Cardiac Conduction Abnormalities in Children with Duchenne’s Progressive Muscular Dystrophy: Electrocardiographic Features and Morphologic Correlates

SHYAMAL K. SANYAL, M.B.B.S., AND WARNER W. JOHNSON, M.D.

SUMMARY The ECGs of 50 boys, 5–18 years old, with Duchenne’s muscular dystrophy were studied for evidence of cardiac conduction system abnormalities. Among the 24 patients with positive findings (48%), most had intraatrial conduction defects: 16 an abnormally prolonged PV, index, 12 a short PR interval with a normal QRS and two coronary sinus rhythm. Five patients had infranodal conduction defects: One had right bundle branch block, three left anterior fascicular block and one right bundle branch block with left anterior fascicular block. Only one child had first-degree atioventricular (AV) block. About one-third of the patients had more than one type of defect. The conduction abnormalities were progressive in some patients.

Morphologic features of the conduction systems of three patients were studied systematically to find correlates for the observed ECG changes. Compared with normal controls matched for age and sex, each of these three hearts showed multifocal areas of degenerative changes, characterized by vacuolization, fatty infiltration, nuclear pyknosis, loss of myofibers and moderate-to-severe fibrosis. These dystrophic changes were similar in all patients and (with differing severity) involved the sinoatrial node, “atrial preferential pathways,” approaches to the AV node, the AV node including the upper portion, the bundle of His, and subendocardial as well as infranodal right and left bundle branches.

Our observations indicate a high prevalence of ECG evidence of cardiac conduction abnormalities in patients with Duchenne’s dystrophy. Multifocal dystrophic involvement of the cardiac conduction system furnishes the anatomic basis for such changes and may account for the persistence of an infantile pattern of accelerated conduction, which may sometimes manifest clinically as Lown-Ganong-Levine syndrome with or without sinus tachycardia.

PATIENTS with Duchenne’s muscular dystrophy (DMD) have a distinctive ECG, characterized by a tall R wave with an abnormal R/S ratio over the right precordial leads and deep but narrow Q waves over leads I, aV, V and V. This classic profile, seen in 70–80% of patients with DMD, has been attributed to multifocal dystrophic involvement of the left ventricular myocardium with a peculiar predilection for the posterobasal segment and contiguous lateral or inferior walls. Other ECG findings, such as short PR interval and left-axis deviation of the mean electrical force, which imply involvement of the cardiac conduction system in the disease, are seldom recognized, and their prevalence is unknown. In a study of 34 patients, Ronan et al. found no atroventricular (AV) or infra-ventricular conduction disturbance and concluded that impairment of AV conduction was an unlikely manifestation of DMD. Perloff et al. in contrast, observed prolonged AV conduction in seven of 35 patients with DMD. Reports of the prevalence of short PR intervals

From the Cardiopulmonary Disease Service, St. Jude Children’s Research Hospital, Memphis, Tennessee, and the Department of Pathology, University of Mississippi Medical Center, Jackson, Mississippi.

Dr. Sanyal’s present address and address for correspondence: Department of Pediatrics, King Faisal University Medical College, Alkhobar Teaching Hospital, P.O. Box 2208, Alkhobar, Kingdom of Saudi Arabia.

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also conflict, ranging from none in a study of 44 patients to five among 17 patients.

To reliably estimate the prevalence and spectrum of conduction defects in patients with DMD, we studied the ECGs of 50 patients for evidence of intraatrial, AV or intraventricular conduction abnormalities. We also assessed the histologic features of the cardiac conduction system in three patients with ECG evidence of conduction defects to establish the morphologic basis for such changes.

Methods

Patients

The study group consisted of 50 patients who were examined at the Clinic for Muscular Disorders at St. Jude Children’s Research Hospital. All were males, ages 5–20 years. In each patient the diagnosis of DMD was made by the attending neurologist on the basis of clinical, biochemical, electromyographic and muscle biopsy findings. During follow-up periods of 5–12 years, a pansystolic blowing murmur (grade III/VI) with maximum intensity over the apical area was noted in three patients; the murmur was conducted toward the left axilla in two of them. In each of these three patients and in four others, auscultatory evidence of an early to mid–non-ejection systolic click suggested mitral valve prolapse (MVP) syndrome. M-mode echocardiography confirmed the diagnosis in each of these seven patients and in four others. Ten patients developed congestive heart failure during the follow-up period; eight of them died.

