A rest and exercise haemodynamic evaluation of a new cardio-selective β -adrenoceptor blocker celiprolol alone and in combination with nitroglycerine in ischaemic heart disease

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1 The symptomatic benefits of combining β -adrenoceptor blockers and nitrates in angina pectoris are well recognised. Their actions on cardiac haemodynamics and volumes when combined have been poorly characterized. Accordingly this study investigated a new cardioselective β -adrenoceptor blocking agent celiprolol and buccal nitroglycerine in 24 patients with angiographically documented coronary artery disease.

2 Following a control period, with confirmed stable haemodynamics, three groups ($n = 8/\text{group}$) of prospectively matched patients, were studied following intravenous celiprolol (8 mg), buccal nitrate (10 mg) or their combination. Haemodynamics and left ventricular ejection fraction (nuclear probe) were determined following each intervention. The actions of each regimen on the haemodynamics of exercise-induced angina were compared by exercise testing in the control state and following each regimen.

3 At rest, celiprolol did not alter haemodynamic parameters. Nitrate therapy reduced left ventricular filling pressure (pulmonary artery occluded pressure—PAOP) and volumes; the ejection fraction and heart rate increased. Combination therapy resulted in a highly significant reduction in left ventricular preload and afterload (PAOP and mean arterial blood pressure) at an increased left ventricular ejection fraction and reduced cardiac volumes; there was a trend to reduce cardiac double product ($\text{HR} \times \text{SBP}$).

4 During exercise celiprolol reduced systolic blood pressure, heart rate and cardiac index; systemic vascular resistance index increased. Nitrate therapy reduced blood pressure and PAOP, and increased ejection fraction. Combination therapy reduced all components of the triple product (heart rate, systolic blood pressure and PAOP) without affecting the other haemodynamic or radionuclide parameters.

5 These data suggest improvements in cardiac function from the combination of celiprolol and nitrate therapy which were not achieved by either agent when used as monotherapy; they afford an interesting insight into the manner in which such widely utilised therapeutic modalities interact in coronary artery disease.

Keywords celiprolol nitroglycerine ischaemic heart disease
 β -adrenoceptor blocker

Introduction

The haemodynamic accompaniments of exercise-induced angina are increases of left ventricular end-diastolic pressure and volume (Parker *et al.*, 1966; Wiener *et al.*, 1968; Mann *et al.*, 1977). Although β -adrenoceptor blocking compounds are effective anti-anginal agents (Prichard *et al.*, 1970; Thadani *et al.*, 1979), they may increase left ventricular end-diastolic pressure and volume, aggravating the underlying haemodynamic disorder (Hendry *et al.*, 1981; Silke *et al.*, 1981; Taylor *et al.*, 1982). Nitrates have been widely used in cardiovascular therapeutics; their anti-anginal action is associated with a reduction in left heart volumes and an improved cardiac ejection fraction (Christenson *et al.*, 1965; Najmi *et al.*, 1967; Parker *et al.*, 1971; McAnulty *et al.*, 1975; Shah *et al.*, 1976; Schwartz *et al.*, 1977; Steele *et al.*, 1978; Slutsky *et al.*, 1983). Logically the combination of β -adrenoceptor blockade and nitrate therapy might be expected to be advantageous in patients with severe coronary artery disease and impaired cardiac pumping function. Celiprolol is a new cardioselective β -adrenoceptor antagonist with ancillary agonist activity (Pittner & Bonelli, 1983). The following study was a between group comparison of the effects of single i.v. doses of celiprolol, buccal nitroglycerine or their combination in patients with stable but reproducible angina pectoris; the comparative effects of each regimen on the haemodynamics of exercise-induced angina were compared using a previously validated model (Taylor *et al.*, 1982).

