ACUTE FULMINANT CARDIOVASCULAR BERIBERI WITH LACTIC ACIDOSIS (SHOSHIN OR ACUTE PERNICIOUS BERIBERI)

MEDICAL GRAND ROUNDS
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I. INTRODUCTION

One year ago in an update on Wernicke's encephalopathy the fact that thiamine deficiency presenting as Wernicke's encephalopathy usually escapes clinical detection even in University Hospitals was stressed. In most instances this disorder was not discovered until the patient reached the autopsy table. In Norway, Germany, Australia and the USA, the correct clinical diagnosis before death was made in only 2.5 to 14% of the cases found at autopsy.

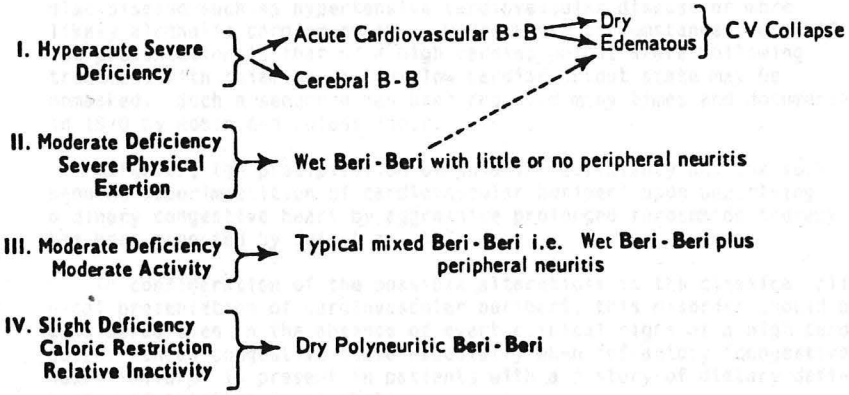
There is also abundant evidence that thiamine deficiency presenting as cardiovascular beriberi similarly is underdiagnosed. Reports indicate that cardiovascular beriberi is not infrequent even in affluent western societies and many of these cases go undiagnosed. This is particularly true of Acute Fulminant Cardiovascular Beriberi with Severe Lacticacidosis, also known as Shoshin or Acute Pernicious Beriberi.

Almost all the textbooks of medicine refer to Shoshin beriberi as a very rare disorder in western countries, yet since 1970 over 80 cases of Shoshin beriberi have been reported. This universally fatal form of thiamine deficiency has a survival rate of 80% to 100% when the disease is recognized and promptly treated. It may be the most common curable form of acute lacticacidosis presenting with plasma lactate in excess of 10 meq/l.

In view of evidence indicating that thiamine deficiency is seriously underdiagnosed, not only in alcoholics with which it is commonly associated but also in a large variety of disorders occurring in non-alcoholics characterized by malnutrition and/or inadequate intake of thiamine, a review of the clinical, cardiovascular, hemodynamic and metabolic consequence of thiamine deficiency is relevant.

II. TYPES OF BERIBERI AND PREDISPOSING FACTORS

Table 1



III. CARDIOVASCULAR BERIBERI - WET BERIBERI

A. CLINICAL PICTURE - Variations In Presentation

Classical cardiovascular beriberi presents as a hyperkinetic high cardiac output venous congestive state with clinical signs of biventricular "failure" (right greater than and preceding the left), including edema, pulmonary congestion, tachycardia, wide pulse pressure, with high venous pressure, rapid circulation time, evidence of arteriolized venous blood, warm skin and pistol shots over large arteries.

As the disease progresses, the blood pressure begins to fall, vasoconstriction of the skin and hands gradually appears and mild cyanosis of the distal extremities may become evident. Only as death approaches does cardiac output fall to low levels.

The most severe form of cardiovascular beriberi (Shoshin) may appear de novo or be superimposed on the usual high cardiac output cardiovascular beriberi. Shoshin beriberi is characterized by life threatening lactic acidosis, very low systemic vascular resistance severe progressive hypotension with impending collapse, acute renal failure, marked distal cyanosis and what appears to be (but is not) a low cardiac output state.

The clinical picture can be modified further by the duration of the venous congestive state. Late in the course of the usual high output beriberi, if shoshin beriberi has not supervened, the clinical picture is altered and cardiovascular beriberi may now mimic ordinary low output biventricular congestive heart failure as cardiac output, although elevated, continues to fall. According to Professor R. B. Blacket (1981) of the University of New South Wales, who has been studying cardiovascular beriberi for the past 35 years, cardiac output is never below normal unless the patient is terminal.

Further variation in the clinical presentation of cardiovascular beriberi occurs when this disease is superimposed on underlying cardiac disease such as hypertensive cardiovascular disease or more likely alcoholic cardiomyopathy. Under these circumstances, even if the presentation is that of a high cardiac output state following treatment with thiamine, a true low cardiac output state may be unmasked. Such a sequence has been reported many times and documented in 1970 by Robin and Goldschlager.

Moreover, the precipitation of thiamine deficiency and the subsequent superimposition of cardiovascular beriberi upon underlying ordinary congestive heart by aggressive prolonged furosemide therapy has been reported by Yui et al, 1978.

In consideration of the possible alterations in the classical clinical presentation of cardiovascular beriberi, this disorder should be considered even in the absence of overt clinical signs of a high cardiac output venous congestive state especially when refractory "congestive heart failure" is present in patients with a history of dietary deficiency of thiamine or alcoholism.

The most quoted, promoted and used criteria for the clinical diagnosis of cardiac beriberi are those of Blankenhorn et al, published in 1946. Unfortunately, these criteria no longer fit the clinical, historical and hemodynamic findings that have evolved in the past 40 years and should no longer be promulgated as the basis for the diagnosis of cardiac beriberi.

Table 2

BLANKENHORN'S CLINICAL CRITERIA FOR CARDIAC BERIBERI

1. cardiomegaly with normal rhythm
2. edema
3. raised venous pressure
4. peripheral neuritis or pellagra
5. non-specific changes on the electrocardiogram
6. no other evident cause for heart disease
7. low dietary thiamine for at least three months
8. improvement of symptoms and reduction of heart size after specific vitamin replacement therapy
9. necropsy findings consistent with beriberi

Blankenhorn et al., 1946

In regard to each of the above criteria, the following information is relevant:

1. Cardiovascular beriberi with high venous pressure, high cardiac output and peripheral edema may occur with a normal size heart.

2. Early in cardiovascular beriberi pitting subcutaneous edema may be absent in the pretibial and sacral areas. Edema first appears in the muscles where multiple functional A-V fistulas occur.

   Also, acute pernicious beriberi (Shoshin) may occur de novo very rapidly before peripheral edema has had time to appear.

3. Venous pressure is also raised in ordinary congestive heart failure. Only when the elevation of venous pressure is coupled with a rapid circulation time is it suggestive of cardiovascular beriberi.

4. As shown in Table I, cardiovascular beriberi can occur before there is any evidence of peripheral neuropathy or pellagra.

5 & 6. Beriberi can be superimposed on a variety of types of heart disease where electrocardiographic alterations are found.

