33. Herbst TJ, Raichle ME, Ferendelli JA: β-adrenergic regulation of adenosine 3′-5′-monophosphate concentration in brain microves-
34. MacKenzie ET, McCulloch J, O'Keane M: Influence of endog-
35. MacKenzie ET, McCulloch J, O'Keane M, Pickard JD, Harper AM: Cerebral circulation and norepinephrine: relevance of the

36. Palmer GC: Diminished adenylate cyclase responses in frontal
37. Reid JL, Zivin JA, Kopin IJ: Central and peripheral adrenergic
mechanisms in the development of deoxyxycorticosterone-saline hy-
38. Lovenberg W, Nagaoka A: Plasma norepinephrine and dopamine
39. Vlachakis ND, Alexander N: Plasma catecholamines and their
40. Kobayashi H, Maoret T, Spano PF, Trabucchi M: Effect of age on

Hemodynamic, Hormonal and Electrolyte Responses
to Prenalterol Infusion in Heart Failure
DREW FITZPATRICK, M.D., HAMID IKRAM, M.D., M. GARY NICHOLLS, M.D.,
AND ERIC A. ESPINER, M.D.

SUMMARY The hemodynamic, hormonal and electrolyte effects of prenalterol, a synthetic selective β1 agonist, were studied in six patients with New York Heart Association functional class II and III heart failure. Prenalterol was infused incrementally at 60, 120 and 240 nmol/min, each rate for 24 hours, producing steady-state plasma prenalterol levels of 52 ± 3, 121 ± 6 and 194 ± 9 nmol/l, respectively (mean ± SEM). Hemodynamic and hormonal measurements were performed before, during and after prenalterol administration under conditions of constant body posture and a regulated intake of dietary sodium and potassium.

Prenalterol induced a statistically significant increase in cardiac index (from 2.6 ± 0.2 to 3.1 ± 0.3 l/min/m²), with parallel increases in stroke index (from 28 ± 2 to 34 ± 2 ml/beat/m²). Forearm blood flow measurements increased (from 2.9 ± 0.5 to 4.1 ± 0.6 ml/min/100 g), while calculated systemic vascular resistance fell, as did pulmonary capillary wedge pressure (from 13.7 ± 1.6 to 10.5 ± 1.7 mm Hg). The drug did not alter heart rate, arterial pressure, right heart pressures or the frequency of ventricular premature beats. Prenalterol increased plasma renin activity (from 2.9 ± 0.8 to 6.6 ± 1.8 nmol/l/hour), angiotensin II (from 59 ± 12 to 89 ± 22 pmol/l), urinary aldosterone excretion (from 41 ± 10 to 78 ± 34 nmol/day) and plasma insulin (from 10.6 ± 2.2 to 19.8 ± 3.9 mIU/l). Circulating catecholamines, cortisol, glucose, glucagon or pancreatic polypeptide did not change. Dose-response studies in five patients showed dose-dependent increments in hemodynamic variables, while hormonal changes plateaued at the second dose level. We conclude that prenalterol infusion augments myocardial contractility, reduces systemic vascular resistance, and stimulates insulin release and the renin-angiotensin-aldosterone system.

NO MAJOR ADVANCE in chronic inotropic treatment for heart failure has taken place since the introduction of digitalis, and the place of this drug for patients in sinus rhythm is still uncertain.1 Several drugs have been investigated.2-4 Reports that a selective β1 agonist, prenalterol, improves myocardial function in patients with heart failure are encouraging, especially because the drug may be effective when given by mouth.5 However, available data relate largely to its administration over a period of minutes only and dose-response information is scarce. Further, the effects of the drug on neurohumoral systems and electrolytes have received scant attention. The present study documents hemodynamic, hormonal and electrolyte changes during 3 days of an incremental prenalterol infusion in six patients with cardiac failure.

Methods
The protocol was approved by the hospital's ethical committee. All patients gave informed written consent. Clinical details of the six patients are summarized in table 1. All had suffered at least one episode of pulmonary edema but had responded to routine treatment. At the time of entrance to the study, their therapy had not changed for at least 3 months. Patient 1 was on perhexilene and disopyramide, which were discontinued 1 week before the study.
The 6-day protocol called for a 2-day "run-in" period, 3 days of prenalterol infusion, and a "run-out" day after the termination of prenalterol therapy. Throughout these days, each patient received a diet of constant sodium (38-45 nmol/day), potassium (51-67 nmol/day) and carbohydrate content. Urine, obtained with an indwelling bladder catheter, was retained as 24-hour collections on ice for electrolyte and hormone analysis. The patients remained semisupine throughout. Blood sampling for hormone and electrolyte measurements and hemodynamic recordings were carried out twice daily at 8:30 a.m. (fasting) and 3:30 p.m. Diogxin and diuretics were administered immediately after the morning recordings, while vasodilator therapy was given both after morning and afternoon recordings. The dose of these medications remained constant for each patient.

