviation.
FC = free carnitine; LCAC = long-chain acylcarnitine; NCP = noncollagenous protein; SCAC = short-chain acylcarnitine.

The results of the invasive and noninvasive cardiac functional evaluation are summarized in Table II. All patients had evidence of abnormal cardiac mechanics. Using the previously defined criteria, 7 patients had dilated cardiomyopathy (Patients 1 to 5, 7 and 8), and 3 had restrictive cardiomyopathy (Patients 6, 9 and 10). No patient had evidence of ischemic or valvular heart disease, hypertension, or concentric or asymmetric left ventricular hypertrophy.

Electrophysiologic evaluation: The results of the noninvasive electrophysiologic evaluation are summarized in Table III. Electrocardiographic documentation of dysrhythmia was obtained in 8 of 10 patients before electrophysiologic study; in Patients 5 and 10, this consisted of ventricular fibrillation documented at the time of sudden cardiac arrest. Patients 4 and 6 did not have electrocardiographic documentation during palpitations or syncope, respectively.

The results of invasive electrophysiologic testing are also presented in Table III. In Patient 2, who had heart block, the site of atrioventricular block was localized below the His bundle recording site, suggesting distal His-Purkinje block. Patient 3 had automatic, ectopic atrial tachycardia[18] (Fig. 1). Patient 9 had atrial flutter. Five patients had inducible sustained ventricular tachycardia that resulted in marked hemodynamic impairment (Fig. 2) and Patient 1 had nonsustained ventricular tachycardia. Patient 4 had no inducible tachycardia or conduction disturbance.

Laboratory evaluation: The hematologic assessment of hepatic, renal and thyroid function was normal in all 10 patients, as were the complete blood counts and electrolytes. The serum CK level was normal in the 9 patients in whom it was measured; serum aldolase was normal in 8 of 8 patients. Fasting serum carnitine and short- and long-chain acylcarnitine concentrations were determined in all 10 patients and were normal in 9 (Table IV). Elevated concentrations of long- and short-chain acylcarnitine were present in the serum of Patient 4. No patient had serum-free carnitine deficiency.

Skeletal muscle evaluation: Electromyograms were abnormal in 2 of the 5 patients examined (Patients 6 and 8). The abnormal electromyograms, most promi-

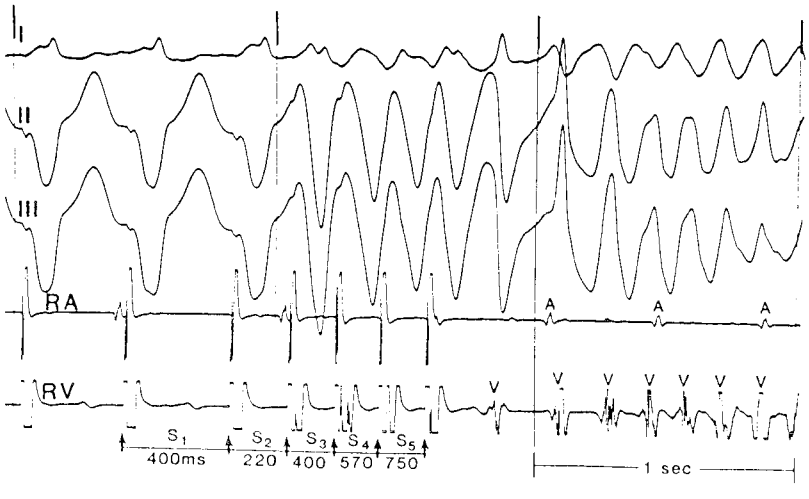

FIGURE 2. Ventricular tachycardia initiation with 4 premature extrastimuli in Patient 6. The 8-beat ventricular-paced train is at 400 ms (150 beats/min). A = atrial electrogram; RA = high right atrial electrogram; RV = right ventricular electrogram; V = ventricular electrogram.

sent in proximal muscles, showed motor units of low amplitude and short duration. These findings suggested a diffuse myopathic process, although these patients had no clinical evidence of muscle weakness.