Methods

Patients

Twenty-four patients with electrocardiographic and angiographic evidence of coronary artery disease were studied. Patients were matched for major clinical and haemodynamic variables and allocated to each drug. The average (s.e. mean) age of the patients was 52 ± 2 years (range 33–67); average duration of angina 15 ± 5 months (range 3–108). Nineteen had suffered a previous myocardial infarction (anterior 9, inferior 10). Chest radiography was normal in all (cardiothoracic ratio 0.46 ± 0.01). Coronary artery narrowing ($> 70\%$ diameter stenosis) was present in 1, 2 or 3 vessels in 4, 11 and 9 of the patients respectively. The anginal workload was 92 ± 12 Watt (range 20–200). Patients with unstable angina pectoris, a myocardial infarction within 3 months of the study, clinical evidence of mitral

regurgitation, and those in whom previous cardio-active medication (with the exception of nitrates) could not be safely discontinued for 72 h prior to these studies were excluded. No patient received nitrate therapy within 12 h or other cardioactive medication within 72 h of the investigations. The purpose of the study was explained to each patient who freely consented to participate; the study was approved by the Hospital Ethics Committee.

Study design

The study was a randomised open haemodynamic and radionuclide evaluation of the comparative effects of celiprolol, buccal nitroglycerine or their combination. Prior to the definitive study patients were familiarised with the technique of supine-bicycle exercise, and the maximum work-load which each could maintain for 4 min determined; the chosen workload, individually titrated for each patient prior to the definitive study, reliably induced angina between 2–4 min of exercise. In each patient the study commenced (15–30 min after blood pool labelling) with the control 4 min of supine bicycle-exercise at the predetermined constant work-load. Haemodynamic and radionuclide measurements were obtained minute by minute. Following circulatory restabilisation (20 min), the control studies at rest were undertaken over 20 min. Four sets of haemodynamic and radionuclide measurements were made in the 3–5 min following each of four injections of 10 ml dextrose-saline into the pulmonary artery. Following this the randomised treatment was administered; this consisted of either celiprolol (8 mg i.v. over 1 min into the pulmonary artery), 10 mg buccal nitroglycerine (Suscard) inserted into the buccal groove or a combination of these. Haemodynamic and radionuclide measurements were recorded between 5–10 min following drug administration. Finally patients were re-exercised at the predetermined bicycle work-load and measurements again made each minute during the exercise period.

Haemodynamic procedures

A narrow bore (7F) Swan-Ganz thermodilution catheter was introduced percutaneously via a median basilic approach in the brachial fossa and advanced into the pulmonary circuit under wave form monitoring control. Systemic arterial pressure was externally transduced via a cannula (Vygon 1.2 mm external diameter) inserted with the Seldinger technique into the brachial artery.

Both pulmonary and systemic pressures were externally transduced (Bell & Howell 4-327-I), zero references being at mid-chest (average 10 cm distance below the horizontal plane of the sternal angle); both pressures were continuously displayed (Simonson and Weel System 8000) and recorded together with the ECG on a high performance ultra-violet recorder (EMI SE6300). Pressures were averaged blind, by an observer not involved in their acquisition, from 30–60 s traces obtained with the recorder run at 30 cm min⁻¹. Thermodilution cardiac output was automatically computed and recorded to facilitate quality control (Gould Statham Computer SP 1435/Recorder SP 2009). The indicator (10 ml dextrose-saline) was aspirated from a reservoir at 0° C and injected with a CO₂ powered gun (OMP 3700). Determinations of cardiac output were in triplicate; each set of measurements followed an initial injection (to allow for catheter warming losses). The variance of this technique in our laboratory is < 6% at rest and < 7% during steady state bicycle exercise. Systemic vascular resistance, stroke volume and left ventricular stroke work were derived from the following formulae and corrected for body surface area.

