Insulin Secretion in Heart Failure

B. SHARMA,* M.B., M.R.C.P., D.C.H. ; P. A. MAJID,† M.B., B.S., M.R.C.P. ; B. C. PAKRASHI,‡ M.B., B.S., M.R.C.P.
J. R. W. DYKES,§ M.B, CH.B., B.SC. ; S. H. TAYLOR,|| M.B., B.SC., M.R.C.P.

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Summary: Insulin secretion tests were carried out before and after treatment in patients with severe congestive heart failure. Before treatment the plasma insulin level and the insulin secretion response to intravenous tolbutamide were significantly reduced in all patients. In patients who made a good clinical recovery the plasma insulin level and the insulin secretion response were significantly improved. Patients who had a poor response to medical treatment showed little improvement in their insulin secretion test. This suppression of insulin secretion is probably due to the reduced blood flow to the pancreas together with a high level of circulating catecholamines.

Introduction

Patients with severe chronic heart failure present a difficult therapeutic problem. Though digitalis, diuretics, and potassium remain the mainstay of conventional treatment, they are often unable to increase appreciably the low cardiac output. The low cardiac output associated with circulatory shock after myocardial infarction is now known to be accompanied by a failure of insulin secretion (Taylor *et al.*, 1969). As a low output state is common to both conditions the facility with which insulin may be released in patients with severe heart failure was investigated.

Methods

Eight patients with severe chronic heart failure were studied (Table I). In two (Cases 3 and 7) this was the result of advanced ischaemic heart disease and in the remainder it was secondary to chronic rheumatic valvular heart disease. The jugular venous pressure was raised and ankle oedema was present in all eight patients, the liver was enlarged in six, and tricuspid incompetence was present in five. All were in atrial fibrillation and chest radiographs showed extensive pulmonary venous congestion. All patients were bedridden and all had had extended periods of treatment with digitalis, diuretics, and potassium. Informed consent for these studies was obtained from all patients.

* Research Fellow, United Leeds Hospitals.
† Senior Wellcome Foundation Research Fellow, Honorary Lecturer in Medicine, University of Leeds.
‡ Senior Ciba Research Fellow, Honorary Lecturer in Medicine, University of Leeds.
§ Lecturer in Chemical Pathology, University of Leeds.
|| Senior Lecturer in Medicine, University of Leeds; Consultant Physician to the United Leeds Hospitals and Leeds Regional Hospital Board.

Design of Investigation

Patients were kept on total bed-rest, and oral therapy with digoxin, frusemide, and potassium was continued throughout the four-week period of the study. Before additional treatment was given, control measurements were made of Pa_{O_2}, Pa_{CO_2}, *p*H, lactate, and pyruvate in the systemic arterial blood. After control samples of venous blood had been taken the insulin secretion test was carried out by injecting 1 g. of tolbutamide intravenously over 10 seconds. Further venous blood samples for plasma insulin and blood glucose measurements were taken at 1, 2, 5, 10, 15, 30, and 60 minutes after the injection.

After these control studies the oral therapy with digoxin, frusemide, and potassium was supplemented by twice-daily intravenous injections of 0·5 g. of aminophylline combined with 80 mg. of frusemide and additional oral potassium supplements of 1·2 g. of potassium chloride daily in all patients. In spite of this treatment two patients died within the first week; the remaining six were restudied in a similar manner to the control studies after four weeks of such treatment. The results of the insulin secretion tests were compared with those obtained in 12 normal male subjects aged 40-65 years.

Laboratory Techniques

Blood gas measurements were made by a polarographic technique and *p*H was determined by a microelectrode method. These measurements were made in duplicate on a direct reading instrument (Electronic Instruments Laboratories Ltd.) The standard deviation between duplicates for Pa_{O_2}, Pa_{CO_2}, and *p*H were 0·63 mm., 1·35 mm., and 0·01, respectively. Blood lactate was measured by the technique of Marbach and Weil (1967), the coefficient of variation at 13 mg./100 ml. being 7%. Blood pyruvate was measured by the method of Gloucester and Harris (1962), the coefficient of variation at 1 mg./100 ml. being 10%. The blood glucose concentration was estimated by an AutoAnalyzer glucose

