Noninvasive assessment of left ventricular function in myotonic muscular dystrophy

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SUMMARY In order to assess left ventricular function, measurements of left ventricular internal dimension and its rate of change have been made by echocardiography in 7 patients with myotonic dystrophy and the three children of one of them, who were clinically normal but had abnormal muscle biopsies. Electrocardiograms and systolic time intervals were also recorded in all. Only one patient had signs of overt heart disease and an abnormal electrocardiogram (type B WPW). Systolic time intervals were normal in all 7 patients. Five subjects had echocardiographic abnormalities, which were of minor degree except in the patient with overt heart disease who had considerable impairment of both systolic and diastolic left ventricular function. Another patient had abnormalities of both systolic and diastolic function; systolic abnormalities occurred alone in one patient and diastolic abnormalities alone in one relative.

It is concluded that patients with myotonic dystrophy and no clinical signs of heart disease may have minor abnormalities of left ventricular function as shown by echocardiography. Echocardiography is more sensitive than systolic time intervals in detecting these abnormalities; both systolic and diastolic function abnormalities, alone or together, can occur. There seems to be no relation between involvement of skeletal and cardiac muscle.

Myotonic muscular dystrophy is a diffuse systemic disorder, which is inherited as an autosomal dominant trait, with appearance in both sexes, generally late onset of symptoms, and slowly progressive evolution. The clinical picture may include involvement of skeletal and cardiac muscle, cataracts, premature frontal baldness, bone changes, testicular atrophy, other mild endocrine abnormalities, and mental deterioration.

Evidence of cardiac disease in patients with myotonic dystrophy is usually found in the electrocardiogram, the most common alterations being P and ST and T wave abnormalities, first degree atrioventricular block, left axis deviation, atrial flutter and fibrillation, bundle-branch block, and premature atrial and ventricular contractions (DeWind and Jones, 1950; Fisch, 1951; Cannon, 1962; Miller, 1962; Payne and Greenfield, 1963; Fearington *et al.*, 1964; Church, 1967). There is still little information on the functional abnormality of cardiac muscle in these patients, because in the majority there is insufficient indication for invasive investigations such as cardiac catheterisation and angiocardiology. It has recently been suggested,

however, that cardiac involvement in myotonic dystrophy is not merely common, but is an integral part of the condition, resulting from the complete expression of the gene towards striated muscle tissue, whether skeletal or myocardial (Schmitt and Schmidt, 1975).

We have, therefore, considered it of interest to study left ventricular function not only in patients with myotonic dystrophy in the early stages, but also in those relatives with no clinical signs of the disease, but who already had pathological changes in skeletal muscle. In order to avoid cardiac catheterisation, we have measured left ventricular dimension non-invasively by echocardiography (Chapelle and Mensch, 1969; Popp *et al.*, 1969); instantaneous left ventricular dimension was measured throughout the cardiac cycle along with its rate of change (Gibson and Brown, 1973).

Patients and methods

Seven patients (2 male and 5 female, age range 10 to 44 years) were studied. All had typical physical findings, and the diagnosis was substantiated by electromyography and positive skeletal muscle biopsies. In addition, the 3 children of one of them,

Table Skeletal muscle, echocardiographic, and mechanocardiographic findings in 7 patients with myotonic dystrophy (cases 1 to 7) and in 3 children with family history of myotonic dystrophy (cases 8 to 10)

Case No.	Sex	Age (y)	Skeletal muscle involvement	Echocardiographic measurements				Systolic time intervals			RR interval
				ESD	EDD	Peak shortening rate*	Peak lengthening rate†	Q-A ₁	LVET	PEP	
				(cm)	(cm)	(s ⁻¹)	(s ⁻¹)	(ms)	(ms)	(ms)	(ms)
1	F	12	Moderate	2.4	3.7	3.2	3.6	310	240	70	660
2	F	12	Mild	2.6	3.7	1.9‡	1.8	370	280	90	860
3	F	10	Mild	2.6	3.5	1.9	3.4	320	245	75	630
4	F	37	Moderate	2.8	4.0	1.7	2.5	390	290	100	780
5	F	44	Moderate	4.0	5.0	1.4	0.8	360	260	100	720
6	M	38	Moderate	3.0	4.1	2.8	2.4	340	250	90	630
7	M	12	Mild	2.5	3.6	2.6	5.0	360	270	90	700
8	F	8	Minimal	2.4	4.0	2.4	3.2	360	280	80	790
9	M	6	Minimal	2.2	3.6	3.4	4.1	310	240	70	600
10	M	11	Minimal	2.4	3.9	3.5	2.0	360	275	85	740

*Normal range: 2.0-3.6 s⁻¹ in children, 1.8-3.2 s⁻¹ in adults.†Normal range: 2.2-5.5 s⁻¹ in children, 2.0-5.5 s⁻¹ in adults.

