Insulin secretion after open-heart surgery with particular respect to pathogenesis of low cardiac output state

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Insulin secretion tests, and measurements of systemic arterial free fatty acids, pyruvate, and lactate were carried out before operation in 6 patients undergoing open-heart surgery for valve replacement. The measurements were serially repeated after operation and the results were related to the clinical state of the patient. In patients developing the clinical picture of a low cardiac output state, the systemic arterial free fatty acid, lactate, and pyruvate levels were all greatly increased and the secretion of insulin severely suppressed. These variables gradually returned to their preoperative levels in parallel with improvement in the clinical state in each patient. The therapeutic implications of these findings are discussed in relation to the use of insulin in the post-operative management of patients undergoing open-heart operation.

The low cardiac output syndrome is a major hazard of the early postoperative period after open-heart surgery, and its onset is associated with a high mortality. Correction of hypovolaemia and the counteraction of depressed left ventricular function by inotropic agents and vasodilator drugs have greatly improved the outlook, but some patients still fail to respond adequately to these measures. The primary fault is one of pumping failure of the heart, and in this respect it is similar to the heart failure associated with naturally occurring disease. The pumping failure associated with cardiogenic shock after myocardial infarction and that associated with severe congestive heart failure have both been found to be accompanied by suppression of insulin secretion (Taylor *et al.*, 1969; Sharma *et al.*, 1970). The following investigation was, therefore, designed to measure the facility with which insulin was released in patients undergoing open-heart operations for valve replacement.

Subjects and methods

Clinical details Six patients undergoing open-heart surgery for mitral or aortic valve replace-

ment were studied. Their personal, clinical, surgical, and laboratory details are listed in Table 1. None was in congestive heart failure at the time of the preoperative studies, though all were severely incapacitated by breathlessness on exertion. Cases 2 and 6 were in sinus rhythm; the remainder were in atrial fibrillation. The chest radiographs and electrocardiographic findings were consistent with the clinical diagnoses and all patients were adjudged good surgical risks. Informed consent for the studies was obtained from all patients.

Design of investigation Measurements were made of the systemic arterial blood gas tensions, pH, free fatty acids, lactate, pyruvate, and glucose immediately before an insulin secretion test was performed; these measurements were made on the day before operation, during the first 12 hours after operation (Day 1), and on the 2nd, 5th, 7th, 14th, and 28th postoperative days. The insulin secretion test was based on the potency of intravenous tolbutamide to release preformed insulin from the beta cells of the pancreas (Seltzer, 1962). The standardization, repeatability, and range of normal values of this test have been reported elsewhere (Saxton *et al.*, 1970). After the control venous sample, 1 g. tolbutamide was injected intravenously over 10 seconds. Further venous blood samples for the measurement of glucose and insulin were taken at 1, 2, 5, 10, 15, 30, and 60 minutes. None of the patients complained of or showed any side-effects after the injection. The results of the insulin secretion tests were compared

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TABLE I Clinical and laboratory details of patients studied

