# Acute Haemodynamic Effects Of Intravenous ICI 153,110 In Congestive Heart Failure

*FEROZ MEMON**
*D METCALFE***
*D. JEWITT***

**Summary**

**Despite recent advances in the pharmacological and mechanical means of supporting ventricular function, congestive heart failure continues to be major cause of morbidity and mortality. Impaired myocardial contractility remains to be a primary feature. Phosphodiesterase inhibition can lead to an increase in cyclic AMP and augment myocardial contractility. The results in this study suggest that the positive inotropic drug may be beneficial for the treatment of Congestive heart failure. Furthermore ICI 153, 110 proves to be effective positive inotropic drug with vasodilating effects and does improve left ventricular performance during acute administration in patients with congestive heart failure.**

**Introduction:**

The present study was designed to evaluate the haemodynamic effects of ICI 153, 110, a phosphodiesterase inhibitor in patients with NYHA class III congestive heart failure. Haemodynamic effects were evaluated by right and left heart catheter.

Nine patients were studied with mean age of 65.1 years. Heart rate remained unchanged. Systemic vascular resistance decreased from mean of 22 to 17 while cardiac output increased from 4.5 to 5.1. Left Ventricular dp/dt increased from 953 mmHg/sec to 1245 mmHg/sec. Left ventricular End diastolic Pressure fell from 21 mmHg to 14mmHg.

The present study reveals that ICI 153, 110 is effective in improving left ventricular performance during acute administration in patients with congestive heart failure. Clinical value of this drug depends on evidence of persistant haemodynamic improvement on long term administration.

A decrease in myocardial contractility is a central patho-physiological event in congestive heart failure. Positive inotropic agents are administered to patients with chronic congesive heart failure on the premise that sufficient reserve cardiac contractility can be stimulated[1]. Despite an extensive search, a perfect inotropic agent has not been developed. Recent efforts have been directed towards investigating potential inotropic agents which possesses the additional desirable effect of vasodilation[2].

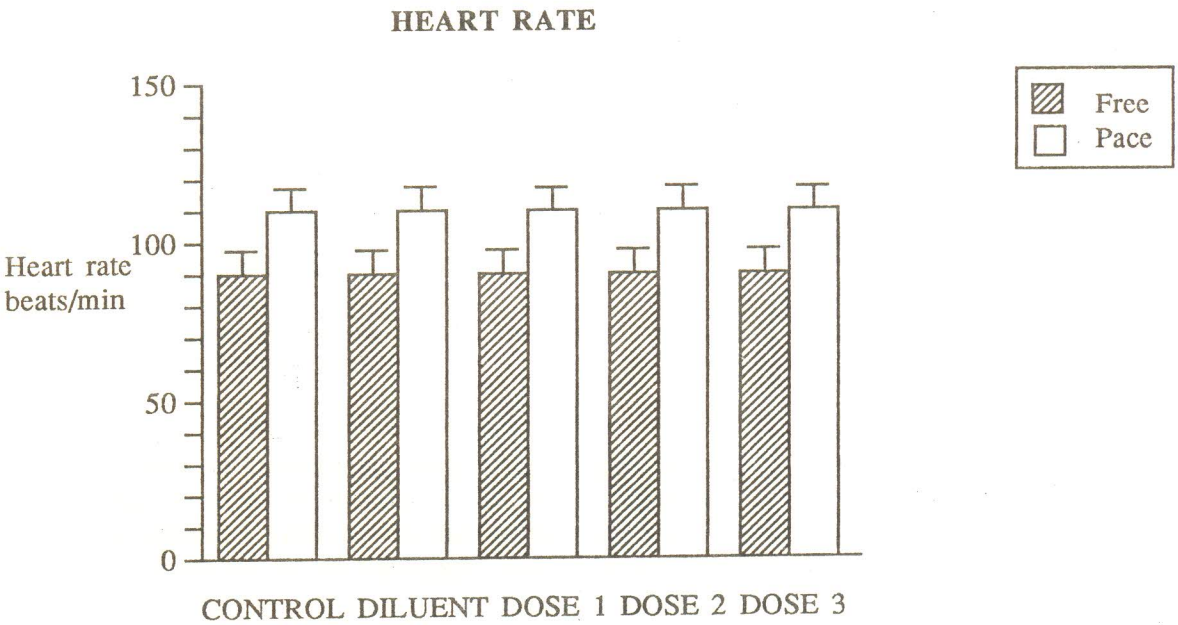
A new class of drugs has now been described that have both potent positive inotropic and vasodilator effects. They are the non glycoside noncate cholamin drugs. A growing body of evidence supports the contention that the effects of these

**TABLE I**

| DOSE 1 (Low Dose) (15-25mg) | DOSE 2 (Intermediate Dose) (40-50mg) | DOSE 3 (High Dose) (65-100mg) |
|---|---|---|
| 15mg(n=2)- 25mg(n=4) | 40mg(n=2)- 50mg(n=7) | 65mg(n=2)- 75mg(n=2) 100mg(n=5) |

n=number of patients receiving given dose.

