Effects of buccal nitrate on left ventricular haemodynamics and volume at rest and during exercise-induced angina

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1 A novel approach has been employed to characterize the effects of a cardioactive drug on left ventricular haemodynamics and volume by simultaneously determining cardiac stroke volume (thermodilution) and left ventricular ejection fraction (nuclear probe).

2 The effects of glyceryl trinitrate were evaluated in 12 patients with angiographically proven coronary artery disease at rest and 3, 7, 15 and 30 min following 10 mg buccal nitroglycerine (Suscard) administration. The impact of the drug on left ventricular haemodynamics and volume during exercise-induced angina was determined by repeating exercise 30 min following drug administration, at the workload that reliably induced angina during control exercise.

3 At rest buccal nitroglycerine reduced systemic arterial pressure, cardiac and stroke volume indices, and increased heart rate. The left ventricular ejection fraction (E.F.) increased; its filling pressure together with end-diastolic and end-systolic volumes were significantly reduced. Compared with control supine-bicycle exercise, the drug reduced mean systemic arterial pressure and left ventricular filling pressure without change in cardiac and stroke volume indices. There was a smaller increase in left ventricular volume during exercise, and the fall in E.F. was attenuated.

4 These data demonstrated differential actions of glyceryl trinitrate on left ventricular function related to the physiological state in obstructive coronary artery disease. These techniques appear to hold promise in the evaluation of the effects of other therapies on left ventricular volume in coronary artery disease.

Keywords buccal nitrate angina haemodynamics left ventricular volume

Introduction

The major haemodynamic action of nitroglycerine is a reduction in left ventricular filling pressure; this has been reported to result in variable alterations in cardiac output and stroke volume (McAnulty *et al.*, 1975; Williams *et al.*, 1975; Shah *et al.*, 1976; Schwarz *et al.*, 1977; Steele *et al.*, 1978; Slutsky *et al.*, 1983). Owing to the technical difficulties involved the majority of studies have been confined to resting evaluation of nitrates with relatively little information available concerning their actions during symptomatic

angina (Christensson *et al.*, 1965; Najmi *et al.*, 1967; Parker *et al.*, 1971).

The Starling effect relates left ventricular performance to sarcomere length or ventricular volume at end-diastole (Braunwald *et al.*, 1984). In clinical practice however, the left ventricular filling pressure is more readily determined than its filling volume; consequently the former is frequently used as an index of filling volume. However substitution of pressure for volume is only valid at an unchanged myocardial com-

pliance. Recent advances in non-invasive echocardiographic and radionuclear imaging techniques now enable the direct measurement of rest and exercise left ventricular volumes (Crawford *et al.*, 1979; Folland *et al.*, 1979; Schiller *et al.*, 1979; Slutsky *et al.*, 1979; Konstam *et al.*, 1981). In the current study they have been derived from the ejection fraction, obtained with a non-imaging nuclear probe, and stroke volume by thermodilution (Ganz & Swan, 1972; Wagner *et al.*, 1976).

The study evaluated the supine rest and exercise effects on cardiac function of buccal glyceryl trinitrate in patients with coronary artery disease.

Methods

Patients

Twelve patients with electrocardiographic and angiographic evidence of stable coronary artery disease were studied. Coronary artery narrowing ($> 70\%$ diameter stenosis) was present in 1, 2, or 3 vessels in two, three and seven of the patients respectively. Ten had suffered a previous myocardial infarction; the predominant site was anterior in 4 and inferior in 6. The mean age was 51 years, range 39–62 years; average angina duration was 32 months (range 3–96). Chest radiography was normal in all (cardiothoracic ratio 0.47: range 0.40–0.53). Patients with unstable angina pectoris, a myocardial infarction within 3 months of the study, and those receiving therapy with cardioactive medication (excluding nitrates) were excluded. 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 an open haemodynamic and radionuclide evaluation of the effects of buccal nitroglycerine 10 mg (Suscard). 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 (77 ± 10 (s.e. mean) Watt) 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 individually predetermined constant work-load. Haemodynamic and radionuclide measurements were obtained minute by minute. Following circulatory re-stabilisation (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 saline into the pulmonary artery. Following this 10 mg buccal nitrate was inserted into the buccal groove and measurements repeated at 3, 7, 15 and 30 min. Finally patients were re-exercised at the predetermined bicycle work-load and measurements again made each minute during the exercise period. No patient received additional nitrate medication within 12 h, or other cardioactive medication within 72 h of these investigations.