Case No.	Age Height (cm.) Type of operation Perfusion time Clinical course	Sex	Weight	Day	Systemic arterial measurements					
					P _a O ₂ (mm. Hg)	P _a CO ₂ (mm. Hg)	pH	Free fatty acids (mEq/l.)	Lactate (mg./100 ml.)	Pyruvate (mg./100 ml.)
1	49 years 165 Mitral valve replacement 49 min. perfusion Good	M	58 kg.	Preop.	74	34.0	7.47	0.245	15.5	0.8
				1	*400	48.5	7.36	0.426	> 50	1.7
				2	*170	43.0	7.42	0.392	28.0	1.6
				3	*154	42.5	7.48	0.334	18.7	1.8
				5	*120	35.5	7.47	0.200	16.9	1.0
				7	85	37.0	7.51	0.194	12.6	0.8
				14	86	34.5	7.53	0.200	10.3	0.9
				28	82	35.5	7.56	0.197	5.6	1.0
2	54 years 170 Aortic valve replacement 59 min. perfusion Good	M	70 kg.	Preop.	82	46.0	7.42	0.336	13.5	1.1
				1	105	57.0	7.40	0.820	27.5	2.1
				2	64	32.0	7.48	0.750	24.0	1.7
				3	66	36.5	7.43	0.730	22.8	1.4
				5	78	39.0	7.42	0.690	20.0	1.6
				7	74	33.0	7.48	0.281	17.3	1.3
				14	78	37.5	7.40	0.193	12.7	1.2
				28	79	41.5	7.41	0.190	5.4	1.0
3	48 years 173 Mitral valve replacement 64 min. perfusion Poor Day 1 Good later	F	74 kg.	Preop.	106	37.0	7.43	0.270	10.0	0.6
				1	*315	53.0	7.36	0.655	> 50	2.0
				2	*175	47.5	7.36	0.427	35.5	1.8
				3	86	45.0	7.43	0.422	18.0	1.5
				5	64	35.0	7.54	0.294	14.7	1.1
				7	65	38.0	7.50	0.220	12.1	0.8
				14	77	35.5	7.47	0.128	6.1	0.7
				28	76	40.5	7.42	0.198	4.9	0.7
4	50 years 156 Aortic and mitral valve replacement 79 min. perfusion Poor	F	69 kg.	Preop.	92	44.5	7.42	0.685	10.5	0.9
				1	*425	44.0	7.42	2.800	34.5	2.3
				2	*335	52.0	7.37	1.835	28.0	2.0
				3	*210	44.5	7.45	1.760	25.0	1.6
				5	54	35.0	7.50	1.400	19.5	1.0
				7	65	34.0	7.47	1.000	13.0	1.1
				14	67	36.0	7.49	0.714	8.5	1.0
				28	76	39.5	7.49	0.695	6.9	0.9
5	51 years 165 Mitral valve replacement 55 min. perfusion Poor	M	54 kg.	Preop.	87	40.5	7.41	0.975	10.5	0.9
				1	*430	49.0	7.39	1.300	> 50	1.8
				2	*194	49.5	7.42	1.085	44.7	1.7
				3	49	48.0	7.48	0.960	31.6	1.8
				5	58	45.0	7.51	0.800	22.6	1.2
				7	50	38.0	7.50	0.896	19.0	0.9
				14	70	33.5	7.50	0.402	16.5	1.0
				28	70	39.0	7.41	0.690	6.2	1.0
6	57 years 170 Aortic valve replacement 68 min. perfusion Poor	M	56 kg.	Preop.	82	39.5	7.44	0.478	12.3	0.8
				1	*390	47.5	7.47	1.310	42.2	2.4
				2	*280	55.0	7.43	0.910	32.9	1.5
				3	*106	60.0	7.39	0.590	26.7	1.7
				5	*110	50.0	7.55	0.440	27.0	1.4
				7	*122	46.0	7.45	0.360	25.0	1.9
				14	63	37.5	7.43	0.240	18.9	1.7
				28	70	39.0	7.51	0.445	14.0	1.3

* On 100 per cent oxygen by face mask at 8 l./min.

with those obtained from 12 normal male subjects aged 40-65 years.

The study was specifically designed not to interfere in any way with the routine postoperative treatment of the patient. All but one patient (Case 2) received oxygen by face mask for some days after operation (Table 1). During the first 3

days after operation all patients routinely received intravenous glucose therapy which probably accounts in part for the very high values of blood glucose observed at this time. Except for the studies during the first 3 postoperative days the insulin secretion tests were carried out in the morning 3 hours after a light meal.