* Department of Cardiology, LMCH, Hyderabad.
** King's College Hospital, London SE5.




drugs are largely due to phosphodiestrase inhibition[3]. ICI 153, 110 (4,5 - dihydro - 6 - [2 - (pyride - 4 - y1) vinyl - 2H - pyridne - 3 - one) is a novel compound with positive inotropic effects on the heart and vasodilator effects on the peripheral blood vessel[4].

The present study was designed to evaluate the cardiovascular effects of ICI 153, 110 in patient with NYHA class III heart failure and to indicate whether this compound has therapeutic value in this group of patients.

**Aims of the Study:**

i) To determine the acute haemodynamic effects of dose of ICI 153, 110 (range 25-100 mg) given intravenously in patients with congestive heart failure NYHA grade-III.

ii) To determine the blood levels of ICI 153, 110 at which haemodynamic assessments are made.

iii) To drive any relationship between blood levels of ICI 153, 110 and haemodynamic effects.

iv) To determine in the same patients. Blood levels following single oral dose of 100mg.

v) Finally to determine the effects, if any, of the doses of ICI 153, 110 on measurement of haematological and biochemical parameters in blood.

**Method**

**Selection of patients**

The patients were recruited from those who presented to the cardiac department of King's college hospital London for investigation during the the period 1987-88 patients were included who:-

i) Were suffering from either ischaemic heart disease or Dilated cardiomyopathy.

ii) Were in grade III cardiac failure (NYHA) that is they had symptoms on minimal exertion.

iii) Were on therapy with diuretic and/or digitalis preparation and not on any other third line therapy.

**Exclusion Criteria**

Patients were not allowed to enter the study. If

i) They were suffering from heart failure due to aortic stenosis or mitral stenosis.

ii) They had evidence of gross hepatic or renal failure.

iii) They were women of child bearing potential.

iv) They had evidence of ventricular arrythmias other than occasional isolated Ventricular Premature Contraction.

v) They were receiving therapy other than digitalis and/or diuretics that could not be withdrawn, e.g. vasodilators.

**Dosing Regimen**

For the first two patients the doses given were:

1st dose 15mg cumulative dose 15mg.
2nddose 25mg cumulative dose 40mg.
3rd dose 25 mg cumulative dose 60mg.

For the next two patients the doses given were:

1st dose 25mg cumulative dose 25mg.
2nd dose 25mg cumulative dose 50mg.
3rd dose 25mg cumulative dose 75mg.

Remaining patients were given following doses:

1st dose 25mg cumulative dose 25mg.
2nd dose 25mg cumulative dose 25mg.
3rd dose 50mg cumulative dose 100mg.

As this was phase two dose ranging study, hence to avoid any potential serious side effect of the drug, initially a lower dose was introduced and was gradually increased in subsequent patient. No higher dose than last regimen was given. There was 15-20 min. interval between each dose. It was decided that for any dose, progression to the next dose would not take place, if

a) The increase in Left Ventricular dp/dt max exceed 25%,

b) Systolic. BP fell below 90mmHg.