1. systemic vascular resistance index = mean arterial pressure (MAP) × 80/cardiac index
2. stroke volume index (SVI) = cardiac index/heart rate
3. left ventricular stroke work index = SVI × (MAP-PAOP) × 0.0136

Radionuclide techniques

The radionuclide studies were undertaken using an ECG-triggered, microprocessor based, non-imaging nuclear probe (Nuclear Stethoscope, Bios Inc., Valhalla, New York), employing previously described techniques (Wagner *et al.*, 1976; Strashun *et al.*, 1981; Links *et al.*, 1982; Lahiri *et al.*, 1984). Patients were injected with 15 mg stannous pyrophosphate (TechneScan PYP kit, Mallinckrodt Diagnostic Products), and 30 min later with red blood cells labelled *in vitro* with 99m-technetium (15 mCi). For each study, the nuclear stethoscope was positioned parallel to the catheter table and at 100 cm distance from the midpoint of the sternal angle. The degree of obliquity and caudal tilt to yield an optimum assessment was determined (usually 20–35 degree LAO with a 10–20 degree caudal tilt). With the probe, in close proximity to the chest, the circumference of the former was traced with an indelible marker on the chest to allow the same probe position to be reliably retained;

rest and exercise studies were undertaken using techniques developed to minimise chest wall motion. All angulations, and probe/chest position were subsequently maintained constant. The area of maximal left ventricular count activity and level of background activity were determined prior to each study using the microprocessor algorithm incorporated in the nuclear probe. Data were acquired in the ECG-gated mode for between 30 and 60 s, to a minimum of 10,000 counts. The left ventricular ejection fraction was determined from the displayed background subtracted left ventricular time-activity curves. This technique has been calibrated in our laboratory; in 20 patients, in whom 10 consecutive resting ejection fractions were determined at 2 min intervals, the average variability was 3.5% (range 0.9–5.7%), and over six determinations during steady state bicycle exercise was 4.6% (range 1.0–11.2).

Left ventricular end-diastolic and end-systolic volume indices were determined from simultaneous ejection fraction and thermodilution stroke output determinations using the equations:

1. ejection fraction = stroke volume index/end-diastolic volume index
2. stroke volume index = end-diastolic volume index – end-systolic volume index

Statistical analysis

The dose response and exercise data were evaluated by analysis of variance of repeated measurements (Biomedical Computer Program 'P' Series, 1979). The significance of the differences between control and post-drug data and between the three regimens was determined from the single value generated with Fisher's multiple comparison procedure (Winer, 1977). All values were judged significant at the conventional level (5%). The baseline haemodynamic variables were analysed for trends of change over the four resting control measurements; none being present the control data has been averaged from the four separate determinations.

Results

These studies were uneventful; no patient complained of adverse reactions. Although these studies were not undertaken with a view to symptomatic assessment, when asked whether there was any appreciable difference between the control and drug studies, five of the celiprolol patients, four of the nitrate and seven on the combination therapy reported that the severity

of perceived angina was less during the drug period.

Comparability of the randomised groups (Table 1)

Patients in each group were well matched for baseline demographic, clinical and haemodynamic variables including age, numbers with and sites of previous infarction, duration of angina, body surface area and weight, cardiothoracic ratio and angiographic severity of coronary artery disease. The anginal workload was similar and the control rest and exercise cardiac performance (assessed from cardiac indices, pulmonary artery occluded pressures and radionuclide ejection fractions) were not significantly different.

Stability of baseline control haemodynamic data

The reproducibility of the baseline control data was adequately demonstrated from the small coefficients of variation of the control measurements. There was no between group difference in the variability of measurements. The average and range of the coefficients of variation during the control period were: systolic blood pressure 1.5% (range 0.4–4.0%), diastolic blood pressure 1.5% (range 0–5.8%), mean blood pressure 1.6% (range 0.6–3.6%), heart rate 2.5% (range 0–6.5%), pulmonary artery occluded pressure 7.5% (range 0–16.5%), cardiac index 3.5% (range 0–10.4%) and left ventricular ejection fraction 2.9% (range 0.9–6.8%). Analysis of variance of the data with trend curve fitting revealed no significant trends of change in any of these variables in any group. Control means have therefore been averaged from these data.

Resting effects of each regimen: (Figure 1, Table 2)

Celiprolol did not alter haemodynamic parameters.