Electrocardiographic Studies

Standard 12-lead ECGs were obtained for each patient with a direct-writing recorder at a paper speed of 25 mm/sec and a voltage standardization of 10 mm/mV. Annual follow-up ECGs over 5–12 years were available for study in all but five cases (table 1). ECGs recorded while the patients had either upper or lower respiratory tract infections or congestive heart failure were excluded from analysis.

Precise electrocardiographic measurements were obtained by using a magnifying lens and calipers. Averaged measurements of three successive cycles were used to determine heart rate, rhythm, mean QRS axis in the frontal plane, morphology of P wave in standard and augmented limb leads and over right and left precordial leads, PR interval (corrected for age and heart rate), duration and amplitude of the P wave over leads II and V₅, the QRS interval, QTc interval, and amplitude and morphology of the Q wave and QRS complex in each lead.

AV and intraventricular conduction characteristics were classified by the revised nomenclature of Hecht et al. Left anterior fascicular block was diagnosed only if the mean electrical axis in the frontal plane was counterclockwise and exceeded −45° with normal initial QRS forces. The terminal P–V₂ index (the algebraic sum of amplitude and duration of the negative component of the P wave over V₂) was determined as reported previously.

Morphologic Examination

The conduction system was studied systematically in hearts from three patients who had ECG evidence of conduction defects and died during follow-up. After noting the gross features of two hearts, we perfused them with either 2.5% glutaraldehyde or 10% formalin using a previously reported technique. The heart of the remaining patient was fixed in 10% formalin in the conventional manner.

To study the sinoatrial (SA) node, we excised a block of tissue approximately 2 × 2 cm from an area that included the superior vena cava at its juncture with the right atrium at the sulcus terminalis, the crest of the atrial appendage and adjacent atrial myocardium. The tissue block was serially sectioned in a longitudinal fashion (cava-atrial) so that epicardium covered one side and endocardium the other. Each section was examined serially by light microscopy until the SA node was identified (fig. 1). Cephalocaudad-oriented blocks about 1.5 cm thick were then excised and sectioned serially; the tenth, eleventh and twelfth sections from each block were stained with hematoxylin-eosin and with Werhof’s elastic and Gomori’s trichrome methods.

Additional sections of the interatrial septum, tissue anterior to the fossa ovalis, the intercaval wall, and the lower portion of the posterior wall of the right atrium were taken so that the intermodal preferential pathways would be included.

The AV node was examined by excising a 2 × 2-cm
### Table 1. Intratrial Conduction Abnormalities in Duchenne's Muscular Dystrophy

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<th>Serial no.</th>
<th>Follow-up*</th>
<th>Age (years)</th>
<th>Heart rate (beats/min)</th>
<th>MEA</th>
<th>PR interval</th>
<th>PV(_1) index</th>
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*Years indicate when the initial and follow-up ECGs were obtained.
†Patients in whom M-mode echocardiography was performed.
‡Predicted values based on data for normal children (% 16 years old; > 16 years old).§Patients in whom morphologic studies of the cardiac conduction system were done.

Abbreviations: MEA = mean electrical axis in the frontal plane; AV = atrioventricular; RBBB = right bundle branch block; LAFB = left anterior fascicular block; MVP = mitral valve prolapse; CHF = congestive heart failure; PV\(_1\) index = algebraic sum of amplitude and duration of the negative component of the P wave over PV\(_1\).
block of tissue with a lateral boundary consisting of an adjacent area from the right atrium and its endocardium, the origin of the tricuspid valve and the left ventricular myocardium. Cephalocaudad-oriented blocks about 1.5 cm thick were excised, sectioned serially and examined until the AV node was identified (fig. 2A). Thereafter, every third, fourth and fifth sections from each block were stained as described above, and the His bundle and right and left bundle branches, including distal portions, were identified (figs 2B–F).

For comparison, hearts obtained from age- and sex-matched normal controls were fixed by the same techniques used in the main study, and the conduction system was examined systematically by the same procedure used for DMD patients.

Results

Electrocardiographic Features

Conduction abnormalities were seen in 24 of 50 patients (48%) (table 1). Twenty-three patients had intraatrial conduction abnormalities, five had infranodal conduction abnormalities and one patient had prolongation of AV conduction. An abnormally prolonged PV index, the most common defect, occurred in 16 patients, five who had congestive heart failure and three who had MVP. (One patient had both MVP and heart failure.) In four instances, heart failure increased the PV index abnormality. Nine patients with an abnormal PV index had neither congestive heart failure nor MVP.