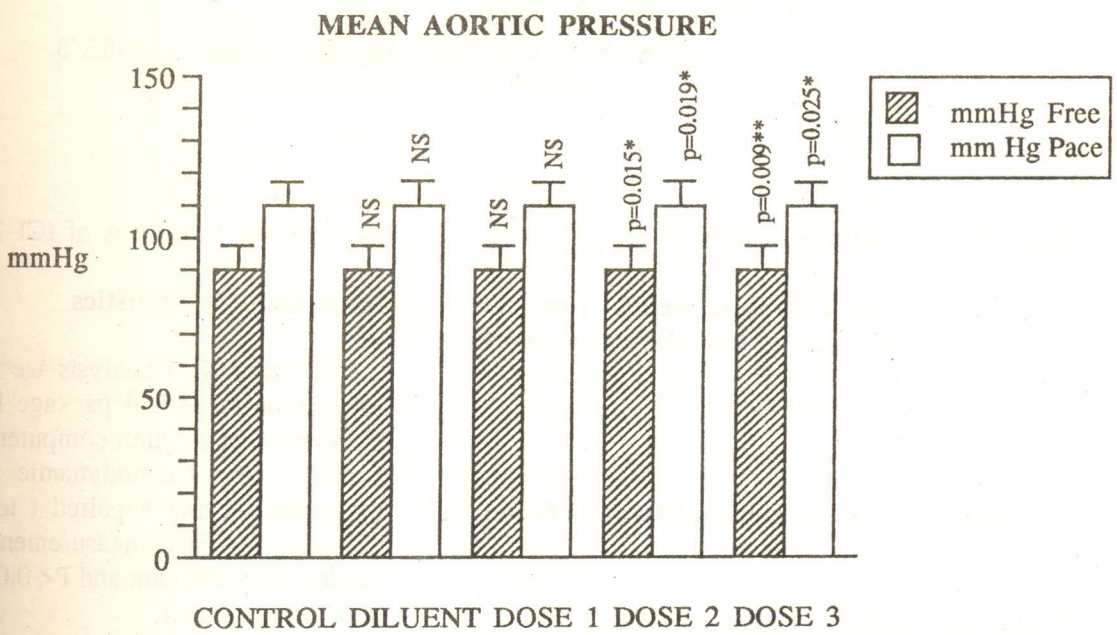
c) Cardiac arrythmias were seen and considered dose related.

d) Any untoward effect occurred which was considered detrimental to the patient.

**Methods of Assessment**

**1. I/v Study**

On the day of the catheter study, the following



procedure was adopted for each patient.

1) **Left Heart Catheterisation**

Using the Seldinger technique a Millar catheter was inserted via the Right femoral artery into LV to make following measurement in spontaneous ans paced heart rate.

a) Left Ventricular dp/dt max.

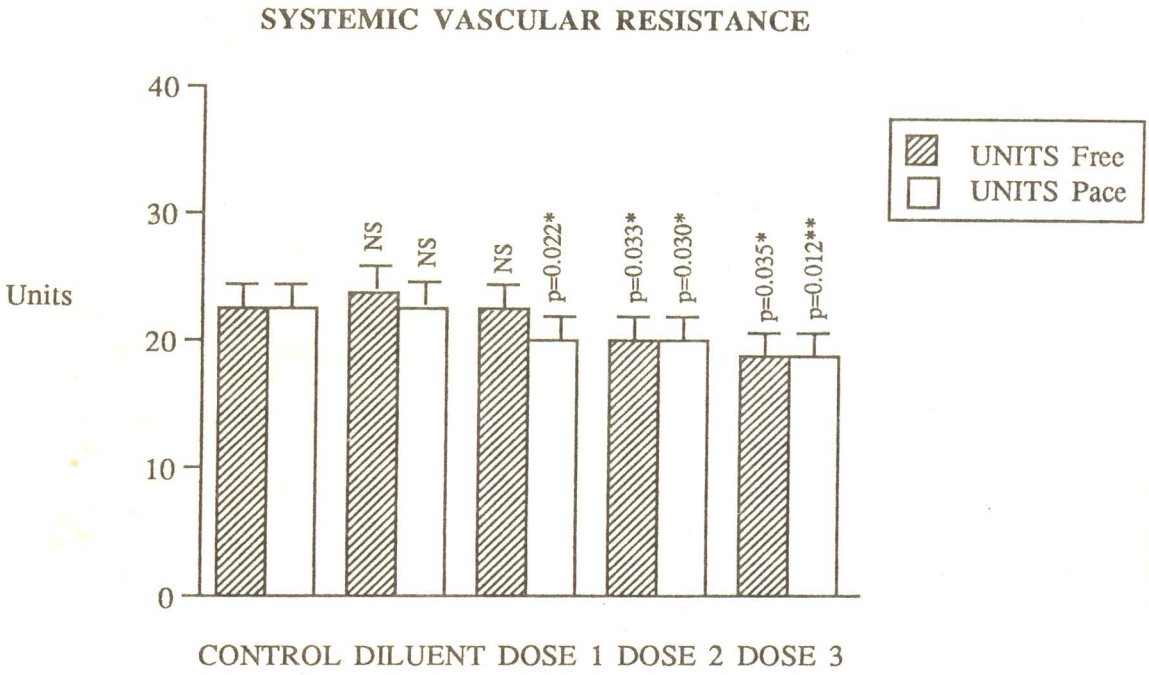
b) Left Ventricular end diastolic pressure.

