CASE REPORT

Fulminating Beriberi Heart Disease with Lactic Acidosis: Presentation of a Case with Evaluation of Left Ventricular Function and Review of Pathophysiologic Mechanisms

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SUMMARY Cardiac beriberi is considered a rare disease in western society. A patient with fulminating Shoshin-type beriberi was studied in the acute phase and found to have severe metabolic acidosis, high output biventricular failure, and markedly low systemic vascular resistance. Red blood cell transketolase activity was abnormally low. Following treatment with thiamine, diuretics, digitalis and oxygen, all abnormalities disappeared.

The historical background of the disease is reviewed along with a discussion of pathophysiologic mechanisms responsible for the hemodynamic profile and lactic acidosis. Angiographic and hemodynamic data on the patient presented suggest relative depression of left ventricular function in the acute phase of beriberi. Since beriberi is uncommonly encountered, emphasis is placed on diagnostic and therapeutic implications of the disease which may not be widely appreciated.

METABOLIC ACIDOSIS and varying degrees of hyperdynamic circulatory states are common in many alcoholic patients. The acidosis may have variable etiologies, including poor tissue perfusion secondary to shock and pancreatitis, alcohol-induced non-diabetic ketoacidosis, ingestion of methyl alcohol or other toxins, abuse of paraldehyde, or coincidental diseases such as diabetes or renal disease. The hyperkinetic circulation is often attributed to alcohol withdrawal and impending delirium tremens, pancreatitis, fever, liver disease, anemia, or other non-specific causes. We recently investigated a patient with striking metabolic acidosis and a hyperdynamic circulatory state caused by acute fulminating cardiac beriberi.

Case Report

The patient, a 36-year-old white male, was admitted into the Lexington Veterans Administration Hospital Outpatient Clinic for chronic alcoholism. He had no previous alcohol-related hospital admissions. He was in good health and was working as a carpenter until 10 days before admission to the clinic, when he noted the onset of pain in his legs and feet, generalized weakness, and intermittent nausea and vomiting. Two days before admission, he developed sudden severe dyspnea, three-pillow orthopnea and paroxysmal nocturnal dyspnea. He also noted night sweats, anorexia, and dark urine during this period. His wife noted purple mottling of his hands and feet. He denied having chest pain, bleeding, cough or fever. He also denied ingesting aspirin, methyl alcohol, ethylene glycol, paraldehyde or other chemicals. There was no history of diabetes or renal disease. His dietary intake, according to his wife, consisted of alcohol and prepackaged "junk foods," such as chips and snacks for the last three to four months. He consumed approximately three pints of vodka per day.

Physical examination revealed an acutely ill, anxious, tachypneic patient in moderate respiratory distress. Blood pressure was 105/60 in the supine position, pulse 136 beats/min, respirations 40/min, and temperature 97°F. There was jugular venous distension at 45°. The lungs were clear to auscultation and percussion. Cardiac examination revealed the PMI to be at the fifth intercostal space in the mid clavicular line. There was a grade 4/6 systolic ejection murmur at the lower left sternal border and apex, and a grade 2/6 early diastolic sound or short murmur at the left sternal border. Carotid and femoral pulses were noted to be weak but of a water-hammer quality. Bilateral femoral bruits were audible. There were no pulses palpable below the femorals and the radial pulses were weak. No hepatosplenomegaly, ascites or edema were noted. There was livedo reticularis of the hands and distal lower extremities. There was no calf tenderness or swelling. Neurologic examination revealed diminished sensation to pinprick and light touch in the lower legs. Proprioception was intact and reflexes were normal.

The initial data base included an electrocardiogram which showed sinus tachycardia and non-specific T wave changes. The admission chest x-ray showed an increase in heart size when compared with a film taken one year earlier. There was mild pulmonary venous congestion (fig. 1). An echocardiogram showed a normal aortic and mitral valve without premature mitral
Figure 1. Chest roentgenograms taken one year before hospitalization (top left), on admission to the hospital (top right), and before discharge 11 days later (bottom). At the time of hospital admission cardiac dilatation and pulmonary vascular congestion were noted. These subsequently resolved on therapy including thiamine.