Prenalterol Administration

The drug was diluted in 5% dextrose and water and infused intravenously in an incremental fashion at 60, 120 and 240 nmol/min, each rate for 24 hours, beginning at 9:00 a.m. The dextrose solution was administered at 10 ml/hour throughout using an IVAC pump. During run-in and run-out days, 5% dextrose was infused at the same rate (10 ml/hour) through the right atrial port of the Swan Ganz catheter. Patient 6 developed acute gout; consequently, the protocol in this case was shortened to 2 days of prenalterol infusion at 60 and 120 nmol/min each for 24 hours, followed by a runout day.

Hemodynamic Measurements

On the morning of the first study day, a triple-lumen Swan Ganz catheter was inserted under strictly sterile conditions into the pulmonary artery for measurements of right-heart pressures and cardiac output. A radial artery was cannulated for arterial pressure monitoring and for blood sampling. Pressures were measured with a P23 Statham transducer (with the midaxillary line as zero reference) and a DR-8 multichannel recorder. Mean pressures were derived by electronic integration. Cardiac output was measured in triplicate with a thermodilution technique (5% dextrose at 1-5°C) and a bedside computer. Hemodynamic recordings, with the exception of forearm blood flow, were made at 8:30 a.m. and 3:30 p.m. daily at the same time as arterial sampling for hormone analysis. Forearm blood flow was measured at 4:00 p.m. each day by plethysmography using a mercury-filled rubber strain gauge. Recorded values represented the average of three determinations with less than 5% variation and were expressed as ml/min/100 g of tissue.

Derived hemodynamic variables were calculated as follows. Stroke work index (SWI) = SI × (MAP - PCWP) ÷ 0.0136 (g-m/m²), systemic vascular resistance (SVR) = 80(MAP - RAP)/CO (dyn-sec·cm⁻²), pulmonary vascular resistance (PVR) = 80(MPA - PCWP)/CO (dyn-sec·cm⁻²), work product = HR × SI × MAP - mean systemic arterial pressure, PCWP = pulmonary capillary wedge pressure, RAP = mean right atrial pressure, MPA = mean pulmonary artery pressure, and SBP = systolic arterial pressure.

Hormone and Electrolyte Measurements

Arterial samples were drawn at 8:30 a.m. and 3:30 p.m. daily to measure plasma renin activity,² angioten-
sin II,¹ aldosterone,₆ cortisol,₉ epinephrine and norepi-
nephrine.¹₀ Fasting plasma glucose (glucose oxidase method) was determined daily at 8:30 a.m., while fasting arterial samples were drawn for measurements of plasma insulin,¹¹ glucagon,¹² and pancreatic polypeptide (by radioimmunoassay using a polyethylene glycol separation technique) at 8:30 a.m. on the second run-in day and again at 8:30 a.m. at the completion of the third day of prenalterol infusion. Urine aldoste-
one¹³ and cortisol² excretion were measured in 24-hour collections by radioimmunoassay and competi-
tive protein binding, respectively. Sodium and potassium in plasma, urine and duplicate diets were determined by flame photometry.

Statistical Methods

Repeated-measures analyses of variance were carried out on all variables using program P2V of the BMDP package. The initial hypothesis tested was that no daily variation occurred, and where variables were measured twice daily, no diurnal variation occurred. For indices exhibiting significant daily variation, further comparisons using t tests, with appropriate mean-square-error terms from analysis of variance, were per-
formed to determine when these changes occurred. In the case of variables measured twice daily, the interaction of days and time of day was clearly nonsignificant; thus, we could compare the daily mean values for each index.

**Figure 1. Hemodynamic indexes in six patients with heart failure before, during and after prenalterol infusion (mean ± SEM).** Recordings during prenalterol were at 3:30 p.m. and 8:30 a.m., after 6½ and 23½ hours of each infusion rate. The discontinuous horizontal lines represent mean "run-in" (pre-prenalterol) levels for each index. The bars with asterisks indicate significant changes from run-in values. *p < 0.05; **p < 0.01. MPA = mean pulmonary artery pressure; PCWP = mean pulmonary capillary wedge pressure; RAP = mean right atrial pressure.

