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Effect of Propranolol on Exercise Tolerance of Patients with Atrial Fibrillation

R. W. BROWN,* M.B., B.S., M.R.A.C.P.; A. J. GOBLE,† M.D., F.R.A.C.P., M.R.C.P.

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Summary: Six patients with atrial fibrillation who were taking digitalis were exercised before and after 30 mg. of propranolol twice daily. Though there was a lower pulse rate at rest and on exercise in all patients, three suffered deterioration of exercise tolerance. It is concluded that propranolol does not improve the exercise tolerance of patients with atrial fibrillation whose resting ventricular rate is controlled with digitalis.

Introduction

It has been shown experimentally in animals that, under exercise conditions, increasing pulse rate is associated with increasing cardiac output up to a critical value, after which diastolic filling of the ventricles is impaired and the cardiac output falls (Corday and Irving, 1961). It is not known at what level the change occurs in human hearts in sinus rhythm, but some physiologists have suggested that it is between 160 and 180/minutes (Rushmer, 1960; Wood, 1968). Ventricular rates during submaximal and maximal exercise are about 10% higher than this in patients with atrial fibrillation who are taking digitalis (Hornstein and Bruce, 1968). Propranolol, which is known to reduce the ventricular rate at rest and during exercise (Harrison *et al.*, 1965; Chamberlain, 1966; Schulman *et al.*, 1967), may improve the exercise tolerance of patients with atrial fibrillation via this mechanism. This improvement might outweigh the negative inotropic action of the drug and produce a net benefit.

A double-blind trial was therefore devised to determine whether the addition of propranolol resulted in clinical improvement in the exercise tolerance of patients with atrial fibrillation taking digitalis.

* Cardiac Registrar.

† Cardiologist.

Royal Melbourne Hospital, Melbourne, Victoria, Australia.

Patients and Methods

Outpatients with chronic atrial fibrillation taking digitalis and whose general medical condition had been stable for some weeks were selected. The clinical details are shown in the Table. Five of the six had rheumatic heart disease and one was euthyroid after radiation therapy for thyrotoxicosis.

The patients continued to take their usual therapy, including digitalis, and were subjected to exercise on three occasions, each a week apart. After the first test they were allocated, by double-blind method, either propranolol 30 mg. twice daily or a placebo for the first week, and were given the alternative after the second test.

Before each exercise test the patients were interviewed, their pulse rate and arterial pressure were taken, and they were examined for signs of cardiac failure. Each patient then undertook the same three levels of exercise on a treadmill at a 5° slope for three minutes. The maximum level achieved by each patient on the first test was attempted at both subsequent tests.

The heart rate and electrocardiograph were monitored throughout the test, and the heart rate over the last 30 seconds was recorded by means of a Royal Melbourne Hospital cardiac cycle counter (Mark II). The arterial pressure was taken immediately the exercise was completed.

Results

Fig. 1 illustrates the difference in heart rate at rest and on exercise with and without propranolol. In the one patient who did not actually exercise at 3 km./hour an estimated pulse rate was determined from the line of best fit on a pulse-rate/work-load graph. In all cases there was a reduction in pulse rate after propranolol, and the mean reduction of pulse rate was 28/minute at rest, 39/minute at 3 km./hour, and 36/minute at the maximum exercise level.

Clinical Details of the Patient

Case No.	Age	Cardiac Disease	Functional Classification†	Maximum Exercise Level (km./hour)	Maximum Pulse Rate (Control)	Patients' Observations After Propranolol	Clinical Observations After Propranolol*
1	54	R.H.D. mitral valvotomy. Hypertension	Class 1	5.25	178	Unchanged	Unchanged
2	34	R.H.D. M.S. M.I.	Class 2	5.0	176	Unchanged	Unchanged
3	44	Controlled thyrotoxicosis	Class 2	6.0	190	Unchanged	Unchanged
4	48	R.H.D. M.S. I.H.D.	Class 2	4.0	184	Noted increased dyspnoea on effort	J.V.P. raised 2 cm.
5	55	R.H.D. M.I.	Class 2	5.0	154	Noted increased effort dyspnoea and P.N.D.	Unable to complete exercise test because of dyspnoea
6	52	R.H.D. M.I.	Class 3	3.5	128	Increased dyspnoea noted during exercise test only	Collapse during exercise test (see text)

* The changes in pulse rate and arterial pressures are set out in Figs. 1 and 2.

