Immediate effects of bumetanide on systemic haemodynamics and left ventricular volume in acute and chronic heart failure

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1 The haemodynamic and radionuclide effects of i.v. bumetanide ($25 \mu\text{g kg}^{-1}$) were prospectively studied in 24 patients with angiographically documented coronary artery disease and either acute exercise-induced (Group I, $n = 12$) or chronic (Group II, $n = 12$) heart failure.

2 Bumetanide at rest increased systemic arterial blood pressure and vascular resistance index; cardiac index and pulmonary artery occluded pressure (PAOP) were reduced at an unchanged heart rate in all patients. The left ventricular ejection fraction fell in patients with normal resting left ventricular filling pressure without change in those with chronic heart failure. The cardiac volumes were unchanged in either group.

3 During constant-load supine bicycle exercise, there were similar effects on systemic arterial pressures, vascular resistance index and PAOP; however the cardiac index was maintained at a reduced left ventricular filling pressure and unchanged ejection fraction and volumes.

4 These data demonstrate immediate mild pressor and vasoconstrictor actions of bumetanide which appear independent of the state of cardiac function; they suggest that any immediate improvement in patient symptomatology following bumetanide may be consequent on the reduction in PAOP; short-term reductions in volume may not occur.

Keywords bumetanide heart failure left ventricular volume haemodynamics

Introduction

The onset of angina pectoris is accompanied by acute but reversible left ventricular failure characterised by increased left ventricular pressure and volume; in chronic heart failure there is long-standing pressure and volume overload (McCans & Parker, 1973; Sharma *et al.*, 1976; Rerych *et al.*, 1978; Nechwatal *et al.*, 1980; Freeman *et al.*, 1981; Manyari *et al.*, 1981; Hakki *et al.*, 1983; Mancini *et al.*, 1983; Manyari *et al.*, 1983; Osbakken *et al.*, 1983; Steingart *et al.*, 1984). It is widely believed that the immediate and long-term benefits of diuretic therapy in such patients are due to reductions in left ventricular filling pressure and volume (Nechwatal *et al.*, 1980). However, the speed of onset and

relative importance of effects on filling pressure and volume in patients with coronary artery disease and LV dysfunction has not been fully evaluated.

Bumetanide is a potent loop diuretic (Bourke *et al.*, 1973; Olesen *et al.*, 1973; Sigurd *et al.*, 1974); it has been reported that an early pressor response, such as occurs following frusemide (Francis *et al.*, 1985), is absent following bumetanide both in normal volunteers (Johnston *et al.*, 1986) and in chronic heart failure (Ziacchi *et al.*, 1981). The following studies attempted to address some of these questions by evaluating the immediate haemodynamic and radionuclide effects of bumetanide in 24 patients with haemo-

dynamic evidence of either mild or severe impairment of left ventricular function.

Methods

Patients (Table 1)

Twenty-four patients with either exercise induced heart failure (Group I; *n* = 12; resting PAOP < 18, exercise PAOP > 25 mm Hg) or chronic heart failure (Group II; *n* = 12; resting PAOP > 18 mm Hg) were studied 12–24 h prior to diagnostic cardiac catheterisation. All patients had electrocardiographic and angiographic evidence of coronary artery disease and 21 of them had previous myocardial infarction. The average age of the patients was 54 ± 9 years (range 36–68). Angina was present in all patients in Group I (average duration 20 months); six patients in Group II had both angina and exertional dyspnoea (average duration 24 months). The average CTR was 0.46 ± 0.05 in Group I and 0.52 ± 0.04 in Group II. All patients in Group II had radiographic evidence (Kostuk *et al.*, 1973) of pulmonary venous congestion (Grade I = 6, Grade II = 5, Grade III = 1). Informed consent was obtained from each patient and the study was approved by the Hospital Ethics Committee.

