Summary
THE regulation of circulatory pressor responses during anti-hypertensive therapy with slow calcium-channel blockers was evaluated in a single-blind placebo-controlled study of two such agents, nifedipine and nicardipine. In twelve patients with stable essential hypertension the dose-response effects of each drug on the resting blood pressure together with the pressor responses induced by skin cold, isometric exertion and dynamic exercise were examined. Nifedipine or nicardipine were administered in a logarithmic dosage schedule of 15, 30 and 60 mg/day with incremental doses at weekly intervals. The effects on resting blood pressure and heart rate at rest and during the three pressor stimuli were measured at each dose level.

Both drugs induced significant dose-related reductions in the resting diastolic blood pressure without change in pulse pressure, accompanied by an increase in heart rate; in the small numbers in the present study there were no significant differences evident between the dose-response effects of nifedipine and nicardipine. There was a small reduction in the systolic pressor response to hand cold on nifedipine; the increases in blood pressure and heart rate induced by hand-grip contraction or sub-maximal treadmill walking were unaffected by either drug. These studies suggest that calcium antagonists, by reducing the resting blood pressure, without impairing the circulatory responses to daily activities, have a potentially important therapeutic role in the management of essential hypertension.

Introduction
Blood pressure varies widely during daily life both in normal subjects and in the hypertensive patient (Pickering, 1968). A number of pressor influences are superimposed on the basic diurnal rhythm; these include those due to dynamic and static exercise, cold or mental stress, either singly or in combination. Except in the case of mental stress there is a clear stimulus-response relationship in both normal and hypertensive subjects; the autonomic mechanisms have been recently reviewed (Taylor, 1981).

The influence of anti-hypertensive agents on the circulatory responses induced by these common daily stimuli is of potential therapeutic importance. The modulation of pressor responses by sympatholytic agents (Taylor et al, 1979; Watt et al, 1980; Taylor, 1980), selective (Nelson et al, 1982) and non-selective (McAllister, 1979) alpha-adrenoceptor antagonists as well as by simultaneous alpha/beta-blockade (Maconochie et al, 1977) has been described. Calcium antagonists which directly relax arterial smooth muscle (Massingham, 1973; Fleckenstein, 1977; Mikkelsen et al, 1979) and thereby reduce peripheral
vascular resistance are effective anti-hypertensive agents in patients at rest (Bartorelli et al., 1978; Lederballe-Pedersen and Mikkelsen, 1978). However, it is not known whether the reduction in resting blood pressure induced by these agents is equally reflected in their ability to suppress the surges in blood pressure that occur in response to dynamic exercise, isometric exertion or in response to cold. This was investigated in the following dose-response comparative study of nifedipine and a newer calcium antagonist, nicardipine (Seki and Takenaka, 1977; Higuchi et al., 1980; Higuchi and Shiobara, 1980).

Method

Patients: Twelve male patients, aged 31-63 years, with essential hypertension (DBP 110±3; range 100-130) were studied. Cardiothoracic ratio was within normal limits in all (range 0.43-0.50). In two patients there was electrocardiographic evidence of left ventricular hypertrophy, in a further two T wave inversion and unifocal ventricular extrasystoles respectively, the remainder had a normal ECG. No patient had clinical or biochemical evidence of any metabolic disease. None had hypercholesterolaemia (>8 mmol/l), hypertriglyceridaemia (>1.7 mmol/l), anaemia (Hb<13.5 g/dl) or any inter-current systemic disorder. No patient had previously received anti-hypertensive medication. The groups were well matched for major variables, although those randomised to nicardipine were somewhat younger (Table I). Informed consent was obtained from each patient and the study was approved by the Hospital Ethics Committee.

Design of Study: The study was a placebo-controlled single blind dose-response design, undertaken on an outpatient basis, with patients randomised to nifedipine or nicardipine prior to the study. Patients were familiarised with the laboratory techniques on a number of occasions beforehand. At each attendance the pressor responses were carried out in the order cold, isometric exertion and dynamic exercise, commencing one hour after the first oral dose of the day. Blood pressure and heart rate were measured at minute intervals throughout each observation period. The study commenced with each patient comfortably reclining for five minutes, following which five control measurements were made at 1 min intervals. The cold pressor response was then carried out by immersion of the right hand in water at 0°C for two minutes. When blood pressure and heart rate had returned to control values, the isometric pressor response was measured also in the recumbent posture. The patient gripped a standard adult (13 x 23 cm) rolled sphygmomanometer cuff, pre-inflated to 10mmHg, with the right hand and raised and maintained the mercury column steady at 100mmHg for 3 minutes. This standardised method of isometric testing has been calibrated in 6 normal volunteers; in repeated tests on 5 separate occasion in each subject, the average (range) of the coefficients of variation in the circulatory response at the end of 3 min static effort was for systolic blood pressure 2.7% (1.7-3.6%), for diastolic blood pressure 4.4% (2.1-7.9%) and for heart rate 3.9% (2.2-6.9%). The pressor response induced by this method in the same 6 volunteers, did not differ significantly from that elicited during 3 min sustained effort at 30% maximum voluntary contraction, using a conventional electrical dynamometer. The magnitude of the pressor response to this static effort was similar in 6 patients with uncomplicated hypertension (Silke and Taylor, 1982).

When the blood pressure and heart rate had returned to control values, the dynamic exercise test was carried out. The patient stood at rest on the treadmill for three minutes and then walked at a pre-determined speed and incline suffic-