Buccal nitrate therapy resulted in small falls in resting systemic arterial systolic blood pressure and cardiac index ($-0.41 \text{ min}^{-1} \text{ m}^{-2}$; $P < 0.05$). The heart rate and left ventricular ejection frac-

Figure 1 Effects of celiprolol (C) and nitrate (N) alone and in combination (CB) on rest and exercise haemodynamic parameters in coronary artery disease. Levels of significance are related to differences from control. ** $P < 0.01$.

tion ($+9\%$; $P < 0.01$) increased. The pulmonary artery occluded pressure, left ventricular volumes and the cardiac stroke work index (-12 g m m^{-2} ; $P < 0.01$) were reduced. The systemic vascular resistance index was unchanged.

Combination therapy resulted in significantly greater falls in resting systolic (-24 mm Hg ; $P < 0.01$) and mean (-14 mm Hg ; $P < 0.01$) arterial blood pressure compared with monotherapy. The cardiac index ($-0.51 \text{ min}^{-1} \text{ m}^{-2}$; $P < 0.01$)

Table 1 Comparability of treatment groups (mean $\pm$ s.e. mean data)

Group (n = 8/Group)	Age (years)	CTR* (%)	Vessels > 70% stenoses			Anginal workload (watt)	Ejection fraction (%)
			1	2	3		
Celiprolol	50 $\pm$ 3	0.48 $\pm$ 0.01	0	5	3	94 $\pm$ 22	50 $\pm$ 3
Nitrate	55 $\pm$ 2	0.48 $\pm$ 0.01	2	2	4	107 $\pm$ 24	52 $\pm$ 4
Combination	52 $\pm$ 4	0.43 $\pm$ 0.01	2	4	2	74 $\pm$ 14	50 $\pm$ 5

*Cardiothoracic ratio

Table 2 Haemodynamic effects at rest (mean $\pm$ s.e. mean)

		Control	Drug	Difference
Systolic blood pressure (mm Hg)	C	130 $\pm$ 4	131 $\pm$ 5	+0.6
	N	146 $\pm$ 8	137 $\pm$ 10	-9.9
	Cmb	147 $\pm$ 9	123 $\pm$ 6	-23.5**
Diastolic blood pressure (mm Hg)	C	73 $\pm$ 2	74 $\pm$ 4	+1.3
	N	82 $\pm$ 5	83 $\pm$ 4	+1.4
	Cmb	78 $\pm$ 5	78 $\pm$ 5	-0.7
Mean blood pressure (mm Hg)	C	94 $\pm$ 3	95 $\pm$ 4	+0.8
	N	104 $\pm$ 6	99 $\pm$ 6	-5.8
	Cmb	102 $\pm$ 7	89 $\pm$ 6	-13.5**
Heart rate (beats min ⁻¹)	C	77 $\pm$ 4	75 $\pm$ 5	-2.4
	N	73 $\pm$ 5	82 $\pm$ 6	+9.3**
	Cmb	77 $\pm$ 4	82 $\pm$ 5	+5.7
Pulmonary artery occluded pressure (mm Hg)	C	13 $\pm$ 1	11 $\pm$ 1	-1.3
	N	11 $\pm$ 1	8 $\pm$ 1	-3.4**
	Cmb	10 $\pm$ 2	6 $\pm$ 2	-3.5**
Cardiac index (l min ⁻¹ m ⁻²)	C	3.8 $\pm$ 0.2	3.6 $\pm$ 0.2	-0.2
	N	3.2 $\pm$ 0.2	2.8 $\pm$ 0.2	-0.4*
	Cmb	3.6 $\pm$ 0.2	3.1 $\pm$ 0.2	-0.5**
Stroke volume index (ml m ⁻²)	C	50 $\pm$ 2	49 $\pm$ 3	-0.9
	N	45 $\pm$ 3	35 $\pm$ 3	-9.2**
	Cmb	48 $\pm$ 3	39 $\pm$ 4	-8.5**
Stroke work index (g m m ⁻²)	C	56 $\pm$ 4	56 $\pm$ 4	+0.6
	N	57 $\pm$ 5	45 $\pm$ 5	-12.0**
	Cmb	60 $\pm$ 4	44 $\pm$ 5	-15.7**
Systemic vascular resistance index (dyn s cm ⁻⁵ m ²)	C	2012 $\pm$ 146	2143 $\pm$ 151	+130.8
	N	2692 $\pm$ 196	2856 $\pm$ 198	+163.7
	Cmb	2325 $\pm$ 205	2319 $\pm$ 215	-5.5
Ejection fraction (%)	C	51 $\pm$ 3	50 $\pm$ 2	-0.8
	N	51 $\pm$ 4	61 $\pm$ 4	+9.4**
	Cmb	50 $\pm$ 5	64 $\pm$ 6	*14.4**
End-systolic volume index (ml m ⁻²)	C	52 $\pm$ 7	51 $\pm$ 6	-0.6
	N	47 $\pm$ 9	26 $\pm$ 6	-21.1**
	Cmb	57 $\pm$ 15	28 $\pm$ 10	-29.6**
End-diastolic volume index (ml m ⁻²)	C	102 $\pm$ 9	101 $\pm$ 8	-1.5
	N	91 $\pm$ 10	61 $\pm$ 8	-30.3**
	Cmb	105 $\pm$ 16	67 $\pm$ 12	-37.9**