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 and Howell 4-327-I), zero reference 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} . Cardiac output was via the thermodilution technique, injection (aspirated via three-way tap from a reservoir at 0°C) of the indicator (10 ml dextrose-saline) was with a CO_2 powered gun (OMP 3700); cardiac output being automatically computed and recorded (Gould Statham Computer SP 1435/Recorder SP 2009). 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 = mean systemic artery pressure (MAP) $\times$ 80/cardiac output
2. stroke volume (SV) = cardiac output/heart rate
3. left ventricular stroke work = SV $\times$ (MAP-PAOP) $\times$ 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). Patients were injected with 15 mg stannous pyrophosphate (Technescan PYP kit, Mallinckrodt Diagnostic Products), and approximately 30 min later with red blood cells labelled *in vitro* with 99m-technetium (15 mCi). Measurements were obtained with the probe positioned over the praecordium in the 35–45 degree left anterior oblique position with a 10–15 degree caudal tilt. The area of maximal left ventricular count activity and level of background activity were determined before each set of haemodynamic measurements using the microprocessor algorithm incorporated in the nuclear probe. Data were acquired in the ECG-gated mode for between 30 and 60, 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 consecutive measurements during constant load supine bicycle exercise 4.6% (range 1.0–11.2%).

Statistical analysis

The dose-response and exercise data were evaluated by analysis of variance of repeated measurements (Biomedical Computer Programs—P Series, 1979). The significance of difference between control and post-drug data was determined from the single value generated with a multiple comparison procedure (Winer, 1971). 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 having been present the control data have been averaged from these four determinations.

Results

These studies were completed without incident in any patient. None complained of adverse reactions during or following any drug dose or period of exercise.

Variability of control haemodynamic measurements

The mean and range of the coefficients of variation for haemodynamic variables over the control period were for systemic mean arterial blood pressure 1.6% (range 0.5–4.3%), heart rate 3.2% (range 1.5–5.7%), cardiac index 5.1% (range 1.9–10.4%), pulmonary artery occluded pressure 10.0% (range 4.6–16.2%) and ejection fraction 3.7% (range 0.8–6.9%). There was no change in haemodynamic variables over the control period; consequently values for each variable have been averaged from the four control values.

Effects of buccal nitrate at rest (Figure 1; Table 1)

At rest there were immediate (3 min) reductions in the pulmonary artery occluded pressure (PAOP: -3 mm Hg; $P < 0.01$), cardiac index (-0.3 l min $^{-1}$ m $^{-2}$; $P < 0.05$), stroke volume index (-9 ml m $^{-2}$; $P < 0.01$), end-systolic volume index (-14 ml m $^{-2}$; $P < 0.01$) and end-diastolic volume index (-22 ml m $^{-2}$; $P < 0.01$), with increases in heart rate ($+9$ beats min $^{-1}$; $P < 0.01$) and left ventricular ejection fraction ($+6\%$; $P < 0.01$). The maximum effects occurred between 7 and 30 min. At 30 min there were reductions in systemic systolic (-20 mm Hg; $P < 0.01$), diastolic (-6 mm Hg; $P < 0.05$) and mean blood pressure (-15 mm Hg; $P < 0.01$), pulmonary artery occluded pressure (-3 mm Hg; $P < 0.01$), cardiac index (-0.4 l min $^{-1}$ m $^{-2}$; $P < 0.01$), stroke index (-10 ml m $^{-2}$; $P < 0.01$), end-systolic volume index (-13 ml m $^{-2}$; $P < 0.01$) and end-diastolic volume index (-21 ml m $^{-2}$; $P < 0.01$). There was an increase in heart rate ($+7$ beats min $^{-1}$; $P < 0.01$).

Effects during dynamic exercise (Figure 2, Table 2)

During dynamic exercise all components of the systemic arterial pressure were significantly lower ($P < 0.01$) with nitroglycerine than during control exercise. The cardiac and stroke volume indices were unchanged but the PAOP was reduced ($P < 0.01$). At 4 min of exercise the ejection fraction was increased ($+12\%$; $P < 0.01$), and the end-systolic volume index (-35 ml m $^{-2}$; $P < 0.01$) and end-diastolic volume index (-36 ml m $^{-2}$; $P < 0.01$) were reduced.