**Results**

**General**

Prenalterol was well tolerated. No serious arrhythmias were observed during the study, and the incidence of ventricular premature complexes, measured at 1-minute intervals at 8:30 a.m. and 3:30 p.m. daily, was not altered by prenalterol administration.

**Hemodynamic Responses (figs. 1 and 2)**

Cardiac index increased significantly, from a pre-treatment mean of 2.6 ± 0.2 l/min/m² to 2.9 ± 0.2, 3.1 ± 0.3, and 3.0 ± 0.2 l/min/m² on subsequent days of prenalterol infusion, then declined to 2.8 ± 0.2 l/min/m² upon cessation of the drug. Stroke index changes paralleled changes in cardiac index, except that run-out values were sustained higher than control values. Forearm blood flow, as measured directly by strain-gauge plethysmography, increased from a baseline of 2.9 ± 0.5 ml/min/100 g of tissue to 4.1 ± 0.6 ml/min/100 g on the second and third prenalterol days, then declined when the drug was withdrawn. These changes in measured forearm blood flow matched stepwise decrements in calculated systemic vascular resistance. Mean pulmonary artery pressures and right atrial pressures were unchanged, but a statistically significant decline in pulmonary capillary wedge pressure was noted during the lowest rate of prenalterol infusion, and was sustained during the final two study days.

Heart rate and arterial pressure did not increase during prenalterol administration, and the product of rate and systolic pressure therefore remained stable. Systemic vascular resistance declined significantly; the calculated pulmonary vascular resistance did not change.

Comparing data from the run-in day and the final infusion day, prenalterol induced clear-cut increases in stroke work index in all patients, with concomitant decrements or little change in pulmonary capillary wedge pressure (fig. 3A). Withdrawal of prenalterol resulted in a decline in stroke work index in all but one case, along with minor and variable changes in wedge pressure (fig. 3B).

**Hormone and Electrolyte Responses (figs. 4 and 5)**

Baseline levels of plasma renin activity, angiotensin II and plasma aldosterone were moderately increased, as might be expected during long-term treatment with diuretics. Prenalterol therapy resulted in a greater than twofold rise in PRA and somewhat lesser increments in angiotensin II and plasma aldosterone. Urine aldosterone increased in a stepwise fashion, as did plasma renin activity. Angiotensin II tended to decline when prenalterol infusion was withdrawn. Cortisol levels, circulating norepinephrine and epinephrine did not change.

Urine sodium excretion tended to decline during prenalterol administration and increased to exceed dietary intake when the drug was withdrawn. These changes and those in body weight were not statistically
significant. Urine potassium equalled dietary intake before prenalterol, then declined during the 3 days of infusion, and then returned to baseline. While these fluctuations were not statistically significant, plasma potassium concentration increased significantly on the final 2 study days.

Fasting plasma insulin levels increased twofold during prenalterol administration. The tendency for fasting glucose levels to rise during the study did not reach statistical significance. No changes in plasma glucagon (216 ± 36 pg/ml on day 2; 253 ± 64 on day 5) or pancreatic polypeptide (318 ± 78 pg/ml on day 2; 531 ± 128 on day 5) were seen.

Dose-Response Data

Dose-response data are available for the five patients studied at each of the three prenalterol infusion rates (table 2). Infusion at 60, 120 and 240 nmol/min produced steady-state prenalterol plasma concentrations of 52 ± 3, 121 ± 6, and 194 ± 9 nmol/l, respectively. Cardiac index, stroke index and forearm blood flow increased in a linear fashion, while pulmonary capillary wedge pressure fell at the lowest infusion rate then remained stable. The increase in plasma renin activity, angiotensin II and aldosterone plateaued during the second day of prenalterol infusion.

Discussion

Therapy of heart failure relies heavily on correction of abnormal fluid accumulation and vascular tone. The primary abnormality in most types of cardiac failure, i.e., impaired myocardial contractility, is less well managed. Digitalis remains the only agent for chronic ambulant therapy. It is a weak inotropic drug compared with the modern synthetic amines but its long-term usefulness in patients in sinus rhythm remains controversial.

