Preliminary Communications

Hypertrophic Cardiomyopathy. An Electrophysiological Study

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Summary: Recordings of the transmembrane action potential of the cardiac myofibril from a patient with hypertrophic obstructive cardiomyopathy showed that the repolarization time was appreciably prolonged and that the maximum rate of follow was grossly reduced. This electrical abnormality is compatible with the late and irregular activation of the ventricular muscle in the disease. Propranolol was found to produce a similar "quinidine-like" effect on the transmembrane action potential in both cardiomyopathic and control tissue.

INTRODUCTION

Hypertrophic obstructive cardiomyopathy is a disease of uncertain aetiology (Goodwin, 1970). Histological studies show massive short irregular fibres with abnormal nuclei. Electromicroscopical studies show a non-specific picture common to other cardiac diseases. The possibility of excessive noradrenaline deposits in the diseased muscle has been postulated (Pearce, 1964). To date no study of the electrophysiological property of this hypertrophic myopathic muscle has been reported.

CASE REPORT AND METHOD

A 42-year-old woman presented with a four-year history of progressive syncopal attacks and dyspnoea on exercise. She had a sharp arterial pulse wave, "a" wave in the jugular venous pulse, forceful left ventricular and presystolic thrust on palpation of the precordium, and, on auscultation, a loud atrial sound and early systolic murmur with reversed split of the second heart sound. The chest x-ray picture was within normal limits. The electrocardiogram showed the QRS voltage changes of left ventricular hypertrophy and wide T waves. The ultrasound cardiogram was diagnostic, with a characteristic early systolic anterior movement of the anterior leaflet of the mitral valve. Cardiac catheterization showed a gradient of 120 mm. Hg. across the left ventricular outflow tract. The left ventricular angiogram was characteristic of hypertrophic cardiomyopathy with moderate mitral regurgitation. The patient was treated with propranolol while awaiting operation.

At operation a firm muscle band was felt below the right coronary cusp of a normal aortic valve. Two incisions were made in the muscle band 5 mm. apart and 5 mm. deep. The intervening muscle was removed and quickly placed in oxygenated Tyrode solution for microelectrode studies. The pressure across the left ventricular outflow tract at the end of the operation was only 10 mm. Hg. The postoperative course was uneventful with good symptomatic improvement.

The excised muscle was studied by a conventional microelectrode technique (Coltart *et al.*, 1970) and the maximum rate of follow was determined by stimulating the tissue with a square pulse of 1 msec. duration at a voltage 1.5 times the stimulus threshold via a bipolar platinum electrode. The effect of increasing dosage of propranolol on the action potential was studied when the tissue was driven at a rate of 60 beats per minute. Propranolol in concentrations of 0.1 to 10 mg./l. was added to the Tyrode solution and continued until changes in the transmembrane potential had stabilized.

RESULTS

The typical ventricular transmembrane action potential from this patient is shown in Fig. 1. A comparison of the electrophysiological properties of the ventricular papillary muscle excised from eight patients undergoing mitral valve replacement (control tissue) and the hypertrophic cardiomyopathic muscle excised in this case is given in Table I. The repolarization time is increased from 302 ± 11.2 msec.

(control tissue) to 498 ± 29 msec. ($P < 0.001$) by a prolongation of the slow phase of repolarization. The maximum rate of rise of the cardiomyopathic tissue was significantly reduced ($P < 0.001$), 186 ± 12 msec. compared with 240 ± 17 msec. in the control studies. All other measurements were similar to the control values. The maximum rate of follow in the cardiomyopathic muscle was 72 beats per minute compared with 160 beats per minute in the control tissue.

TABLE I.—Difference Between the Action Potential of the Hypertrophic Cardiomyopathic and Control Human Cardiac Cell

	Time to Repolarize to 90% (msec.)	Resting Potential (mV)	Magnitude of Action Potential (mV)	Overshoot (mV)	Maximum Upstroke Velocity (V/sec.)
Control	302 ± 11.2	95 ± 6.2	117 ± 6.5	21 ± 2.3	240 ± 17
Hypertrophic cardiomyopathy	498 ± 29	94 ± 4.5	120 ± 10.2	25 ± 4.2	186 ± 12

Control = Mean $\pm$ S.E. of 8 tissue studies of left ventricular papillary muscle. Hypertrophic cardiomyopathy = Mean $\pm$ S.E. of 10 separate cells of excised muscle.

The effect of propranolol 10 mg./l. on the contour of the transmembrane action potential of the cardiomyopathic and control tissue is shown in Table II. This concentration was chosen because intermediate concentrations of propranolol had little significant change in the cardiomyopathic tissue. There is a significant reduction ($P < 0.05$) in the rate of rise of the action potential in both tissues after propranolol. There is a tendency to a reduction in the repolarization time, but this is not significant in the control tissue.

DISCUSSION

The clinical history and signs in this patient are characteristic of hypertrophic obstructive cardiomyopathy (Goodwin, 1970). The reduction in the outflow gradient, which was the object of the operation, is similar to the results reported by Morrow *et al.* (1968) in 25 patients, using the same approach.