Levels of significance relate to differences from control: * $P < 0.05$, ** $P < 0.01$.

C—Celiprolol; N—Buccal NTG 10 mg; Cmb—Combination

and PAOP were reduced without change in heart rate or systemic vascular resistance index. The left ventricular ejection fraction (+14%; $P < 0.01$) increased; its end-diastolic and end-systolic volume indices fell. Both the cardiac stroke work index (-16 g m m^{-2} ; $P < 0.01$) and the cardiac double-product were reduced (-8.8% ; $P = 0.07$).

Effects during dynamic exercise: (Figure 2, Table 3)

Compared with control exercise, celiprolol monotherapy reduced systolic (-18 mm Hg ;

$P < 0.05$) blood pressure, cardiac index ($-1.3 \text{ l min}^{-1} \text{ m}^{-2}$; $P < 0.01$), heart rate ($-15 \text{ beats min}^{-1}$; $P < 0.01$) and cardiac double-product (-19.7% ; $P = 0.006$). Exercise systemic vascular resistance index increased ($+209 \text{ dyn cm s}^{-5} \text{ m}^2$; $P < 0.01$); PAOP and left ventricular volumes were unaltered.

Buccal nitroglycerine significantly reduced exercise systemic arterial blood pressure. There was a trend to reduce the exercise cardiac index ($-0.6 \text{ l min}^{-1} \text{ m}^{-2}$; $P = 0.06$) at unchanged heart rate. The exercise left ventricular ejection fraction increased (+12%; $P < 0.05$) with a highly significant fall in PAOP (-12 mm Hg ;

Figure 2 Effects of celiprolol (C) and nitrate (N) alone and in combination (CB) on cardiac double-product at rest and during supine bicycle exercise in coronary artery disease. Levels of significance are related to differences from control.

$P < 0.01$). The decreases in left ventricular volume indices did not achieve conventional significance levels. The exercise double-product fell (-14.6% ; $P = 0.005$).

Combination therapy significantly reduced exercise systemic arterial blood pressure and heart rate (-12 beats min^{-1} ; $P < 0.01$) but the cardiac index was maintained compared with control exercise. There was a highly significant fall in exercise PAOP (-12 mm Hg; $P < 0.01$) and cardiac double product (-20.1% ; $P < 0.01$). The other haemodynamic variables were unchanged.