Prenalterol, a synthetic selective β1 agonist, is free of several of these disadvantages. It can be given orally, and therefore is a potential substitute for digitalis for the ambulant management of cardiac failure. Short-term studies have confirmed its inotropic action and freedom from acute toxicity, but few data are available on the dose-response characteristics of the drug in heart failure patients. Its effect on important neurohumoral systems and electrolytes in cardiac function must be clarified. This information is crucial because the long-term efficacy of the drug will be determined by these changes.

Our study confirms that prenalterol increases cardiac output and stroke work while decreasing the left ventricular filling pressure. This is the hallmark of an inotropic drug. The effect appears to be dose-dependent, increasing in a linear fashion and declining rapidly when the infusion is discontinued. Some residual elevation of stroke output remains which may be of therapeutic significance. In this regard, the persistence of inotropic activity for as long as 3 months has been reported after dobutamine infusion. Heart rate did not alter significantly with increasing doses of prenalterol confirming the lack of an important chronotropic action. Similarly, there was no change in the arterial pressure and the pressure-rate product, which is an indirect measure of myocardial oxygen demand. This important facet of the drug’s action requires confirmation by direct measurement, because the indirect as-
cessment of cardiac oxygen requirements may be fallacious. It is almost impossible to separate vasodilator from inotropic effects of a drug in the intact human. In isolated heart muscle studies, prenalterol has been shown to have definite inotropic properties. Awan et al. reported that prenalterol induces vasodilatation on the basis of a fall in calculated systemic vascular resistance. Our data support their observations. Furthermore, forearm blood flow measurements confirm vasodilatation in this vascular bed. Vasodilatation has been reported with other inotropic drugs, including terbutaline, amrinone and pibuterol. This effect is only prominent in cardiac failure patients, being absent in animals and healthy volunteers. Awan et al. suggest that this vasodilatation may be due to the improvement in cardiac output resulting in withdrawal of inappropriately raised sympathetic tone. Our study did not address the underlying mechanism, but the lack of any change in circulating catecholamines suggests that sympathetic influences were not major determinants. Another possibility is β₂-mediated vasodilatation, since presumably this drug is only a relatively selective β₂ agonist. Whatever the reason, this vasodilator action is likely to be beneficial because it would tend to offset the vasoconstriction that is common in cardiac failure. It thus supplements the inotropic action by afterload reduction.

Our study demonstrates activation of the juxtaglomerular apparatus with release of renin during prenalterol infusion. Since stimulation of β receptors augments renin release, this effect of prenalterol is not surprising. That this action of prenalterol may be physiologically important is confirmed by concomitant increments in plasma angiotensin II and aldosterone levels. Several important questions are raised by these data. First, cardiac function was maintained and even

![Figure 3](image-url)  
**Figure 3.** Changes in stroke work index (SWI) and in mean pulmonary capillary wedge pressure (PCWP) with the introduction of prenalterol therapy (A) and upon withdrawal of the drug (B). In panel A, data from the run-in day for each patient are compared with those during the third prenalterol infusion day, while in panel B results from the third day of prenalterol administration are compared with the subsequent day after discontinuation of the drug. In panel B, data from two patients fell on the same line. The asterisk represents the patient who developed acute gout.

![Figure 4](image-url)  
**Figure 4.** Hormone data before, during and after prenalterol in six patients (mean ± SEM). (For plasma and urine aldosterone values, n = 5.) In the sixth patient, who received only two infusion rates of the drug, plasma aldosterone levels were 922, 1490, 3030 and 3336 pmol/l and urine aldosterone excretion values were 85, 92, 247 and 392 nmol/day on run-in, first, second infusion days and run-out days, respectively. The discontinuous horizontal lines represent mean run-in values for each index. Bars with asterisks indicate statistical significance (*p < 0.05, **p < 0.01) compared with run-in levels.
enhanced despite the vasoconstrictor action of angiotensin II. This suggests that the inotropic and vasodilating actions of prenalterol were powerful enough to overcome any increase in afterload, at least in the short term. Second, it is not clear whether activation of the renin-angiotensin-aldosterone system is sustained during long-term therapy. If it is, a decline in cardiac output due to increased afterload and accumulation of fluid secondary to elevated aldosterone levels may occur, leading to blunting or a loss of therapeutic response. Blockade of the renin-angiotensin system by means of a converting enzyme inhibitor may then be required to maintain the initial therapeutic effect.

