Skeletal muscle pathology in chronic heart block

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SUMMARY Skeletal muscle samples, mainly from the deltoid, were studied morphologically and histochemically in 35 patients with chronic heart block and from nine elderly control subjects. The average age of the first group was 67.7 (range 11-94) years. Abnormalities were present in 20 cases, no difference being found between patients with idiopathic and secondary heart block. In 15 samples there was increased oxidative enzyme activity in some muscle fibres, and in six there was fibre type grouping. Six had unexplained type II fibre atrophy and two had a predominance of type I fibres. Tubular aggregates were conspicuous in one biopsy specimen, and in another, rod bodies were found. Minor abnormalities were also seen in the control group. In the absence of any consistent pattern many of these changes were attributed to ageing.

Cardiac conduction disturbances are a recognised feature of some neurological disorders, and complete heart block has been described in association with dystrophia myotonica (Litchfield, 1953), with scapuloperoneal dystrophy (Mawatari and Katayama, 1973), and with the oculocranio somatic syndrome (Kearns and Sayre, 1958; Olson *et al.*, 1972). A recent survey of a large group of patients with chronic heart block attending cardiac clinics showed that such cases were rare, and, in the remainder, neurological assessment shed no light on the aetiology of the conduction disturbance (Lambert and Fairfax, 1976).

Postmortem studies of cases of chronic heart block have demonstrated that the most common finding is fibrosis selectively replacing the Purkinje fibres, and this has been described as a 'myopathy' of the conducting system (Lenègre, 1964). In animals, some histochemical similarities exist between the Purkinje fibres of the heart and the type II fibres of skeletal muscle (Snijder and Meijer, 1970). Skeletal muscle has not, however, been systematically studied in patients with chronic heart block. Muscle morphology and histochemistry were therefore examined in a series of patients with complete heart block to determine whether any abnormality of skeletal muscle was present in these cases.

Patients and methods

Thirty-five consecutive patients admitted for pace-

maker implantation with chronic atrioventricular block were studied. Informed consent was obtained from each subject. A full neurological assessment was made and serum creatine phosphokinase was measured. A skeletal muscle specimen was taken under local anaesthesia, usually from the deltoid muscle, during implantation of the pacemaker. The sample was processed using conventional techniques (Dubowitz and Brooke, 1973). Morphological detail was demonstrated by the modified Gomori trichrome method (Engel and Cunningham, 1963); the histochemical methods used were: adenosine triphosphatase reaction at pH 9.4 (Padykula and Herman, 1955); succinic dehydrogenase (Nachlas *et al.*, 1957); NADH-tetrazolium reductase (Novikoff *et al.*, 1961); phosphorylase (Takeuchi and Kuriaki, 1955); periodic acid Schiff (PAS), and Sudan black.

A control series of deltoid muscle specimens was obtained as soon as possible *post mortem* from nine patients aged over 65 years who had died from causes other than heart block.

Results

The 35 patients studied, 24 men and 11 women, were aged between 11 and 94 with a mean of 67.7 years. In 11 cases a recognised cause of heart block was present. These included: aortic valve disease (3), cardiomyopathy (2), familial heart block (2), and congenital heart block (1). There were also single cases of chronic heart block secondary to ischaemic heart disease, to sarcoidosis, and to septal

Received for publication 6 October 1976

calcification in association with Paget's disease. In the remaining 24 patients the disorder was idiopathic.

No examples of those neurological disorders known to be associated with heart block were identified in this series, but unrelated neurological abnormalities were found in 21 patients including both those with idiopathic and those with secondary heart block. Twenty of these patients were aged 60 years or more. The commonest abnormalities were: cervical spondylosis (5), deafness (4), absent ankle reflexes (4), sensory impairment of the legs (3), impaired upward gaze (3), and ptosis (2). There were single examples of Parkinson's disease, trigeminal neuralgia, and traumatic hemiparesis.