Study design

The study was a single-blind within group evaluation of the haemodynamic and radionuclide effects of bumetanide (25 µg kg⁻¹ i.v.) in patients with coronary artery disease and either reversible (PAOP < 18 mm Hg at rest and > 25 mm Hg during exercise) or with chronic heart failure (PAOP > 18 mm Hg at rest). 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 was determined. Angina or dyspnoea was reliably induced during the fourth minute of exercise in all patients. Previous therapy, which included β-adrenoceptor blockers, nifedipine, short or long-acting nitrates and frusemide was withdrawn 36–48 h before the study. In each patient the study commenced with the control 4 min supine bicycle-exercise at the individually predetermined constant work-load during which haemodynamic and radionuclide measurements were obtained minute by minute. Following circulatory restabilisation (20 min), four sets of control studies at rest were undertaken over a 16 min period. Haemodynamic and radionuclide measurements were made in the 2–4 min follow-

Table 1 Patient characteristics

Age (years)	Previous myocardial infarction	Cardio-thoracic ratio	Pulmonary venous congestion (grade)	Number of vessels (> 70% diameter stenosis)	Ejection fraction (%)	Work load (watts)	Bumetanide dose (mg)
Group I: Exercise induced heart failure							
52 (38–66)	9 Ant 4 Inf 5	0.46 (0.39–0.51)	0 = 12	1 = 5 2 = 3 3 = 4	49 (28–79)	75 (35–200)	1.82 (1.7–2.1)
Group II: Chronic heart failure							
55 (41–68)	12 Ant 9 Inf 3	0.52 (0.46–0.61)	1 = 6 2 = 5 3 = 1	1 = 0 2 = 2 3 = 10	34 (11–47)	62 (20–150)	1.76 (1.4–2.1)

Ant = Anterior, Inf = Inferior. Ranges are given in parenthesis.

ing injection of 10 ml saline into the pulmonary artery. Bumetanide $25 \mu\text{g kg}^{-1}$ was then injected into the central circulation over 1 min and haemodynamic and radionuclide measurements were recorded 7, 15 and 30 min later. Finally patients were re-exercised for 4 min at the pre-determined work-load and measurements were again made each minute during the exercise period.

Radiographic measurements

Measurement of cardiothoracic ratio and assessment of pulmonary venous congestion was obtained from a 2 m standing posteroanterior chest X-ray, performed prior to haemodynamic and radionuclide studies in all patients and assessed with a standardised technique (Kostuk *et al.*, 1973). Angiographic left ventricular ejection fraction was calculated from the planimetric measurement of end-systolic and end-diastolic frames of the cine angiogram in the right anterior oblique projection. The average variability of this technique was less than 5%. Coronary artery obstruction was defined as narrowing of greater than 70% in any of the major coronary vessels.

Haemodynamic measurements

The heart rate was measured from the electrocardiograph (CM5). Pulmonary vascular pressures were measured through a narrow bore (7F) balloon-flotation thermodilution catheter (Gould Inc SP 5107) introduced percutaneously via a median basilic approach in the brachial fossa and advanced into the pulmonary circuit under wave form monitoring control so that inflation of the balloon resulted in replacement of the pulmonary artery pressure record by a typical pulmonary wedge tracing (pulmonary artery occluded pressure—PAOP). Systemic arterial pressure was measured 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 (Gould Statham P23 ID), zero reference being at mid-chest level below the horizontal plane of the sternal angle; and continuously displayed and recorded together with the ECG on a high performance ultra-violet recorder (EMI SE 6300). 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 index was measured by the thermodilution technique and was automatically computed and recorded (Gould Statham Computer SP 1435/Recorder SP2009); injection (aspirated via three-way tap from a reservoir at

0°C) of the indicator (10 ml dextrose 5%) was with a constant velocity CO_2 powered gun (OMP model 3700). This system is linear *in vitro* and the variance of the technique in our laboratory is $< 6\%$ at rest and $< 7\%$ during steady state bicycle exercise. Systemic vascular resistance, stroke and left ventricular stroke work indices were derived from the following formulae:

1. systemic vascular resistance (SVRI) = mean systemic artery pressure (MAP) $\times 80/\text{cardiac index}$.
2. stroke index (SI) = cardiac index/heart rate.
3. left ventricular stroke work index (SWI) = SI $\times (\text{MAP} - \text{PAOP}) \times 0.0136$.

Radionuclide measurements

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 patient lying on the catheter table. The probe was positioned over the praecordium in the 30–35 degree left anterior oblique position with a 10–15 degree caudal tilt. The area of maximal left ventricular count and level of background activities were determined before the definitive 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/10 ms. 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 the average variability (Silke *et al.*, 1986) during 10 consecutive resting ejection fraction determinations at 2 min intervals was 3.5% (range 0.9–5.7) and over six consecutive measurements during constant load supine 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 cardiac index determinations using the equations:

1. ejection fraction = stroke volume index/end-diastolic volume index $\times 100$
2. stroke volume index = end-diastolic volume index – end-systolic volume index

Statistical analysis

The variability of the measurements in the resting control period was determined from the coefficient of variation and expressed as a percentage of the mean. The baseline haemodynamic variables were analysed for trends of change over the resting control measurements (Dixon & Brown, 1979); none being present the control data were averaged from the four separate determinations.

