An Ultrastructural Basis for Electrocardiographic Alterations Associated with Duchenne’s Progressive Muscular Dystrophy

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SUMMARY
Electrocardiographic abnormalities were identified in 63 (84%) of 75 patients with Duchenne’s progressive muscular dystrophy. A tall R wave over V场面 with an abnormal R/S ratio was seen in 64% of the patients, a deep and narrow Q wave > 4 mm over leads I, II, and V5, in 44%, sinus tachycardia in 32% and right axis deviation in 16%. Other ECG abnormalities included an abnormal PV, index in 14% of patients and a short P-R interval in 6%.

Ultrastructural characteristics of the heart were determined for two patients with characteristic electrocardiographic abnormalities. Common to both hearts was a total loss of thick as thin myofilaments, which gave a “moth-eaten” appearance to the myofiber. This feature, combined with preservation of the transverse tubular system, formed the most characteristic ultrastructural finding and was seen most consistently in the posterobasal area of the left ventricle. Alterations of Z-band material; accumulation of mitochondria, occasionally containing electron-dense bodies and showing loss or discontinuity of cristae; dilatation of sarcoplasmic reticulum with striking ectasia of cisternae; depletion of glycoprotein particles; a paucity of lipoid or lipochrome granules; and the absence of virus-like particles were other consistent ultrastructural features. Comparison of skeletal and cardiac muscle disclosed identical subcellular changes. These observations support the contention that the distinctive ECG pattern associated with Duchenne’s dystrophy results from multifocal degenerative changes involving myocardium, predominantly the posterobasal region of the left ventricle and the posterior papillary muscle.

ELECTROCARDIOGRAPHIC (ECG) ABNORMALITIES in patients with Duchenne’s progressive muscular dystrophy are well defined but their genesis, although the subject of much interest, is still unclear. Frankie and Rosser, on the basis of histologic findings in cardiac tissue, recently suggested that these changes result from a generalized cardiomyopathy characterized by a peculiar distribution of fibrosis and other degenerative changes. Thus far, a comparable subcellular pattern of degenerative changes has not been reported. Our purpose in this communication is (i) to describe the ultrastructural characteristics of myocardial cells in patients with Duchenne’s muscular dystrophy, (ii) to compare the changes in cardiac muscle with those in skeletal muscle, and (iii) to speculate as to the role of these myocardial changes in the genesis of electrocardiographic abnormalities in patients with this disease.

Materials and Methods

Standard 12-lead electrocardiograms were obtained for 75 patients with Duchenne’s progressive muscular dystrophy during follow-up observations at the Clinic for Muscular Disorders at St. Jude Children’s Research Hospital. All patients were males ranging in age from 5 to 18 years with a median of 11.5 years. In each patient, the diagnosis of muscular dystrophy was established on the basis of clinical, biochemical and muscle biopsy findings. None of the patients had evidence of upper or lower respiratory tract infection or congestive heart failure at the time the electrocardiograms were obtained. A pansystolic blowing murmur, grade III/IV, was noted in four patients. In each of these patients, the maximum intensity of the murmur was heard over the apical area, and in two it was conducted toward the axilla as well. An early-to-mid, non-ejection systolic click was heard in five patients.

All electrocardiograms were obtained with a direct writing recorder at a paper speed of 25 mm/sec and a voltage standardization of 10 mm per mV. Precise electrocardiographic measurements were obtained by using a magnifying lens and calipers. Averaged measurements, from three successive cycles, were used to determine heart rate, rhythm, mean electrical axis in the frontal plane, duration and amplitude of P wave in leads II and V1, P-R interval (corrected for age and heart rate), QRS interval, corrected Q-T interval, duration, and amplitude of QRS and Q complexes in each lead. The Q/R and R/S ratios were also determined. The size of the left atrium was assessed for each patient by measuring the PV index (the negative component of the P wave) as described by Reynolds et al. and others.

Two patients, 10 and 12 years of age, died during follow-up. Their hearts were removed within 1–3 hours after death and were immediately perfused with glutaraldehyde by a procedure, described below, that permitted fixation of the entire organ. The hearts of two additional patients, neither of whom had Duchenne’s dystrophy or any evidence of myocardial diseases, were also removed within 3 hours of death and fixed by the same technique as used in the main study.