Serum creatine phosphokinase levels were normal in 28 out of 29 patients, and in the only subject with a raised level (284 IU/l) no neurological abnormality was found.

SKELETAL MUSCLE MORPHOLOGY

Morphological examination of the 35 muscle specimens from patients with chronic heart block showed no microscopic evidence of muscular dystrophy. There was also no inflammatory infiltration present in any of the specimens. The patient with sarcoidosis had a normal muscle biopsy although sarcoid granulomata were present in skin lesions and there was evidence of pulmonary, myocardial, and visceral involvement.

The proportion of type II fibres in the deltoid muscle specimens varied from 17 to 66% with a

mean of $46.0\% \pm 11.5$ (SD). The mean percentage of type II fibres in the postmortem control series was $31.3\% \pm 9.5$ (SD) with a range of 20-49% (Fig. 1). In two patients with idiopathic heart block and in three controls, the proportion of type II fibres was less than 24%, quoted as the lower 95% confidence limit for this muscle in young adults (Johnson *et al.*, 1973).

Fifteen of the 35 muscle specimens were normal, 10 of these being from patients under 70 years of age. In the remaining 20 biopsy specimens one or more abnormalities were found (Table).

In 15 patients (14 of whom were over 70 years of age) increased subsarcolemmal staining was demonstrable in some fibres using the succinic dehydrogenase reaction (Fig. 2) and some of these appeared similar to 'ragged-red' fibres (Engel, 1971) using the Gomori trichrome stain. Increased staining of these abnormal fibres was seen with Sudan black (Fig. 3). In none of the specimens did 'ragged-red' fibres comprise more than 1% of the total muscle fibres.

Rod bodies were seen in some fibres (Fig. 4) in an 80-year-old man with calcific aortic valve disease, Paget's disease, and polymyalgia rheumatica treated by steroids; increased subsarcolemmal staining and type II fibre atrophy were also present.

Tubular aggregates (Fig. 5) were identified in 20% of the skeletal muscle fibres in a 62-year-old man with unexplained cardiomyopathy and aortic incompetence. He had complained of recurrent leg cramps and on examination showed slight wasting and weakness of both quadriceps femoris muscles. Tubular aggregates were present in this muscle and were also found three months later in the pectoralis major. Further samples were obtained on a third occasion during an operation for aortic valve replacement: the rectus abdominis and muscle from the atria and ventricles were examined histochemically and by electron microscopy (Dr D. Landon) but tubular aggregates could not be identified in any of these specimens.

Six muscle biopsy specimens (3 from patients with cervical spondylosis) showed grouping of fibre

Fig. 1 Proportion of type II fibres of deltoid muscle in idiopathic (open circles) and secondary (closed circles) heart block and in elderly controls (triangles).

Table Skeletal muscle abnormalities found in 20 specimens from patients with chronic complete heart block

Irregular distribution of oxidative enzyme activity
Type grouping
Type 2 fibre atrophy
Type 1 fibre predominance
Rod bodies
Tubular aggregates
Central nuclei increased

Fig. 2 *Deltoid muscle from a patient with idiopathic heart block showing increased subsarcolemmal staining by the succinic dehydrogenase reaction ($\times 180$).*

Fig. 3 *Abnormal fibres in the deltoid muscle of the same patient using the Sudan black stain ($\times 110$).*

Fig. 4 Rod bodies present in deltoid muscle of a patient with secondary heart block and polymyalgia rheumatica (Trichrome stain $\times 280$).

Fig. 5 Tubular aggregates in skeletal muscle of a patient with heart block and cardiomyopathy (Deltoid muscle, phosphofructokinase stain $\times 180$).

types. Six other specimens, including two from patients with aortic valve disease, showed unexplained atrophy of type II fibres. Increased central nuclei (15%) were the sole abnormality found in deltoid muscle from a 46-year-old man with vitiligo and chronic heart block possibly of autoimmune aetiology (Fairfax and Leatham, 1975).