All patients had histologic or histochemical abnormalities of their skeletal muscle (Table V), although all biopsy specimens appeared normal with routine hematoxylin-eosin staining. Except for Patient 4, who demonstrated mild fiber type IIb atrophy by histochemical analysis, no patient had histologic findings suggestive of disuse. In the other 9 patients, histochemical evaluation of the skeletal muscle was normal. However, in 5 patients increased lipid was present in type I fibers, as detected by the oil red 0 or Sudan black stains (Fig. 3). In these 5 patients and in the other 5 patients, increased lipid droplets were present by electron microscopic examination in type I fibers (Fig. 4). Additionally, at the ultrastructural level, an increased amount of endomysial fibrosis was present in 9 patients (Fig. 5). Patient 1 did not have endomysial fibrosis. Three patients had abnormalities of mitochondrial morphology. Patients 4 and 6 had subsarcolemmal mitochondrial aggregates. Patient 3 had normal numbers and distributions of mitochondria, but their shapes were widely varied and unusual. All electron microscopic specimens had normal myofibrillar structure and normal glycogen content.

The determination of an increase in lipid droplets on electron microscopy was made by visual inspection of the photomicrographs. In previous reports[15,19] and in our experience, lipid droplets are uncommon in normal skeletal muscle. In the biopsy specimens obtained from our patients with dysrhythmias, the presence of an increased number of lipid droplets was obvious but more subtle than previously described in lipid myopathies.[20,21]

All patients had biochemical analysis of their skeletal muscle that demonstrated normal concentrations of free carnitine and short-chain acylcarnitine. Long-chain acylcarnitine was decreased compared with control values from our laboratory in 9 of 10 patients (Table IV).

TABLE V Skeletal Muscle Analysis

Case	Light Microscopy	Histochemistry	Electron Microscopy
1	Normal	Normal	↑ Lipid
2	↑ Lipid (type I)	Normal	↑ Lipid
3	Normal	Normal	↑ EF ↑ Lipid
4	↑ Lipid (type I)	Mild atrophy (type IIb)	↑ EF ↑ Lipid
5	↑ Lipid (type I)	Normal	↑ EF ↑ Lipid
6	↑ Lipid (type I)	Normal	↑ EF ↑ Lipid
7	Normal	Normal	↑ EF ↑ Lipid
8	Normal	Normal	↑ EF ↑ Lipid
9	↑ Lipid (type I)	Normal	↑ EF ↑ Lipid
10	↑ Lipid (type I)	Normal	↑ EF ↑ Lipid ↑ EF

EF = endomysial fibrosis.

Discussion

The initial manifestations of cardiomyopathy in the young patients we studied were due to uncommon dysrhythmias. In our experience, the occurrence of ventricular tachycardia, primary atrial tachycardia, or infra-Hisian heart block in young patients suggests the presence of cardiomyopathy. The principal observation in these patients is the association of previously unrecognized dilated or restrictive cardiomyopathy with laboratory evidence (histologic and biochemical) of skeletal myopathy without clinically apparent muscle

FIGURE 3. Skeletal muscle from Patient 5 stained for fat droplets (**arrow**) showing the increased lipid staining present by light microscopy in 5 patients. Oil red 0 stain; magnification × 875, reduced by 33%.

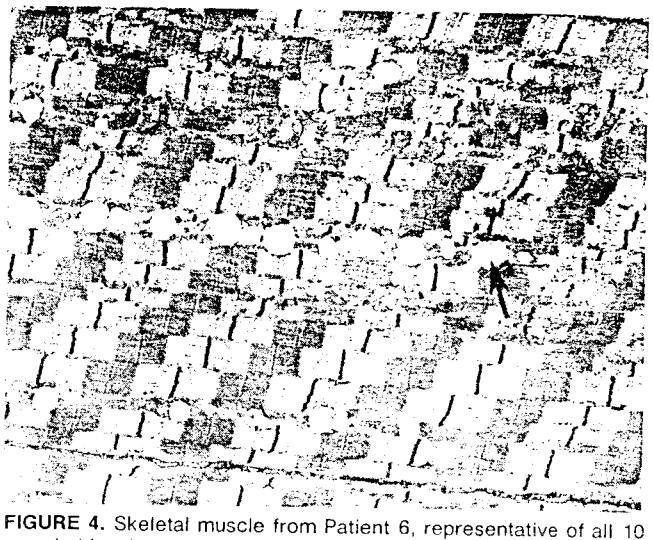

FIGURE 4. Skeletal muscle from Patient 6, representative of all 10 muscle biopsies showing increased number of lipid droplets (**arrow**) in type I muscle fibers by electron microscopy. Magnification × 24,000, reduced by 33%.

weakness. Although these findings do not permit an explanation of the relation between cardiac and skeletal myopathy, they support the concept that in these patients, cardiomyopathy is not an isolated problem, but rather one manifestation of a generalized myopathy.

