TABLE 1—Mean ($\pm$ S.D.) Blood Lignocaine Levels ($\mu\text{g/ml}$) after Injection

Solution	5 min	10 min	15 min	30 min	45 min	60 min	90 min	120 min	180 min	240 min
2%	0.21 $\pm$ 0.24	0.34 $\pm$ 0.24	0.59 $\pm$ 0.26	0.76 $\pm$ 0.39	0.95 $\pm$ 0.60	0.67 $\pm$ 0.40	0.70 $\pm$ 0.50	0.42 $\pm$ 0.23	0.28 $\pm$ 0.18	0.22 $\pm$ 0.25
10%	0.25 $\pm$ 0.21	0.46 $\pm$ 0.32	0.61 $\pm$ 0.39	0.52 $\pm$ 0.22	0.61 $\pm$ 0.20	0.52 $\pm$ 0.12	0.44 $\pm$ 0.15	0.34 $\pm$ 0.10	0.23 $\pm$ 0.05	0.17 $\pm$ 0.04

TABLE 2—Number of the 10 Volunteers Complaining on Injection

Complaints	2% Lignocaine	10 ml NaCl	10% Lignocaine	2 ml NaCl
Fullness, pain, or burning sensation	6	7	2	4

concentrations are considered. Five subjects, however, achieved a blood level in excess of this, the highest being 2.5 $\mu\text{g/ml}$.

These low mean levels in volunteers, however, contrast with those found on injection under anaesthesia and in studies on patients with myocardial infarction (Scott *et al.*, 1968; Bellet *et al.*, 1969). They are not, however, completely unexpected since another volunteer study involving 2.4 mg/kg into the vastus lateralis showed comparable low blood levels (Meyer and Zelechowski, 1970). The different levels achieved in the "physiological volunteer" as compared with the "non-physiological patient" may be due to variation in cardiac output, muscle perfusion, or other factors influencing the pharmacokinetics of lignocaine. Hepatic blood flow and function may also be altered during these non-physiological states. The range of individual blood levels found in both volunteer and patient studies confirm that, whereas therapeutic levels can often be achieved, accurate blood levels cannot be forecast.

Since, however, a 10% solution is a smaller volume to produce discomfort, achieves similar lignocaine blood levels to a

lower concentration, and shows no apparent local complications, it is a suitable concentration for clinical use. It has been held that highly concentrated solutions of local anaesthetics are particularly toxic, but blood level studies have failed to confirm this (Braid and Scott, 1965), as has the present study.

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Cardiac Beriberi: Two Modes of Presentation

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Summary

Two patients suffering from cardiovascular beriberi presented with different clinical manifestations. One had the classical features of a high cardiac output with raised jugular venous pressure and gross oedema. The other was in fulminating heart failure with clinical evidence of a low cardiac output but no peripheral oedema. The latter type of beriberi (shoshin) is rare. Cardiovascular beriberi has a high mortality when untreated. Both patients responded dramatically to thiamine, and this emphasizes the importance of considering thiamine deficiency as a cause of heart failure even when the cardiac output is low.

Introduction

Beriberi is due to deficiency of thiamine, a vitamin which is a cofactor in a variety of important biochemical reactions

(Williams, 1961). It is common in rice-eating communities but occurs sporadically in Western countries where it is usually associated with chronic alcoholism or, more rarely, with dietary faddism. It presents in two major forms in adults—the "dry," in which features of peripheral neuropathy predominate, and the "wet" or cardiac beriberi, in which oedema is prominent. The cardiac form has been recognized for centuries in the Far East and India, but its occurrence in the West has been adequately documented only since 1937, when Weiss and Wilkins established the importance of thiamine deficiency in the production of cardiovascular disturbance in alcoholics.

Cardiac beriberi classically presents as a high output state with raised jugular venous pressure and peripheral oedema (Wood, 1968). Less commonly it presents as fulminating heart failure with evidence of a low cardiac output, and this form has been given the name "shoshin" beriberi. "Sho" in Japanese means acute damage and "shin" means heart (Wolf and Levin, 1960). Only one case has previously been recorded in Britain (Wood, 1939).

We describe here two cases of cardiac beriberi. One presented with clinical evidence of a very low cardiac output; the other had a high cardiac output, and cardiorespiratory studies showed several interesting features. In both cases the response to thiamine was dramatic, emphasizing the importance of recognizing these syndromes.