closure. Dimensions of all cardiac chambers were within normal limits. Arterial blood gases on room air revealed a pH of 7.05, pO₂ 91 mm Hg, and pCO₂ 10 mm Hg. Hematocrit was 41%, white blood cell count 12,000/cu mm with a normal differential, and platelet count 210,000/cu mm. Glucose was 190 mg%, BUN 14 mg%, chloride 91 mEq/l, potassium 3.9 mEq/l, sodium 142 mEq/l, and CO₂ < 5 mEq/l. A serum lactate level was 24 mEq/l (normal range 0.5-2.2). A toxicology screen was negative for methanol, ethanol, ethylene glycol, salicylate and barbiturate. The whole blood transketolase activity was 0.67 IU/g Hg (laboratory normal 0.75-1.3).*

Additional laboratory data included a T-4 of 4.8 µg/dl (normal 4.5-11.5) and T-3 resin uptake of 42% (normal 25-36%). Total proteins were 5.4 g%, albumin 3.3 g%. Calcium was 8.2 mg%, creatinine 1.6 mg%, total bilirubin 3.8 mg%, LDH 356 µl/ml (normal 100-225), SGOT 248 µl/ml (normal 10-40). Serum magnesium level was 1.8 mg% (normal 1.8-2.6).

Blood and urine cultures were negative.

The patient was initially treated with intravenous fluids, bicarbonate and broad spectrum antibiotics. However, because of signs of worsening biventricular failure, severe oliguria and persistent acidosis despite bicarbonate, emergency cardiac catheterization was performed.

Initial catheterization data are shown in table 1. The left ventriculogram revealed a vigorous and symmetrically contracting ventricle without mitral regurgitation (fig. 2). The aortic root injection revealed the aortic valve to open asymmetrically without aortic regurgitation. An abdominal aortogram was performed to evaluate the renal arteries and distal blood flow, as no pulses below the femoral were noted. The study showed patent abdominal aorta, renal arteries and iliac arteries with rapid dye washout.

On the basis of the patient’s history of alcoholism, nutrition, peripheral neuropathy, low systemic vascular resistance, high cardiac output with biventricular failure, lactic acidosis, and lack of other known causes of high output failure, the diagnosis of Shoshin-type beriberi heart disease was made. He was

*Performed at Bio-Science Laboratories, Los Angeles, California using the method of Smeets' based on measurement of NADH consumption.
treated subsequently with a loading dose of 1 mg of digoxin, 8 mg of morphine, 200 mg of intravenous thiamine, and 45 mEq of bicarbonate. After beginning digoxin and thiamine, the patient had a marked drop in the bicarbonate requirement needed to correct his acidosis, utilizing 360 mEq of bicarbonate for 18 hours before thiamine and only 45 mEq over the next 24 hours. The patient responded to the above management with a marked increase in urine output, correction of acidosis, reduction in pulmonary-capillary wedge pressure, and improvement in skin color and respiratory pattern. The balloon-tipped flotation catheter was left in place for 48 hours following the initial catheterization. Repeat hemodynamic measurements and Fick cardiac output determinations were performed on day 3 (table 1, column 2). Cardiac output, vascular resistance, and pressures were still abnormal but were markedly improved from the initial catheterization.

The patient continued to show clinical improvement over the next several days, using only thiamine and multivitamins as medications. He received no digoxin after his initial loading dose until the eighth hospital day when he received 0.25 mg/day. A final right and

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**TABLE 1. Cardiac Catheterization Data Over a Three Day Period**

<table>
<thead>
<tr>
<th></th>
<th>6/14</th>
<th>6/16</th>
<th>6/24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>125</td>
<td>100</td>
<td>58</td>
</tr>
<tr>
<td>Pressures (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right atrium</td>
<td>21</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>40/20</td>
<td>33/12</td>
<td>16/2</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>40/20</td>
<td>33/21</td>
<td>16/8 T3</td>
</tr>
<tr>
<td>Pulmonary-capillary wedge</td>
<td>22</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>115/22</td>
<td>150/86</td>
<td>140/8</td>
</tr>
<tr>
<td>Aorta</td>
<td>100/50</td>
<td>87/67</td>
<td>109/83</td>
</tr>
<tr>
<td>Arterio-venous oxygen difference (vol %)</td>
<td>1.45</td>
<td>1.92</td>
<td>4.04</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>23</td>
<td>14.30</td>
<td>5.61</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>13.3</td>
<td>8.31</td>
<td>3.55</td>
</tr>
<tr>
<td>End-diastolic volume index (ml/m²)</td>
<td>114.3</td>
<td>98.1</td>
<td></td>
</tr>
<tr>
<td>End-systolic volume index (ml/m²)</td>
<td>31.7</td>
<td>34.0</td>
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<tr>
<td>Stroke volume index (ml/m²)</td>
<td>82.6</td>
<td>64.1</td>
<td></td>
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<tr>
<td>Ejection fraction (%)</td>
<td>72</td>
<td>65</td>
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<tr>
<td>Ejection time (sec)</td>
<td>0.18</td>
<td>0.33</td>
<td></td>
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<tr>
<td>Mean circumferential fiber shortening range (circumference/sec)</td>
<td>2.25</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>Systemic vascular resistance (dyne/sec/cm⁵)</td>
<td>160</td>
<td>543</td>
<td>1483</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (dyne/sec/cm⁵)</td>
<td>24</td>
<td>61</td>
<td>71.2</td>
</tr>
<tr>
<td>Stroke work index* (g-m/m²)</td>
<td>88</td>
<td>118</td>
<td></td>
</tr>
</tbody>
</table>