Twelve patients, each with a normal QRS duration,
had a short PR interval; in two cases the PR interval returned to normal within 3–5 years of follow-up. Coronary sinus rhythm, characterized by negative P wave in leads II, III and aV₃, and a normal PR interval.

was found in two patients only; in both, the direction and morphology of P became normal during follow-up (fig. 3).

Five patients had infranodal conduction defects: one patient had right bundle branch block and three patients had a left anterior fascicular block. Right bundle branch block and, later, left anterior fascicular block developed in a child who initially had a normal QRS duration and normal mean electrical axis in the frontal plane (fig. 4). One child had first-degree AV block. Nine of the 24 patients (37%) had more than one type of conduction defect.

**Morphologic Findings**

Morphologic changes of the cardiac conduction system — multifocal areas of fibrosis, vacuolization and fatty infiltration involving the entire conduction system — were similar in all three patients studied morphologically. Histologic specimens from normal controls did not show dystrophic changes.

**SA Node**

Myofibers varied in size and showed vacuolization, fatty encroachment and nuclear pyknosis (fig. 5). There were focal areas of fibrosis and a decrease in

**Figure 2.** Histologic features of the atrioventricular node (AVN). His bundle and origin and course of left and right branches of the bundle of His (BH) in a normal control. (A) The relationship among right atrium (RA), input fibers (IF). AVN and BH; the latter is partially encircled by central fibrous body (CFB). IVS = interventricular septum. (B) The division of the BH into left and right bundle branches (LBB and RBB). (C) Origin and course of the LBB. (D) Distal LBB beneath left ventricular (LV) endocardium (E). (E) Proximal and (F) distal RBB deep within right ventricular (RV) myocardium. Hematoxylin-eosin stain; magnification (A) × 19, (B) × 25, (C) × 90, (D) × 40, (E) × 40 and (F) × 10.

**Figure 3.** Serial electrocardiographic tracings from a patient with Duchenne’s muscular dystrophy showing coronary sinus rhythm characterized by inversion of P wave in leads II, III and aV₃ in 1967 and a return to normal sinus rhythm during follow-up.
sarcoplasmic staining (fig. 5C). Similar changes were noted in approaches to the SA node and atrial preferential pathways. The SA node artery was normal.

**Approaches to AV Node**

Focal areas of fibrosis, fatty infiltration and vacuolization were noted. The AV nodal artery was normal.

**AV Node**

Multifocal areas of moderate-to-severe fibrosis, loss of myofibers and vacuolization of cells involved the nodal area, including its upper portion (fig. 6).

**AV Bundle**

Focal areas of fibrosis, fatty infiltration and vacuolar degeneration involved both the penetrating portion and the branching portion of the AV bundle. No connections between atrial septal musculature and the bundle were found (fig. 7).

**Left Bundle Branch**

Multifocal areas of dystrophic changes involved both the proximal and the peripheral portions of the left bundle. The changes included loss of myofibers, myofiber splitting with variation in size and staining of myofibers, fibrosis and vacuolization (figs. 8A–C).

**Right Bundle Branch**

Areas of fibrosis, vacuolization of cells, myofiber splitting with variation in size and staining of myofibers and loss of myofibers involved the first, second and third portions of the right bundles (fig. 9).

No anomalous connections were observed between atria and the conduction system.

**Discussion**

Cardiomyopathy with a peculiar predilection for the posterobasal segment of the left ventricle and adjacent areas is an integral part of DMD. Although such involvement may explain the distinctive ECG profile that characterizes DMD, namely, a tall R wave over V1 and deep Q waves over V5, it does not account for the conduction defects and raises the possibility that dystrophic changes may involve the conduction system. Our observations establish that ECG evidence of conduction abnormalities is common, that the prevalence of such changes is higher than previously recognized, and the multifocal dystrophic involvement provides the morphologic correlate for the electrocardiographic findings.

An increase in terminal negative force of the P wave over lead V1, resulting in an abnormal PV index, was seen in 16 of the 24 children who presented with ECG abnormalities.
abnormalities. An abnormal prominence of P terminal forces in children with DMD could be related to several factors: an interatrial or left atrial conduction defect, left atrial enlargement, progressive thoracic deformity or left atrial hypertension associated with diminished left ventricular compliance.