- Rt. atrial Pressure.

c) Blood Pressure.

d) Heart Rate.

Baseline measurements of haemodynamic Parameters as outlined above were made and a sample of venous blood taken for estimation of ICI 153, 110 (a blanks). The first dose was injected then and 15 min later haemodynamic measurement were repeated and a second sample taken for estimation of ICI 153, 110. Same procedure was adopted for the 2nd and 3rd doses of ICI 153, 110.




2) **Right Heart Catheterisation**

This was performed via right femoral vein and measurements were made at free and paced heart rate of:

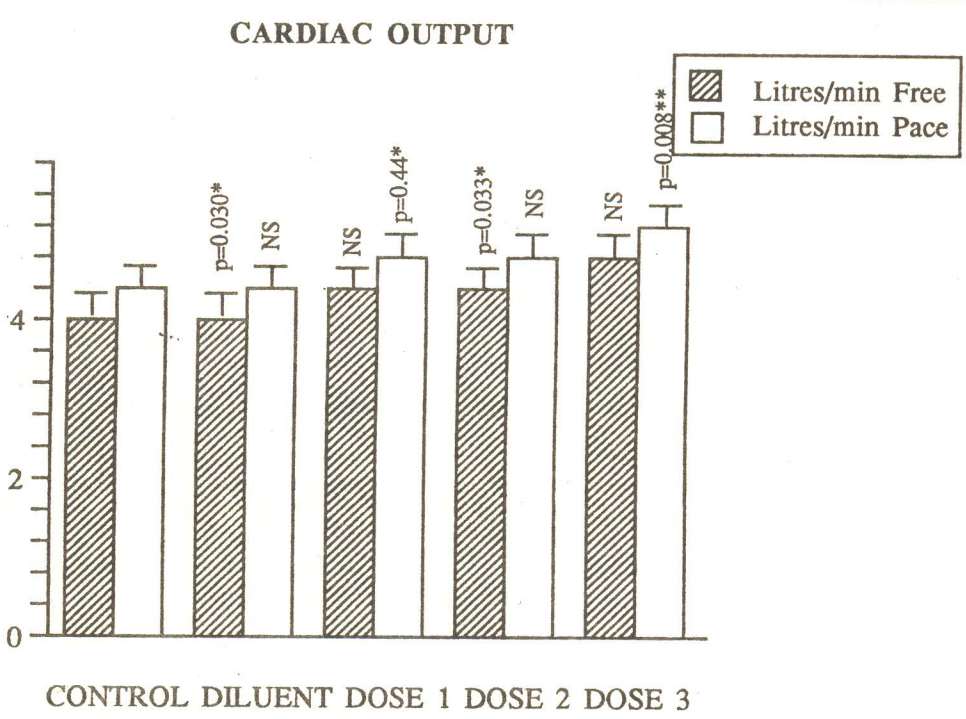
- Cardiac output.

- Pulmonary arterial Systolic and diastolic Blood Pressure.

- Pulmonary capalary wedge pressure.

**Data Analysis Statistics**

For statistical analysis we utilised the SP SS/PC &, the statistical package for IBM PC of the University of London computer. Statistical significance of the haemodynamic measurements was determined using a paired t test. A p value was obtained for each measurement, $P< 0.05$ was regarded as significant and $P< 0.005$ was regarded as highly significant.