Perfusion Technique

A modified pump was tightly fitted to a glass container filled with glutaraldehyde, 2.5%, at 4°C. The free end of a plastic tube that led to the pump outlet was then cannulated into the proximal aorta. An angiocatheter was inserted into this tube with the tip of the catheter lying at the level of coronary ostia; the other end of the angiocatheter was connected to a mercury manometer. The heart was suspended in perfusion fluid in a second container, and the free end of another plastic tube, which led to the pump inlet, was placed under the fluid that surrounded the heart.

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Clamps were then removed from both tubes and the pump motor was activated, forcing the perfusion fluid into the aorta and the coronary vessels. After circulating through the coronary system, the fluid drained into the container in which the heart was suspended, and then suctioned, through the second tube, back to the pump for recirculation. Each heart was perfused for a period of 4 hours. During the entire period, the perfusion pressure was maintained at 100 mm Hg; the temperature of the perfusion fluid was maintained at 4°C.

**Examination of Tissue**

All four hearts (two normal and two from patients with Duchenne’s dystrophy) were studied systematically. Multiple sections were taken from different areas of the organ, that is, the four chambers, papillary muscles, interventricular septum, free wall of both ventricles and atria, and posterobasal areas of the left and right ventricles. For light microscopy, tissues were fixed in 10% formalin and processed in a standard manner. For ultrastructural studies, sections of perfused-fixed tissue, less than 1 mm thick, were made with a Porter-Blum ultratome, postfixed in OsO4 in Millonig’s phosphate buffer, dehydrated in ethanol and propylene oxide, and embedded in plastic embedding media (“Spurr”). Five or more sections of tissue from each area of the four hearts were sectioned at a thickness of 0.5 to 1 micron and stained with toluidine blue. Ultrathin sections (approximately 9 nm each) were stained with uranyl acetate and lead citrate and examined with a Siemens’ Elmskop I electron microscope.

To examine the coronary artery system, we obtained multiple sections from the left and right coronary arteries throughout their epicardial distributions and from the intramural arteries of the atria and ventricles, including the small arteries that supply the sinoatrial and atrioventricular nodes. For three patients with Duchenne’s muscular dystrophy, sections of skeletal muscle were examined for ultrastructural characteristics. In each instance, the specimens were obtained antemortem by muscle biopsy and immediately submerged in 2.5% chilled glutaraldehyde. Further steps for processing and examination of these specimens were identical to those described above for electron-microscopic study of cardiac tissue.

**Results**

**Electrocardiographic Features**

Electrocardiographic abnormalities were noted in 63 (84%) of the 75 patients studied. A tall R wave in lead V1, exceeding the upper limit of normal for age, and an abnormal R/S ratio, exceeding 1.5, were the most common ECG findings, appearing in 64% of the patients. A deep, narrow Q wave > 4 mm in leads I, aV3, and/or V6 and Vs was observed in 44% of the patients, sinus tachycardia in 32% and right axis deviation in 16%. Other ECG abnormalities included an abnormal PV1 index > 0.016 in 14% of the patients, a short P-R interval in 10% and left axis deviation in 6%.

The two patients in whom histologic and ultrastructural characteristics of the heart were studied both had characteristic electrocardiographic abnormalities. Their heart rates were 120 and 110 beats per minute, respectively. The mean electrical axis in the frontal plane in one patient was +78° and +110° in the other. The amplitudes of the R wave over V1 were 14 and 16 mm with S waves of 1 and 2 mm, respectively. Deep, narrow Q waves exceeding 4 mm over leads I, aV6, V5, and V4 were noted in both patients. The patient with right axis deviation had, in addition, a negative P wave in V1 with an abnormal PV1 index of 0.03.

**Gross and Histologic Findings**

Both hearts showed cardiomegaly. Patchy white areas were seen over the epicardial surface of the ventricular free walls, and — on cut sections — over the left ventricular myocardial surface and the midportion of the interventricular septum. The endocardium appeared normal.