† New York Heart Association.

Abbreviations: I.H.D. = Ischaemic heart disease. R.H.D. = Rheumatic heart disease. M.S. = Mitral valve stenosis. M.I. = Mitral valve incompetence. P.N.D. = paroxysmal nocturnal dyspnoea. J.V.P. = Jugular venous pressure.

The reductions in systolic blood pressure after propranolol at the same exercise levels is shown in Fig. 2. The mean reduction at rest was 21 mm. Hg, at 3 km./hour 28 mm. Hg, and at the maximum level of exercise 39 mm. Hg.

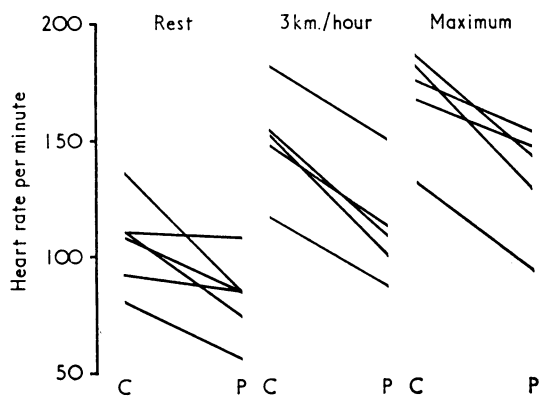


FIG. 1.—Pulse rate at rest and two exercise levels. C = Control (placebo). P = Propranolol.

Three of the six patients noted definite worsening of their exercise tolerance and all three had objective evidence of deterioration.

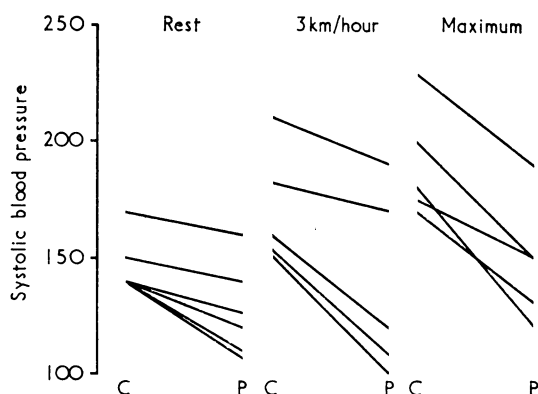


FIG. 2.—Arterial pressure at rest and two exercise levels. C = Control (placebo). P = Propranolol.

One (Case 4) reported increased dyspnoea on effort and on examination was found to have raised jugular venous pressure. He was able to complete the exercise test. Another (Case 5) noted increased effort dyspnoea and suffered an episode of paroxysmal nocturnal dyspnoea. He was unable to reach his previous level of exercise because of dyspnoea. He had no clinical signs of cardiac failure. The third patient (Case 6) developed a supraventricular tachycardia during the test after taking the placebo. Despite suppression of this arrhythmia by propranolol, she still noted increased dyspnoea and collapsed with severe dyspnoea, cough, and pallor at the highest exercise level. In this patient satisfactory measurements of pulse and

blood pressure were not obtained at that test, and her exercising results are not included in Figs. 1 and 2.

In view of the definite clinical deterioration in three of the six patients and lack of symptomatic improvement in the others, the trial was abandoned.

Discussion

Since half the patients deteriorated clinically and none improved, it is concluded that the addition of propranolol does not improve the exercise tolerance of patients with atrial fibrillation taking digitalis at the pulse levels attained in the trial. As the rate at which tachycardia interferes with diastolic filling is not known, the patients under test may not have exceeded this level. Therefore, since cardiac output increases with increasing pulse rates up to this unknown critical level, the reduction in pulse rate may well have been harmful. There is some evidence that this critical rate in fact may be over 200 in normal hearts and even in patients with mitral stenosis—a group in particular who should benefit from a longer diastolic period (Åstrand *et al.*, 1963; Graybiel, 1964; Rowlands *et al.*, 1965). The negative inotropic action of the drug also cannot be ignored, and cases of cardiac failure attributed to the use of the drug have already been reported (Epstein and Braunwald, 1966; Conway *et al.*, 1968).

The clinical deterioration in three of the six cases is consistent with the laboratory findings of Schulman *et al.* (1967) and of Cumming and Carr (1966), who detected a reduction in cardiac output with exercise, after administration of propranolol to patients with mitral stenosis and atrial fibrillation.

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