TABLE 2 Results of insulin secretion test in patients undergoing open-heart operations

Case No.	Time (min.)	Preop.		Day 1		Day 2		Day 3		Day 5		Day 7		Day 14		Day 28	
		Ins.*	Glu.†	Ins.	Glu.	Ins.	Glu.	Ins.	Glu.	Ins.	Glu.	Ins.	Glu.	Ins.	Glu.	Ins.	Glu.
1	C	21	60	37	286	76	115	51	186	237	104	109	72	138	80	63	89
	1	97	58	184	295	179	104	116	172	374	98	351	80	574	72	177	89
	2	268	70	285	214	323	102	227	164	537	100	514	83	581	69	368	90
	5	267	60	264	264	413	104	264	232	596	94	517	76	541	66	338	85
	10	226	65	269	270	408	92	274	186	609	90	486	69	493	54	282	75
	15	218	56	184	306	392	88	292	192	595	86	476	43	452	49	212	63
	30	30	32	133	246	404	58	266	176	541	66	213	40	115	30	89	50
	60	30	30	116	144	193	52	76	103	189	32	47	30	48	25	36	42
2	C	30	78	54	126	34	76	48	96	45	100	208	117	26	84	25	72
	1	313	75	188	113	225	73	217	94	287	98	390	117	276	78	251	72
	2	312	75	213	109	219	72	212	95	285	102	369	110	292	74	287	73
	5	311	73	223	101	211	74	230	94	197	103	334	107	221	72	180	70
	10	288	68	215	104	184	73	188	90	173	88	339	92	216	68	143	65
	15	278	63	235	98	166	70	203	80	144	83	325	86	183	62	157	58
	30	193	49	199	78	140	64	140	74	112	60	285	70	103	46	158	49
	60	70	47	190	62	63	46	86	70	36	45	266	66	48	44	28	38
3	C	103	63	46	196	163	128	174	106	37	81	351	62	59	80	176	88
	1	312	55	74	190	192	122	252	104	105	73	357	64	66	76	230	88
	2	324	59	88	215	180	120	284	101	141	78	437	58	142	78	309	89
	5	313	55	97	207	218	120	307	100	211	74	459	52	266	74	349	89
	10	275	50	74	203	217	115	332	98	302	73	457	56	262	75	365	87
	15	240	43	57	180	212	114	333	95	315	70	462	54	243	72	342	84
	30	198	33	53	186	214	112	333	85	328	63	432	49	217	60	305	70
	60	162	23	35	208	173	100	213	52	144	48	379	47	75	46	150	48
4	C	52	80	26	216	83	100	33	68	23	77	15	76	45	76	30	73
	1	210	75	30	214	139	97	66	68	39	77	67	81	173	80	175	72
	2	220	75	32	184	181	90	97	68	52	82	71	86	272	78	168	73
	5	176	70	44	188	160	87	103	68	84	80	71	86	172	72	115	71
	10	141	63	44	176	160	85	118	65	89	78	68	84	143	70	93	69
	15	114	60	49	176	187	82	132	63	77	76	95	81	110	66	86	64
	30	107	52	46	180	158	73	99	58	71	70	85	74	66	54	49	50
	60	45	49	26	190	120	69	59	53	30	68	58	69	40	44	28	40
5	C	24	89	26	175	160	105	156	128	42	98	48	92	50	100	34	66
	1	329	86	36	170	156	93	149	110	190	95	67	86	252	95	337	64
	2	362	92	57	165	155	96	181	110	280	94	176	88	458	98	440	63
	5	335	90	56	108	175	95	193	108	355	96	308	86	517	90	415	62
	10	267	88	46	160	170	95	192	103	353	94	288	86	509	86	464	60
	15	197	76	49	165	165	93	247	101	371	90	336	74	473	83	440	59
	30	118	56	64	172	163	92	265	95	313	82	151	63	380	56	340	46
	60	32	50	28	163	160	100	213	88	311	68	44	50	58	50	93	38
6	C	25	72	22	251	61	110	41	108	54	120	24	98	109	134	149	133
	1	294	68	21	235	53	109	27	107	127	118	102	92	344	130	323	130
	2	207	72	32	242	97	108	37	115	200	118	110	92	411	120	396	125
	5	225	66	47	239	124	103	73	116	330	116	150	94	428	124	480	119
	10	180	66	65	237	120	93	77	103	268	110	155	92	392	106	364	114
	15	195	60	71	233	121	101	83	115	170	108	149	88	421	102	350	103
	30	143	50	62	229	111	107	90	116	163	96	112	80	366	96	253	90
	60	57	34	71	224	93	96	69	105	103	80	91	62	296	82	117	52