Discussion

Technical considerations

In the current study, left ventricular volume indices were derived from ejection fraction data

Figure 1 Haemodynamic and volumetric effects (mean $\pm$ s.e. mean) of buccal nitrate (10 mg) in coronary artery disease at rest. Levels of significance relate to differences from control (C) values. * $P < 0.05$, ** $P < 0.01$.

using a non-imaging scintillation device. This nuclear probe is an inexpensive, portable device for rapidly determining left ventricular ejection fraction. It is positioned to count left ventricular and background activity using an inbuilt microprocessor algorithm, and will then derive ejection fraction and associated indices of left ventricular function in a beat-to-beat or ECG multiple-gated mode. In this study data were collected in the ECG multiple-gated mode. Several groups of investigators have demonstrated the accuracy of ejection fraction as determined by this technique (Bacharach *et al.*, 1977; Berger *et al.*, 1981; Strashun *et al.*, 1981; Lahiri *et al.*, 1984; McCarthy & Makler, 1985).

The computerised measurement of blood flow and cardiac index by thermodilution is a well validated clinical procedure (Forrester *et al.*, 1972; Sorenson *et al.*, 1976; Hoel, 1978). Stroke volume index may be simply derived; since ejection fraction is the ratio of stroke volume to end-diastolic volume, left ventricular end-diastolic volume index was calculated from simultaneous measurements of stroke volume index and ejection fraction.

These derived indices are however subject to several sources of error. Firstly there are those due to the inherent variability of both techniques; in our laboratory the resting variability of the ejection fraction measurement by the nuclear

Table 1 Haemodynamic and volumetric effects of buccal nitrate at rest (mean $\pm$ s.e. mean)

	Control 0 (min)	3	Buccal nitrate 10 mg		30
			7	15	
Systolic blood pressure (mm Hg)	149 $\pm$ 6	142 $\pm$ 7	139 $\pm$ 7*	133 $\pm$ 6**	129 $\pm$ 7**
Diastolic blood pressure (mm Hg)	81 $\pm$ 3	83 $\pm$ 3	82 $\pm$ 3	78 $\pm$ 2	75 $\pm$ 2*
Mean blood pressure (mm Hg)	105 $\pm$ 4	101 $\pm$ 4	98 $\pm$ 4	95 $\pm$ 3**	90 $\pm$ 3**
Heart rate (beats min ⁻¹)	73 $\pm$ 4	82 $\pm$ 4**	85 $\pm$ 4**	82 $\pm$ 4**	80 $\pm$ 4**
Pulmonary artery occluded pressure (mm Hg)	11 $\pm$ 1	8 $\pm$ 1**	8 $\pm$ 1**	8 $\pm$ 1**	8 $\pm$ 1**
Cardiac index (l min ⁻¹ m ⁻²)	3.4 $\pm$ 0.2	3.1 $\pm$ 0.2*	3.0 $\pm$ 0.2**	3.0 $\pm$ 0.2**	3.0 $\pm$ 0.3**
Stroke volume index (ml m ⁻²)	47 $\pm$ 2	38 $\pm$ 3**	36 $\pm$ 3**	37 $\pm$ 3**	37 $\pm$ 3**
Stroke work index (g m m ⁻²)	59 $\pm$ 4	48 $\pm$ 4**	44 $\pm$ 4**	44 $\pm$ 4**	42 $\pm$ 4**
Systemic vascular resistance index (dyn s cm ⁻⁵ m ⁻²)	2548 $\pm$ 148	2709 $\pm$ 161	2734 $\pm$ 165	2629 $\pm$ 156	2588 $\pm$ 184
Ejection fraction (%)	56 $\pm$ 3	62 $\pm$ 4**	64 $\pm$ 3**	62 $\pm$ 3**	59 $\pm$ 3
End systolic volume index (ml m ⁻²)	41 $\pm$ 6	27 $\pm$ 6**	22 $\pm$ 4**	24 $\pm$ 4**	28 $\pm$ 5**
End-diastolic volume index (ml m ⁻²)	87 $\pm$ 7	65 $\pm$ 7**	58 $\pm$ 6**	61 $\pm$ 5**	66 $\pm$ 7**