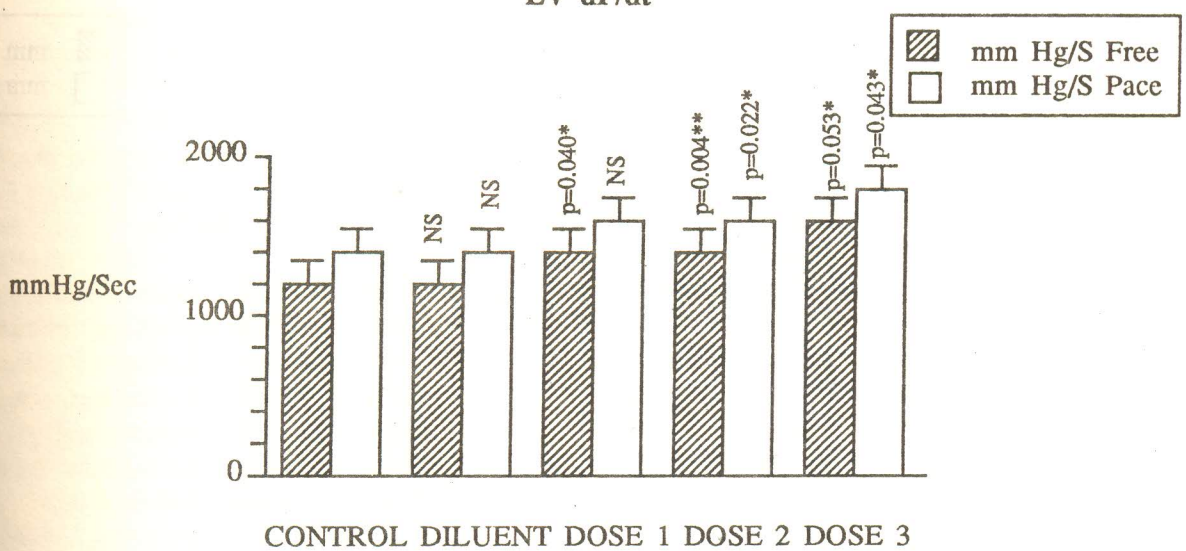


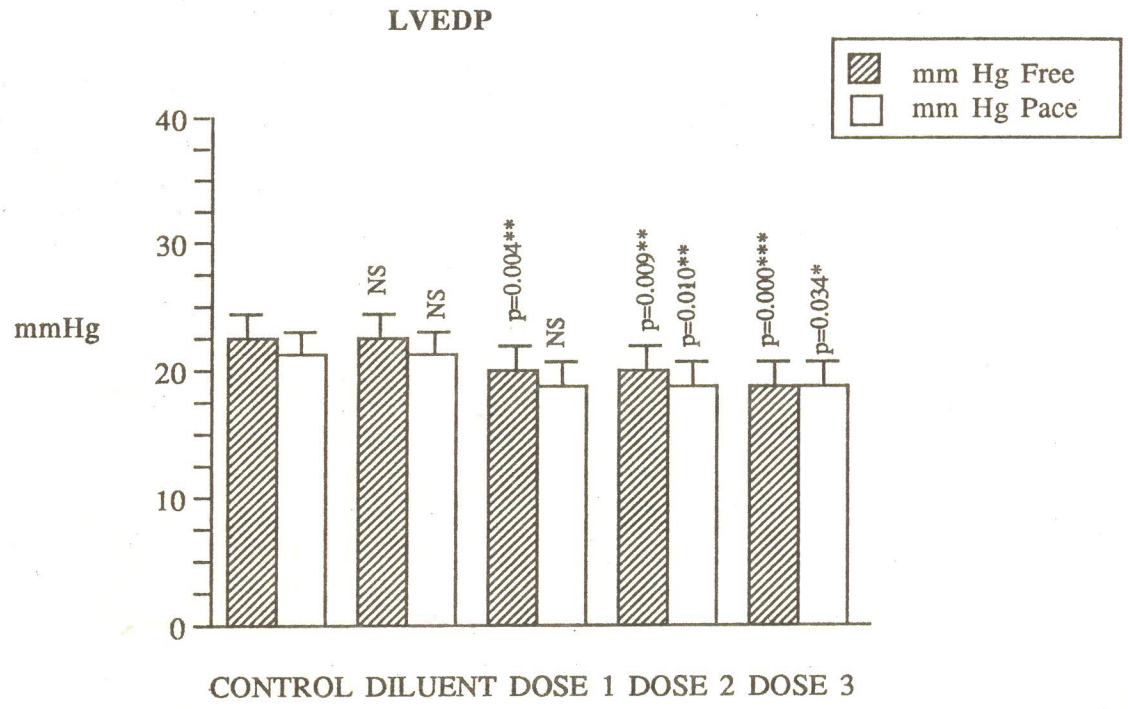

**Results**

**Patient Characteristics**

Nine patients were studied with the mean age of 65.1 years (range 47-74 years). All the patients with congestive heart failure were either in class III or IV of NYHA. Male to female ratio was 1:1.5 Male being 5 and 4 female. The primary aetiology was coronary artery disease in 8 patients one of them having concomitant hypertension, one was suffering from dilated cardiomyopathy (table).

Heart rate remained unchanged. Mean Aortic pressure fell significantly. SVR also decreased significantly. Cardiac output increased with every dose, at baseline being 4.5 and at third dose 5.6.

