

Massive Insulin Hypoglycemia and Capillary Vascular Physiology in Man

John W. Lovett Doust, M.B., B.Sc.,* and Marta E. Salna, M.D.,† Toronto

The vascular responses attending major insulin hypoglycemic reactions in man have been reviewed by Kalinowsky and Hoch,¹ Bellak,² and others, but the special role of the capillary and other small vessels has received little attention. The importance of this role is implied in the investigations made on the influence of insulin in coma-provoking doses in regard to brain metabolism, the literature on which has been reviewed by Himwich,³ and since the capillary system is the final common path by which energy is transferred between blood elements and tissue cells.^{4, 5}

This paper is concerned with the acute responses of the minute vasculature of two nondiabetic human subjects receiving massive doses of insulin five times weekly, over a three-month period. The more chronic vascular effects of this sequential experience of hypoglycemia are reported elsewhere.⁶

PROCEDURE

Clinical Material. The subjects were two white male schizophrenics. Patient A was aged 21 years and diagnosed as a catatonic; Patient B was 23 years old and diagnosed as a paranoid schizophrenic. Each was investigated for three months prior to the administration of insulin in order to determine his baseline status. The two patients were then followed through a course of hypoglycemic episodes, brought about by injections of up to 600 units of regular insulin, resulting in sixty sopor reaction states and forty-six coma states in Patient A, and fifty-seven sopors and thirty comas in Patient B. Duration of coma was five minutes per treatment initially, but was allowed progressively to endure up to thirty minutes on any one occasion in each patient. Interruption of the hypoglycemia was accomplished routinely by the oral route in the early sopor stages,

by gastric tube in the later sopor and light coma stages, and intravenously in the later deep coma episodes.

METHODS

Acral blood flow in the arterioles was estimated indirectly by skin temperature measurements taken from the dorsum of the fingers near the nail fold. A Baird-Hardy dermal radiometer was used. Capillary blood flow was measured directly as the rate per second of corpuscular streaming in the nailfold skin capillary loops under microscopic observation, timing being achieved by stroboscopic control in accordance with a method recently introduced.⁷ Capillary blood pressure was estimated as the skin-color-disappearance-pressure by means of a glass Hooker capsule affixed to the dorsum of the subject's hand. If rather rigid standards are adopted for this technic, the results⁸ agree well with those obtained by the Landis⁹ direct micro-cannulation method in which the intubated nailfold skin capillary loops were used as the site for examination. Capillary blood-oxygen saturation was estimated oximetrically, using the spectroscopic technic,^{4, 10} and again taking readings from the nailfold skin. Tissue edema was measured by a simple water-displacement plethysmograph attached to the terminal phalanx of the index finger. A Leitz incident-light capillary microscope was used to inspect the functional anatomy of the nailfold skin vasculature and note was taken of the morphology of the minute vessels,¹¹ as well as the dynamic changes in their tone, the occurrence of extravascular hemorrhages, etc. Arterial pressure was estimated routinely with a mercury sphygmomanometer.

Each of the above investigations was carried out kinetically and serially on both patients, (1) during the three-month pre-insulin observation period; (2) throughout the hypoglycemic episodes and continuing until consciousness was regained following the glucose interruption; (3) five hours post-insulin after the glucose interruption when the patients had fully recovered from their hypoglycemic experience.

In addition, spot checks were made of the blood

From the Department of Psychiatry, University of Toronto, Toronto, Canada.

*Associate Professor, Department of Psychiatry, University of Toronto Medical School, Toronto, Canada.

†Research Associate, Department of Psychiatry, University of Toronto Medical School, Toronto, Canada.

glucose levels,¹² both fasting during the initial baseline resting period and later at the clinical peaks of the insulin response. Similar observations were made of the blood specific gravity, using the Van Slyke and associates,¹³ and Phillips et al.¹⁴ copper sulphate falling drop method, to derive estimates of plasma protein, hemoglobin and hematocrit variation. Statistical significance was assayed by the analysis of variance technic and computation of the correlation ratio (η^2), the latter providing a useful index of the extent to which the variation is dependent upon the individual monitor employed.

RESULTS AND DISCUSSION

These are displayed in the accompanying tables and figure. In every case in table 2 the mean values of the variable investigated are given for each of four phases of the patient's hypoglycemic experience and its interruption by glucose while, for comparison, similar mean values are displayed for the relevant pre- and post-insulin conditions.