*Computed as (left ventricular systolic pressure-left ventricular end-diastolic pressure) (stroke index) (0.0136).
left heart catheterization was performed on the 10th hospital day. All hemodynamic parameters had returned to normal (table 1, column 3). A chest x-ray at this time showed return of heart size to normal (fig. 1).

The patient has been observed for four months in the outpatient department with treatment of thiamine alone. He is asymptomatic without evidence of heart disease. Follow-up transketolase assay has not yet been obtained.

**Discussion**

Beriberi heart disease, originally described in the orient by Aalsmeer and Wenkebach and by Keefer, is considered relatively uncommon in the west. Classically, beriberi has been divided into two major types: a "dry" form, in which features of peripheral neuropathy predominate, and a "wet" form, in which signs and symptoms of right-sided heart failure with normal or high cardiac output are the presenting features. Rarely, a fulminant or "pernicious" variant, termed Shoshin beriberi (from the Japanese sho meaning acute damage and shin meaning heart), may occur with severe biventricular failure, metabolic acidosis, variable cardiac output with vascular collapse, peripheral cyanosis and death. This case represents the second case reported in western literature of this fulminant variant which has been studied hemodynamically in both the acute and recovery stage.

The myocardial and peripheral hemodynamic abnormalities in beriberi have been frequently investigated. Keefer described the syndrome of cardiac insufficiency in beriberi as characterized by fatigue, palpitations, shortness of breath, edema, and cardiomegaly with a "diffuse and feebly" apical impulse and minimal neurologic signs. After reviewing the literature available at that time, Keefer felt that thiamine deficiency causes "changes in the heart muscle which are characterized by cardiac enlargement and deficient contractile power." He also felt that the mild neurologic involvement allowed greater muscular exercise by the patient, placing even greater demands on the myocardium, as opposed to the patient with predominant neurologic manifestations and mild cardiac involvement. At about the same time, Aalsmeer and Wenkebach proposed that a deficiency of thiamine leads to a disturbance in metabolism which results in absorption of water by skeletal muscle and myocardial tissue with a secondary depression of contractility and heart failure.

The observation that widespread peripheral vasodilatation, with resultant arteriovenous shunting, may play a significant role in the pathophysiology of the disease was originally made by Wenkebach and by Weiss and Wilkins. Wenkebach reported a return to normal of the widened pulse pressure following administration of Pitressin, and felt that arteriolar dilation was responsible for the accelerated circulation and hyperkinetic state. Blacket and Palmer described regional perfusion abnormalities characteristic of the clinical presentation in these patients. They reported very low peripheral vascular resistance, muscular vasodilatation with cutaneous vasoconstriction, elevated splanchnic flow, and reduction of renal blood flow and glomerular filtration rate. The findings of mottled cutaneous cyanosis and severe oliguria in our patient, despite patent renal arteries and high cardiac output, are clearly compatible with their observations and have been reported in one other patient.

The exact mechanism of the loss of arteriolar vascular resistance is unknown, but it is felt to be directly related to the biochemical lack of thiamine. Both Lahey and Akbarian reported return of systemic vascular resistance toward normal within 30-90 minutes following intravenous administration of thiamine. The direct relationship of thiamine to the peripheral vascular lesion is also supported by the fact that in one patient administration of methoxamine failed to increase systemic vascular resistance in the acute phase, whereas after thiamine, methoxamine produced a marked rise in systemic resistance. Several authors have shown that the systemic vascular resistance returns to normal within one to two weeks of treatment with thiamine. Wagner suggested that abnormally low systemic vascular resistance which returns to normal within two weeks of thiamine therapy is definitive proof of beriberi heart disease.