7. Patients have been reported to develop even lethal cerebral or cardiovascular beriberi as early as 9 to 27 days on a thiamine deficient diet. Recently 3 cases of Shoshin beriberi were reported to have developed within 14 days of starting

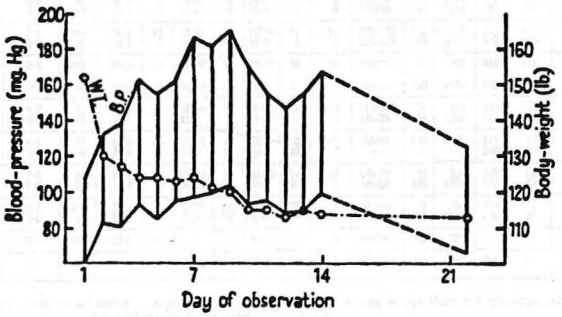
total parenteral nutrition (TPN).

8. While in general patients with cardiovascular beriberi rapidly improve with thiamine therapy, a salutory response need not occur at once and the clinical condition can worsen temporarily because of the development of hypertension.

   This development of a transitory (may last days to weeks) but at times severe hypertension commonly occurs during thiamine therapy and may precipitate acute pulmonary edema or worsen the ongoing pulmonary congestion.

   Indeed the occurrence of hypertension during thiamine therapy supports the diagnosis of cardiovascular beriberi. An example is shown below.

Fig. 1 - J.H. Walters, 1953



Case 3. Blood-pressure and body-weight.

B. HEMODYNAMIC FINDINGS

According to Campbell (1984) and others the primary disorder affecting the cardiovascular system in beriberi is a peripheral one i.e. loss of systemic vascular resistance. "It is therefore an error to regard beriberi as a cardiac disease. It should be called cardiovascular beriberi not beriberi heart disease".

Although the cardiac output is very high and systemic vascular resistance is low, not all the organs share equally in the augmented cardiac output. The circulation in cardiovascular beriberi is disordered. Some areas such as muscle receive the bulk of the cardiac output whereas others vital areas including kidney and brain have decreased organ flow.

1. Cardiac Output and Systemic Vascular Resistance

Table 3 - from Blacket & Palmer, 1960

HÆMODYNAMIC DATA AT REST IN 16 PATIENTS WITH BERI-BERI, SOME STUDIED BEFORE AND AFTER TREATMENT.

Case	Age	Sex	B.S.A. sq. metres	Arterial blood % sat.	A-VO_2 Difference vols. %	Ventilation l. BTPS min./m²	O_2 consumption ml. STP min./m²	Cardiac index l./min./m²	Pulse rate	Stroke vol. ml. min./m²	Pressures (mm. Hg) P.C.	Pulm. Art. Abs.	Pulm. Art. Mean	Rt. vent. Abs.	Rt. vent. Mean	Rt. auric Mean	Brachial art. Abs.	Brachial art. Mean	Resistance dynes sec. cm.⁻⁵ System	Pulmonary Total	Pulmonary Art'lar	Work LV / Work RV	P.C.V	Plasma vol.	Loss of weight with recovery (Kg.)
1	37	M	1·75	95	3·1	—	133	4·3	120	52·6	—	—	—	29/4	14	4	120/60	80	576	—	—	—	—	—	8·6
days after thiamine			—	95	3·7	—	122	3·3	90	36·3	—	—	—	20/0	6	0	110/85	92	1268	—	—	—	—	—	—
2	25	M	1·71	87	1·9	5·1	155	15·5	88	176·0	20	40/26	30	39/21	25	20	—	100	—	90	30	8·9	—	—	8·6
days after B_1			—	97	4·5	3·1	125	2·8	80	34·5	—	20/8	12	20/1	6	0	140/80	100	1700	204	—	8·0	—	—	—
3	34	M	1·69	98	1·7	5·9	152	9·0	90	100·0	—	—	—	47/22	30	18	128/72	98	579	—	—	—	50	—	18·1
4	35	M	1·78	95	3·5	5·4	147	4·2	88	47·2	—	47/25	32	47/19	—	19	145/80	102	896	400	—	4·4	45	6·32	11·3
days after B_1			—	98	3·5	4·9	143	4·1	95	43·2	10	41/15	25	35/−2	12	3	172/86	110	1171	274	164	4·5	46	3·89	—
5	41	M	1·76	94	4·7	5·1	163	3·5	60	57·4	14	42/13	22	40/5	13	5	180/100	132	1664	288	185	7·0	54	—	5·0
B_1 given 3 days before study.																									
days after B_1			1·76	—	3·7	4·5	135	3·7	80	45·4	4	26/10	12	28/0	9	0	165/90	116	1450	150	90	—	55	—	—
days after B_1			1·80	94	4·2	4·1	128	3·0	90	33·9	1	16/4	10	20/0	6	0	125/95	110	1599	145	130	11·0	58	—	—
6	36	F	1·53	89	2·9	3·8	152	5·2	97	53·6	20	35/16	27	40/9	18	6	165/103	126	1199	220	200	5·0	46	3·40	8·6
days after B_1			—	95	4·1	4·4	148	3·6	88	51·6	—	15/3	6	18/2	5	−1	145/92	104	1554	89	74	14·3	50	2·32	—
7	32	F	1·59	88	2·9	4·7	136	4·7	104	45·3	16	42/20	31	37/9	22	8	135/75	100	980	330	160	3·7	36	3·05	9·1
8	44	M	1·87	93	2·4	4·0	121	5·0	95	52·4	—	30/8	19	27/3	13	1	125/72	100	850	165	—	5·0	40	4·12	—
days after B_1			—	92	2·9	4·3	129	4·4	98	54·7	8	20/6	10	30/0	8	0	125/84	110	1099	88	80	10·2	42	3·44	2·3
days after B_1			—	95	3·1	4·5	130	4·3	100	43·5	4	17/6	10	17/0	9	0	150/98	124	1224	99	75	12·0	45	3·84	—
9	34	M	1·72	95	2·1	5·9	156	7·2	104	70·6	17	55·20	35	57/14	33	14	200/110	132	749	222	114	5·5	42	—	12·0
days after B_1			—	96	4·3	3·5	118	2·7	90	30·2	7	21/8	15	20/0	6	0	200/125	152	2584	392	136	9·7	—	—	—
10	30	M	1·86	90	2·1	7·2	175	8·4	123	68·8	14	57/27	37	60/11	28	10	130/83	97	443	188	117	3·3	50	3·45	3·2
B_1 given 1 day before study																									
days after B_1			—	94	4·5	4·5	145	3·3	95	33·9	5	48/15	25	48/1	20	0	130/86	108	1438	332	266	4·1	48	3·31	—
11	24	M	2·10	91	3·6	4·1	171	4·7	90	52·3	22	57/26	35	58/15	26	16	195/105	120	863	283	149	5·2	—	—	26·3
days after B_1			—	96	4·2	3·5	120	2·9	88	36·1	1	15/5	9	16/−2	4	−2	126/78	94	1252	120	106	8·5	—	—	—
12	46	M	1·66	94	4·0	4·6	173	4·3	95	45·8	13	28/13	19	22/—	8	−1	145/90	110	1221	211	67	4·9	32	4·47	5·4
days after B_1			—	95	5·3	4·8	136	2·6	110	23·5	5	25/8	13	30/3	10	1	—	—	—	342	149	—	38	3·80	—
13	31	M	1·72	94	2·2	5·8	155	7·0	84	83·7	21	40/24	31	40/15	24	12	130/75	98	528	205	66	3·6	44	4·01	10·0
days after B_1			—	93	2·8	—	108	3·8	58	38·4	7	24/10	14	24/5	10	2	140/80	100	1210	170	85	7·8	49	2·65	—
14	41	M	1·63	92	1·8	5·3	172	9·6	112	72·4	6	37/20	28	37/9	20	7	90/60	70	356	154	112	3·3	—	—	—
days after B_1			—	93	3·7	3·4	151	3·6	48	75·5	9	23/9	13	23/0	4	0	160/90	108	1466	176	81	7·8	—	—	—
15	41	M	1·62	92	1·5	5·3	186	12·3	100	123·5	—	—	—	36/5	23	4	150/85	100	399	—	—	—	35	3·23	5·0
16	56	M	—	90	3·9	—	196	—	70	—	—	36/10	16	36/3	12	3	150/64	90	1390	256	—	—	40	—	—