Previous reports have noted concomitant cardiomyopathy and clinical manifestations of skeletal myopathy. Norris et al[22] first reported 4 patients with cardiomyopathy in whom clinically apparent skeletal muscle weakness later developed. Histologic examination of the skeletal muscle in their patients demonstrated a dystrophic process, with an increase in endomysial fibrosis and a fatty infiltration and replacement in muscle examined. Not all areas of the muscle were uniformly affected. Isaacs and Muncke[23] evaluated 3 patients who presented with clinical evidence of both cardiomyopathy and skeletal muscle weakness. Electromyography was abnormal in all 3 patients, and histologic examination of the skeletal muscle showed ultrastructural abnormalities of mitochondria, myofibrillar loss and vacuolization. Kearns-Sayre syndrome (a constellation of abnormalities including progressive external ophthalmoplegia, facial and peripheral muscle weakness, and retinal pigmentation) is another example of clinically apparent skeletal muscle weakness with later appearance of clinical manifestations of cardiomyopathy. In this syndrome, the cardiomyopathy is manifest as an abnormality of atrioventricular conduction progressing to third-degree (infra-Hisian) heart block. Ultrastructural examination of the skeletal muscle[24] and cardiac muscle[25] in patients with Kearns-Sayre syndrome has demonstrated an increased number of structurally abnormal mitochondria. Other well-recognized disorders in which skeletal muscle weakness is associated with the subsequent appearance of cardiomyopathy include myotonic dystrophy,[26] limb girdle dystrophy[27] and Duchenne's muscular dystrophy.[27] Thus, from these reports the association between clinically apparent cardiac and skeletal myopathy a pears not to be uncommon.

FIGURE 5. Skeletal muscle by electron microscopy from Patient 4, showing increased number of lipid droplets (arrow) surrounded by excessive and variably shaped mitochondria (M) with increased endomysial connective tissue (C). Magnification × 9,000, reduced 33%.

Shafiq et al[6] and Smith et al[8] studied skeletal musc in patients with cardiomyopathy, but no clinical ev dence of skeletal myopathy. In 6 patients with cardi myopathy, Shafiq et al[6] found that skeletal musc histologic characteristics appeared normal by routir light microscopy, but histochemical and electron m croscopic abnormalities were present in all (includir lipid infiltration and increased interstitial connectiv tissue in 1 patient). Smith et al[8] studied 11 patients wit hypertrophic cardiomyopathy. Eight of 11 patients ha abnormalities of their skeletal muscle by histochemic or electron microscopic evaluation. These abnormalitie included core or target fibers and abnormalities i number, localization and structure of the mitochondri A spectrum of mitochondrial abnormalities was presen ranging from minor ultrastructural changes to signif cant mitochondrial proliferation and structural alter ations. There were also increased numbers of lipi droplets in the muscle fibers with mitochondrial ab normalities. Although no patient had clinical evidenc of skeletal muscle weakness, electromyograms wer abnormal in 10 patients.

These reports relating cardiac to skeletal myopathy detected by clinical or laboratory means, confirm tha a broad spectrum of abnormalities exists. The patient we studied, presenting with cardiomyopathy manifes as dysrhythmias and with laboratory evidence of skel etal myopathy, fit into such a spectrum. It is not clear however, to what extent the spectrum of clinical mani festations of cardiac and skeletal myopathy is in fluenced by differences in cause or time of observatior in the disease course. Many previously described pa tients had severe congestive heart failure at the time o their skeletal muscle evaluation, thus raising the issue of whether the observed skeletal muscle abnormalities were secondary to heart failure or to a poor nutritiona status. None of our patients were cachectic, and only 1 had moderate congestive heart failure; no patient ap peared chronically ill. Therefore, it appears unlikely that the skeletal myopathy in our patients was sec ondary to cardiac disease, but rather occurred con currently as another manifestation of a generalized myopathy.