The histologic appearance of cardiac tissues ranged widely, from areas with essentially normal morphology to those containing grossly abnormal changes. The spectrum of histologic abnormalities (fig. 1) were the same in both patients and consisted of multifocal degenerative changes of varying severity, involving ventricular myocardium, interventricular septum, papillary muscles and atria. The most severe changes involved the posterobasal region of the left ventricle, while minimal changes were seen in the atrial musculature.

Fibrosis was the most common histologic feature of tissues containing severe alterations (fig. 2). There was marked variability in the size and shape of myofibers: some were atrophic and surrounded by fibrosis and islands of fat, whereas some of the adjacent fibers were normal and others were hypertrophic. No inflammatory cells were seen. Sections of large and smaller intramural arteries, including those supplying sinoatrial and atrioventricular nodes, were normal.

**Ultrastructural Characteristics**

**Contractile Elements**

The myofibrils varied greatly in morphology from one area of a myofiber to another. All myofibrils of a particular cell generally showed the same degree of damage, ranging from small, localized osmiophilic areas to complete loss of striations and dissolution of filaments.

Myofibrillar lysis was characterized by a loss of myosin as well as actin filaments and disorganization of Z-band material. Even in areas of minimal depletion, the absolute numbers of thick and thin filaments were conspicuously decreased. In more severely affected areas, a complete loss of myofibrillae — hence, of all myofilaments — was apparent. These areas of myofibrillar loss, present in a subsarcolemmal position as well as deep within the myofiber, were patchy in distribution, giving a “moth-eaten” appearance to the myofiber (figs. 3, 4). In areas of myofibrillar loss, the Z-band material showed marked alterations (fig. 5) consisting of Z-band widening, extension into the sarcocmere, subsarcolemmal accumulations, clumping and, occasionally, splitting of the Z-band.

**Transverse Tubules**

The loss of myofilaments contrasted very sharply with the status of T tubules, which were preserved and could be readily seen extending across the area of myofibrillar loss (figs. 3, 4).

This combination of changes, namely, patchy areas of
total myofibrillar loss, giving a "moth-eaten" appearance to the myofiber, coupled with preservation of transverse tubular system, was the most consistent ultrastructural finding in both patients. These changes were most prominent in the left ventricular posterobasal area, followed by posterior papillary muscle, interventricular septum, right ventricle and atrial musculature, in order of decreasing severity.

**Mitochondria**

Compared to normal cardiac muscle cells, mitochondria in the dystrophic area were increased in number and showed a spectrum of structural changes, including minimal swelling, partial loss or discontinuity of cristae, and the occasional presence of electron-dense bodies (fig. 6). Myelin figures were extremely rare and stacked cristae were not seen.

**Sarcomplasmic Reticulum**

The sarcoplasmic reticulum was usually dilated with striking ectasia of the cisternae in some instances. Cisternal dilatation, when present, was seen in relation to the T system in the region of Z bands. In rare instances, they were seen in relation to other intracellular structures, such as the nucleus.

**Nucleus**

The structure of nuclei in cells in the dystrophic area did not differ greatly from that of nuclei in unaltered cardiac muscle cells. The chromatin material was in part margined and in part finely dispersed. Clumping of chromatin material or intranuclear filaments was not seen. Virus-like particles were absent in the nucleus and in the cytoplasm.

**Sarcolemma**

Sarcolemmal changes were rare. When present, they consisted of cystic spaces bounded by outer and inner layers of sarcolemma and the presence of subsarcolemmal debris.

**Other Cytoplasmic Constituents**

Other cytoplasmic structures, such as glycogen granules, lipid droplets and lipochrome pigments, were extremely rare in areas of myofibrillar loss.