uplicate determinations of cardiac output were made in all cases. Agreement between duplicates was better than 0·5 l/m²min. and the results from the first determination were used throughout

In Blacket & Palmer's classical study, cardiac output in 13 cases prior to thiamine treatment averaged 12.5 l/min (range 7.1 - 26.0 l/min). This was associated with a concomitant low mean systemic vascular resistance of 680 dynes/sec/Cm^{-5} which rose following thiamine treatment to 1491 as cardiac output fell to 5.9 l/min.

This low systemic vascular resistance was the consequence of marked peripheral vasodilation within the musculature producing multiple of functional A-V fistulas, leading to augmented venous return and high cardiac output. The low systemic vascular resistance correlates negatively with the cardiac output.

The pathogenesis of the lack of arteriolar tone is unknown, but certainly appears to be related to the biochemical blocks produced by thiamine deficiency since the reports of Lahey et al (1953), Akbarian et al (1966) and Robin et al (1970) have shown a rapid return of systemic vascular resistance towards normal within

37 to 90 minutes of intravenous thiamine therapy.

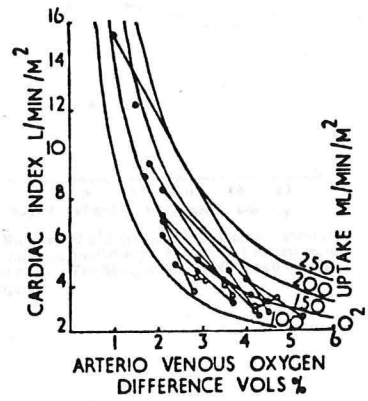
Moreover, many reports indicate that the hypotension, arteriolar vasodilation and low systemic vascular resistance characteristic of cardiovascular beriberi and especially Shoshin beriberi are not responsive to most vasoconstrictors including dopamine, dobutamine, methoxamine and norepinephrine (Anderson et al 1985, Engbers et al 1984, LaSelve et al 1986, Thomas et al 1985, Wolf & Levin 1960 and Fond et al 1980)

The increase in cardiac output was mainly the consequence of a high stroke volume which averaged 123 ml/beat (range 72-301) and fell during thiamine treatment to 72 ml/beat.

2. Mixed A-VO_2

While in ordinary low output congestive heart failure the mixed A-VO_2 is elevated by contrast in high output cardiovascular beriberi the mixed A-VO_2 is low as seen in fig. 2.

Fig. 2 - From Blacket & Palmer, 1960



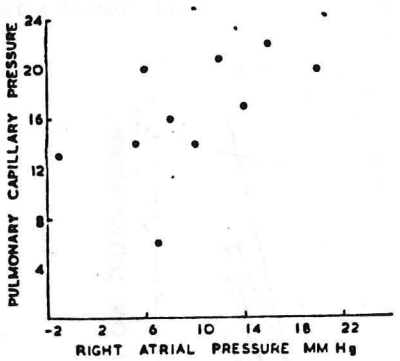
Cardiac index and arteriovenous oxygen difference at rest before treatment (●) and after recovery (○). Isopleths of oxygen uptake are also shown.

Mean mixed A-VO_2 averaged only 2.7 vol % (range 1.1-4.0) and rose after therapy to 3.9 vol %.

3. Right Atrial and Pulmonary Capillary Pressures

Mean right atrial pressure was 9.0 mm Hg, varied from 1-21 and fell on treatment to 0.25 mm Hg. Pulmonary capillary wedge pressure averaged 16 mm Hg, ranged from 6-22 and after thiamine fell to 6. The higher the right atrial pressure, the higher the pulmonary capillary pressure.

Fig. 3 - From Blacket & Palmer, 1960



Right atrial and left atrial (pulmonary capillary) mean pressure (millimetres of mercury) at rest in untreated cases. The filling pressures of the two ventricles rise together.

C. EVIDENCE FOR DISORDERED CIRCULATION WITH ABNORMAL ORGAN BLOOD FLOW

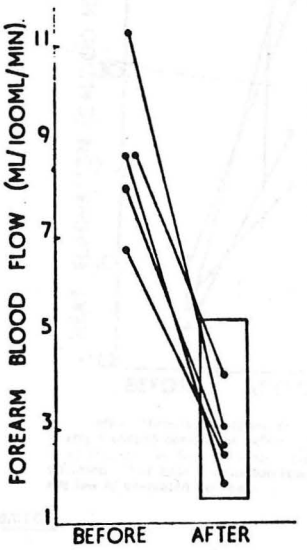
1. Blood Flow to the Musculature

Most authorities agree that the large increase in cardiac output which averaged 13.3 L/min in a large series of 25 cases of cardiovascular beriberi was the consequence of a very low systemic vascular resistance (mean 637 dynes-sec-cm^{-5}).

This decrease in vascular resistance occurred mainly in the musculature where multiple functional A-V fistulas occurred. This is evidenced by as much as a 3 to 5 fold increase in forearm muscle blood flow despite vasoconstriction in the skin and hand.

The functional A-V shunts in the muscles accounts for the fact that edema occurs there first prior to any peripheral pitting edema.

Fig. 4 - from Blacket & Palmer, 1960



Forearm blood flow before treatment and after recovery in five patients. The normal range is enclosed in the rectangle. The forearm flow is high in the untreated disease.

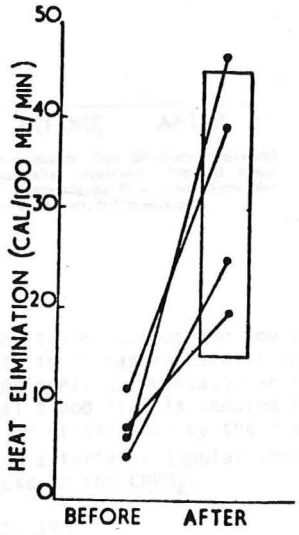
2. Blood Flow to the Skin

Early in mild cardiovascular beriberi the skin is often flushed and warm. Capillary pulsations in the fingertips were first noted by Wencheback in 1934.

As the vascular resistance in the muscles decreases and blood pressures falls despite a high cardiac output intense vasoconstriction in the skin follows, often with cyanosis of the extremities.