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Case 1

A 30-year-old Negro student, who had arrived in Britain nine months previously, was admitted to hospital having suddenly developed severe breathlessness, weakness, and pain in the chest and upper abdomen. He was confused, but it seemed he had been well until three months earlier when facial swelling and ankle oedema appeared and persisted for several weeks. He had also noted occasional palpitations and pain in the feet. He had continued to attend college until the morning of his admission. He denied taking alcohol excessively, but large numbers of beer bottles had been found in his room. It seemed that his diet was monotonous and much of it was carbohydrate.

He was restless and agitated. His oral temperature was only 35°C, and his extremities were cold. He was dyspnoeic but not orthopnoeic; respirations 36/min, pulse rate 70/min, blood pressure 110/60 mm Hg. Peripheral pulses were faint, the jugular venous pressure was raised, but there was no peripheral oedema. The heart was enlarged and there was a prominent right ventricular impulse and an accentuated pulmonary second sound. A triple rhythm was audible at the left sternal edge. Crepitations were heard at both lung bases and the liver was enlarged (3 cm) and tender. Tendon reflexes were absent in all limbs, but lack of co-operation precluded full neurological examination.

Investigations.—Haemoglobin 14.5 g/100 ml; sedimentation rate 1 mm/hr (Westergren); white cell count 14,000/mm³; blood urea 38 mg/100 ml; serum potassium 5.2, sodium 130, chloride 91 mEq/l; aspartate transaminase 450 IU/l; hydroxybutyrate dehydrogenase 640 IU/l; serum cholesterol 70 mg/100 ml; protein 6.6 g/100 ml (albumin 4.9 g). The urine contained protein. X-ray examination showed a large heart and congested lung fields. E.C.G. was normal apart from a prominent J-wave consistent with the low body temperature.

The cause of the severe cardiac failure was not immediately apparent. He was treated with intravenous frusemide, intramuscular digoxin, and a small dose of morphine for restlessness. He passed 300 ml of urine, but over the next 24 hours the blood pressure dropped to 80/50 and urine flow ceased. The blood urea and serum potassium rose and 15 g of Resonium A was given orally. The possibility of beriberi was considered and was thought unlikely because of the clinical evidence of a low cardiac output, but 12 hours after 100 mg of thiamine, given intravenously as a therapeutic trial 24 hours after admission, the pulse was stronger and the blood pressure rose to 135/80. The clinical picture of a low cardiac output was replaced by a hyperkinetic state with warm skin, bounding pulses, and an active heart. Third heart sounds were heard over both ventricles and there was a loud systolic ejection murmur. The cardiac output, measured within 48 hours after the administration of thiamine, was 10.3 l/min. Urine began to flow (after 32 hours of anuria) and in the next 72 hours he passed over 10 l; the weight fell from 58.0 to 51.8 kg. Despite the diuresis the blood urea continued to rise for several days but then fell. With the initial diuresis the serum potassium fell from 6.2 to 3.7 mEq/l, and an attack of nodal tachycardia was attributed to this and to digoxin which had been continued orally. Normal rhythm returned with oral potassium, and digoxin was stopped.

The development of the high output state was associated with a severe and incapacitating burning and tenderness of the skin of the distal part of the legs. Over a period of several days all clinical evidence of circulatory and renal abnormality cleared. Evidence of mild peripheral neuropathy remained though the dysaesthesia improved. The cardiac output three weeks after admission was also normal. The patient was discharged, but failed to attend for follow-up.

Case 2

A 62-year-old white man presented with breathlessness on effort, ankle swelling, and a poor memory. Symptoms had been present for several months. He had lived alone for six years, ate irregularly, and consumed large quantities of beer. His previous health had been excellent.

He was euphoric and confused, and there was evidence of scurvy, with petechiae and perifollicular haemorrhages over both shins and a positive Hess test. The extremities were warm with bounding peripheral pulses. The pulse rate was 72/min and blood pressure 150/65. The jugular venous pressure was raised with gross peripheral oedema. Surprisingly, the heart was not enlarged and

no triple rhythm or heart murmur was heard. The chest was clear but the liver was enlarged 3 cm below the costal margin. There was no abnormality of the cranial nerves, but hyperaesthesia, muscle tenderness, and loss of vibration sense were found distally in the legs; ankle jerks were absent. The haemoglobin was 12.0 g/100 ml and total serum protein 5.6 g/100 ml (albumin 2.6 g); these figures were attributed to haemodilution. The cardiothoracic ratio was normal on radiological examination and there was a small right pleural effusion. The E.C.G. was normal. Red cell transketolase was 22 IU/l (normal range 34-90) with a thiamine pyrophosphate effect of 76% (normal 3.5-40); platelet ascorbate level was 2.5 µg/10⁹ platelets (normal 3-14).