Beta receptors modulate the release of many hormones, including those concerned with glucose homeostasis. We observed a significant increase in plasma insulin levels during the present study. Although animal data suggest that the adrenoceptors responsible for enhancing insulin secretion are the $\beta_1$ type, our results and those of Rönn et al., who observed an increase in insulin during prenalterol administration in normal volunteers, suggest either that stimulatory $\beta_1$ receptors exist on the pancreatic $\beta$ cell, or that prenalterol has sufficient $\beta_1$ agonist action to release insulin. Alternatively, prenalterol may primarily increase blood sugar levels, inducing release of endogenous insulin. Although we saw no significant change in glucose, glucagon or pancreatic polypeptide levels, it appears prudent to monitor blood glucose during future long-term studies of prenalterol.

Since insulin reportedly increases myocardial contractility in cardiac failure it is interesting to speculate whether the increase in plasma insulin observed in our study contributed to the inotropic effect of prenalterol.

In conclusion, prenalterol infusion in six patients with heart failure increased cardiac index and stroke index in a dose-response fashion without adversely affecting heart rate, arterial pressure or right-heart pressures. Forearm blood flow rose in a stepwise fashion during the incremental infusion of prenalterol. Activation of the renin-angiotensin-aldosterone axis was observed, and if sustained during long-term prenalterol treatment, could offset, in part, the beneficial hemodynamic effects.

Acknowledgment

We thank Sarah Jones for technical help, Sister Creek and nurses of the recovery ward, special test sisters, dietitians, the biochemistry department and the technicians in the endocrine department for their assistance. We also thank Paula Gilson for typing the manuscript; Dr. Elizabeth Wells for statistical analysis; the staff of the photography department for preparing the figures; Dr. George Moore of Astra for supplying prenalterol; and Dr. J. Ashley and E. Sainsbury, B.Ph., for

Table 2. Dose-Response Data in Five Patients

<table>
<thead>
<tr>
<th>Infusion rate (nmol/min)</th>
<th>Steady-state prenalterol plasma concentration (nmol/l)</th>
<th>Cardiac index (L/min/m²)</th>
<th>FBF (ml/mm/100 g tissue)</th>
<th>PCWP (mm Hg)</th>
<th>PRA (nmol/l/hour)</th>
<th>Angiotensin II (pmol/l)</th>
<th>Aldosterone (pmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>—</td>
<td>2.4 ± 0.3</td>
<td>2.9 ± 0.7</td>
<td>13.7 ± 1.6</td>
<td>2.2 ± 0.6</td>
<td>55 ± 16</td>
<td>526 ± 93</td>
</tr>
<tr>
<td>60</td>
<td>51.9 ± 3.3</td>
<td>2.7 ± 0.4</td>
<td>3.3 ± 0.4</td>
<td>10.5 ± 1.7</td>
<td>3.6 ± 1.0</td>
<td>71 ± 20</td>
<td>589 ± 74</td>
</tr>
<tr>
<td>120</td>
<td>121.3 ± 6.2</td>
<td>2.8 ± 0.4</td>
<td>3.7 ± 0.8</td>
<td>11.5 ± 1.6</td>
<td>4.6 ± 1.5</td>
<td>77 ± 23</td>
<td>664 ± 70</td>
</tr>
<tr>
<td>240</td>
<td>194 ± 8.5</td>
<td>3.0 ± 0.4</td>
<td>4.0 ± 0.6</td>
<td>11.0 ± 1.6</td>
<td>4.5 ± 1.5</td>
<td>70 ± 21</td>
<td>659 ± 84</td>
</tr>
<tr>
<td>Run-out</td>
<td>—</td>
<td>2.6 ± 0.3</td>
<td>3.4 ± 0.5</td>
<td>10.7 ± 1.4</td>
<td>3.9 ± 1.3</td>
<td>69 ± 23</td>
<td>638 ± 78</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

Abbreviations: FBF = forward blood flow; PCWP = pulmonary capillary wedge pressure; PRA = plasma renin activity.
analysis of drug levels. The study received support from the Medical Research Council of New Zealand.

References

9. Murphy BEP: Some studies of the protein-binding of steroids and their routine micro and ultramicro measurement of various steroids in body fluids by competitive protein-binding radioassay. J Clin Endocrinol Metab 27: 973, 1967
Hemodynamic, hormonal and electrolyte responses to prenalterol infusion in heart failure.
D Fitzpatrick, H Ikram, M G Nicholls and E A Espiner

Circulation. 1983;67:613-619
doi: 10.1161/01.CIR.67.3.613

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/67/3/613