Blacket and Palmer estimated skin blood flow by measuring the rate of heat elimination from the hand. Prior to treatment with thiamine heat elimination was very low and rose 3 to 5 fold after treatment.

Fig. 5 - from Blacket & Palmer, 1960



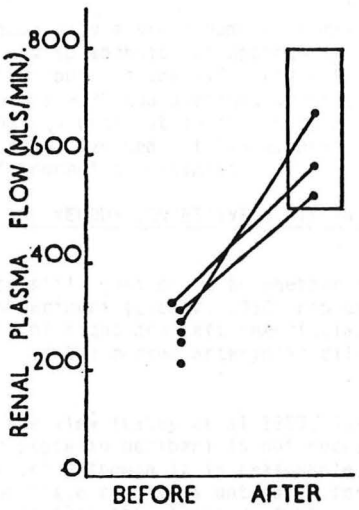
—Heat elimination from the hand under nearly standard conditions before treatment and after recovery in four patients. Normal range enclosed. The heat elimination (and hand flow) are low in untreated beri-beri.

3. Renal Hemodynamics

Measurements of glomerular filtration rate and renal plasma flow in several studies have revealed evidence of intense renal vasoconstriction. In Blacket and Palmer's studies GFR and RPF averaged only 68 and 266 ml/min respectively despite cardiac outputs as high as 20 l/min.

The fall in blood pressure that marks the beginning of acute fulminant beriberi with lacticacidosis (Shoshin) is associated with oliguria, azotemia and anuria.

Fig. 6 - from Blacket & Palmer, 1960



—Renal plasma flow (diodone clearance) before and after treatment. Normal range enclosed. Renal plasma flow (and glomerular filtration rate) are reduced in beri-beri.

4. Cerebral Blood Flow

Despite the high cardiac output and low systemic vascular resistance characteristic of cardiovascular beriberi, cerebral vasoconstriction is present, cerebrovascular resistance is increased and cerebral blood flow is reduced significantly producing a fall in oxygen utilization by the brain ($CMRO_2$). This is evidenced by a widened arterial - jugular venous oxygen difference ($A\text{-}JVO_2$) and a decrease in the $CMRO_2$.

Table 4 - from Madison & Sensenbach, 1951

MEAN CHANGES IN CEREBRAL BLOOD FLOW AND METABOLISM IN SEVEN PATIENTS WITH CARDIOVASCULAR BERIBERI DURING THIAMINE TREATMENT

	CBF	$A\text{-}JVO_2$	$CMRO_2$
	ml/100 gm/min	vol/100 ml	ml/100 gm/min
pre rx	32	8.67	2.71
early rx	46	6.97	3.12
late rx	56	6.77	3.66
controls	61	6.59	4.01

5. Splanchnic Blood Flow

Although only a small number of measurements have been made, the liver and splanchnic bed apparently do not share in the vasoconstriction found in the skin, kidneys and brain. Splanchnic blood flow was high and averaged about 2000 ml/min. These data suggest that in contrast to the reduced splanchnic blood flow of ordinary congestive heart failure, hepatic flow in cardiovascular beriberi is normal or elevated.

D. THE NATURE OF THE VENOUS CONGESTIVE STATE IN BERIBERI - PRESENT CONTROVERSIES

Controversy still goes on as to whether the venous congestive state found in beriberi (Eichna, 1960) represents cardiac failure with true depression of right and left ventricular function or is solely the consequence of the marked arteriolar dilatation and enhanced venous return.

Many hold the view (Lahey et al 1953, Sharpey-Schafer 1961) that the congestive state in beriberi is not necessarily the consequence of myocardial failure although it is reasonable that failure may occur if the high output state continues untreated for a prolonged period of time. Others consider the elevated right and left ventricular end diastolic and pulmonary capillary wedge pressures as unequivical evidence myocardial failure.

As Blacket & Palmer have pointed out, the high stroke volumes achieved in the most florid cases of beriberi at rest are higher than in other hyperkinetic states and may even be twice as high as in vigorous exercise in normal subjects.

It is apparent that despite this so called "cardiac failure", the thiamine deficient myocardium performs remarkably well. At times it can produce a cardiac output of 36 l/min, with a stroke volume of 400 ml/beat (Kozam et al 1972). Moreover on exercise this subject was capable of increasing his cardiac output to 46 l/min - hardly a failing myocardium despite elevated right ventricular end diastolic and pulmonary capillary wedge pressure.

Finally, at times when cardiovascular beriberi is superimposed on low output alcoholic cardiomyopathy a high output state may supervene as a consequence of the unloading produced by the thiamine deficient state. This does not suggest that thiamine deficiency worsens myocardial function (Robin & Goldschlager, 1970).

Table 5 - from Robin & Goldschlager, 1970 - BERIBERI SUPERIMPOSED ON ALCOHOLIC CARDIOMYOPATHY

High output failure

Parameters	*Baseline*	*Exercise (180 Kg.-M./min.)*	*Ouabain (1 mg. I.V.)*	*Thiamine (300 mg. I.V.)*	*Thiamine + exercise (180 Kg.-M./min.)*
Heart rate (beats/min.)	100	120	100	92	134
Right atrial pressure (mm. Hg)	(12)	(15)	(15)	(7)	(4)
Right ventricular pressure (mm. Hg)*	50/12	60/15	55/15	30/7	30/4
Pulmonary artery pressure (mm. Hg)	50/20 (35)	60/30 (45)	55/30 (40)	30/15 (20)	30/30(20)
Pulmonary resistance (dynes sec. cm.$^{-5}$/M.^{2})	333	424	361	356	235
RV dp/dt (mm. Hg/sec.)	250	330	256	310	365
Right ventricular work (Kg.-M./min./M.^{2})	5.1	6.4	5.7	1.5	2.3
Pulmonary capillary pressure (mm. Hg)	(16)	(25)	(18)	(10)	(7)
Left ventricular pressure (mm. Hg)*	140/18	140/25	135/20	130/10	140/7
Aortic pressure (mm. Hg)	140/60 (80)	140/40 (90)	135/40 (90)	130/80 (100)	140/70 (100)
Cardiac index (L./min./M.^{2})	5.4	6.3	5.4	4.5	6.8
Stroke index (c.c./min. M.^{2})	54	71	54	46	55
Peripheral vascular resistance (dynes sec. cm.$^{-5}$/M.^{2})	857	847	857	1,776	1,176
LV dp/dt (mm. Hg/sec.)	1,450	1,190	1,510	1,700	2,150
Left ventricular work (Kg.-M./min./M.^{2})	13.9	14.0	13.5	7.0	11.3
Coronary blood flow (c.c. min./100 Gm. L.V.)	157	155	155	110	115
Myocardial oxygen extraction (vol.%)	4.2	4.3	4.5	9.5	9.6
Myocardial oxygen consumption (c.c./min./100 Gm. L.V.)	6.6	6.7	7.0	9.5	11.3

Abbreviations: RV dp/dt = maximal rate of right ventricular pressure rise; LV dp/dt = maximal rate of left ventricular pressure rise.
* All ventricular diastolic pressures are end-diastolic pressures.