* Plasma insulin (μ unit/ml.).

† Blood glucose (mg./100 ml.).

Laboratory techniques Blood gas measurements were made by a polarographic technique, and pH was determined by a micro-electrode method. The polarographic measurements were made on a gas-calibrated direct reading instrument (Electronic Instruments Laboratories Ltd.); the standard deviation between duplicates for P_{aO_2} ,

P_{aCO_2} , and pH 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. was 7 per cent. Blood pyruvate was measured by the method of Gloster and Harris (1962); the coefficient of variation at 1 mg./100 ml. was 10 per cent.

Total free fatty acids were estimated colorimetrically by the method of Laurell and Tibbling (1967) after extraction by the method of Duncombe (1963); the coefficient of variation at 0.5 mEq/l. was 7 per cent. The blood glucose concentration was estimated by an 'Autoanalyser' glucose oxidase technique (Morley, Marks, and Dawson, 1966); the coefficient of variation at 106 mg./100 ml. was 5 per cent. Immunoreactive insulin was measured by the double-antibody radioimmunoassay method of Hales and Randle (1963), employing the reagents and oxoid membrane filter supplied by the Radio Chemical Centre at Amersham. The standards were based on crystalline bovine insulin using a calibration range 0–500 μ units/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 μ units/ml., was ± 3.3 , ± 7.4 , ± 9.7 , and ± 12.3 μ units/ml., respectively. All measurements were made in duplicate.

Measurements and calculations A quantitative measure of the 'total' insulin secretion was estimated by calculating the separate areas under the plasma curves for the first 10 minutes and for the whole hour after the tolbutamide injection. Statistical analyses were based on orthodox methods (Fisher, 1944).

Results

Studies before operation Before operation the systemic arterial blood gas tensions and pH were within the normal range in all 6 patients (Table 1). The arterial free fatty acid level was within normal limits except in one patient (Case 2) in whom it was raised. The systemic arterial blood lactate was raised in one patient (Case 1) before operation but was within normal limits in the remainder. The arterial pyruvate level was raised in one patient (Case 2); in the remainder it was within normal limits. The resting values of arterial blood gas tensions, pH, free fatty acids, and lactate and pyruvate were consistent with the clinical and circulatory state of these patients. The insulin secretion response after tolbutamide was within the normal range in all 6 patients (Fig. 1 and Table 2). The control blood glucose level was within the normal range in all 6 patients. The fall in blood glucose level during the 60 minutes after the injection of tolbutamide averaged 48 per cent (range 38–64%) compared with a fall of 51 per cent in normal subjects, and reflects the normal output of insulin in all these patients before operation.

Studies after operation Two patients (Cases 1 and 2) made excellent progress after operation, and at no time gave rise to concern.

FIG. 1 Insulin secretion response to intravenous tolbutamide in two patients before and after open-heart operation. The range in 12 normal subjects (mean ± 2 SD) is cross-hatched.

One patient (Case 3) presented clinical signs of a low output state on Day 1 but thereafter made excellent clinical progress. The 3 remaining patients (Cases 4, 5, and 6) had a difficult and prolonged postoperative course and all 3 presented the clinical picture of the low cardiac output syndrome in the immediate postoperative period. Case 4 was seriously ill for more than a week. Case 5 was seriously ill for the first 48 hours after operation but then rapidly improved. Case 6 was seriously ill for 72 hours after operation before improvement began.