‡Abnormal values are in italics.

aged 6, 8, and 11 years, were also included in the study. Though these children had no clinical signs of myotonic dystrophy, muscle biopsies showed a selective hypotrophy and predominance of type I muscle fibres; ultrastructural studies showed dilatation of the sarcoplasmic reticulum and T tubules and sarcoplasmic masses without myofibrils within the muscular fibres. These findings were consistent with a very early stage of the disease (Scelsi *et al.*, 1977). The degree of skeletal muscle involvement was arbitrarily classified as *minimal* when only ultrastructural abnormalities were present, *mild* when muscular weakness and wasting only affected facial and proximal muscles, and *moderate* when muscular weakness and atrophy were generalised but interfered little with normal activity: there were no *severe* cases, in whom extreme difficulty in movement would have been present (Table).

Chest x-ray films and electrocardiograms were obtained in all the subjects, and systolic time intervals were also recorded as described by Weissler and associates (1968), immediately before the echocardiographic study. Total electromechanical systole (Q-A₂), left ventricular ejection time (LVET), and pre-ejection period (PEP) were measured to the nearest 5 ms in at least 5 cardiac cycles and the means calculated.

Echocardiographic measurements were made with a Smith Kline Ekoline 20 ultrasonoscope, using a 2.25 MHz 1.25 cm transducer, and in all cases a simultaneous electrocardiogram was recorded. Clear continuous echoes of the endocardium were obtained on the left side of the septum and the posterior wall. The subjects were studied in the supine position or turned slightly to

the left, with the transducer in the 3rd, 4th, or 5th interspace.

DIGITISATION

Echocardiograms were digitised as described by Gibson and Brown (1973), using a Summagraphics digitiser and a Prime 300 computer system at Brompton Hospital, London. Data points were generated for the endocardium of the septum and the posterior wall, together with calibration signals representing 0.5 s, 1 cm, and the RR interval of the beat to be studied. From the digitised data, using an incremental plotter, plots were made of left ventricular dimension (D), rate of change of dimension (dD/dt), and normalised rate of change of dimension (1/D × dD/dt) = Vcf in s⁻¹ (Fig. 1). End-diastolic dimension was taken as that synchronous with the QRS complex of the electrocardiogram, and end-systolic dimension as the minimum of the left ventricular dimension curve. Peak systolic and diastolic rates of wall movement were estimated in normalised form. The echocardiographic and mechanocardiographic data are given in the Table.

CONTROL VALUES

Control values for the systolic time intervals were taken from a previous study of 260 normal subjects aged 11 to 54 years, in which the limits of variation were assessed by the tolerance ellipse method (Rampulla *et al.*, 1973).

The echocardiographic data were compared with those obtained in a normal population of 28 children, age range 6 to 12 years (T. F. Tse, unpublished observations), and in a normal population of 12 older subjects (Venco *et al.*, 1977). Normal ranges

Fig. 1 Computer output of digitised echocardiogram from case 8 showing (from below) the original data showing septum and posterior wall, left ventricular dimension, rate of change of dimension (dD/dt), and normalised rate of change of dimension. The cross on the dimension trace marks mitral valve opening.

for peak shortening and lengthening rate of left ventricular internal dimension are given in the footnote to the Table.

Results

(1) CLINICAL

Only one patient with myotonic dystrophy had clinical evidence of significant cardiac involvement, with dyspnoea on effort, an apical pansystolic

Fig. 2 Tolerance ellipses and regression lines of pre-ejection period (PEP) relative to heart rate in 130 normal men and 130 normal females. The dots represent the values obtained in the subjects of the present study.

murmur of grade 3/6, slight cardiomegaly on x-ray examination, and an electrocardiogram showing type B WPW pattern. All the remainder had normal chest x-ray films and electrocardiograms, though 2 had a soft systolic murmur.

(2) SYSTOLIC TIME INTERVALS

PEP and LVET were within normal limits in all 10 patients, as shown in Figs 2 and 3.