Blood Flow in the Minute Vessels. Table 2 gives the changes found for corpuscular rate in the nailfold skin capillaries and probable cutaneous arteriolar flow as determined by skin temperature fluctuation respectively. Figure 1 illustrates graphically the corpuscular flow changes of the distal hairpin loops and focuses attention on the hypoxic implications of the coma state. Not only is cellular respiration impaired by depriving the cell of

its glucose requirements; direct molecular oxygen delivery is also delayed. In Patient A (table 2) arteriolar blood flow inhibition follows precisely the pattern set by flow in the true capillaries, but in Patient B this is not so and the paradoxical rise in skin temperature at the deep coma phase, and at a time when corpuscular

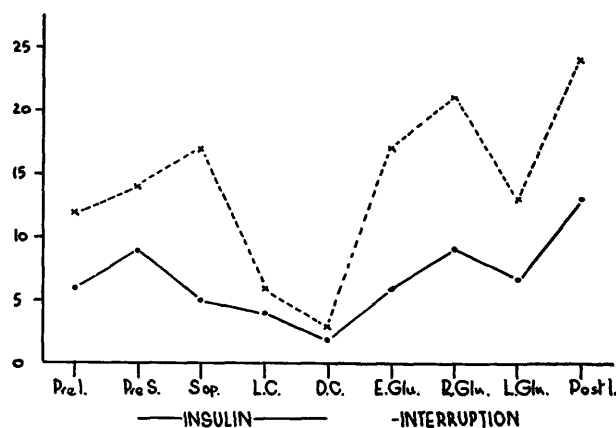


FIG. 1. Mean capillary blood flow in Patient A (continuous line) and Patient B (dotted line). Ordinates: rate of flow (corpuscles per second); abscissa (reading from left to right): Pre-insulin baseline levels; pre-sopor state following insulin injection; hypoglycemic sopor; light coma; deep coma; initial response to 33.3 per cent glucose administration; "rebound" effect of absorbed glucose; later acute effects of glucose; "post-insulin" (levels obtained 5 hours following interruption of the hypoglycemic coma).

TABLE 1
Mean changes brought about by insulin in blood sugar, plasma protein, hematocrit and hemoglobin content

Time (fasting)	Blood sugar (mg. per cent) Patient		Plasma protein (gm. per cent) Patient		Hematocrit (per cent) Patient		Hemoglobin (gm. per cent) Patient	
	A	B	A	B*	A	B*	A	B*
Pre-insulin	85.000 (s=12.5) (N=4)	69.000 (s=6.5) (N=3)	8.047 (s=.4) (N=25)		46.591 (s=1.6) (N=23)		15.817 (s=.5) (N=23)	
Insulin			7.797 (s=.3) (N=30)	7.923	47.900 (s=2.3) (N=28)	48.805	16.282 (s=.8) (N=28)	16.579
Sopor	28.625 (s=9.1) (N=8)	30.556 (s=10.2) (N=9)						
Coma	23.125 (s=8.5) (N=16)	23.333 (s=12.1) (N=12)						
Difference			-0.250		+1.345		+0.465	
t test			5.124		4.854		4.927	
d.i.			53		49		49	
P			<.001		<.001		<.001	

*No specific gravities were available on the pre-insulin blood in the case of Patient B.

TABLE 2
Effect of various stages of hypoglycemia on capillary vascular variables and finger volume