The systemic arterial blood gas tensions and pH showed no consistent changes during the postoperative period due to the routine treatment with oxygen by face mask and correction of any fall in systemic arterial pH with parenteral sodium bicarbonate. The systemic arterial free fatty acid, lactate, and pyruvate measurements all showed a consistent pattern of change after operation. There was a considerable increase in all three variables during the immediate postoperative period, with a gradual return to their original preoperative level during the succeeding 28 days. The extent of the changes in these three variables correlated well with the clinical state of these patients (Table 1). The insulin secretion test likewise showed a close relation with the clinical state of the patient (Fig. 1 and Table 2). The two patients (Cases 1 and 2) who had an uninterrupted clinical recovery showed normal insulin secretion tests throughout the postoperative period. Case 3 was seriously ill on Day 1 and at this time she showed a severe suppression of insulin secretion. Her rapid improvement during the succeeding days was accompanied by a rapid return to normal in the insulin secretion test. The clinical state of

the patient and the facility with which tolbutamide released insulin was closely correlated in the three patients who had a poor postoperative course. The insulin secretion response was nearly completely suppressed in the immediate postoperative period and only returned to normal in parallel with the improvement in their clinical state (Fig. 2). It is of interest to note that in 5 of the 6 patients there was an overshoot in insulin response, as compared with their own pre-operative test, at some time during the post-operative course.

Discussion

These studies show a clear-cut correlation between the clinical state of the patient after open-heart operation, and the ability to secrete insulin in response to the intravenous injection of tolbutamide. The correlation is similar to that reported for the low cardiac output states occurring in patients with cardiogenic shock after myocardial infarction (Taylor *et al.*, 1969; Allison, Chamberlain, and Hinton, 1969) and in severe congestive heart failure (Sharma *et al.*, 1970). The mechanisms responsible for this suppression of insulin secretion are unknown, but a common factor in all of these patients is the low cardiac output.

In the experimental animal a large fall in cardiac output is invariably accompanied by a correspondingly large fall in splanchnic blood flow (Selkurt, Alexander, and Patterson, 1947; Selkurt and Brecher, 1956; Levy, 1958; Gregg, 1962). This fall in splanchnic and presumably pancreatic blood flow may prevent an adequate stimulus reaching the insulin-secreting beta cells. A second possible factor in the suppression of insulin secretion relates to the increased sympathetic drive and raised levels of circulating catecholamines that immediately follow a large fall in cardiac output. The catecholamines, and particularly adrenalin, have been shown not only to cause pathological changes specifically located in the beta cells of the pancreas (Loubatières *et al.*, 1965) but also to suppress insulin both in animals (Kris *et al.*, 1966; Hertelendy *et al.*, 1966; Altszuler *et al.*, 1967) and in man (Porte *et al.*, 1966; Karam *et al.*, 1966; Majid *et al.*, 1970). In patients who develop a low cardiac output state after open-heart surgery, both conditions are present, and together may account for the suppression of insulin release observed.

The therapeutic implications of these findings are worthy of comment. Myocardium damaged by ischaemia depends for its energy production on the metabolism of glucose

FIG. 2 Average total insulin secretion response to intravenous tolbutamide in 12 normal subjects and 6 patients before and after open-heart operation.

(Owen, Thomas, and Opie, 1969). If such damage is accompanied by loss of ability to secrete insulin, cardiac performance may be further severely impaired. In addition, the correlation between the severity of the circulatory illness and the increase in the free fatty acids observed in the present studies agrees with the earlier findings of Oliver, Kurien, and Greenwood (1968) who showed a correlation between the plasma level of free fatty acids and the incidence of serious dysrhythmias and disorders of conduction after myocardial infarction. In both instances the administration of insulin may possibly produce clinical improvement, and these findings suggest that its use in patients developing the low output syndrome after open-heart operations should be more thoroughly investigated.

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