(3) ECHOCARDIOGRAPHY

Left ventricular dimensions at end-systole and end-diastole were normal in all subjects. Peak shortening rate, however, was reduced in 4 of the 7 patients with clinical disease, but not in the 3 children. In 2 of the patients and in 1 of the clinically unaffected children, peak diastolic lengthening rate was also reduced. These abnormalities were slight, except in case 5, in which there was clinical evidence of significant cardiac involvement. This patient also had type B WPW syndrome, but abnormalities of septal

Fig. 3 Tolerance ellipses and regression lines of left ventricular ejection time (LVET) relative to heart rate in 130 normal men and 130 normal women. The dots represent the values obtained in the subjects of the present study.

Fig. 4 Computer output of digitised echocardiogram from case 2. The layout is similar to that of Fig. 1. There is a considerable reduction in peak shortening and lengthening rate of left ventricular dimension.

movement (DeMaria *et al.*, 1976; Hishida *et al.*, 1976) were not present. Thus, 5 of the 10 subjects studied had some functional abnormality of left ventricular contraction or relaxation alone or together. Fig. 4 is from a patient (case 2) with impairment of both Vcf and lengthening rate.

Discussion

Cardiac involvement in myotonic muscular dystrophy was described by Griffith in 1911 and since then many other reports have appeared. Character-

istically, cardiac abnormalities are recognised when the clinical manifestations of the disease are well advanced, but they are often the primary cause of death (Wolintz *et al.*, 1966). Necropsy studies have shown no characteristic histological pattern, but a varying amount of myocardial replacement with fat or fibrous tissue may occur (Fisch and Evans, 1954; Slatt, 1961; Cannon, 1962; Holt and Lambert, 1964). In addition, there is no apparent relation between the histological findings and the clinical severity of the heart disease (Holt and Lambert, 1964).

An abnormal electrocardiogram is usually considered the most important clue to the diagnosis of heart disease in such patients, but this was not the case in our series, where the electrocardiogram was abnormal in only one. This differs from previous experience, where electrocardiographic abnormalities have been commonly observed and may even precede changes in the skeletal muscle (Kuhn, 1960; Payne and Greenfield, 1963; Petkovich *et al.*, 1964; Wolintz *et al.*, 1966). The most likely explanation for this discrepancy lies in the very young age of almost all our subjects, 7 out of 10 being below 13 years of age.

A more specific and sensitive diagnostic tool seems necessary in the early stages of the disease. Fumagalli and Savoldi (1960) recorded systolic time intervals in 4 patients with myotonic dystrophy and found abnormal prolongation of isovolumic contraction time in all of them. However, systolic time intervals were normal in all our patients, including the one with clinical signs of heart disease (case 5), indicating the low sensitivity of this diagnostic procedure.

In the present study, therefore, we used echocardiography to assess left ventricular function. Left ventricular dimension at end-systole and end-diastole can be measured directly from the echocardiogram. These measurements were normal in all patients, including case 5 with clinical evidence of left ventricular disease. Further information can be obtained by digitisation of the original records, allowing peak rates of changes of dimension in systole and diastole to be calculated. Abnormalities of these were found in 4 patients with myotonic muscular dystrophy and in 1 child with a family history of the disease and an abnormal muscle biopsy, though there were no clinical signs of skeletal muscle involvement. Both contraction and relaxation of the left ventricle were involved, just as skeletal muscle shows the abnormalities of dystrophin and myotonia, affecting strength of contraction and velocity of relaxation, respectively. These findings, together with the normal internal dimensions of the ventricles, show that functional ab-

normalities of the heart appear well before anatomical abnormalities are clinically apparent.

Moreover, as was observed by Holt and Lambert (1964), no close relation seems to exist in our cases between involvement of skeletal and cardiac muscle; for example, case 1 was one of the most clinically affected patients, but no abnormalities of left ventricular function were apparent on echocardiography, and case 10, who had no clinical signs of myotonic dystrophy, had slight impairment of left ventricular relaxation.

In conclusion, echocardiography seems to be a useful method in the early diagnosis of cardiac involvement in patients with myotonic muscular dystrophy, when electrocardiograms and systolic time intervals are normal and even when no clinical abnormalities are present. Follow-up studies, which can easily be accomplished with this non-invasive technique, will probably cast some light on the natural history of cardiac involvement in myotonic muscular dystrophy.

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