The resting dose-response data were analysed by analysis of variance of repeated measurements partitioning the variance between patients, time and groups. The significance of difference between control and post-drug data, within each and between groups was assessed from the single value generated with a multiple comparison procedure (Winer, 1971). The control and post-drug exercise values were compared with a similar procedure. All values were judged significant at the conventional level (5%).

Results

The studies were uneventful; no patient complained of adverse reactions. Although these investigations were not undertaken with a view to symptomatic assessment, when asked whether there was any appreciable difference between the control and post-drug studies, three Group I and five Group II patients stated that the severity of perceived exertional dyspnoea and angina was less during the drug period.

Comparability of the randomised groups
(Table 1)

The baseline demographic, clinical and haemodynamic variables were similar for each group with some exceptions. The control resting and exercise PAOP were significantly higher and the rest and exercise cardiac index and ejection fraction lower in Group II than in Group I patients; however the average workload maintained over 4 min supine bicycle exercise was similar.

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: Group I: systolic blood

pressure 1.8% (range 0.4–2.5%), diastolic blood pressure 1.8% (range 0.6–3.5%), mean blood pressure 2.1% (range 0.5–5.1%), heart rate 1.9% (range 0–5.5%), pulmonary artery occluded pressure 8.5% (range 0–22%), cardiac index 2.9% (range 1.3–5.3%), and left ventricular ejection fraction 3.2% (range 1.2–5.4%); Group II: systolic blood pressure 1.9% (range 0.8–2.9%), diastolic blood pressure 1.7% (range 0–2.9%), mean blood pressure 2.1% (range 0.7–4.8%), heart rate 1.8% (range 0–5%), pulmonary artery occluded pressure 3.2% (range 0–9.3%), cardiac index 4.0% (range 2.2–5.3%) and left ventricular ejection fraction 6.6% (range 1.6–11.7%).

Analysis of variance of the data with trend curve fitting revealed no significant trends of change in any of these variables in either group. Control mean values have therefore been averaged from these data.

Bumetanide dose

The average dose of intravenous bumetanide was in Group I, 1.82 mg (range 1.7–2.5 mg) and in Group II, 1.76 mg (range 1.4–2.1 mg). The average diuresis (timed voided collection) over the 30 min period was similar in both groups (Group I, 454 ± 32 ml; Group II, 511 ± 34 ml).

Effects at rest (Table 2, Figure 1)

The effects of bumetanide were similar in both groups. The reductions in cardiac index and PAOP were associated with increase in systemic arterial pressures and vascular resistance index. The heart rate was unchanged. There was a small reduction in the resting stroke volume index (-6 ml m^{-2} $P < 0.01$) and left ventricular ejection fraction (-5% : $P < 0.01$) in Group I patients. Left ventricular volumes were unchanged in either group.

Effects during dynamic exercise (Table 3, Figures 2 and 3)

The pressor action of bumetanide with the reduction in PAOP were evident in both groups during exercise. Systemic vascular resistance index increased in Group II. There were small but insignificant reductions in cardiac and stroke volume indices and derived ventricular volumes were unchanged.

Effects on left ventricular function response
(Figure 4)

Both at rest and during exercise, bumetanide altered the overall relationship between stroke