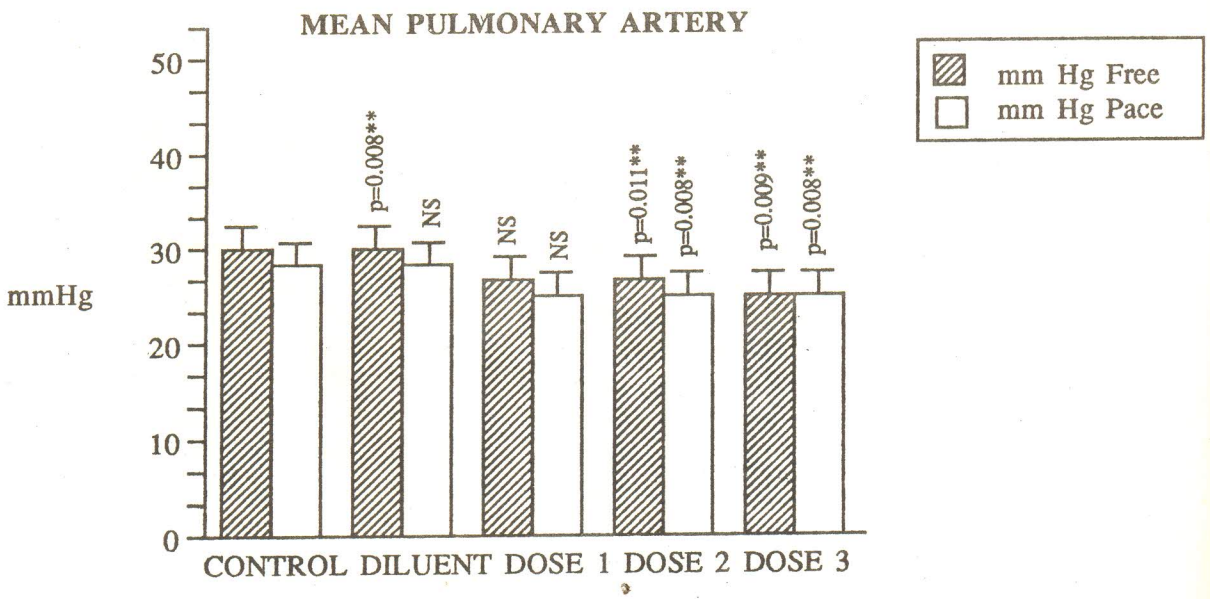





Left Ventricular dp/dt increased gradually with increase in dose. Mean at base line was 953 mmHg/sec. while at 3rd dose was 1277 mmHg/sec. With increase in dose LVEDP fell significantly from 21 base line to 14 mmHg after the 3rd dose. Mean pulmonary arterial pressure fell from 29 mmHg to 20 mmHg at 3rd dose.

**Blood Level**

Blood concentration of ICI 153, 110 were increased in 6 patients (table). Initial dose of 15mg showed mean blood level of 0.26 ug/ml while cumulative dose of 40mg showed blood con of 0.68 ug/ml and dose of 65mg achieved 1.12 ug/ml.



Finally cumulative dose of 100mg showed blood level of the drug to 2.0 ug/ml. Hence there was a dose related peak response of blood levels.

The biochemical and haematological screening was within hormal range.

**Discussion**

Impaired myocardial contractility is a primary feature of congestive heart Failure. Use of inotropic agents to stimulate the depressed myocardium may give symptomatic improvement to patients with congestive heart failures[5]. Digitalis is still most widely used cardiotonic agent but doubt about its efficacy in patient with sinus rhythm[6] and its modest inotropic effect in long term follow up study has led to its reduced use[7]. This controversy has led to continued search for therapeutic alternative. B-adrenergic receptor agonists in addition to augmenting cardiac contractility can bring about peripheral vasodilatation and achieve unloading effect upon heart[8] catacholamines as a whole have potential for arrythmogenesis and development of tolerance[9] and their primary limitation by requiring i/v administration[10].

Because of these disadvantages, active consideration has been given to new orally active group of non sympathomimetic non glycoside inotropic agents that inhibit cardiac phosphodiesterase[11]. Amrinone is one of these drugs, proved effective in short term acute i/v administration[12] but has been limited in clinical use because of its potential to produce thrombocytopenia and arrythmias that precludes its clinical use orally[13]. Milrinone is more potent than Amrinone and shows promising results with long term treatment[14] but needs to be taken 4-5 times/day and does not improve prognosis of patient with advanced congestive heart failure[15].