**Histologic and Ultrastructural Features of Control Hearts**

Hearts obtained from two control subjects were perfused and examined by techniques identical to those used for study of hearts from patients with Duchenne's dystrophy. The ultrastructural and histologic features of the control hearts were very similar to those described for myocardium studied by standard methods. There was no evidence of alterations in Z-band material, myofibrillar lysis, or loss of thick or thin filaments. A well-developed transverse tubular system was the characteristic ultrastructural feature of the ordinary working cells of the ventricular myocardium. Slight mitochondrial swelling with disruption of cristae were

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**Figure 1.** Histologic features of interventricular septum. (a) Thin fibrous band (indicated by black square) separating right from left ventricular myocardium of the septum. H & E stain, ×12. (b) Higher magnification of the fibrous band showing fibrous connective tissue separating and replacing myofibers. H & E stain, ×600.
observed in both hearts. The only abnormal histologic changes were those of minimal postmortem autolysis. The close similarity of morphologic features disclosed by this comparison validated the perfusion technique used in our study.

Comparative Ultrastructure of Skeletal and Cardiac Muscle

A comparison of ultrastructural characteristics between skeletal muscle and cardiac muscle disclosed an identical pattern, namely, myofibrillar loss lending a "moth-eaten" appearance to the myofiber, coupled with well-preserved T tubules.

Comments

Originally described by Ross,\textsuperscript{13} the histologic alterations of myocardium in patients with Duchenne’s progressive muscular dystrophy are now well established.\textsuperscript{7,14-17} The purpose of our study was to identify subcellular changes in the

Figure 2. Histologic features of left ventricular myocardium from the posterobasal area. Note especially the multifocal degenerative changes of myofibers, some of which are replaced by fibrous and adipose tissues. H & E stain, \(\times\) 65.

Figure 3. Ultrastructural characteristics of left ventricular myofiber from posterobasal area in the first patient. Note the multifocal irregular areas characterized by a total loss of thick as well as thin myofilaments, which lends a "moth-eaten" appearance to the myofiber, and preservation of sarcotubular system extending from the sarcoplasm across the areas of myofibrillar loss. \(\times\) 14,000.
myocardial cells of such patients. These features, which have not been reported previously, consisted of varying degrees of myofibrillar loss, alterations in mitochondria and sarcoplasmic reticulum, depletion of glycogen particles, a paucity of lipid or lipofuscin granules, the absence of virus-like particles and the preservation of nuclear morphology and the transverse tubular system.

In recent years, ultrastructural evidence of myofibrillar loss has been found in association with diverse forms of myocardial damage. The various conditions that produce myofibrillar lysis are customarily divided into three different groups18 — depending on the class of myofilament, either myosin (thick filaments) or actin (thin filaments), that is primarily affected. Preferential loss of thin filaments has been typically associated with hypokalemia19 with multiple episodes of hypoxia,20 and with the use of antimalarial drugs such as plasmocid.21 By contrast, preferential loss of thick filaments has been reported in the following conditions: congenital heart diseases associated with an obstruction of the right ventricular outflow tract;22 administration of isoproterenol;23 experimentally induced pressure or volume overloading; glucose-insulin-potassium therapy in patients with myocardial infarction;24 late stages of cardiac hypertrophy with asymmetrical hypertrophic cardiomyopathy (ASH)25 or aortic valvular disease26 and administration of anthracycline drugs for treatment of neoplastic diseases, as recently reported by Buja et al.27, 28 and others.29 The myofibrillar loss in our patients with Duchenne’s muscular dystrophy, however, involved both thick and thin filaments. In areas of minimal involvement, the absolute number of myofilaments was decreased, producing a diffuse pattern. In more severely affected areas, there was complete disappearance of both thick and thin filaments, lending a “moth-eaten” appearance to the myofiber. This ultra-

FIGURE 4. Ultrastructural characteristics of left ventricular myofiber from the posterobasal area in the second patient. Dystrophic changes are identical to those seen in the first patient. X 14,000.

FIGURE 5. Z-band alterations in left ventricular myofiber from the posterobasal area. Note especially fragmentation (a, X 20,000) and widening and splitting of Z-band material (b, X 8,500).
structural feature has not been described in any of the other clinical entities typically associated with preferential loss of either thick or thin filaments.

Recently, Ferrans et al. reported an unusual form of infantile cardiomyopathy that manifests clinically as severe, eventually fatal cardiac arrhythmias and is characterized pathologically by a distinctive type of multifocal degenerative change of the cardiac muscle cells. These cells lose both thick and thin filaments, undergo marked mitochondrial hyperplasia and assume a rounded shape similar to that of histiocytes. Unlike the cardiac muscle cells of our patients, in which the transverse tubular system is preserved, these histiocytes lacked a sarcotubular system.