Table 6 - from Robin & Goldschlager, 1970 - SAME PATIENT NINE DAYS AFTER TREATMENT OF BERIBERI

Low output failure

Parameters	*Baseline*	*Exercise (150 Kg.-M./min.)*	*Thiamine (300 mg. I.V.)*	*Ouabain (1 mg. I.V.)*	*Ouabain + Exercise (150 Kg.-M./min.)*
Heart rate (beats/min.)	110	115	120	92	110
Right atrial pressure (mm. Hg)	(10)	(14)	(10)	(5)	(5)
Right ventricular pressure (mm. Hg)*	80/10	82/14	80/10	35/5	40/5
Pulmonary artery pressure (mm. Hg)	80/30 (40)	82/30 (45)	80/30 (40)	35/20 (25)	40/20 (30)
Pulmonary resistance (dynes sec. cm.$^{-5}$/M.^{2})	2,000	1,714	2,000	645	572
RV dp/dt (mm. Hg/sec.)	110	130	120	220	380
Right ventricular work (Kg.-M./min./M.^{2})	1.1	1.6	1.1	1.3	2.0
Pulmonary capillary pressure (mm. Hg)	(16)	(25)	(20)	(12)	(10)
Left ventricular pressure (mm. Hg)*	130/15	130/25	135/20	130/10	130/10
Aortic pressure (mm. Hg)	130/80 (105)	130/80 (105)	135/75 (100)	130/80 (105)	130/70 (100)
Cardiac index (L./min./M.^{2})	1.6	2.1	1.6	3.1	4.2
Stroke index (c.c./min./M.^{2})	17	21	16	34	38
Peripheral vascular resistance (dynes sec. cm.$^{-5}$/M.^{2})	5,250	4,000	5,000	2,710	1,905
LV dp/dt (mm. Hg/sec.)	975	1,000	1,100	1,600	2,000
Left ventricular work (Kg.-M./min./M.^{2})	2.6	3.4	2.7	4.8	6.6
Coronary blood flow (c.c./min./100 Gm. L.V.)	92	105	90	90	115
Myocardial oxygen extraction (vol.%)	9.0	8.6	9.2	9.0	9.2
Myocardial oxygen consumption (c.c./min./100 Gm. L.V.)	8.3	9.2	8.3	8.1	10.6

Abbreviations: RV dp/dt (mm. Hg/sec.) = maximal rate of right ventricular pressure rise; LV dp/dt = maximal rate of left ventricular rise.
*All ventricular diastolic pressures are end-diastolic pressures.

I leave the precise definition of the venous congestive state in beriberi to my cardiology colleagues. However, all would agree that despite the high cardiac output in beriberi until just prior to death, the circulation is disordered and various vital organs suffer inadequate circulation.

IV. ACUTE FULMINANT CARDIOVASCULAR BERIBERI WITH LACTICACIDOSIS (Shoshin or Acute Pernicious Beriberi)

A. Introduction

As mentioned earlier, acute fulminant beriberi, a rapidly lethal disease most often goes undiagnosed. This is the result of two main factors.

One is the unfamiliarity of most phyicians with this disorder. Repeated statements are made in the literature and in texbooks of medicine that this lethal form of beriberi is rare in the western world. In 1981 Ikram et al, in a review in the Quarterly Journal of Medicine, stated that this "fulminant variety of beriberi is very rarely seen in Western countries." Similarly, Grossman & Braunwald in Braunwald's 4th edition of his Textbook of Cardiovascular Medicine (1984) reported that in the western world this fulminant form of beriberi "is quite uncommon."

The second major reason that the acute fulminant form remains underdiagnosed is that it is not widely appreciated by physicians that this disorder is characterized by a severe lacticacidosis which often is the predominant part of the clinical picture.

That thiamine deficiency is a cause of a severe yet curable lacticacidosis is not mentioned in most review articles on lacticacidosis and in most textbooks of medicine. Even Cohen & Woods' scholarly book entitled "Clinical and Biochemical Aspects of Lactic Acidosis" (1976) does not mention thiamine deficiency as a cause of this disorder. Nor was thiamine deficiency discussed as cause of severe lacticacidosis in Dr. Harry Jacobson's Medical Grand Rounds on Lacticacidosis in 1983.

Indeed, Dr. Jacobson erroneously stated that severe acidosis, due to lactic acid alone, is uncommon in alcoholics. It is precisely when a thiamine deficient alcoholic drinks alcohol that he is most likely to develope severe lethal lacticacidosis as a manifestation of his thiamine deficiency.

Acute fulminant cardiovascular beriberi with severe lacticacidosis is not a rare disorder. Indeed, it may be the most common form of curable lacticacidosis that presents with blood lactate levels in excess of 10 meq/l.

Since 1970, twenty-three articles have appeared from 10 different countries reporting at least 80 cases of Shoshin beriberi. In the last 10 years alone 60 patients with this disorder have been reported in 18 articles from 10 countries. Seventy percent of all these cases

were reported from Australia and the Netherlands where physicians are more alert to this potentially catastrophic illness.

Dr. Charles Campbell from Australia who reported seeing 30 patients with fulminant cardiovascular beriberi between 1977 and 83 sadly stated that "lives are lost because physicians are unfamiliar with the severe lacticacidosis of acute pernicious beriberi."

In a recent article from the Netherlands, Majoor (1982) claimed that since 1970 he has seen 22 cases of cardiovascular beriberi. Of these, 15 patients (68%) presented with the severe lacticacidosis of shoshin beriberi. Now that they are aware of the disease at his hospital they diagnose 3 new cases each year.

B. CLINICAL PRESENTATION

The clinical picture is that of acute severe life threatening cardiovascular collapse and what clinically appears to be (but is not) a very low cardiac output state. The patients complain of severe shortness of breath, intense thirst and often precardial distress or pain. They are restless, agitated and at times confused. Complicating the picture at times is excruciating abdominal pain in the right upper quadrant or epigastic region suggesting an abdominal emergency, especially in view of the marked leukocytosis (30,000-80,000) that is not infrequently found. Severe intense hepatic venous congestion is the most likely cause of the pain.

On physical examination the patients are distressingly hyperpneic, often without orthopnea. There is cardiomegaly but the lungs initially may be free of rales. Only later may pulmonary edema supervene. Collapse is apparent from the hypotension, tachycardia and distal cyanosis with cold extremities. The jugular veins are distended but the circulation time is rapid. There may be no obvious pitting subcutaneous edema, yet the patient may lose more than 6 kg when thiamine is given (muscle edema). When superimposed on ordinary wet beriberi anascarca may be present. Early on, the heart may appear hyperkinetic but later lose these features only to regain them again during thiamine treatment.

Oliguria advancing to anuria is common. Laboratory examination reveals a high anion gap acidosis. Blood lactate levels are very high averaging 17 meq/l. BUN and creatinine are frequently elevated and may worsen initially during treatment.

C. HEMODYNAMIC FINDINGS

Despite the differences in the clinical presentation from that of ordinary cardiovascular beriberi the hemodynamic alterations in the acute fulminant form are similar though more extreme. Although a low cardiac output state seems clinically apparent, the cardiac output is in fact elevated averaging 12.7 l/min and is the same order of magnitude as ordinary cardiovascular beriberi.

Systemic vascular resistance (mean 414 dynes/sec/cm^{-5}), mixed

A-VO_2 (1.5 vol %), stroke volume (104 ml/beat) and blood pressure (92/52) are lower than that found in the milder form of cardiovascular beriberi.