Therapy with thiamine and ascorbic acid was started the day after admission with clear evidence of a diuretic response after four days, and over 10 days the weight fell from 82 to 66 kg with loss of oedema and a rise of haemoglobin and plasma protein levels to normal. The pleural effusion cleared but there was little change in heart size. Evidence of mild peripheral neuropathy persisted and there was no improvement in memory; clinical recovery was otherwise complete.

Cardiopulmonary data were obtained on admission and four weeks after treatment (see Table). Standard methods were used for respiratory function tests (Bates and Christie, 1964). The initial

Cardiopulmonary Data in Case 2

	On Admission	4 Weeks Later	Expected Values
<i>Haemodynamic Data before and after Thiamine</i>			
Height (cm)	166	166	
Weight (Kg)	81	69	
Body surface area	189	176	
Pulse rate (min ⁻¹)	68	80	
Stroke volume (ml)	230	72	
Brachial artery pressure (mm Hg)	147/66	140/70	
Right atrial pressure (mm Hg)	10	4	
Right ventricular pressure (mm Hg)	57/10	25/3	
Pulmonary artery pressure (mm Hg)	57/25	19/12	
Pulmonary capillary pressure (mm Hg)	—	5.5	
Cardiac output (litres min ⁻¹)	15.6	5.8	
Systemic vascular resistance (dynes cm ⁻⁵)	514	1,380	
<i>Respiratory Function Studies before and after Thiamine</i>			
Forced expiratory volume in 1 second (ml)	2,200	3,200	3,000
Forced vital capacity (ml)	2,800	3,800	4,100
Transfer factor by single breath carbon monoxide method (ml min ⁻¹ /mm Hg)	12	25	24
Minute ventilation (l. min ⁻¹)	13.5	8.9	—
Oxygen consumption (ml min ⁻¹)	302	256	—
Arteriovenous oxygen difference (ml/100 ml)	1.9	4.4	—
Arterial O ₂ tension (mm Hg)	62	93	>82
Arterial CO ₂ tension (mm Hg)	31	37	35-45
Arterial pH	7.48	7.42	7.35-7.45
Alveolar-arterial O ₂ difference breathing air (mm Hg)	52	14	<25
Alveolar-arterial O ₂ difference breathing O ₂ (mm Hg)	140	20	<50
Right-to-left shunt (% cardiac output)	18.0	1.2	<3.0
Arterial-alveolar N ₂ difference (mm Hg)	16	9	<12

haemodynamic picture was of a high cardiac output with increased stroke volume and a low peripheral vascular resistance. Though oxygen consumption was raised before thiamine was given the arteriovenous oxygen difference was low since the increased cardiac output was disproportionately high relative to metabolic requirements. Right atrial, right ventricular, and pulmonary arterial pressures were high. The arterial pressure tracing during the Valsalva manoeuvre did not show the square wave response characteristic of severe heart failure. Though there was little change in the pulse rate expiratory effort was accompanied by a fall in the pulse pressure which rapidly rose again when normal respiration was resumed.

Respiratory function was impaired in several respects. There was moderate arterial hypoxaemia and a respiratory alkalosis. The low vital capacity indicated a mild restrictive ventilatory defect, but there was no evidence of airways obstruction. A defect of pulmonary gas exchange was shown by the high alveolar-arterial O₂ difference breathing air. Pulmonary transfer factor was much reduced. A high level of right-to-left shunting was calculated from the data obtained during oxygen breathing and additional ventilation-perfusion inequality was found by an increased arterial-alveolar nitrogen difference (Farhi *et al.*, 1963). Thus multiple factors contributed to the arterial hypoxaemia. All abnormalities of cardiopulmonary function resolved after thiamine therapy.

Discussion

The diagnosis in these cases is strongly supported by the history of dietary inadequacy and excessive intake of alcohol, peripheral neuropathy, mental confusion, and the dramatic response to thiamine. Furthermore, erythrocytes from the second patient had a low red cell transketolase activity which was stimulated by the addition of thiamine pyrophosphate.