Levels of significance relate to difference from control

* $P < 0.05$, ** $P < 0.01$

probe is 3.5%, while that for the thermodilution cardiac index is 4%. Further errors may result both from attenuation of counts from regions of the left ventricle most distant from the probe during ventricular dilatation, as well as from changes in background counts during exercise. Although care was taken to measure the level of background activity at the start of each intervention, it was impractical to remeasure it during exercise. An increased pulmonary blood flow during exercise would be expected to increase background activity; indeed Okada *et al.* (1980) have demonstrated that lung activity increases as left ventricular filling pressure rises. Thus the possibility that towards the end of each exercise period, background activity would be higher than at rest, with an underestimate of the background-subtracted left ventricular ejection fraction, cannot be excluded. Despite these theoretical objections, Lahiri *et al.* (1984) have demonstrated good correlation between 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; and McCarthy & Makler (1985) have recently reported correlation coefficients of 0.96 and 0.93 for the reproducibility of probe-derived ejection fractions and their correlation with gamma-camera data respectively, in patients with coronary artery disease. Moreover the left ventricular volumes cal-

culated 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 (Rackley *et al.*, 1970; Feild *et al.*, 1972; Links *et al.*, 1982; McKay *et al.*, 1984).

Haemodynamic response

Nitrates consistently reduce left ventricular filling pressure in patients with coronary artery disease, but the resultant left ventricular function response has been variable (Christensson *et al.*, 1965; Najmi *et al.*, 1967; Parker *et al.*, 1971; McNulty *et al.*, 1975; Shah *et al.*, 1976; Schwarz *et al.*, 1977; Steele *et al.*, 1978; Slutsky *et al.*, 1983). Shah *et al.* (1976) demonstrated that nitroglycerine reduces indices of cardiac function in patients with coronary artery disease and low or normal left ventricular filling pressures, but causes no deterioration or even improvement in those with high filling pressures. It was therefore predicted that the rest and exercise effects of glyceryl trinitrate on cardiac function in patients with stable coronary artery disease would differ, with deterioration at rest, in the presence of a normal left ventricular filling pressure, but no deterioration or possibly an improvement on exercise as filling pressure rose above normal. This hypothesis was confirmed in the present

Figure 2 Comparative haemodynamic and volumetric effects (mean $\pm$ s.e. mean) of buccal nitrate (10 mg ---) in coronary artery disease at rest. Levels of significance relate to differences from control (—) values. * $P < 0.05$, ** $P < 0.01$.

study. At rest the reduction in pulmonary artery occluded pressure (-3 mm Hg) was accompanied by reduced cardiac and stroke volume indices. In contrast on exercise, greater reductions in pulmonary artery occluded pressure (-13 mm Hg) occurred without deterioration in cardiac and stroke volume indices; this is presumably because suboptimal filling pressures

were not generated. These findings are similar to those of Najmi *et al.* (1967) and are of interest in that they show the contrasting and apparently contradictory actions of buccal glyceryl trinitrate producing detrimental effects of cardiac function at rest but benefit on exercise.

The derived measurements of left ventricular volume index showed that both systolic and dia-

Table 2 Haemodynamic and volumetric effects of buccal nitrate during dynamic exercise (mean $\pm$ s.e. mean)