Status		Capillary blood flow (corpuscles/sec.)		Skin temperature (°F)		Capillary blood pressure (mm.Hg)		Arterial pulse pressure (mm.Hg)	
		Patient		Patient		Patient		Patient	
		A	B	A	B	A	B	A	B
Pre-insulin	Mean	6.00	12.32	91.84	95.36	41.92	43.03	35.86	30.56
	s	7.3	13.3	3.7	1.6	12.9	13.1	11.8	6.7
	N	190	93	59	29	198	95	35	14
Pre-sopor	Mean	9.20	13.83	93.83	93.66	40.47	28.40	80.00	57.50
	s	1.9	8.4	1.6	1.2	14.6	8.4	8.2	12.6
	N	5	6	13	19	17	10	7	4
Sopor	Mean	4.97	16.92	90.84	91.36	21.93	21.58	96.74	60.00
	s	3.4	8.8	1.9	1.7	12.8	6.7	28.5	7.3
	N	29	13	38	24	40	19	43	28
Light coma	Mean	3.97	6.29	89.00	88.15	40.26	50.00	105.83	60.00
	s	4.2	6.5	1.4	3.4	24.4	0	19.7	18.7
	N	38	7	11	6	19	3	12	5
Deep coma	Mean	2.10	3.29	87.05	93.24	54.00	—	103.33	62.00
	s	2.2	5.3	1.4	0.5	8.9	—	40.8	16.4
	N	42	7	12	5	5	—	6	5
Early glucose	Mean	6.34	17.00	88.38	90.45	37.13	27.50	83.68	57.14
	s	8.3	14.8	4.3	3.8	35.5	7.5	15.7	13.8
	N	32	8	25	21	23	8	19	7
Rebound glucose	Mean	9.36	21.33	88.07	91.27	18.61	18.18	66.09	43.00
	s	8.8	13.4	4.7	3.0	5.1	1.4	18.0	16.4
	N	33	9	26	21	23	11	23	10
Late glucose	Mean	6.59	13.33	84.42	88.25	26.11	34.00	56.43	45.00
	s	6.5	6.2	5.4	2.9	13.1	4.9	10.1	11.9
	N	29	6	25	11	19	4	14	8
Post-insulin	Mean	13.43	24.39	93.27	94.40	34.25	35.11	44.32	39.46
	s	9.5	15.2	2.7	1.8	12.7	12.7	8.2	8.2
	N	131	101	32	52	143	92	37	28
F ratio		16.029	6.651	17.937	21.381	14.593	10.794	49.396	18.717
d.f.		8/520	8/241	8/232	8/179	8/478	7/234	8/187	8/100
n ²		.198	.181	.382	.489	.196	.227	.679	.600
P		<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001

motion in the capillaries is almost at a standstill, suggests the operation of a shunt mechanism which bypasses these vessels in this patient. If such were the case, a similar anomaly might be expected in the blood-oxygen saturation of the minute vessels in Patient B and table 2 lends support to this assumption.

Intravascular Pressures. Table 2 also compares the capillary blood pressure and arterial pulse pressure variations during insulin hypoglycemia. The resting pressures of both patients are characteristic of those found in schizophrenia,^{8, 15} and only approximate healthy values under the influence of the glucose interruption. Progressive hypoglycemia would seem to influence capillary pressure in a biphasic fashion, a trough at the sopor stage being given by both patients. This dip is not seen to disturb the steady widening of the pulse pressures although the extent of this change is less evident in Patient B than in Patient A.

Tissue Volume and Other Changes. Digital tissue waterlogging is suggested in table 2 as occurring se-

quentially with deepening coma and raises the question of its source. Relative oxygen-lack increases capillary permeability to plasma,^{16, 17} and even to whole blood.¹⁸ According to Starling's hypothesis, the colloid osmotic pressure of the plasma proteins nicely balances the hydrostatic pressure within the capillary blood vessels. The increase in capillary pressures in insulin coma (table 2) would thus favor extravasation of fluid into the tissues in a fashion identical to its occurrence at rest in the schizophrenic process itself.⁸ Further confirmation of these mechanisms was given by the falling plasma protein and rise in hematocrit and hemoglobin values (table 1) and by the microscopic observations on capillary tone made during the investigation reported here. Characteristic of these was primarily their changeableness. In both patients deepening hypoglycemia was accompanied by rapid alterations of capillary tone from extremes of vasoconstriction to similar vasodilatation, circumstances suggesting an intermittent facilitation of fluid transudation at least in the acral site of examination.

SUMMARIO IN INTERLINGUA

Hypoglycemia Inducite per Doses Massive de Insulina e su Effectos Super le Physiologia del Vasos Capillar in Humanos

1. Es reportate le acute responsas de duo nondiabetic subjectos human a massive doses de insulina administrate cinque vices per septimana durante un periodo de tres menses. Le responsas esseva studiate in tanto que illos se manifestava in alterationes occurrente in le vasculatura capillar.

2. Esseva constatate que le fluxo corpuscular in le capillares cutanee se relentava significative e progressivamente como function del disveloppamento de coma hypoglycemic. Le fluxo se reaccelerava quando glucosa esseva administrate e le coma esseva interrompate. Variationes del temperatura cutanee occurreva plus o minus parallelmente a iste alterationes, lo que indicava un simile influenza super le fluxo de sanguine arteriolar. Un augmento del volumine digital occurrente con le declaration del coma indicava un invasion aquose del histos e accompagniava un parve sed significative reduction del saturation oxygenic del sanguine capillar, un augmento del pression de sanguine capillar, decrescite nivellos de proteina plasmatic, un augmento del hematocrite e del contento de hemoglobina, e certe satis characteristic alterationes in le tono del minute vasos observate per medios capillaroscopic.