The clinical presentation of the second patient was classical; the gross oedema, high jugular venous pressure, and high cardiac output have been reported by many workers (Burwell and Dexter, 1947; Campbell *et al.*, 1951; Lahey *et al.*, 1953; Iseri *et al.*, 1954; Olson, 1958; Lessard *et al.*, 1959; Blacket and Palmer, 1960; Sharpey-Schafer, 1961; Wagner, 1965; Akbarian *et al.*, 1966; Brink *et al.*, 1966; Byrne-Quinn and Fessas, 1969). The picture of fulminating low output heart failure presented by our first patient is less well documented. Only a few cases have been recorded outside the Far East and India, but it is possible that this may not reflect the true incidence. The absence of the classical high output state might well lead to diagnostic error, and since death supervenes rapidly without appropriate treatment necropsy would not reveal the cause of the heart failure.

There are few satisfactory clinical descriptions of shoshin beriberi (Platt, 1958) but a composite clinical picture can be drawn from a small number of detailed reports of individual cases (12 including our own) (Hashimoto, 1937; Wood, 1939; Blankenhorn *et al.*, 1946; Crawford, 1952; Blacket, 1955; Wolf and Levin, 1960; Raman, 1964; Brink *et al.*, 1966). The features included a predominance of young men; history of excessive alcohol intake; a variable length of history before a rapid deterioration to the acute stage. The latter was marked by extreme dyspnoea and retrosternal pain, with cyanosis, poor peripheral pulses, a systolic blood pressure invariably below 90 mm Hg, and absent knee and ankle jerks. The pulse rate was not always raised and peripheral oedema might be slight or even absent. There was a definite polymorph leucocytosis, but no striking electrocardiographic abnormalities. Death occurred between 5 hours and 2 days after admission in 5 of the 12 patients. Of the 7 survivors 4 passed through a phase of high cardiac output before returning to normal cardiovascular status. It is clearly different from the more common form of high output beriberi. Response to thiamine is equally as rapid and complete but in untreated cases death occurs rapidly. Early diagnosis is therefore necessary, but most descriptions of cardiac beriberi mention only the high output presentation of the disease.

The high right atrial pressure and gross peripheral oedema found in beriberi have led to the concept that this condition is a cause of high output cardiac "failure." In our second patient the heart was not enlarged, auscultatory features of ventricular failure were absent, and the response to the Valsalva manoeuvre was not the "square wave" response of severe heart failure. Lahey *et al.* (1953) and Sharpey-Schafer (1961) argued that the congestive state in beriberi is not necessarily a consequence of myocardial failure, though it is clearly possible that ventricular failure may occur if the high output state persists. Sharpey-Schafer showed that the peripheral veins were constricted in beriberi. He attributed the high central venous pressure found in this condition not to cardiac failure but to the combination of peripheral venoconstriction and the increase in blood volume which occur. Venous constriction would also lead to an increase in the pressure gradient between the peripheral and central venous systems (Lahey *et al.*, 1953); a pronounced increase in capillary pressure would result. This would help to explain why the gross oedema found in beriberi seems disproportionate to the more modest rise in jugular venous pressure. The rise

in blood and extracellular fluid volume would also increase oedema since the colloid osmotic pressure would fall. In our second patient the serum albumin on admission was only 2.6 g/100 ml but rose to 3.6 g/100 ml after diuresis.

The diagnosis of cardiac beriberi can be made only if it is suspected on clinical grounds since there are no common routine diagnostic tests. Partial confirmation of high output beriberi can be obtained by demonstrating the presence of a high cardiac output and stroke volume and a low peripheral resistance plus a favourable therapeutic response to thiamine. The test for transketolase activity is of particular value in providing more specific evidence of thiamine deficiency. Transketolase is an enzyme of the hexose monophosphate shunt pathway which catalyzes the reaction D-xylulose 5-phosphate + ribose 5-phosphate → 3-phosphoglyceraldehyde + sedoheptulose 7-phosphate. It requires thiamine pyrophosphate as a co-factor. Transketolase activity can be measured in erythrocytes *in vitro*. In the presence of thiamine deficiency not only is erythrocyte activity low but there is a striking enhancement when thiamine pyrophosphate is added to the system (Brin, 1962).

The mortality of untreated cardiac beriberi is high, and in view of the harmless nature of the treatment a good case could be made for the routine administration of thiamine to all patients in whom heart failure is present without clear evidence of the cause.

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