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

	Group	Control	Post-drug		
			7	15	30 (min)
Systolic blood pressure (mm Hg)	I	136 $\pm$ 6	139 $\pm$ 6	144 $\pm$ 7**	143 $\pm$ 7**
	II	128 $\pm$ 5	131 $\pm$ 5	135 $\pm$ 5**	135 $\pm$ 5**
Diastolic blood pressure (mm Hg)	I	76 $\pm$ 4	80 $\pm$ 3	84 $\pm$ 4**	83 $\pm$ 5**
	II	77 $\pm$ 4	79 $\pm$ 4	81 $\pm$ 3**	80 $\pm$ 3*
Mean blood pressure (mm Hg)	I	99 $\pm$ 4	102 $\pm$ 5	107 $\pm$ 5**	105 $\pm$ 5*
	II	96 $\pm$ 4	97 $\pm$ 4	100 $\pm$ 4**	100 $\pm$ 4**
Heart rate (beats min ⁻¹)	I	74 $\pm$ 3	74 $\pm$ 3	73 $\pm$ 3	73 $\pm$ 3
	II	87 $\pm$ 5	88 $\pm$ 6	87 $\pm$ 5	87 $\pm$ 5
Pulmonary artery occluded pressure (mm Hg)	I	11 $\pm$ 1	10 $\pm$ 1*	10 $\pm$ 1*	9 $\pm$ 1**
	II	25 $\pm$ 2	22 $\pm$ 1**	23 $\pm$ 2*	21 $\pm$ 2**
Cardiac index (l min ⁻¹ m ⁻²)	I	3.4 $\pm$ 0.2	3.1 $\pm$ 0.2*	2.9 $\pm$ 0.2**	2.9 $\pm$ 0.2**
	II	2.9 $\pm$ 0.2	2.8 $\pm$ 0.1	2.7 $\pm$ 0.1*	2.7 $\pm$ 0.1*
Stroke volume index (ml m ⁻²)	I	46 $\pm$ 2	41 $\pm$ 2**	40 $\pm$ 3**	40 $\pm$ 2**
	II	34 $\pm$ 3	34 $\pm$ 3	33 $\pm$ 3	32 $\pm$ 2
Stroke work index (g m m ⁻²)	I	55 $\pm$ 4	51 $\pm$ 3	52 $\pm$ 4	52 $\pm$ 3
	II	33 $\pm$ 4	35 $\pm$ 4	34 $\pm$ 3	35 $\pm$ 3
Systemic vascular resistance index (dyn s cm ⁻⁵ m ²)	I	2432 $\pm$ 203	2895 $\pm$ 336*	3128 $\pm$ 311*	3131 $\pm$ 349**
	II	2758 $\pm$ 198	2844 $\pm$ 203	3065 $\pm$ 202**	3078 $\pm$ 189**
Ejection fraction (%)	I	54 $\pm$ 6	50 $\pm$ 4	47 $\pm$ 4**	49 $\pm$ 5*
	II	34 $\pm$ 4	34 $\pm$ 4	33 $\pm$ 4	34 $\pm$ 4
End-systolic volume index (ml m ⁻²)	I	52 $\pm$ 13	48 $\pm$ 9	55 $\pm$ 12	49 $\pm$ 9
	II	77 $\pm$ 12	79 $\pm$ 13	75 $\pm$ 11	73 $\pm$ 12
End-diastolic volume index (ml m ⁻²)	I	98 $\pm$ 14	89 $\pm$ 10	95 $\pm$ 14	88 $\pm$ 9
	II	111 $\pm$ 11	113 $\pm$ 12	108 $\pm$ 10	105 $\pm$ 11

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

Group I—Exercise induced heart failure.

Group II—Chronic heart failure.

Figure 1 Resting haemodynamic and radionuclide effects (mean $\pm$ s.e. mean) of i.v. bumetanide (25 $\mu\text{g kg}^{-1}$) in patients with exercise induced (—, Group I) and chronic (---, Group II) heart failure. Levels of statistical significance relate to differences from control. * $P < 0.05$, ** $P < 0.01$.