TABLE I.—*Details of Patients Studied*

Case No.	Sex and Age	Clinical Response to Therapy	Before/After Therapy	Systemic Arterial Blood Analysis				
				*p*H	Pa_{O_2} mm. Hg	Pa_{CO_2} mm. Hg	Lactate mg./100 ml.	Pyruvate mg./100 ml.
1	F. 40	Good	Before	7·52	30	24	11·6	1·5
			After	7·50	68	30	5·3	0·5
2	M. 49	Good	Before	7·19	27	30	12·6	1·1
			After	7·46	58	34	4·3	0·8
3	M. 58	Good	Before	7·32	52	37	10·5	1·2
			After	7·41	74	36	6·1	0·5
4	M. 51	Poor	Before	7·49	46	33	23·3	1·4
			After	7·50	60	32	17·5	0·8
5	F. 54	Poor	Before	7·45	50	30	16·4	1·4
			After	7·41	52	29	13·6	0·8
6	M. 46	Poor	Before	7·51	46	34	13·5	0·8
			After	7·47	50	33	10·4	0·5
7	F. 48	Died	Before	7·29	44	31	19·3	1·6
8	F. 40	Died	Before	7·51	38	21	26·2	1·9

oxidase technique (Morley *et al.*, 1968). At a blood glucose concentration of 106 mg./100 ml. the coefficient of variation was 4·6%. Immunoreactive insulin was estimated in duplicate by a modification of the method of Hales and Randle (1963) using the reagents and Oxoid membrane filter supplied by the Radio Chemical Centre, Amersham. The standards were based on crystalline bovine insulin, a calibration range of 0-500 μunits/ml. being used. The average fasting value of 57 μunits/ml. in the normal subjects is higher than that of 6-27 μunits/ml. given by Hales and Randle (1963) using crystalline human insulin in a calibration range 0-200 μunits/ml. The standard deviation of the assay method calculated from the differences between 200 duplicate determinations in each of the concentration ranges 0-45, 50-99, 100-199, and greater than 200 μunits/ml. was ± 3·3, ± 7·4, ± 9·7, and ± 12·3 μunits/ml. respectively.

Measurements and Calculations

The "total" insulin secretion was estimated quantitatively by calculating the separate areas under the plasma curves for the first 10 minutes and for the whole hour following the tolbutamide injection. Statistical analyses were based on orthodox methods (Fisher, 1946).

Results

Before Treatment.—All patients showed a normal blood glucose level and a significantly low control plasma insulin value compared with the series of 12 normal subjects ($P < 0.05$). The average value of 21 μunit/ml. of insulin in these patients, however, is of a similar order to that observed in normal subjects reported by others (Hales and Randle, 1963). In addition all showed a significant degree of suppression of insulin release in response to intravenous tolbutamide as compared with the normal subjects (Fig. 1, Table II). In the latter insulin output in response to the tolbutamide was accompanied by a mean fall in blood glucose level of 51% over the 60-minute test period. In patients in heart failure the corresponding fall was significantly smaller, being 16% over the test period ($P < 0.05$) (Fig. 2).

After Treatment.—Six patients were restudied after four weeks of intensive medical treatment. In three (Cases 1-3) the clinical response was good with complete resolution of the peripheral oedema, disappearance of the raised jugular venous pulse, and diminution of the pulmonary venous congestion. This improvement was accompanied by improvement in the systemic arterial blood gas tensions, *p*H, and lactate and pyruvate measurements (Table I), and by a return to normal in the control plasma insulin level and in the insulin secretion response to tolbutamide (Fig. 3). The normal insulin output in these three patients was accompanied by a mean fall of 42% in blood glucose level during the 60-minute test period, whereas before treatment the mean fall was only 16% (Fig. 3, Table II). In three patients (Cases 4-6) the clinical

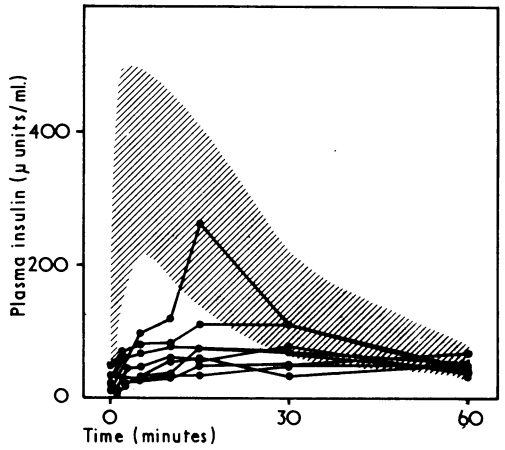

FIG. 1.—Insulin secretion response to intravenous tolbutamide in eight patients in severe chronic congestive heart failure. The range in 12 normal subjects (mean ± 2 S.D.) is cross-hatched