**PATIENT CHARACTERISTICS**

| No. | Initials | Sex | Age Yrs. | Height Cms. | Weight Kg. | B.S.A. Sq. m. | Aetiology |
|---|---|---|---|---|---|---|---|
| 1. | K.C. | F | 68 | - | 72.3 | - | CCM |
| 2. | R.H. | M | 57 | 166 | 74 | 1.82 | CAD |
| 3. | A.P. | M | 71 | 178 | 80 | 1.92 | CAD |
| 4. | W.S. | M | 67 | 178 | 87.5 | 2.0 | CAD |
| 5. | A.P. | M | 64 | 178 | 112.5 | 2.25 | CAD + HT |
| 6. | M.W. | F | 74 | 157 | 54.6 | 1.53 | CAD |
| 7. | A.J. | M | 47 | - | 78.5 | - | CAD |
| 8. | M.C. | F | 67 | 168 | 58.8 | 1.65 | CAD |
| 9. | D.B. | F | 71 | 155 | 67.4 | 1.66 | CAD |

The present study shows that the heart rate is unchanged, while the drug has caused significant dose related increases in peak positive dp/dt, indicating increased myocardial contractility. The significant reduction in right and left heart filling pressure indicates that both preload and afterload are decreased, with a resulting increase in cardiac output and cardiac index suggesting improved

cardiac performance.

A change in peak positive Left Ventricle dp/dt is a commonly used reference for determining changes in myocardial contractility but must be interpreted with caution in the setting of changes in loading conditions. Decrease in preload and afterload may both result in a decrease in peak positive dp/dt, whereas an increase in heart rate can cause an increase in dp/dt[16]. Based on significant reduction in right and left heart pressures and mean aortic pressure, it is highly likely that both preload and after load fell, while the heart rate did not change. Therefore the observed increase in dp/dt could not be related to changes in loading conditions or heart rate, as then it would tend to have reduced the magnitude of left ventricular dp/dt[17&18]. The reduction in ventricular loading with no change in heart rate should prevent any increase in myocardial oxygen demand[19]. Hence the improvement in left ventricular dp/dt seen during study suggests a positive inotropic effect of ICI 153, 110 and it improves left ventricular performance without increasing the metabolic cost to the myocardium.

All the changes in haemodynamic parameters were observed taking place gradually with each dose of ICI 153, 110, maximum effects being achieved after the third dose. Increase in drug levels in the blood produced beneficial haemodynamic effects without producing any undesirable effect. Similar effects were observed after the oral dose of 100mg given orally 24-48 hours after initial i/v acute study. Serum drug level effectively maintained peak levels at 12 hours, when it started falling.

The Biochemical and haemotological data of all the patients were within normal limits, following both acute and oral therapy. The drug was well tolerated and no undesirable or toxic effects were observed. There was no evidence of arrythmias of any sort.

## Conclusion & Implications

The study population was small and the haemodynamic effects were observed in acute study. It could not be documented whether tachyphylaxis occurs in response to its inotropic effects with long term use. Due to short term nature of the i/v study, no information could be gathered regarding duration of action of the drug when administered by this route. The results in this study suggest that the positive inotropic drug may be beneficial for the treatment of Congestive heart failure. Furthermore ICI 153, 110 proves to be effective positive inotropic drug with vasodilating effects and does improve left ventricular performance during acute administration in patients with congestive heart failure.

Despite optimal current therapy with digitalis, potent diuretics and vasodilators, patients with severe chronic congestive heart failure remain symptomatic and generally face a progressive declining clinical course with rapidly fatal outcome[20]. The aim of treatment is essentially amelioration of the symptoms and prolonged survival. The clinical value of this drug in the management of congestive heart failure will depend on evidence of persistent haemodynamic improvements on long term administration in patients and documentation of the absence of toxicity during chronic therapy.

If the loading conditions of the failing heart have been optimised by the use of vasodilators, left ventricular performance can be improved by positive inotropic therapy. In failing heart, the presence of contractile reserve has been demonstrated by the phenomenon of extra systolic potentiation[21]. PDE inhibitors have the combination of vasodilator and positive inotropic effect, hence these agents are also known as "Inodilators". Most trials are conducted for observing acute haemodynamics over a short period. From the point of view of patient the essential end points of positive inotropic therapy are prolonged survival and/or improvement of symptoms.

Hence there is a need to demonstrate the long term benefits from PDE inhibitors as it is important to determine that these agents do not exert deleterious effects on myocardial function or patient survival during long term use. Whether a mixed positive inotropic and vasodilator agent (Inodilator) will in future be developed and be shown to improve symptoms, quality of life survival remain to be established. To date, among PDE inhibitors, only

Enoximone has shown premise without haemotological side effects, however the basic question as to whether or not they will improve cardiovascular performance without side effects on survival is improved.