THE FINDINGS IN 15 CASES OF THE ACUTE FULMINANT FORM OF BERIBERI RECENTLY HAVE BEEN SUMMARIZED BY MAJOOR & HILLEN (1982) AS SEEN IN TABLE 7 BELOW.

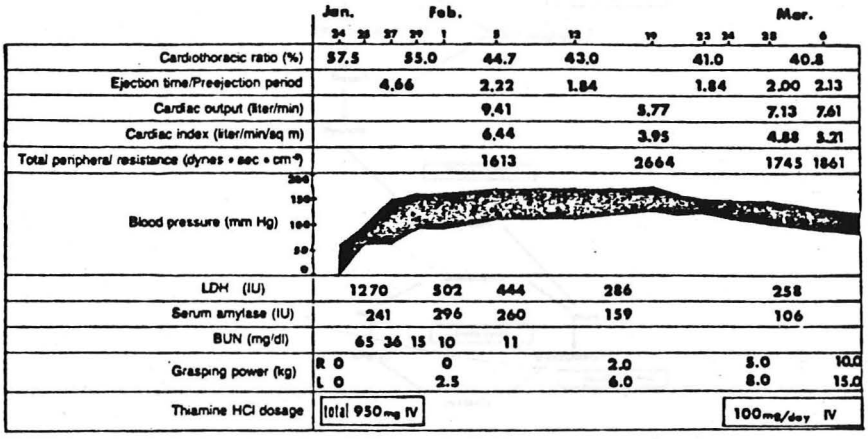
GEGEVENS VAN PATIËNTEN MET BIJGIJN-BERIBERI MET METABOLE (LACTAAT)ACIDOSE UIT DE LITERATUUR EN UIT RECENTE EIGEN WAARNEMINGEN

Onderzoek van	*Patiënt, geslacht en leeftijd*	*Bloeddruk kort na opneming (mmHg)*	*Pols kort na opneming (slagen per min.)*	*Ademhalingsfrequentie (per min.)*	*Druk rechter atrium (mmHg) (normaal tot + 8)*	*Centraal veneuze druk (cm H_2O) (normaal: R-4½ tot R-8½)*	*Hartminuutvolume l/min.*	*Laagste arteriële pH (normaal 7,38-7,43)*	*Daarbij behorende Pco^1 (norm. 4,5-6,0)*	*Lactaat mmol/l (normaal 0,7-1,8)*	*Oedeem (gew. verlies tijdens observatie)*
Jeffrey e.a. (7)	A.m.42	85/55	140	35	+21	–	17.2	7.09	<1.95	6.7	(–10.4 kg)
King e.a. (11)	B.m.40	50/?	120	snel	–	+28.5	–	7.16	1.73	15.7	(–6.4 kg)
Singh (12)	C.v.20	60/40	140	snel	–	↑	–	7.07	1.9	*	geen
	D.m.40	80/40	100	snel	–	↑	–	6.9	1.9	*	gering
Majoor (13,14)	E.m.32	80/25	115	30	+14	R+½	9.0	7.14	2.73	24.5	(–2.6 kg)
Attas e.a. (15)	F.m.36	105/60	136	40	+21	–	23.0	7.05	1.33	24.0	geen
Trunet e.a. (16)	G.v.38	115/75	104	snel	+30	–	10.2	7.10	2.52	11.2	(–15 kg)
Fond e.a. (17)	H.m.30	110/70→ 90/55	140	40	+20	–	10.5	6.98	1.60	?	geen
	J.m.40	75/40	?	snel „Kussmaul"	+13	–	11.7	7.33	1.62	13.0	geen
Majoor e.a. St. Radboudzh Nijmegen	K.m.32	75/50	92	40	+30	R-1?	16.3	7.08	1.60	↑**	+
	L.m.39	90/50	100	24→32	+18 tijdens herstel	>R+10	5.8 tijdens herstel	7.28	2.20	10.4	(–15.4 kg)
Hillen e.a. Catharina zh Eindhoven	M.m.44	80/40	132	52	+26	R+4	12.8	6.90	1.70	17.0	(–8.0 kg)
	N.v.54	55/2	95	40	–	±R+10	7.6 tijdens herstel	7.18	3.2	9.8	++
	O.m.55	80/55	150	24	+18	–	12.8	7.29	2.27	11.5	+
Cluysenaer St Elisabeth zh Amersfoort***	P.m.30	110/75	120	snel	–	R+1	–	6.84	3.6	18.5	(–17.6 kg)

*Bij deze patiënten werd alleen pyruvaat bepaald. Dit was 700, resp. 890 µmol/l (normaal 60-115 µmol/l).
**Bepaling in arteriëel bloed misleidt; wél was de lactaatuitscheiding in de eerste urineportie 0.260 mmol/mmol creatinine (normaal 0.010-0.058 (18)).
***Gaarne zeggen wij collega Cluysenaer dank voor zijn bereidwilligheid deze gegevens voor dit artikel af te staan.

All these circulatory abnormalities return towards normal after thiamine therapy. At times the picture of collapse is rapidly transformed into a clinical presentation of a hyperkinetic high output state with warm skin, bounding pulse and hyperactive heart. (King et al, 1972; Seta et al, 1981; Majoor, 1978; McIntyre & Stanley, 1971)

Fig. 7 - from Seta et al, 1981



. Clinical course ET/PEP shows elevated rate in phase 2, depressed rate in phase 3, and return to normal rate after recovery. Cardiac output also shows high output in phase 2, decreased output in phase 3, and normal output after recovery.

D. LACTICACIDOSIS

1. Pathogenesis of the lacticacidosis

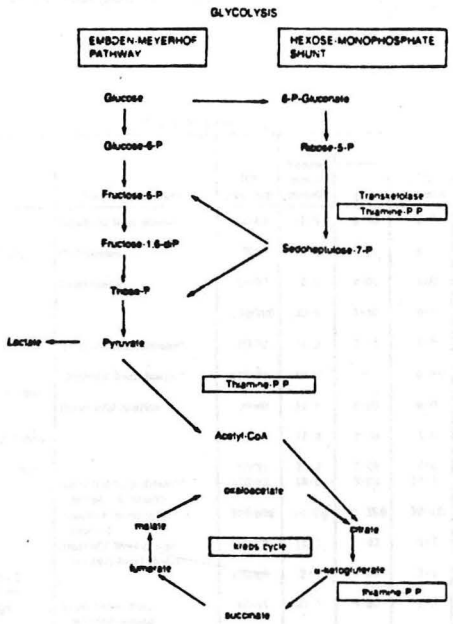
The lacticacidosis characteristic of acute pernicious beriberi is the consequence of two major factors:

One is the regional hypoperfusion secondary to thiamine deficiency

Second is the block in the metabolism of pyruvate resulting from thiamine deficiency.

These metabolic blocks are shown in fig 8.

Fig. 8 - from Van Eps & Schouten, 1985



. Schematic representation of the Emden-Meyerhof pathway and Krebs' citric acid cycle.