Discussion

This study described the haemodynamic profiles of celiprolol, buccal nitroglycerine and their combination at rest and during exercise in stable coronary artery disease. It is important to stress the factors influencing the results of such comparative studies as well as the relevance and limitations of such exercises. The study was designed as a between group study, comparing the change in haemodynamic variables induced by celiprolol, nitrate or combination both at rest and during exercise. Although it may be argued that a better method of assessment would be a sequential assessment technique, where each patient received each treatment, there are also problems with this type of study methodology. Following a period of dynamic exercise at sub-maximal workloads, 20 min must be allowed for haemodynamic recovery (Verma *et al.*, 1984). This inevitably introduces the risk of an order effect on haemodynamic variables, as previously demonstrated (Silke *et al.*, 1986). In this study we elected for a between group assessment

as all therapies can be assessed at approximately the same time in terms of pharmacodynamic activity. Of course important prerequisites for valid comparison in this study design are comparable patients with well matched baseline demographic, clinical and haemodynamic parameters. We believe that these considerations were adequately fulfilled in the current study.

The methodology utilised has been well validated. The computerised measurement of blood flow and cardiac index by thermodilution (Forrester *et al.*, 1972; Sorenson *et al.*, 1976; Hoel, 1978) is a reliable technique; in our laboratory its variability is $< 6\%$ at rest and $< 7\%$ during constant load bicycle exercise (Verma *et al.*, 1984). The left ventricular ejection fraction data was obtained with a non-imaging nuclear probe in the ECG multiple-gate mode. Several groups of investigators have validated this methodology (Wagner *et al.*, 1976; Bacharach *et al.*, 1977; Berger *et al.*, 1981; Strashun *et al.*, 1981; Links *et al.*, 1982; Lahiri *et al.*, 1984). There is a high level of correlation between the standard gamma camera and nuclear probe-derived ejection fractions in normal volunteers, with a mean (s.d.) difference of only 0.3% (2.60) and 2.3% (5.02) at rest and peak exercise (Lahiri *et al.*, 1984). Both the reproducibility (c.v. at rest $< 4\%$; exercise $< 6\%$) and accuracy (against angiographic EF%: $r = 0.85$; $P < 0.001$) of this technique in our laboratory have been established. Since ejection fraction is the ratio of stroke volume to end-diastolic volume, left ventricular end-diastolic volume index can be derived from simultaneously measured stroke volume index and ejection fraction. It appears that the left ventricular volume calculated at rest and during dynamic exercise in the present series were similar to those derived by conventional gamma-camera and biplane cineangiography techniques in patients with equivalent coronary artery disease (Links *et al.*, 1982; Rackley *et al.*, 1970; Feild *et al.*, 1972; McKay *et al.*, 1984).

The doses and routes of drug administration were those which have been previously demonstrated to result in substantial pharmacodynamic effects (Silke *et al.*, 1985a, 1986); the route of drug administration was selected based on ease of administration and laboratory convenience. These considerations suggest that our data reliably describe the acute pharmacodynamic actions of celiprolol, nitrate and their combination in coronary artery disease.

Haemodynamic effects

Previous studies have in general demonstrated reduction in cardiac performance following

Table 3 Haemodynamic effects during supine bicycle exercise (mean $\pm$ s.e. mean)