Table 3 Haemodynamic effects of bumetanide during exercise

	Group	Control		Post-drug	
		Rest	Exercise (4th min)	Rest	Exercise (4th min)
Systolic blood pressure (mm Hg)	I	136 ± 6	173 ± 6	143 ± 7**	178 ± 8
	II	128 ± 5	154 ± 7	135 ± 5**	158 ± 6
Diastolic blood pressure (mm Hg)	I	76 ± 4	87 ± 5	83 ± 5**	90 ± 5*
	II	77 ± 4	81 ± 3	80 ± 3*	85 ± 3**
Mean blood pressure (mm Hg)	I	99 ± 4	120 ± 6	105 ± 5*	125 ± 6*
	II	96 ± 4	105 ± 4	100 ± 4**	109 ± 4**
Heart rate (beats min ⁻¹)	I	74 ± 3	96 ± 3	73 ± 3	96 ± 4
	II	87 ± 5	114 ± 5	87 ± 5	111 ± 5
Pulmonary artery occluded pressure (mm Hg)	I	11 ± 1	26 ± 2	9 ± 1**	16 ± 1**
	II	25 ± 2	35 ± 1	21 ± 2**	29 ± 2**
Cardiac index (l min ⁻¹ m ⁻²)	I	3.4 ± 0.2	5.3 ± 0.4	2.9 ± 0.2*	5.0 ± 0.3
	II	2.9 ± 0.2	4.0 ± 0.2	2.7 ± 0.1*	3.8 ± 0.2
Stroke volume index (ml m ⁻²)	I	46 ± 2	53 ± 4	40 ± 2**	52 ± 2
	II	34 ± 3	37 ± 3	32 ± 3	36 ± 3
Stroke work index (g m m ⁻²)	I	55 ± 4	69 ± 7	52 ± 3	76 ± 5
	II	33 ± 4	35 ± 4	35 ± 3	39 ± 4
Systemic vascular resistance index (dyn s cm ⁻⁵ m ²)	I	2432 ± 203	1968 ± 204	3131 ± 349**	2129 ± 221
	II	2758 ± 191	2143 ± 123	3078 ± 189**	2353 ± 156*
Ejection fraction (%)	I	54 ± 6	39 ± 4	49 ± 4*	39 ± 3
	II	34 ± 4	25 ± 3	34 ± 4	28 ± 3
End-systolic volume index (ml m ⁻²)	I	52 ± 13	99 ± 17	49 ± 9	90 ± 14
	II	77 ± 12	120 ± 12	73 ± 12	104 ± 14
End-diastolic volume index (ml m ⁻²)	I	98 ± 14	153 ± 19	88 ± 9	142 ± 15
	II	111 ± 11	156 ± 12	105 ± 11	140 ± 13

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

Group I—Exercise induced heart failure.

Group II—Chronic heart failure.

Group I

Figure 2 Exercise haemodynamic and radionuclide effects (mean $\pm$ s.e. mean) of i.v. bumetanide (25 μ g kg⁻¹) in patients with exercise induced heart failure. Levels of statistical significance relate to differences from control. * $P < 0.05$, ** $P < 0.01$; ---- control, — drug.

volume index and end-diastolic volume and pressure. In patients with normal pressures, the reduction in PAOP at rest was associated with a reduced stroke index; similar reductions in PAOP in heart failure patients were not associated with reductions in stroke index. In neither group was the end-diastolic volume index altered. During exercise PAOP was reduced in both groups without change in stroke volume or end-diastolic volume indices.

Discussion

This study described the haemodynamic and radionuclide effects of bumetanide in patients with either acute reversible or chronic heart failure due to coronary artery disease. It is important to remember that the study design, patient population, method of exercise and technical methods may influence the outcome and our conclusions. We relied on haemodynamic stability being present over the study period; the repro-

ducibility of this test situation has been previously described (Verma *et al.*, 1984). The methods utilised are accurate, reproducible and of sufficient sensitivity to characterise small pharmacodynamic changes. The techniques for the computerised measurement of blood flow and cardiac index by thermodilution have been well documented (Forrester *et al.*, 1972; Ganz & Swan, 1972; Sorenson *et al.*, 1976; Hoel, 1978); in our laboratory the variability of cardiac index by this technique is $< 6\%$ at rest and $< 7\%$ during constant load supine bicycle exercise (Silke *et al.*, 1986). The left ventricular ejection fraction data were obtained with a non-imaging nuclear probe in the ECG multiple-gated mode. Several groups of investigators have validated this technique (Berger *et al.*, 1981; Lahiri *et al.*, 1984; McCarthy & Makler, 1985). A high level of correlation between the standard gamma camera and nuclear probe-derived ejection fractions in normal volunteers has been demonstrated (Lahiri *et al.*, 1984; McCarthy & Makler, 1985). Our variability is $< 4\%$ at rest and $< 6\%$ during

Group II

Figure 3 Exercise haemodynamic and radionuclide effects (mean $\pm$ s.e. mean) of i.v. bumetanide ($25 \mu\text{g kg}^{-1}$) in patients with chronic heart failure. Levels of statistical significance relate to differences from control. * $P < 0.05$, ** $P < 0.01$; ---- control, — drug.

exercise; it is accurate against angiographically determined ejection fraction in coronary patients ($n = 40$, $r = 0.85$, $P < 0.001$). Since ejection fraction is the ratio of stroke volume to end-diastolic volume, the combination of these two techniques allows left ventricular volumes to be derived. Although there are theoretical limitations with the use of the nuclear probe during exercise (due to its narrow field of view in relationship to the dilated left ventricle or changes in background activity), our calculated volumes are similar to direct measurements using gamma camera or biplane cineangiographic techniques in patients with equivalent coronary disease (Rackley *et al.*, 1970; Feild *et al.*, 1972; Links *et al.*, 1982; McKay *et al.*, 1984).