The effects of left atrial hypertension on P terminal forces in V1 are controversial. Some have reported a significant positive correlation between left atrial pressure and magnitude of the negativity of P terminal forces in V1, others have not identified such a relationship. Although in four of our patients, the PV1 index abnormality worsened after the onset of congestive heart failure, probably because of an increase in left ventricular filling pressure, no changes in terminal P forces were noted after cardiac decompensation in six other patients. Nine patients with an abnormal PV1 index did not have congestive heart failure. This lack of a consistent correlation between ECG evidence for left atrial abnormality and left atrial pressure or volume overload suggests that other factors may contribute to the genesis of abnormal PV1 index. Josephson et al. in a recent study correlating left atrial size and pressure as well as intraatrial conduction time, reported that only prolongation of intraatrial conduction time was consistently related to abnormal P terminal negativity over V1. We previously reported that focal areas of fibrosis at the cellular level and a total loss of thick and thin myofilaments at the subcellular level, involving (with differing severity) all four cardiac chambers, including the left atrium, characterize the cardiomyopathy that forms an integral part of DMD. That such fibrosis may prolong intraatrial conduction and provide a basis for abnormal PV1 index in patients with DMD seems reasonable.

Ronan et al. and Fitch and Ainger suggested that infranodal and AV conduction defects in patients with DMD are rare. Our observations do not support this
suggestion. Five patients showed ECG evidence of infranodal conduction defect; three had left anterior fascicular block. One child gradually developed right bundle block and then left anterior fascicular block. Whether patients with this combination will develop chronic complete AV block as they age is speculative.

A short PR interval and normal QRS duration were seen in about one-fourth of our patients. The genesis of short PR interval in children with DMD is not known. Although this could represent a normal variant of childhood, a partial or complete bypass of the AV node through anomalous connections, as reported by Mahaim and Benatt, James and Anderson et al., could decrease the physiologic delay of the conduction of the cardiac impulse and thus shorten the PR interval. A normal QRS complex with no initial slurring does not suggest the presence of Mahaim fibers in our patients. Histologic examination did not disclose posterior internodal tract, paraspecific fibers or other anomalous connections between atria and conduction system.

AV nodal bypass due to an anomalous tract is not the only explanation for accelerated conduction in our patients. A decrease in normal physiologic delay in the region of the AV node is another possibility. Our findings indicate that multifocal areas of dystrophic changes involve the AV node, including its upper portion. Since the upper portion is the usual site for nodal delay, dystrophic involvement of this area could decrease this delay. Moreover, dystrophic involvement of the AV node may alter the infranodal conduction pattern so that one group of fibers would conduct faster than the other, resulting in a functional longitudinal dissociation of the AV node. The net result may be persistence of the infantile pattern of accelerated conduction that may manifest electrocardiographically as short PR interval.

**Clinical Implications**

During childhood, the basic intracardiac intervals increase as the conduction system matures. Such changes account for the characteristic decrease in heart rate during this period. Multifocal dystrophic involvement of the conduction system could retard the normal maturation process with persistence of the in-

**Figure 6.** Histologic features of atrioventricular node in Duchenne's muscular dystrophy. Note vacuolization (black arrow and black circle). Hematoxylin-eosin stain; magnification × 195.

**Figure 7.** Histologic features of the His bundle in Duchenne's muscular dystrophy. (A) Loss of myofibers with replacement by fibrous tissue (black arrow). (B) Similar changes, i.e., loss of myofibers, fibrosis and vacuolar changes, are seen in the His bundle from another patient. Hematoxylin-eosin stain; magnification (A) × 40; (B) × 200.
fantile pattern of accelerated conduction that may manifest clinically as sinus tachycardia. In addition, dystrophic involvement of the intranodal fibers may produce a functional longitudinal dissociation of the AV node, partial block and reentry mechanism that

**Figure 8.** Histologic features of the left bundle branch in Duchenne’s muscular dystrophy. (A) Marked degree of vacuolization (black arrows). (B) Other changes include splitting of myofibers (white arrow). (C) Fibrosis (F); degenerating myofibers (black arrows) and splitting of myofibers (thin black and white arrows). Hematoxylin-eosin stain; magnification (A) × 560; (B) and (C) × 350.

**Figure 9.** (above) Histologic features of the right bundle branch (RBB) in Duchenne’s muscular dystrophy. Note dystrophic changes characterized by areas of degenerative myofibers (black arrows), disappearing myofibers (open arrows) and fibrosis (F). Hematoxylin-eosin stain; magnification × 560.
may result in rapid heart rate in patients with DMD. If substantiated, this proposed electrophysiologic basis for cardiac conduction defects would aid in the understanding of arrhythmogenesis and provide a pharmacologic rationale for selecting appropriate antiarrhythmic drugs for children with DMD.

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