In addition to infantile cardiomyopathy, there are certain other conditions in which cardiac cells may lose both thick and thin myofilaments, for instance, alcoholic cardiomyopathy,31,32 “beer drinker’s” heart,33,34 rheumatic heart disease,35 “iron heart”,36 viral cardiomyopathy37 and cardiac sarcoidosis.38 In each of these conditions, however, the ultrastructural features of the heart differ from those seen in our study of Duchenne’s dystrophy. In patients with alcoholic cardiomyopathy or “beer-drinker’s” heart, the cardiac cells contain an abundance of lipid droplets, glycogen granules and lipochrome pigments. In patients with rheumatic heart disease, the most striking changes are evident in the left atrial muscle fibers. As reported by Fenoglio and Wagner,35 the connective tissue stroma of the left atrium and mitral valve in patients with rheumatic heart disease show extensive deposition of collagen and elastic fibers. By contrast, in patients with Duchenne’s muscular dystrophy, the most extensive degenerative changes involve the left ventricular myocardium. Finally, iron deposits and virus-like particles, as reported in “iron heart”36 and viral cardiomyopathy,37 respectively, were not seen in our patients.

Recently, Auger and Chenard reported persistent Z-band material in areas of myofibrillar loss in “beer-drinker’s” heart. We did not observe such changes in Duchenne’s muscular dystrophy; rather the spectrum of alterations in Z-band material consisted of widening and extension, clumping and, occasionally, splitting of the bands. The significance of these changes is not clear. Whether certain alterations, such as thickening or symmetrical extension of Z-band material into adjacent areas of sarcomeres, indicate sarcomerogenesis, as suggested by Legato,39 while other alterations, such as clumping and fragmentation of Z-band material represent degenerative changes associated with early myofibrillar lysis,40 remains speculative. Subsarcolemmal filaments, as described by Posche in cardiac hypertrophy, were not seen in our study.

The close similarities between histologic alterations of cardiac and skeletal muscle cells in patients with Duchenne’s muscular dystrophy have been pointed out by several investigators.41-44 Our observations indicate that such similarities extend to the subcellular level as well. Thus, we believe that myocardial cells in patients with Duchenne’s muscular dystrophy are characterized by a constellation of ultrastructural findings — namely, myofibrillar loss (thick as well as thin filaments), resulting in a “moth-eaten” appearance of the myofiber; preservation of the transverse T system and nuclear structures in the areas of myofibrillar loss; dilatation of sarcoplasmic reticulum; a conspicuous paucity of lipid droplets and lipofuscin or glycogen granules; and the absence of virus-like particles.

A distinctive electrocardiographic pattern, consisting of tall R waves over V1 with R/S ratio exceeding 1 and deep but narrow Q waves over leads I, aV, and V, has been consistently reported in 80-90% of patients with Duchenne’s dystrophy and was seen in most of our patients, including the two whose hearts were studied for histologic and ultrastructural characteristics. Although these ECG abnormalities may closely simulate a myocardial infarction pattern, there are certain differences. In patients with Duchenne’s dystrophy, the Q waves are deep and narrow, unlike the broad Q waves of patients with myocardial infarction. In addition, the vectorcardiographic studies do not reflect abnormal initial forces, but do point toward a diffuse myocardial involvement. The recent histologic obser-
tions of Frankel and Rosser further substantiate the hypothesis that generalized cardiomyopathy forms an integral part of Duchenne's dystrophy. These investigators have shown that in patients with this disorder, the histologic evidence of degenerative changes initially begin at the posterobasal segment of the left ventricle, subsequently spread to involve the outer third of the left ventricular free wall and, finally, manifest as diffuse transmural fibrosis. In addition, they have noticed varying degrees of involvement of the interventricular septum.