Whitaker et al[28] described a patient with skeletal muscle weakness and abnormal skeletal muscle electron microscopy (increased lipid and abnormal mitochondria), who was found to have a deficiency of free carnitine in muscle but normal serum carnitine concentrations. Their patient also had a diminished rate of utilization of palmitate. Both of these findings suggest that fatty acid metabolism was abnormal in this patient's skeletal muscle. Tripp et al[9] described a fulminant form of cardiomyopathy due to carnitine deficiency; results of skeletal muscle histologic and biochemical examination of patients with carnitine deficiency revealed massive lipid accumulation. Similar skeletal muscle histologic abnormalities (i.e., lipid myopathy) have been demonstrated in patients with normal and mildly decreased skeletal muscle carnitine concentrations,[29] and in patients with normal skeletal

muscle carnitine but with carnitine-palmityl-transferase deficiency.[30] Thus, similar histologic findings may arise from different defects in lipid metabolism. In our patients, none of whom had total serum or skeletal muscle carnitine deficiency, 9 of 10 had decreased skeletal muscle long-chain acylcarnitine and the skeletal muscle histology suggested a lipid myopathy distinct from that of carnitine deficiency.

Endomysial fibrosis, detected with electron microscopy in 9 of 10 patients, suggests chronicity.[15] We also observed abnormal mitochondrial numbers, size or distribution in 3 patients. These observations, plus those of increased lipid droplets and decreased skeletal muscle acylcarnitine esters, suggest that a systemic metabolic defect involving lipid utilization may be present. A spectrum of metabolic abnormalities related to lipid metabolism or transport may be the basis for the varied clinical manifestations of cardiac and skeletal myopathy. We no not know whether this is a congenital or acquired metabolic abnormality, but detailed study of the electrophysiologic, biochemical, and histologic features of cardiac and skeletal muscle of family members of affected patients may give clues to the basis of the metabolic abnormality.