In this study patients were demographically similar, but formed two distinct groups in terms of baseline clinical and haemodynamic parameters; the latter were stable at baseline prior to administration of bumetanide as evident from the small coefficient in control haemodynamic

variables. The major between group differences in left ventricular filling pressures and ejection fraction indices reflected the severity of the underlying derangement of left ventricular function.

Bumetanide is a potent natriuretic (Bourke *et al.*, 1973; Sigurd *et al.*, 1974); following i.v. administration onset of diuresis is within 10 min with a peak effect by 30–45 min (Sigurd *et al.*, 1975; Marcantonio *et al.*, 1982). The dosage selected for these studies ($25 \mu\text{g kg}^{-1}$) was estimated to compare on a 40:1 ratio to frusemide (Asbury *et al.*, 1972; Ostergaard *et al.*, 1972; Olesen *et al.*, 1973; Ramsay *et al.*, 1978).

Previous studies with bumetanide in ischaemic disease have centered on the diuretic actions in chronic cardiac failure; the circulatory pharmacodynamic effects have received little attention (Asbury *et al.*, 1972; Olesen *et al.*, 1973; Davies *et al.*, 1974; Sigurd *et al.*, 1975; Kubik *et al.*, 1976; Abrahamsen, 1977). However, unlike the acute pressor actions of frusemide which may be attributable to release of angiotensin II (Johnston

Figure 4 Effects (mean $\pm$ s.e. mean) of i.v. bumetanide ($25 \mu\text{g kg}^{-1}$) on resting and exercise left ventricular function in patients with exercise induced (Group I) and chronic (Group II) heart failure. Levels of statistical significance relate to differences from control. * $P < 0.05$, ** $P < 0.01$; ---- control, — drug.

et al., 1983), bumetanide has been reported to be without such immediate effects after its acute administration to normal volunteers (Johnston *et al.*, 1986) and in chronic heart failure (Ziacchi *et al.*, 1981). In the present study however, a clear pressor response was elicited in both groups of patients; the magnitude of the response appeared similar to earlier observations of our group on the acute effect of frusemide in acute heart failure following myocardial infarction (Nelson *et al.*, 1983). There are at least two possible explanations for the differences between the present study and previous descriptions of bumetanide's acute pharmacodynamics. Both Ziacchi *et al.* (1981) and Johnston *et al.* (1986) used a maximum of $500 \mu\text{g}$; these lower doses may have failed to activate renin release. Alternatively our invasive methods, due to their small variability, may have possessed a greater power to detect the limited pressor effect. Notwithstanding these differences, our findings suggest that, at clinically relevant dosages, mild pressor effects can be detected; this may suggest the constriction of the arteriolar bed as has been reported in experimental studies with bumetanide (Brogden *et al.*, 1975) and clinical studies with intravenous frusemide (Francis *et al.*, 1985).

In the present study at the same time as the increase in systemic arterial pressure and vascular resistance, bumetanide reduced resting left ventricular filling pressure by 2–4 mm Hg and

cardiac index between $0.2\text{--}0.5 \text{ l min}^{-1} \text{ m}^{-2}$ in both groups of patients. The early reductions in left heart filling pressure may be due to venodilator effects as previously described for frusemide (Dikshit *et al.*, 1973; Nelson *et al.*, 1983). The ejection fraction and stroke volume index fell only in patients with normal initial left ventricular filling pressure; it is possible that this reflected suboptimal levels of left ventricular filling pressure in these patients. These data appear in accord with the limited haemodynamic data (Abrahamsen, 1977; Ziacchi *et al.*, 1981) already existing on bumetanide. Similar effects were apparent during dynamic exercise. The ventricular function curve relating stroke volume index to filling pressure, showed a beneficial shift during exercise in both groups of patients.

These results demonstrate that the effects of the acute administration of i.v. bumetanide were independent of baseline haemodynamic status. Thus the results were broadly similar to the previously described actions of frusemide. Although benefit was demonstrated, the reduction in left heart volumes following acute therapy with bumetanide was not statistically significant. It is however possible that longer term therapy is required to demonstrate such effects or that there was inadequate statistical power in this test situation. Our data suggest that there is a rational basis for undertaking additional longer term studies.

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