3. Es presentate un breve discussion del implicationes metabolic de iste constatationes.

ACKNOWLEDGMENTS

This work was supported in part by a grant from the Insulin Fund of the University of Toronto and in part by funds from the Province of Ontario under the Mental Health Grants Programme of the Department of National Health and Welfare, Ottawa, Canada.

REFERENCES

- ¹ Kalinowsky, L. B., and Hoch, P. H.: Shock Treatment and other Somatic Procedures in Psychiatry. New York, Grune and Stratton, 1946.
- ² Bellak, L.: Dementia Praecox. New York, Grune and Stratton, 1948.
- ³ Himwich, H. E.: Brain Metabolism and Cerebral Disorders. Baltimore, Williams & Wilkins Co., 1951.
- ⁴ Lovett Doust, J. W.: Spectroscopic and photo-electric oximetry in schizophrenia, and other psychiatric states. *J. Ment. Sc.* 98:143-60, Jan. 1952.
- ⁵ Lovett Doust, J. W.: Physiological factors underlying therapeutic success in mental disorders. *Canad. M. A. J.* 69: 108-14, Aug. 1953.
- ⁶ Lovett Doust, J. W., and Salna, M. E.: The effects of repeated insulin hypoglycaemia on capillary and tissue metabolism in man. *Canad. Psychiat. A. J.* 1:35-42, Jan. 1956.

Blood O ₂ saturation				Plethysmography (ccH ₂ O)	
R.S.	per cent	R.S.	per cent	Patient	
Patient		Patient		A	B
A		B			
24.9	(92)	22.2	(91)	4.68	4.78
11.2		11.9		0.5	0.3
331		128		35	8
19.0	(90)	21.1	(91)	4.34	4.63
4.2		5.5		0.4	0.3
2		9		7	4
15.6	(89)	17.1	(90)	4.53	4.99
4.2		5.1		0.4	0.2
34		21		16	8
15.3	(89)	15.8	(89)	5.17	4.86
5.9		4.1		0.6	0.2
42		28		3	5
9.7	(87)	15.8	(89)	5.25	5.50
2.5		3.0		0.5	0
21		27		6	2
20.1	(91)	20.3	(91)	4.48	4.50
6.8		6.7		0.6	0.4
45		15		8	6
34.4	(95)	35.6	(95)	4.22	5.00
8.7		8.3		0.3	1.1
44		36		11	4
26.4	(93)	26.2	(93)	4.44	—
5.6		7.9		0.5	—
22		31		5	—
29.3	(93)	26.7	(93)	4.32	4.23
9.9		7.8		0.4	0.5
244		156		40	27
28.305		28.346		4.820	4.965
8/777		8/442		8/122	7/56
.226		.383		.240	.381
<.001		<.001		<.001	<.001

SUMMARY

1. The acute responses of two nondiabetic human subjects to massive doses of insulin five times weekly for a three-month period are reported in terms of changes occurring in the capillary vasculature.

2. It was found that corpuscular flow rates in the skin capillaries fell significantly and progressively as hypoglycemic coma developed. Speed was regained when glucose was given and the coma interrupted. Skin temperature variations roughly paralleled these changes and suggested a similar influence on arteriolar blood flow. An increase in finger volume with the onset of coma indicated a waterlogging of the tissues and accompanied a small but significant fall in capillary blood-oxygen saturation, a rise in capillary blood pressure, decreased plasma protein, a rise in hematocrit and in hemoglobin content, and some rather characteristic changes in the tone of the minute vessels as observed capillaroscopically.

3. The metabolic implications of these findings are discussed briefly.

⁷ Lovett Doust, J. W., and Salna, M. E.: A stroboscopic method for estimating nailfold capillary blood flow in the skin of man. *J. Nerv. Ment. Dis.* 121:511-15, June 1955.

⁸ Lovett Doust, J. W.: The capillary system in patients with psychiatric disorders: increased "capillary blood pressure" in neurosis and psychosis and its relation to some correlates of anoxaemia. *Arch. Neurol. Psychiat.* 74:137-43, Aug. 1955.