If superimposed on the block in the metabolism of pyruvate characteristic of thiamine deficiency an acute alcoholic debauch is added, then severe lacticacidosis supervenes because of the increase in $NADH_2$ and the reduction of NAD which occurs in liver cells during the oxidation of alcohol to acetaldelyde and then to acetate.

Under these circumstances pyruvate is reduced to lactate and the metabolism of lactate produced in the regions of vascular hypoperfusion is inhibited thereby raising serum lactate to life threatening levels.

2. <u>The Magnitude of the Lacticacidosis</u>

The severity of the lacticacidosis can be seen from Campbell's report (1984) of 18 cases seen between 1977 and 1983. These data are shown in table 8.

In the 16 cases where measurements were made prior to thiamine therapy pH averaged 7.07 (range 6.78 - 7.49). Seventy-five percent of the subjects had a pH of 7.11 or less. The mean lactate level was 17.8 meq/l and ranged from 8.5 - 28.2 meq/l. Lactate levels of 15 meq/l or more was present in 75% of the cases.

Table 8 - from Campbell, 1984

CLINICAL DATA

Case	Sex/age	Symptoms	Associated disease	BP (mm Hg)	Venous lactate (mmol/l)	Arterial				
						pH	HCO_3 (mmol/l)	BE (minus)	pO_2 (mm Hg)	pCO_2 (mm Hg)
1	M/28	Epigastric pain <1 day; not SOB, thirst	Alcoholic liver disease*	90/60	16·5	6·78	2·7	33·3	118	20
2	F/47	Fever, cough, sputum 1 day; SOB <1 day	Pneumonia	70/?	19·5	7·11	4·4	23·4	102	5
3	M/28	Epigastric pain 4 days; vomiting; not SOB	Pancreatitis	94/70	18·0	7·01	3·0	28·0	129	10
4	M/48	Central chest pain, vomiting 1 day		150/100	20·6	7·49	5·1	12·2	156	6·5
5	M/64	Increasing SOB several days	Alcoholic liver disease*	80/70	11·2	7·13	7·0	20·7	121	20
6	M/44	Abdominal pain, vomiting 1 day; SOB <1 day	Alcoholic liver disease*	110/70	19·0	–	4·4†	–	–	–
7	F/31	Collapsed; moaning shouting	Peripheral neuritis	70/40	11·4	7·09	6·0	22·4	120	21
8	M/30	Unwell 5 days; vomiting 4 days. SOB, thirst ½ day		100/70	17·2	7·16	3·0	22·7	106	9·1
9	M/24	Unwell abdominal pain 5 days		80/55	28·2	7·05	2·6	27·0	147	10
10	M/36	SOB, thirst <1 day; drinking heavily	Alcoholic liver disease* peripheral neuritis	110/60	18·8	7·03	13·1	6·2	115	13
11	M/35	Chest and abd. pain. SOB thirst ? 1 day	Anaemia, peripheral neuritis	100/60‡	14·0‡	7·28‡	10·4‡	19·9‡	136‡	24·5‡
12	M/38	Unwell ?2 wk, chest pain, SOB, thirst	Alcoholic liver disease* beriberi heart disease	85/70	23·0	6·92	4·4	28·4	61	21·5
13	M/38	Abd pain 3 days, vomiting 1 day; SOB, thirst <1 day		100/60	7·4‡	7·09	3·4	24·5	107	11·2
14	M/39	SOB, cough, fever 3 days; thirst	Acute bronchitis, infected wound	90/65	20·5	7·00	7·1	20·2	95	19
15	M/22	Unwell 1 wk; lying in bed of river 2 days	Bronchiectasis, cor pulmonale, CCF	95/60	23·0	7·04	5·6	24·6	49	22
16	M/25	Cough, SOB (2nd admission)	Bronchiectasis, cor pulmonale, CCF	120/80	13·3	6·99	4·2	26·6	132	17
17	M/31	Swelling of legs 2 wk; cough, SOB, vomiting 1 day	Alcohol beriberi heart disease, CCF	100/70	15·6	6·98	12·0	21·0	53	13
18	M/32	SOB 1 day (severe jaundice) (2nd admission)	Liver failure, alcoholic liver disease	100/60	8·5	7·35	11·0	11·9	116	21

*Alcoholic liver disease = serum albumin <31 g/l, serum bilirubin >44 μmol/l, other liver function tests abnormal.
†venous blood ‡morning after admission. SOB = short of breath; CCF = congestive cardiac failure; BE = base excess.

3. Response to therapy

The lacticacidosis and collapse of acute fulminant beriberi responds not at all to bicarbonate and vasopressor agents. If thiamine is not given, mortality rate is 100% (Campbell 1984, Thirunavukkarasu, 1979).

In contrast the response to thiamine is rapid and spectacular. What had been a uniformly fatal condition despite correction of the acidosis with bicarbonate and at times dialysis and support of the blood pressure becomes a rapidly reversible disorder when thiamine is administered intravenously.

Table 9 - from Fond et al, 1985 - Example of the failure of vasopressors and bicarbonate to control the lacticacidosis

- Observation n° 1. Résultats des gaz du sang artériel et des dosages biochimiques (sang veineux). Le traitement par la thiamine remplace le traitement par la dopamine et le bicarbonate à partir de la 4e heure.

Heures après admission	*Admission*	*4 heures*	*8 heures*	*24 heures*
Traitement	← Ventilation assistée →			
	← FiO_2 = 1 →	←	FiO_2 = 0,6 →	
	← Dopamine →			
			← Thiamine 1 mg/min →	
	← 500 mEq HCO_3^- →			
Température (°C)	36°4	35°8	37°3	37°4
PHa	7,07	7,05	7,65	7,66
PaO_2 (KPa)	15,6	11,9	9,9	12,3
Pa CO_2 (KPa)	2,9	3,6	3,5	3,9
HCO_3^- (mEq/l)	7,5	6	23,1	27,9
Lactate (mmol/l)	16	22,9	6,5	3,6
Pyruvate (mmol/l)	NF	NF	0,39	0,18

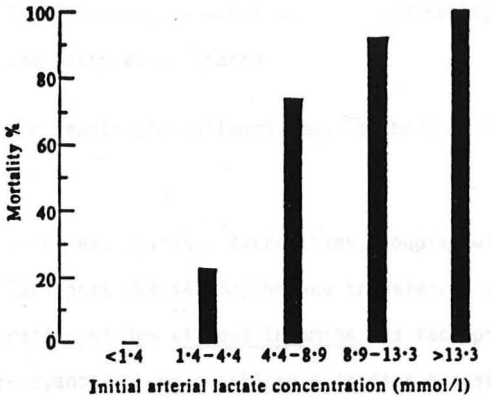
Table 10 - from Fond et al, 1985 - Example of the rapid response of the lacticacidosis to thiamine therapy

- Observation n° 2. Résultats des gaz du sang artériel et des dosages biochimiques (sang veineux). Le traitement par sérum salé hypertonique commence à partir de la 2e heure.

Heures après admission	*Admission*	*2 heures*	*10 heures*	*36 heures*
Traitement	Thiamine 100 mg IV		Sérum salé hypertonique restriction hydrique	
	←	O_2 masque	→	
PHa	7,22	7,48	7,49	7,48
PaO_2 (KPa)	22	16,7	21,5	9,6
Pa CO_2 (KPa)	3,8	3,8	3,8	4,4
HCO_3^- (mEq/l)	15,5	21,3	25,7	27
Lactate (mmol/l)	11	2,51	2,67	1,73
Pyruvate (mmol/l)	0,16	NF	0,07	NF

4. Comparison of the mortality rates of the lacticacidosis of "shock" compared with the lacticacidosis of acute fulminant beriberi.