		Control	Drug	Difference
Systolic blood pressure (mm Hg)	C	185 $\pm$ 10	167 $\pm$ 4	-17.8*
	N	196 $\pm$ 14	171 $\pm$ 10	-24.5**
	Cmb	179 $\pm$ 12	159 $\pm$ 10	-20.5*
Diastolic blood pressure (mm Hg)	C	84 $\pm$ 2	83 $\pm$ 2	-1.5
	N	93 $\pm$ 3	82 $\pm$ 4	-10.8**
	Cmb	86 $\pm$ 6	79 $\pm$ 5	-6.9**
Mean blood pressure (mm Hg)	C	116 $\pm$ 4	111 $\pm$ 3	-5.5
	N	127 $\pm$ 5	110 $\pm$ 5	-17.1**
	Cmb	117 $\pm$ 9	103 $\pm$ 6	-13.5**
Heart rate (beats min ⁻¹)	C	115 $\pm$ 6	100 $\pm$ 5	-15.0**
	N	111 $\pm$ 8	108 $\pm$ 8	-3.2
	Cmb	111 $\pm$ 7	98 $\pm$ 4	-12.4**
Pulmonary artery occluded pressure (mm Hg)	C	24 $\pm$ 2	25 $\pm$ 2	+1.4
	N	28 $\pm$ 6	16 $\pm$ 3	-11.8**
	Cmb	23 $\pm$ 5	11 $\pm$ 3	-11.5**
Cardiac index (l min ⁻¹ m ⁻²)	C	7.2 $\pm$ 0.3	5.9 $\pm$ 0.3	-1.29**
	N	6.4 $\pm$ 0.8	5.7 $\pm$ 0.6	-0.63
	Cmb	5.8 $\pm$ 0.6	5.7 $\pm$ 0.5	-0.14
Stroke volume index (ml m ⁻²)	C	64 $\pm$ 3	60 $\pm$ 2	-3.8
	N	57 $\pm$ 5	53 $\pm$ 4	-3.8
	Cmb	53 $\pm$ 5	58 $\pm$ 5	+4.9
Stroke work index (g m m ⁻²)	C	80 $\pm$ 4	69 $\pm$ 3	-10.3
	N	80 $\pm$ 12	69 $\pm$ 7	-11.4
	Cmb	69 $\pm$ 9	72 $\pm$ 6	+3.4
Systemic vascular resistance index (dyn s cm ⁻⁵ m ²)	C	1304 $\pm$ 71	1513 $\pm$ 77	+208.7**
	N	1765 $\pm$ 208	1648 $\pm$ 167	-116.3
	Cmb	1717 $\pm$ 214	1546 $\pm$ 176	-171.8*
Ejection fraction (%)	C	37 $\pm$ 2	38 $\pm$ 4	+1.3
	N	41 $\pm$ 4	53 $\pm$ 5	+11.9**
	Cmb	35 $\pm$ 5	43 $\pm$ 6	+7.7
End-systolic volume index (ml m ⁻²)	C	114 $\pm$ 14	107 $\pm$ 15	-7.2
	N	86 $\pm$ 11	53 $\pm$ 10	-33.1
	Cmb	113 $\pm$ 21	97 $\pm$ 24	-16.1
End-diastolic volume index (ml m ⁻²)	C	178 $\pm$ 16	167 $\pm$ 17	-11.0
	N	143 $\pm$ 13	106 $\pm$ 12	-36.9
	Cmb	166 $\pm$ 21	155 $\pm$ 25	-11.2

Levels of significance relate to differences from control: * P < 0.05, ** P < 0.01

C—Celiprolol; N—Buccal NTG 10 mg; Cmb—Combination

intravenous β -adrenoceptor blockade in patients with stable coronary artery disease (Svendsen *et al.*, 1979; 1981; Taylor *et al.*, 1982). Such cardio-depression is a direct consequence of withdrawal of cardiac sympathetic support; however it may be offset if the β -adrenoceptor antagonist possesses ancillary cardio-stimulating pharmacological properties (Prichard *et al.*, 1970; Thadani *et al.*, 1979; Taylor *et al.*, 1982). The nature of these cardio-stimulating properties of celiprolol is at present debated; however the drug induces mild increase in cardiac index and left ventricular ejection fraction at rest but β -

adrenoceptor blocking effects during dynamic exercise (Silke *et al.*, 1986). In the present study, resting cardiac parameters were unaffected; however its β -adrenoceptor blocking actions were clearly evident during dynamic exercise both in the celiprolol alone group (decreased heart rate, systolic BP and cardiac index) and in the combination group (decreased heart rate).