In the postmortem series satisfactory fibre typing could be obtained up to 48 hours after death using the ATPase reaction, but poor results were obtained using the other histochemical methods, and morphological detail was not satisfactorily demonstrated. The specimens examined all showed various abnormalities, including type I fibre predominance, type II fibre atrophy, fibre-type grouping, and irregular subsarcolemmal staining for oxidative enzymes.

Discussion

Patients with heart block in association with overt neuromuscular disease form a clinically recognisable small group which accounts for less than 1% of all cases of chronic atrioventricular block (Lambert and Fairfax, 1976). This previous study, and a review of the literature, indicates that these neurological diseases are predominantly multisystem disorders, such as dystrophias myotonica, rather than the 'true' muscular dystrophies. For example, in the oculocraniosomatic syndrome, in addition to ophthalmoplegia and muscular weakness there is ataxia, pigmentary retinal degeneration, nerve deafness, and shortness of stature (Drachman, 1968). Mitochondrial abnormalities have been described affecting sweat glands (Karpati *et al.*, 1973), cerebellum (Schneck *et al.*, 1973), and skeletal muscle (Olson *et al.*, 1972), the latter giving rise to the 'ragged-red' appearance with the trichrome stain.

In the present study the finding of morphological abnormalities of skeletal muscle in secondary heart block and in the control samples led us to the conclusion that the changes observed in patients with idiopathic heart block are unrelated to the aetiology of their conduction disturbance. Furthermore, although there are some histochemical similarities between type II skeletal muscle fibres and the Purkinje tissue (Snijder and Meijer, 1970), no specific abnormality of type II muscle fibres has been identified in this study. Immunohistochemically, the Purkinje tissue has recently been shown to be more comparable to cardiac muscle and to the type I fibres of skeletal muscle than to type II fibres (Fairfax and Doniach, 1976).

This study is the most comprehensive survey of the morphology and histochemistry of skeletal

muscle from elderly living subjects. It indicates that abnormalities of skeletal muscle are common in this age group.

Our pathological results are similar to those noted in a postmortem study of skeletal muscle in the elderly (Jennekens *et al.*, 1971): these authors attributed the changes observed to disuse, inadequate nutrition, myopathic change of undetermined cause, and neurogenic factors. Our subjects were active and well nourished. Careful examination gave no indication of any clinical myopathy but minor neurological abnormalities and multiple disease processes were common. This makes it difficult to evaluate the changes found in the skeletal muscle of elderly people, even in the context of detailed clinical and biochemical information.

In those patients in whom discrete abnormalities were identified, their significance remains uncertain. Tubular aggregates, which are known to occur in hypertrophic myocardium (Maron and Ferrans, 1974), have been described in skeletal muscle in a number of clinical conditions, including one elderly subject with cramps and muscle stiffness (Morgan-Hughes *et al.*, 1970). Similarly, rod bodies were originally described in association with a mild non-progressive myopathy of infancy (Shy *et al.*, 1963), but these have subsequently been identified in other disorders, including the collagen diseases (Engel, 1967). It is interesting, therefore, that our patient had polymyalgia rheumatica.

Ultrastructural studies have shown that increased staining for succinic dehydrogenase, one of the oxidative mitochondrial enzymes, usually corresponds to the presence of increased numbers of mitochondria, and these may also show morphological and biochemical abnormalities (Afifi *et al.*, 1972). Abnormal mitochondria and lipid accumulations patchily distributed in skeletal muscle are a consistent feature of oculocraniosomatic syndrome in which heart block occurs (Olson *et al.*, 1972). The frequent finding of these changes in muscle from elderly, but not from younger subjects suggests that this phenomenon may also be a feature of ageing.

We thank Dr H. Johnson, St. Thomas' Hospital, for providing postmortem material; Dr D. Landon, National Hospital for Nervous Diseases, for electron microscopy; and Dr A. Leatham for encouragement in the study. We also thank Mrs J. Batts, Miss M. Ellison, and Miss R. J. Biles for technical and secretarial assistance.

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