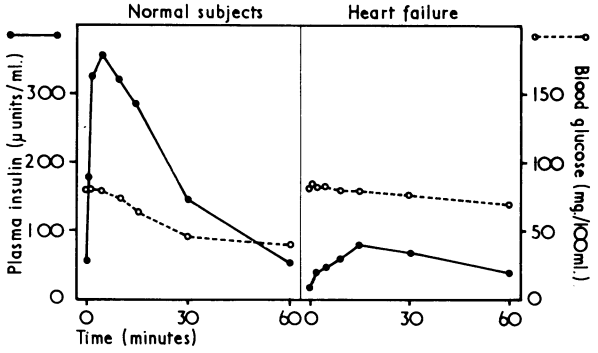

FIG. 2.—Averaged values of plasma insulin and blood glucose after intravenous tolbutamide in 12 normal subjects and eight patients in congestive heart failure.

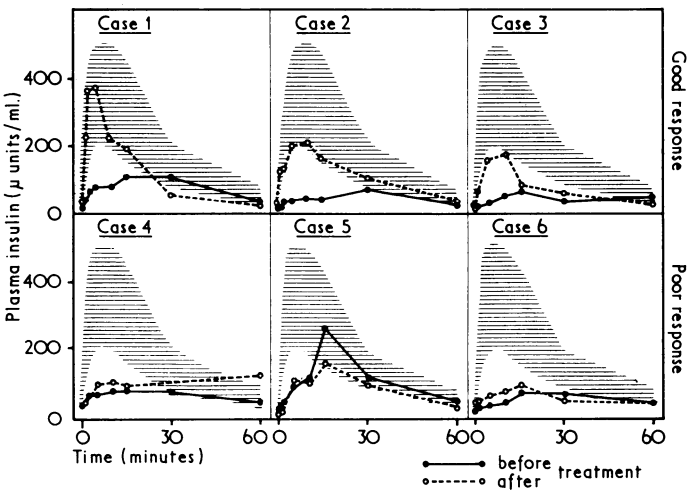

FIG. 3.—Insulin secretion response to intravenous tolbutamide before and after treatment in patients with congestive heart failure. The range in 12 normal subjects (mean ± 2 S.D.) is cross-hatched.

TABLE II.—*Insulin (μunits/ml.) and Glucose (mg./100 ml.) Values in Patients with Heart Failure before and after Treatment*

	Time in Minutes after Injection of Tolbutamide													
	0		1		2		5		10		15		30		60	
Heart Failure before Treatment (8 Cases)																
Insulin	*21±3	(8)	*33±4	(11)	*41±7	(20)	*49±10	(28)	*61±11	(31)	*80±25	(72)	*70±9	(26)	42±5	(13)
Glucose	82±6	(16)	84±6	(18)	83±7	(19)	84±6	(19)	82±6	(18)	81±7	(20)	*76±8	(22)	*69±2	(16)
Heart Failure after Treatment—Good Response (3 Cases)																
Insulin	29±3	(6)	127±58	(100)	188±91	(157)	236±68	(118)	193±18	(31)	138±35	(61)	70±18	(32)	33±1	(2)
Glucose	77±6	(10)	76±5	(9)	77±4	(7)	75±4	(8)	71±4	(7)	62±8	(14)	49±5	(9)	45±6	(11)
Heart Failure after Treatment—Poor Response (3 Cases)																
Insulin	26±8	(14)	*40±12	(21)	*45±13	(23)	*94±13	(22)	*97±11	(20)	116±27	(47)	84±14	(25)	58±32	(56)
Glucose	81±5	(8)	79±6	(11)	79±6	(11)	81±6	(10)	78±7	(12)	72±7	(12)	63±10	(17)	51±9	(16)
Normal Subjects (12 Cases)																
Insulin	57±13	(44)	177±41	(142)	323±49	(171)	357±41	(144)	321±42	(145)	286±42	(146)	141±20	(68)	54±10	(35)
Glucose	83±3	(10)	82±3	(11)	82±3	(11)	80±3	(11)	74±4	(12)	65±4	(12)	43±3	(10)	41±2	(8)

Data expressed as mean ± variance of mean, with standard deviation of observations in parentheses.
*Significantly different from mean of normal subjects ($P < 0.05$).

response to therapy was poor. After four weeks they still had severe heart failure. Though their peripheral oedema had been considerably reduced by treatment their jugular venous pressure was still raised and the chest radiographs showed no significant change in the pulmonary venous congestion. Moreover, the improvement in the systemic arterial blood gas and lactate and pyruvate measurements was much less than in the patients with a good clinical response (Table I). Nevertheless, the control plasma insulin level had increased and the insulin secretion response had improved, though the total response was still significantly impaired (Fig. 3 and Table II).