The prognosis of lactic acidosis in patients in shock is shown below in Fig. 9 from Cohen & Woods, 1976.



The relationship between mortality and initial blood lactate concentration in patients with shock (after Peretz *et al.*, 1965). The figure depicts the relationship between mortality and arterial blood lactate concentrations based on a study of fifty-two patients.

Patients presenting with lactate levels above 8.9 meq/l had a mortality rate greater than 96%. In contrast 94% of patients with lacticacidosis secondary to thiamine deficiency had blood lactate levels higher than 8.9 meq/l, yet the mortality rate was 13%. A survival rate even greater than 87% can be expected if the condition is promptly recognized and appropriately treated.

Table 11 - COMPARISON OF THE MORTALITY RATES IN 73 CASES OF ACUTE FULMINANT BERIBERI WITH LACTICACIDOSIS (SHOSHIN) AND 52 CASES OF LACTICACIDOSIS NOT (?) ASSOCIATED WITH BERIBERI

	Lactate Level meq/l	Mortality Rates Thiamine Therapy		
		treated		none
Lacticacidosis	8.9 - 13.3			96%
	13.4 or greater			99+%
Shoshin Beriberi	17.1	recovered	87%	
	70% 13 or more	died	13%	100%
	94 % greater than 9			

Case Report

G.N., a 39 year old Hispanic man, presented to PMH about 1 year ago with severe abdominal pain, profound shortness of breath and confusion of 2 hours duration and died 10 hours later in severe lactic acidosis and collapse despite massive bicarbonate, fluid and vasopressor therapy.

History revealed previous good health plus alleged moderate beer drinking and occasional binge drinking.

In the surgical E.R., because he had cyanotic extremities, coupled with a pulse 120, BP 116/74, and marked tachypnea (RR 44/min) he was transferred to the Medicine ER. Following the administration of D_5W without thiamine his tachypnea increased and he became more cyanotic. He sustained a cardiac arrest with asystole and despite immediate resusicitation, he remained comatose, hypotensive, and hypothermic.

He was found to have ophthalmoplegia, marked jugular venous distention, bilateral rales, soft abdomen, markedly enlarged liver (10 cm below the costal margin) and cyanosis of the extremities with minimal lower extremity edema. Laboratory tests revealed hyponatremia, a bicarbonate of 10, an anion gap of 25, Cr 1.2, T.P. 7.4, albumin 3.1, glob. 4.4, T bilirubin 3.4, amylase 70, PT 16.4, PTT 46.4. Wbc was 43,000 with left shift. Chest x-ray showed a globular enlarged heart with bilateral hilar and basilar infiltrates indicative of CHF. Despite 10 amps (440 mEq) of bicarbonate his pH remained less than 7.1 and arterial lactate was 26 mEq/l.

He was treated for septic shock with antibiotics, steroids, vasopressors, and biacarbonate. No thiamine was administered. Despite aggressive therapy he remained acidotic and hypotensive and died 10 hours after admission.

Post mortem revealed Wernicke's encephalopathy, cardiovascular beriberi, alcoholic hepatis superimposed on cirrhosis.

Clinically and at post mortem this was a classical case of thiamine deficiency manifested by acute fulminant cardiovascular beriberi with lactic acidosis and Wernicke's Encephalopathy superimposed on alcoholic liver disease.

V. CONDITIONS ASSOCIATED WITH THIAMINE DEFICIENCY

1. Chronic Alcoholism
2. Malnutrition from any cause
3. Persistent Vomiting:
   - Hyperemesis Gravidarum
   - Pyloric Stenosis
   - Cancer of the Stomach
   - Gastric Plication and Gastroplasty
4. Food Faddism
5. Refeeding after prolonged starvation
6. Glucose infusions in thiamine depleted patients
7. Prolonged parenteral nutrition
8. Tumors of the lymphoid - hemopoietic system
9. Intravenous high dose nitroglycerin
10. Ingestion of large doses of antacids
11. Long-term furosemide therapy

These conditions were covered in extensive detail in my Medical Grand Rounds on Wernicke's Encephalopathy on April 17, 1986. However, recently acute pernicious beriberi with lacticacidosis was precipitated in a young woman with hyperemesis gravidarum (Anderson et al, 1985) and in 5 patients receiving total parenteral nutrition. In the latter, fulminant beriberi with lacticacidosis occurred within 2 weeks of starting TPN in three of the five patients (Anderson et al, 1985, LaSelve et al, 1986, Velez et al, 1985).

VI. TREATMENT OF CARDIOVASCULAR BERIBERI AND ACUTE FULMINANT BERIBERI WITH LACTICACIDOSIS

Shoshin beriberi has emerged as a not infrequent medical emergency which if diagnosed promptly is eminently treatable. (Seftel, 1972). Haines in 1937 claimed that the treatment of Shoshin beriberi with intravenous thiamine must be one of the most dramatic responses to treatment seen in medicine.

Since acute fulminant beriberi is a potentially reversible disorder if treatment is instituted immediately whereas death is the certain outcome of late or no treatment, this disorder is a true medical emergency and intravenous thiamine must be administered at once.

Every chronic alcoholic and malnourished patient should receive prophylactic treatment since acute fulminant beriberi with lacticacidosis may be precipitated by a few liters of intravenous fluids containing glucose or in a short time after starting parenteral therapy.

In consideration of the many possible alterations in the classical clinical presentation of cardiovascular beriberi, this disorder should be considered even in the absence of overt clinical signs of a high cardiac output venous congestive state especially when "congestive heart failure" is present in patients with a history of dietary deficiency or alcoholism.

All patients presenting in collapse with severe lacticacidosis should be treated with intravenous thiamine especially if there is a history of, or physical findings indicating malnutrition, alcoholism or a deficient intake of thiamine.

Thiamine should initially be administered daily by the intravenous route in doses of at least 100-300 mg along with therapeutic doses of B complex. Thereafter, 100 mg plus B complex should be administered intravenously on a daily basis. Later the intramuscular route can be used.

Do not depend on oral thiamine therapy since malnutrition seriously decreases thiamine absorption and those patients who are poor absorbers of thiamine are the ones most likely to develop the deficiency state.

Hypomagnesemia and hypophosphatemia must be treated at once since both are essential for the phosphorylation of thiamine to the coenzyme thiamine pyrophosphate. Additionally, there is evidence indicating that either transketolase apoenzyme production may be diminished or the joining of the coenzyme to the apoenzyme may be decreased in magnesium depletion.

IT IS MOST IMPORTANT TO BE CONSTANTLY ALERT TO THE POSSIBILITY OF THIAMINE DEPRIVATION IN ANY SICK PATIENT WHERE CLINICAL FINDINGS OR HISTORY SUGGEST THIS DEFICIENCY AND THEN TO TREAT IT AT ONCE WITH LARGE DOSES OF INTRAVENOUS THIAMINE AND B-COMPLEX.

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