References

1. **Maron BJ, Roberts WC, Edwards JE, McAllister HA Jr, Foley DD, Epstein SE.** Sudden death in patients with hypertrophic cardiomyopathy: characterization of 26 patients without functional limitation. Am J Cardiol 1978; 41:803–810.
2. **Naccarelli GV, Prystowksy EN, Jackman WM, Heger JJ, Rahilly GT, Zipes DP.** Role of electrophysiologic testing in managing patients who have ventricular tachycardia unrelated to coronary artery disease. Am J Cardiol 1982;50:165–171.
3. **Benson DW Jr, Benditt DG, Anderson RW, Dunnigan A, Pritzker MR, Kulik TJ, Zavoral JH.** Cardiac arrest in young, ostensibly healthy patients: clinical, hemodynamic, and electrophysiologic findings. Am J Cardiol 1983;52: 65–69.
4. **Shabetai R.** Cardiomyopathy: how far have we come in 25 years, how far yet to go? J Am Coll Cardiol 1983;1:252–263.
5. **Meerschwam IS, Hootsman WJM.** An electromyographic study in hypertropic obstructive cardiomyopathy. In: Hypertrophic Obstructive Cardiomyopathy. Ciba Foundation Symposium. London: J & A Churchill, 1971: 55–62.
6. **Shafiq SA, Sande MA, Carruthers RR, Killip T, Milhorat AT.** Skeletal muscle in idiopathic cardiomyopathy. J Neurol Sci 1972;15:303–320.
7. **Neustein HB, Lurie PR, Dahms B, Takahashi M.** An X-linked recessive cardiomyopathy with abnormal mitochondria. Pediatrics 1979;64:24–29.
8. **Smith ER, Heffernan LP, Sangalang VE, Vaughan LM, Flemington CS.** Voluntary muscle involvement in hypertrophic cardiomyopathy: a study of eleven patients. Ann Intern Med 1976;85:566–572.
9. **Tripp ME, Katcher ML, Peters HA, Gilbert EF, Arya S, Hodach RJ, Shug AL.** Systemic carnitine deficiency presenting as familial endocardial fibroelastosis: a treatable cardiomyopathy. N Engl J Med 1981;305:385–390.
10. **Goodwin JF.** The frontiers of cardiomyopathy. Br Heart J 1982;48:1–8.
11. **Akhtar M, Damato AN, Batsford WP, Ruskin JN, Ogunkelu JB.** A comparative analysis of antegrade and retrograde conduction patterns in man. Circulation 1975;52:766–778.
12. **Benditt DG, Benson DW Jr, Klein GJ, Pritzker MR, Kriett JM, Anderson RW.** Prevention of recurrent sudden cardiac arrest: role of provocative electropharmacologic testing. J Am Coll Cardiol 1983;2:418–425.
13. **Pearson DJ, Chase FJA, Tubbs DK.** The assay of (−)-carnitine and its o-acyl derivatives. Methods Enzymol 1969;14:612–622.
14. **McGarry JD, Foster DW.** An improved and simplified radioisotopic assay for the determination of free and esterified carnitine. J Lipid Res 1976; 17:277–281.
15. **Dubowitz V, Brooke MH, Neville HE.** Muscle Biopsy: A Modern Approach. Philadelphia: WB Saunders, 1973.
16. **Lowry OH, Rosebrough NJ, Fair AL, Randall RJ.** Protein measurement with the Folin phenol reagent. J Biol Chem 1951;192:265–275.
17. **Popp RL.** M-mode echocardiographic assessment of left ventricular function. Am J Cardiol 1982;49:1312–1318.
18. **Scheinman MM, Basu D, Hollenberg M.** Electrophysiologic studies in patients with persistent atrial tachycardia. Circulation 1974;50:266–273.
19. **Neville HE.** Ultrastructural changes in diseases of human skeletal muscle. In: Vinken PJ, Bruyn GW, eds. Handbook of Clinical Neurology. Amsterdam: North-Holland Publishing, 1979:63–123.
20. **Engel AG, Siekert RG.** Lipid storage myopathy responsive to prednisone. Arch Neurol 1972;27:174–181.
21. **Boudin G, Mikol J, Guillard A, Engel AG.** Fatal systemic carnitine deficiency with lipid storage in skeletal muscle, heart, liver, and kidney. J Neurol Sci 1976;20:313–325.
22. **Norris FH Jr, Moss AJ, Yu PN.** On the possibility that a type of human muscular dystrophy commences in myocardium. Ann NY Acad Sci 1966; 138:342–353.
23. **Isaacs H, Muncke G.** Idiopathic cardiomyopathy and skeletal muscle abnormality. Am Heart J 1975;90:767–773.
24. **McComish M, Compston A, Jewitt D.** Cardiac abnormalities in chronic progressive external ophthalmoplegia. Br Heart J 1976;38:526–529.
25. **Charles R, Holt S, Kay JM, Epstein EJ, Rees JR.** Myocardial ultrastructure and the development of atrioventricular block in Kearns-Sayre syndrome. Circulation 1981;63:214–219.
26. **Prystowsky EN, Pritchett ELC, Roses AD, Gallagher J.** The natural history of conduction system disease in myotonic muscular dystrophy as determined by serial electrophysiologic studies. Circulation 1979;60:1360–1364.
27. **Perloff JK, de Leon AC Jr, O'Doherty D.** The cardiomyopathy of progressive muscular dystrophy. Circulation 1966;33:625–648.
28. **Whitaker JN, DiMauro S, Solomon SS, Sabesin S, Duckworth WC, Mendell JR.** Corticosteroid-responsive skeletal muscle disease associated with partial carnitine deficiency. Studies of liver and metabolic alterations. Am J Med 1977;63:805–815.
29. **Snyder TM, Little BW, Roman-Campos G, McQuillen JB.** Successful treatment of familial idiopathic lipid storage myopathy with L-carnitine and modified lipid diet. Neurology (NY) 1982;32:1106–1115.
30. **Cumming WJK, Hardy M, Hudgson P, Walls J.** Carnitine-Palmityl-Transferase deficiency. J Neurol Sci 1976;30:247–258.