In contrast the published literature has shown that nitrates consistently reduce left ventricular filling pressure in patients with coronary artery disease, but the resultant impact on cardiac pumping has been variable (Christenson *et al.*,

1965; Najmi *et al.*, 1967; Parker *et al.*, 1971; McAnulty *et al.*, 1975; Shah *et al.*, 1976; Schwartz *et al.*, 1977; Steele *et al.*, 1978; Slutsky *et al.*, 1983). Shah *et al.* (1976) demonstrated that nitroglycerine resulted in a deterioration of cardiac index in patients with coronary artery disease and low or normal left ventricular filling pressures, but caused no deterioration or even improvement in those with high filling pressures. It was therefore not unexpected that the rest and exercise effects of nitroglycerine on cardiac function in patients with stable coronary artery disease might differ, with a fall in cardiac index at rest, in the presence of a normal left ventricular filling pressure, but without change in cardiac index or possibly an improvement on exercise as filling pressure rose above normal. This was indeed confirmed in the present study. At rest the reduction in pulmonary artery occluded pressure (-3 mm Hg) was accompanied by a reduced cardiac stroke volume index. In contrast on exercise, greater reductions in pulmonary artery occluded pressure (-12 mm Hg) occurred without change in this variable. These findings are similar to those of Najmi *et al.* (1967) and are of interest in that they show the dependence of the actions of nitrate on the absolute level of the left ventricular filling pressure. The derived measurements of left ventricular volume index showed that both systolic and diastolic chamber size increased on exercise, and that buccal nitrate significantly reduced chamber size both at rest and on exercise. The exercise cardiac double-product was also reduced.

The combination of celiprolol and nitrate did in the main produce predictable interactive effects although there were some unanticipated findings. Thus combination therapy resulted in similar increases in left ventricular ejection fraction and similar decreases in PAOP, left ventricular volumes and cardiac stroke work index to nitrate monotherapy. The reflex increases in heart rate, in response to the blood pressure reduction on nitrate monotherapy, were attenuated on combination therapy.

However there was a greater fall in systolic and mean arterial pressure on combination therapy than would have been predicted based on the effects of monotherapy. Two explanations are possible; either it represented a group 'sensi-

tivity' effect or was a true drug interactive effect. The lack of any discrepancy in systemic arterial pressure on exercise between nitrate monotherapy and combination therapy would suggest the latter explanation; it is possible that the substantial reduction in blood pressure was similar to the haemodynamics of nitrate syncope, when excessive reductions in cardiac preload lead to suboptimal cardiac filling and hypotension. Attenuation of the compensatory reflex sympathetic response by intercurrent β -adrenoceptor blockade would be expected to exaggerate any such tendency. In this regard the lowest PAOP values were attained on combination therapy, perhaps supporting this explanation.

During dynamic exercise the reductions in left ventricular afterload (systemic arterial blood pressure) and in the left ventricular filling pressures were similar to those on nitrate monotherapy; exercise cardiac output was better maintained with a higher stroke index compared with nitrate monotherapy.

Taken together these results demonstrated the nature of the haemodynamic advantages from the combination of celiprolol and nitrate therapy in stable angina pectoris. At rest left ventricular preload and afterload were reduced, associated with an increased left ventricular ejection fraction and a fall in its volumes. Cardiac stroke work index was reduced, the cardiac double-product tended to fall. During dynamic exercise, all components of the cardiac triple product (heart rate $\times$ BP $\times$ PAOP) were reduced without change in ejection fraction and stroke work index. The extrapolation from such short-term observations to longer term clinical therapy must be guarded; however it should be noted that seven of eight patients in the present study claimed considerable symptomatic benefit from the combination. Further investigation of the possible haemodynamic and symptomatic benefits of this combination appear merited.

We wish to thank the nursing and technical staff of the Department of Medical Cardiology for their help, and Mrs A. Richmond for statistical advice. We wish to acknowledge financial support from the Yorkshire Regional Health Authority, West Riding Medical Research Trust and from Revlon U.K.

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(Received 20 March 1986,
accepted 1 August 1986)