⁹ Landis, E. M.: Micro-injection studies of capillary blood pressure in human skin. *Heart* 15:209-28, May 1930.

¹⁰ Ray, G. B.: The measurement of reduction time of blood in the capillaries of the skin. *Amer. J. Physiol.* 147:622-29, Dec. 1946.

¹¹ Lovett Doust, J. W.: The capillary system in patients with psychiatric disorder: the ontogenetic structural determination of the nailfold capillaries as observed by photomicroscopy. *J. Nerv. Ment. Dis.* 121:516-26, June 1955.

¹² Harding, Y. J., and Downs, C. E.: Notes on a Shaffer-Somogyi copper reagent. *J. Biol. Chem.* 101:487-92, July 1933.

¹³ Archibald, R. M., and Eder, H. A.: The estimation of

plasma protein concentration from plasma specific gravity. *J. Biol. Chem.* 183:331-47, 349-60, Mar. 1950.

¹⁴ Phillips, R. A., Van Slyke, D. D., Hamilton, P. B., Dole, V. P., Emerson, K., and Archibald, R. M.: Measurement of specific gravities of whole blood and plasma by standard copper sulphate solutions. *J. Biol. Chem.* 183:305-30, Mar. 1950.

¹⁵ Hoskins, R. G.: *The Biology of Schizophrenia*. London, Chapman & Hall, Ltd., 1946.

¹⁶ Starr, I.: Production of albuminuria by renal vasoconstriction in animals and man. *J. Exper. Med.* 43:31-51, Jan. 1926.

¹⁷ Landis, E. M.: Micro-injection studies of capillary permeability. III. The effect of lack of oxygen on the permeability of the capillary wall to fluid and to the plasma proteins. *Amer. J. Physiol.* 83:528-42, Jan. 1928.

¹⁸ Lovett Doust, J. W.: The capillary system in patients with psychiatric disorder: diminished capillary resistance in neurosis and psychosis as shown by the Göthlin positive pressure test. *J. Clin. Exper. Psychopathol.* 16:272-80, Dec. 1955.

Hunger and Appetite

Physiologists, in studying the activities of the gastrointestinal system, have found it valuable to distinguish between hunger and appetite. Hunger may be recognized by two components. The first is a generalized weakness which may be related to sensory nerve impulses from the alimentary canal, and perhaps occasionally to lowered blood sugar.^{1, 2}

The second component is a more definite perception in the epigastric region, consisting of intermittent sensations of tension or pressure of brief duration. These hunger pangs are usually associated with appetite but may be independent of it. The physiological basis for hunger contractions appears to be inherited with relatively little modification from the experiences of the individual. These contractions have a fixed pattern (thirty minutes activity with one and a half to two hours rest) which does not vary markedly whether the period of abstinence from food is prolonged or short. A starving man will become weaker but not more uncomfortable. It is said that a man can live without food for five weeks but cannot survive lack of water more than five to ten days. Hunger of this type is stopped by solids in the stomach even though they may not be highly nourish-

ing. The mechanism of the hunger contractions is not clearly understood. They are not dependent upon the extrinsic motor nerves, because they are evident even after these nerves to the stomach are cut. Blood sugar level may be a factor but contractions may occur while the contents of the last meal are still in the stomach.

Appetite, while often accompanying hunger, may be present without it. One may want to continue eating an excellent meal long after hunger has been satisfied. The components for appetite are principally psychological and are the result of the past experiences of the individual. We learn to like and dislike foods from our earliest days, and often these patterns are thoroughly fixed in adult life. The nature of the memories associated with the early ingestion of food will determine preferences in a manner independent of logical considerations, and hence will be puzzling to the physician who is attempting a rational therapy for a patient with nutritional problems. If we remember the old adage about there being no disputing matters of taste, or the wide variations in diet among the various nations of the earth, it will be easier to tolerate the food vagaries of our patients.

From the book *Modern Nutrition in Health and Disease* edited by Michael G. Wohl, M.D., and Robert S. Goodhart, M.D. Philadelphia, Lea & Febiger, 1955, Chapter "The Psychology of Appetite"

by Henry W. Brosin, M.D., p. 76.

¹ Carlson: *The Control of Hunger in Health and Disease*. Chicago, University of Chicago Press, 1916.

² Carlson and Johnson: *The Machinery of the Body*. Chicago, University of Chicago Press, 1948.