		Rest	1	Duration of exercise (min)			
				2	3	4	
Systolic blood pressure (mm Hg)	C	149 $\pm$ 6**	182 $\pm$ 9**	187 $\pm$ 9**	190 $\pm$ 9**	194 $\pm$ 10**	
	D	129 $\pm$ 7	170 $\pm$ 9	175 $\pm$ 9	177 $\pm$ 9	176 $\pm$ 9	
Diastolic blood pressure (mm Hg)	C	81 $\pm$ 3**	89 $\pm$ 3**	91 $\pm$ 3**	91 $\pm$ 2**	92 $\pm$ 2**	
	D	75 $\pm$ 2	83 $\pm$ 3	83 $\pm$ 3	83 $\pm$ 2	83 $\pm$ 3	
Mean blood pressure (mm Hg)	C	105 $\pm$ 4**	120 $\pm$ 5**	124 $\pm$ 5**	125 $\pm$ 4**	127 $\pm$ 4**	
	D	90 $\pm$ 3	108 $\pm$ 4	111 $\pm$ 4	112 $\pm$ 4	111 $\pm$ 3	
Heart rate (beats min ⁻¹)	C	73 $\pm$ 4**	103 $\pm$ 5**	106 $\pm$ 5**	108 $\pm$ 5**	109 $\pm$ 6	
	D	80 $\pm$ 4	107 $\pm$ 5	110 $\pm$ 6	109 $\pm$ 6	110 $\pm$ 6	
Pulmonary artery occluded pressure (mm Hg)	C	11 $\pm$ 1*	19 $\pm$ 3**	22 $\pm$ 4**	25 $\pm$ 4**	27 $\pm$ 4**	
	D	8 $\pm$ 1	12 $\pm$ 2	14 $\pm$ 2	14 $\pm$ 2	14 $\pm$ 2	
Cardiac index (l min ⁻¹ m ⁻²)	C	3.4 $\pm$ 0.2**	5.9 $\pm$ 0.4	6.2 $\pm$ 0.4	6.4 $\pm$ 0.4	6.5 $\pm$ 0.6	
	D	3.0 $\pm$ 0.3	5.3 $\pm$ 0.4	5.7 $\pm$ 0.5	6.1 $\pm$ 0.5	6.5 $\pm$ 0.7	
Stroke volume index (ml m ⁻²)	C	47 $\pm$ 2**	58 $\pm$ 3*	59 $\pm$ 3*	59 $\pm$ 3	60 $\pm$ 4	
	D	37 $\pm$ 3	50 $\pm$ 3	52 $\pm$ 3	56 $\pm$ 3	59 $\pm$ 5	
Stroke work index (g m m ⁻²)	C	59 $\pm$ 4**	80 $\pm$ 6*	83 $\pm$ 8*	83 $\pm$ 8	84 $\pm$ 9	
	D	42 $\pm$ 4	66 $\pm$ 6	69 $\pm$ 6	75 $\pm$ 6	78 $\pm$ 7	
Systemic vascular resistance index (dyn s cm ⁻⁵ m ⁻²)	C	2548 $\pm$ 148	1702 $\pm$ 119	1689 $\pm$ 128	1662 $\pm$ 123	1671 $\pm$ 144	
	D	2588 $\pm$ 184	1721 $\pm$ 123	1664 $\pm$ 134	1570 $\pm$ 130	1525 $\pm$ 146	
Ejection fraction (%)	C	56 $\pm$ 3	53 $\pm$ 4*	49 $\pm$ 4**	46 $\pm$ 3**	43 $\pm$ 4**	
	D	59 $\pm$ 3	58 $\pm$ 5	57 $\pm$ 5	55 $\pm$ 4	55 $\pm$ 4	
End-systolic volume index (ml m ⁻²)	C	41 $\pm$ 6*	54 $\pm$ 7*	67 $\pm$ 8**	74 $\pm$ 9**	88 $\pm$ 14**	
	D	28 $\pm$ 5	44 $\pm$ 9	46 $\pm$ 9	50 $\pm$ 8	53 $\pm$ 7	
End-diastolic volume index (ml m ⁻²)	C	87 $\pm$ 7**	112 $\pm$ 7*	126 $\pm$ 9*	133 $\pm$ 10**	147 $\pm$ 15**	
	D	66 $\pm$ 7	93 $\pm$ 10	98 $\pm$ 10	106 $\pm$ 9	111 $\pm$ 10	

C = Control (no drug); D = drug (buccal nitrate 10 mg): Levels of significance relate to differences between C and D

* $P < 0.05$, ** $P < 0.01$.

stolic chamber size increased on exercise, and that buccal nitrate significantly reduced chamber size both at rest and on exercise. Despite the potential sources of error in cardiac volume determinations discussed above, the directional change in volume data was consistent with the haemodynamic data.

This study demonstrated that buccal glyceryl trinitrate reduced left ventricular filling pressure in a group of patients with stable coronary artery disease. The effect on cardiac function was variable. Cardiac and stroke volume indices were reduced at rest when the filling pressure was normal, but remained unchanged on exercise when the filling pressure was elevated. It is therefore important to recognise the different

effects that buccal nitrate produces on cardiac function at rest and on exercise in this group of patients. The measurements of left ventricular volume index derived from the nuclear probe ejection fraction and thermodilution blood flow showed directional changes consistent with changes in the haemodynamic data. Further investigation of the usefulness of this technique for assessing left ventricular volume and function appears merited.

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