## References:


1. Applefield M.M; Newman K.A., Grove W.R., et al. Out patient dobutamine and dopamine infusion in the management of congestive heart failure clinical experience in 21 patients. Am Heart J 1987; 114(3): 589-595.

2. Leier C.V. General overview and uptake of positive inotropic therapy. Am J Med. 1986; 81 (Suppl. 4c): 40-45.

3. Colluci W.S., Wright R.F., Braunwald E. New positive inotropic agents in the treatment of congestive heart failure. Mechanism of action and recent clinical developments (second of two parts). N Engl J Med. 1986; 314(6): 349-58.

4. Data sheet for clinical investigators. Imperial Chemical Industries plc (ICI) clinical research department. 1986.

5. Sonnenblick E.H., Mancini D.M., LeJemtel T.H. New positive inotropic drugs for treatment of Congestive Heart Failure. Am J. Cardiol 1985; 55: 41-A 44A.

6. Chamberlain D.A. Digitalis: where are we now. Br. Heart J 1985; 54: 227-33.

7. Mulrow C.D., Feussner J.R., Veloz: R. Re-evaluation of Digitalis Efficacy. New light on old leaf. Annals of Inter. Med. 1984; 101: 113-117.

8. Anderson J. L., Askins J.C., Lutz J.R., et al. Occurrence of ventricular arrhythmias in patients receiving acute and chronic infusions of Milrinone. Am Heart J 198; III (3): 466-474.

9. Sonnenblick E.H., Frishman W.H., LeJemtel T.H. Dobutamine: A new synthetic cardio active sympathetic Amine. N Eng J Med. 1979; 300(1): 17-22.

10. Applefield M.M., Roffman D.S. Digitalis and other positive catacholamine like Inotropic agents in the management of Congestive heart failure. Am J Med 1986; 80 (Suppl. 2B): 40-45.

11. Colluci W.S., Wright R.F., Braunwald E. New positive Inotropic agents in the treatment of congestive heart failure. Mechanism of action and recent clinical developments. N Engl. J Med. 1986; 314(5): 290-299.

12. Treadway Go. Clinical safety of I/v Amrinone: A Review. Am J Cardiol 1985; 56; 39B-40B.

13. Goldstein R.A., Geracis. A., Dougherty A.H., Naccarell: G.V. Electrophysiologic effects of Milrinone in patients with congestive heart failure. Am J Cardiol 1986; 57: 624-628.

14. Simonton C.A., Chatterjee K. Daly P., Rutman H. Milrinone in congestive heart failure. Acute and chronic haemodynamic and clinical evaluation. J Am Coll Cardiol 1985; 6(2): 453-459.

15. Baim D.S., Collucci W.S., Mourad E.S., Braunwald E. Survival of patients with severe congestive heart failure treated with oral Milrinone. J. Am Coll Cardiol-1986; 7(3): 661-670.

16. Mason D.T. Usefulness and limitations of rate of intraventricular pressure (dp/dt) in the evaluation of myocardial contractility in man. Am J Cardiol 1969; 23: 516-527.

17. Ludmer P.L., Wright R.F., Braunwald E., Collucci W.S. Separation of the direct myocardial and vasodilator actions of Milrinone administered by an intracoronary technique. Circulation 1986; 73(1): 130-137.

18. Jaski B.E., Fifer H.A., Wright R.F., Braunwald E., Colucci W.S. Positive inotropic and vasodilator actions of Milrinone in patients with severe congestive heart failure. Dose response relationships and comparison to nitroprusside. J Clin Invest 1985; 75: 643-649.

19. Gage J., Rutman H., LeJemtal T.H. Additive effects of Dobutamine and Amrinone on myocardial contractility and ventricular performance in patients with severe heart failure. Circulation 1986; 74(2): 367-373.

20. McKee P.A., Castelli, W.P., McNamara P.M., Kannel W.B. The natural history of congestive heart failure. The Framingham Study. N. Engl: J Med. 1971; 285: 1441-1446.

21. Dyke S.H., Sonnen E.H., Gorlin R., Colu R.F. Detection of latent function in acutely ischemic myocardium in dogs; comparison of pharmocologic inotropic stimulation and post extra systolic potentiation (PESP) Circ. Res 1975; 36: 490-497.