TABLE III.—*Total Insulin Secretion after Intravenous Tolbutamide*

Patient Group	No. of Cases	Insulin Output (units/ml./min.)	
		10 minutes	60 minutes
Heart failure before treatment ..	8	*0·30 ± 0·087 (0·207)	*2·53 ± 0·525 (1·486)
Heart failure after treatment—good clinical response	3	1·65 ± 0·524 (0·908)	4·14 ± 0·980 (1·698)
Heart failure after treatment—poor clinical response	3	*0·50 ± 0·071 (0·123)	*3·36 ± 0·690 (1·196)
Normal subjects	12	2·53 ± 0·399 (1·175)	7·31 ± 0·990 (3·429)

*Significantly different from mean of normal subjects ($P < 0·05$).

Quantitative Comparisons.—Insulin secretion in the 10- and 60-minute periods after the tolbutamide stimulus was estimated quantitatively by calculating the respective areas under the plasma insulin curves; the results in the patients before and after treatment are compared with those in normal subjects of the same age group in Table III. Before treatment all patients had a severely depressed insulin output during both the 10- and 60-minute periods. In those who made a good clinical response to treatment the mean outputs at 10 and 60 minutes were increased and not significantly different from those of normal subjects ($P > 0·20$ and $P > 0·10$ respectively). In the patients who made only a limited clinical recovery the insulin outputs at 10 and 60 minutes were still both significantly impaired compared with those of normal subjects ($P < 0·02$ and $P < 0·05$ respectively).

Discussion

Thus severe heart failure is accompanied by a suppression of insulin secretion even in response to such a potent secretory stimulus as intravenous tolbutamide. The serial studies also showed a direct correlation between the degree of circulatory improvement and the improvement in the insulin output response. A similar association occurs in the low cardiac output state associated with cardiogenic shock due to myocardial infarction (Taylor *et al.*, 1970) and in that following open-heart surgery (Majid *et al.*, 1970a). Hence suppression of insulin secretion is an integral part of the syndrome of severe heart failure.

Many mechanisms may be involved in this suppression, but probably two factors are largely responsible. A large fall in cardiac output is invariably accompanied by a reduced blood flow to the regional vascular territories; this is followed by increased sympathetic drive and increased output of adrenomedullary catecholamines (Tomomatsu *et al.*, 1963; Chidsey *et al.*, 1965). The resulting severe reduction in splanchnic, and presumably pancreatic, blood flow may lead to a suppression of insulin release by preventing an adequate secretory stimulus reaching the beta cells. In addition, the increased levels of circulating catecholamines may also play a significant part in the suppression of insulin release, for catecholamines are a potent suppressor of the normal insulin response to a secretory stimulus in both animals (Hertelendy *et al.*, 1966; Kris *et al.*, 1966; Altszuler *et al.*, 1967) and man (Karam *et al.*, 1966; Porte *et al.*, 1966; Majid *et al.*, 1970b). Loubatieres *et al.* (1965) also showed that adrenaline selectively damages the pancreatic beta cells. These two factors of low pancreatic blood flow and increased levels of circulating catecholamines may together play a major part in the suppression of insulin release in severe heart failure.

The therapeutic implications of these findings deserve consideration. Though digitalis and diuretics are still of major importance in the treatment of heart failure, their role is particularly limited in patients in whom the disease is both chronic and severe. The suppression of insulin secretion in these patients may possibly aggravate the heart failure by interrupting the normal carbohydrate metabolic cycle in the heart. Though studies of the effect of insulin on cardiac function in severe heart failure do not appear to have been made, our findings suggest that such studies may have important therapeutic applications.

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Requests for reprints should be addressed to Dr. S. H. Taylor, Department of Medicine, the General Infirmary, Leeds LS1 3EX.

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