The control action potentials in the study have been shown to resemble closely the normal canine action potential (Coltart *et al.*, 1970). Propranolol decreased the velocity of depolarization to a similar extent in both cardiomyopathic and control tissue, in common with the effect produced by other antiarrhythmic agents (Szekeres and Williams, 1962; Hoffman, 1966; Williams, 1966; Coltart and Meldrum, 1970). The grossly prolonged repolarization time in the hypertrophic cardiomyopathic fibre and the decrease in rate of rise of the

Fig. 1.—Typical hypertrophic obstructive ventricular transmembrane action potential. The horizontal line indicates zero potential; the middle trace depicts the intracellular potential. The upper trace shows the output from the differentiator; the depth of the spike is proportional to dv/dt of the intracellular record.

TABLE II.—Effect of Propranolol 10 mg./l. on Contour of Transmembrane Action Potential of Ventricular Fibres of Hypertrophic Cardiomyopathic and Control Human Cardiac Tissue

	Resting Potential (mV)	Amplitude (mV)	Duration (msec.) Measured to Repolarization Within 5 mV of Resting Potential	Upstroke Velocity (V/sec.)
Control (5)	96	122	310	235
After propranolol 10 mg./l.	96	121	300	195
Hypertrophic cardiomyopathy (6)	95	120	500	186
After propranolol 10 mg./l.	95	118	440	148

Values are mean of the number of preparations studied in the control and number of different cells in the cardiomyopathic tissue (number in parentheses).

action potential cannot be explained on the basis of present speculative concepts of transmembrane electrolyte concentrations or ionic fluxes. A block in the normal potassium transmembrane permeability would delay repolarization and

FIG. 2.—Typical human (control) ventricular transmembrane action potential. The horizontal line indicates zero potential; the superimposed middle traces depict intracellular potentials at slow and fast sweep speeds. The upper trace first shows the stimulus artefact followed by the output from the differentiator; the depth of the spike is proportional to dv/dt of the intracellular record.

prolong the refractory period; an antiarrhythmic property. A restraint on potassium permeability, however, would be expected to reduce the resting potential but this was unchanged in the present study.

Hypocalcaemia increases the duration of repolarization of the action potential mainly by prolonging the rapid early phase of repolarization and only to a lesser extent the slower and later phase as seen in the cardiomyopathic tissue. The effect of hypocalcaemia would be exaggerated by hypomagnesaemia. It therefore seems unlikely that an abnormal transmembrane permeability of any one of these electrolytes could explain the observed action potential, but a combination of a deficient flux of all three could be postulated.

Freedberg *et al.* (1970) have shown in the atria of thyroidectomized rabbits that the duration of the repolarization phase was greatly prolonged, yet it was shortened in the

atria of another group rendered thyrotoxic. The patient in this study was euthyroid. The prolonged repolarization in hypertrophic cardiomyopathy might be expected to give a prolonged Q-T interval in the electrocardiogram. No such change was observed in the present case, and prolonged Q-T intervals have not been reported in this condition. We have, however, shown that there is a poor correlation between the Q-T interval as measured from the electrocardiogram and the duration of the action potential (Coltart *et al.*, 1970).

Normal subjects can generally respond with 1:1 A-V conduction to atrial rates up to 200/min. Linhart *et al.* (1965) found an average basal functional refractory period of 350 msec. in patients without abnormalities of A-V conduction, which would thus allow maximum rates of follow of 170/min. This agrees well with the maximum rate of follow of 160/min. in the control human tissue in this study, the difference being possibly due to the diseased state of the papillary muscle excised from these patients undergoing mitral valve replacement.

The gross reduction in the maximum rate of follow to 72/min. in the hypertrophic cardiomyopathic muscle shows an inability of this tissue to shorten its effective refractory period and would explain the late and irregular sequence of propagation of the activation impulse through the ventricular cavity previously supposed to be due to discrete myocardial fibrosis or stretching of the conduction tissue.

Meerscham (1969) reported delayed and polyphasic action potentials from the skeletal muscle of patients with hypertrophic cardiomyopathy. He suggested that there might be a generalized myopathy even though these people rarely manifest any skeletal muscle disability. Thus there is further evidence for an electrophysiological abnormality in this disease.

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Medical Memoranda

Recurrent Meningitis

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Meningitis appears to have been previously unreported as a complication of decubitus ulcers; in the case described it occurred in association with sacral or perineural cysts. It is suggested that the association of sacral cysts with osteomyelitis of the adjacent sacrum as the result of decubitus ulceration may have facilitated entry of infection to the subarachnoid space.

CASE REPORT

A 43-year-old spinster with an 18-year history of seropositive rheumatoid arthritis causing little disability developed active hepatitis in August 1968. Three months later she had staphylococcal septicaemia, which apparently arose from a primary focus of infection in a toe, and this illness was complicated by acute renal failure and jaundice. The infection responded well to penicillin, and renal function returned to normal on a conservative regimen. She was started on prednisone 20 mg. daily to control the hepatitis. During the initial period of her illness she was semicomatose and immobile, and by the fifth day a decubitus