Our observations are in complete accord with theirs and indicate that the most extensive cellular and subcellular changes involve the posterobasal portion of the left ventricle followed by, in order of decreasing severity, involvement of the posterior papillary muscle, interventricular septum, and free wall of the right ventricular wall, with only minimal changes in the right or left atrium. Furthermore, these ultrastructural changes show a broad spectrum that extends from areas with only a minimal loss of actin and myosin filaments to others that show extensive changes characterized by total myofibrillar loss and replacement by collagen fibers. Several investigators have suggested that such changes in cellular structure of the myocardium can produce a loss of epicardial forces and result in an anterior shift of the QRS forces that may manifest as tall R waves over right precordial leads. Since the dystrophic changes in skeletal and cardiac muscle in patients with Duchenne's muscular dystrophy are progressive, it is possible that during early stages of the disease the dystrophic changes of the myocardium are minimal and produce little alteration in the epicardial forces. This would explain the normal electrocardiograms in several of our patients. Progression of the disease, on the other hand, may be associated with increasing myofibrillar loss, which could produce significant alterations in epicardial forces. A predilection of these dystrophic changes for the left ventricle, especially the posterobasal area, would explain a progressive anterior shift of QRS forces, producing taller R waves with an abnormal R/S ratio over the right precordial leads, the most common electrocardiographic abnormalities in patients with Duchenne’s muscular dystrophy. Replacement of normal cardiac tissue by fibrosis, with lateral extension of scarring, may explain the presence of Q waves in these patients, as suggested by Perloff et al. In addition, our preliminary observations indicate that dystrophic changes may involve the conduction system as well, and thus provide a basis for the left axis deviation and short P-R interval in some of our patients. Finally, papillary muscle involvement may produce papillary muscle dysfunction, mitral regurgitation, and left atrial enlargement. Whether the abnormal PV index, present in 14% of our patients, reflects such left atrial enlargement or is an expression of an inter- or intra-atrial conduction defect associated with the basic disease process, remains speculative.

Thus, our ultrastructural observations support the contention that the classical electrocardiographic profile in patients with Duchenne’s muscular dystrophy results from multifocal degenerative changes of the cardiac muscle, predominantly in the left ventricle. Furthermore, these degenerative changes of the heart, at both the cellular and subcellular levels, are identical to those seen in skeletal muscle. Whether or not these focal dystrophic areas of the heart in patients with Duchenne’s progressive muscular dystrophy are genetically predetermined, as suggested by Ronan et al., needs further careful evaluation.

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References

Multiple Dipole Electrocardiography

A Comparison of Electrically and Angiographically Determined Left Ventricular Masses

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SUMMARY In 1969, a new method was published for estimating the mass of electrically active muscle in the left ventricle (electrical LVM). The present paper reports a prospective test of this method, using a series of 113 patients. These patients were believed not to have had myocardial infarctions, so that their electrical LVM should equal their anatomic LVM, which was independently determined from LV biplane angiograms. In fact, the correlation coefficient between electrical LVM and angiographic LVM was \( r = 0.85 \), and the root mean square deviation of electrical LVM, relative to the angiographic LVM, was 66 grams. It was concluded that the electrical LVM estimate had an accuracy of about one-third of an average normal LVM.

A method of estimating left ventricular muscle mass (LVM) from electrocardiographic data was previously reported.\(^1\) In that study, data from a series of 72 patients, for whom LVM was known from biplane angiograms, were used. It was shown that the standard error of the electrocardiographic estimate of LVM was 49 grams. However, the study was partly retrospective in nature, since the estimation procedure was not completely specified independently of the patient data reported. More specifically, the values of the two parameters used in the procedure were determined by these same data. A sharp distinction between developing the method, and testing it, was not maintained.

If a stringent test of the method is desired, it is necessary to obtain additional data, which had in no way been involved in the development of the method, and test the performance of the method prospectively. The present paper reports such a study, in which the exact, unmodified procedure specified by the original study was applied to data from a new series of 113 patients, none of whom had been involved in the original study.\(^1\) Using this series, it will be shown that the root mean square (RMS) deviation of the LVM estimate is about 66 grams, about one-third of the average mass of LV in normal males.

Methods

The electrocardiographic method has been reported earlier and will be only briefly outlined here. Electrocardiographic data from 126 electrodes are reduced, using a
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