The most unsettled aspect of beriberi heart disease is the possibility of a myocardial lesion in addition to a peripheral vascular lesion. Early investigators felt that primary myocardial dysfunction was the dominant feature of the disease. Pathologic changes, including interstitial myocardial edema, cloudy vacuolization of myocardial fibers, fatty degeneration and lack of inflammatory cells have been reported, but these changes are nonspecific. Later investigators felt that heart failure was merely a secondary phenomenon due to the increased work load placed on the heart by peripheral shunting. Recent studies have suggested that there may be both a myocardial component as well as a peripheral vascular lesion. Akbarian has shown that correction of the peripheral vascular resistance seemed only to unmask the myocardial disease by changing volume work into pressure work. The response of the myocardium to thiamine seems to lag behind the response of the peripheral vasculature. This is felt to be one mechanism for the well-documented syndrome of low cardiac output development after treatment of high cardiac output with thiamine. Robin felt that the rise in right and left ventricular dp/dt following thiamine was supportive evidence of the necessity of thiamine for adequate myocardial function.

Possible mechanisms for impairment of myocardial function include altered coronary perfusion, impaired myocardial energy production, and the coexistence of other diseases known to affect the myocardium. Studies of coronary blood flow in beriberi are few and have reported variable findings, ranging from high flow with low coronary resistance to low flow and high coronary resistance. Although quantitative coronary flow was not measured in our patient, subjective estimates during coronary angiography suggested in-
creased flow rates compatible with low coronary resistance.

Direct impairment of myocardial energy production has been proposed as one possible mechanism of the heart failure seen in beriberi. Thiamine is required as a cofactor for energy production via the Krebs cycle at two steps: oxidative decarboxylation of pyruvate to acetyl coenzyme A and of alpha ketoglutarate to succinyl coenzyme A. Impaired myocardial energy production might reasonably be expected to alter ventricular performance. Brink and associates studied myocardial energy production and metabolism in two patients with cardiac beriberi, one of whom had the fulminant Shishin variety with low cardiac output. They concluded that energy supply to the myocardium in beriberi is largely through metabolism of fats rather than carbohydrates. Oxidative phosphorylation appeared to be intact. Thus, although depressed myocardial function secondary to impaired energy production is an attractive hypothesis, it has not yet been clearly demonstrated.

Few studies of ventricular function in patients with beriberi have been reported. The most consistent finding has been elevation of right and left ventricular end-diastolic pressures. It has been the classic view that right ventricular failure alone is the dominant feature of the disease. Numerous studies, however, have documented a significant elevation of left ventricular end-diastolic and pulmonary-capillary wedge pressures when directly measured. Indices of myocardial contractility have only rarely been measured. Robin reported normal right and left ventricular dp/dt during the high output phase, although both parameters did initially increase following thiamine. As their patient developed low cardiac output following initial treatment, dp/dt became severely depressed. When directly measured, left ventricular work has been reported to be increased if patients were studied in a high output state, but depressed during the low output or fulminant phase.

Our patient represents the only reported case where angiographic evaluation of left ventricular function was performed. When studied during the acute phase of his illness he showed evidence of relatively depressed left ventricular function. In the presence of abnormally low systemic vascular resistance and aortic pressure (reduced afterload), one would expect to find high values for the ejection phase indices of left ventricular function (ejection fraction and mean circumferential fiber shortening rate) if myocardial function were not impaired in our patient these indices were within the normal range. During the recovery period systemic vascular resistance increased markedly with only insignificant decreases in ejection phase indices, suggesting that ventricular function may have been inappropriately low for the state of afterload. Figure 3 illustrates the change in left ventricular function in this patient between initial catheterization (at right) and after thiamine therapy. Thus therapy resulted in a higher stroke work index from a lower left ventricular end-diastolic pressure. This strongly suggests that the patient experienced a relative depression of myocardial contractility during the acute phase of his disease that responded to therapy with thiamine. This represents the first patient where both angiographic and hemodynamic data confirm the presence of a relative depression of left ventricular function during the acute phase of beriberi heart disease.

In addition to beriberi heart disease, coexistent diseases may contribute to a relative depression of left ventricular function. Beriberi in western society is almost exclusively a disease of alcoholics. The direct toxic effect of alcohol on the myocardium and the syndrome of alcoholic cardiomyopathy are well-known. It has been proposed by Seftel that the persistence of cardiomegaly following treatment of beriberi with thiamine is evidence of coexisting alcoholic myocardial disease. This may also explain the low output congestive state that occasionally develops following ini-
tial treatment with thiamine. The fact that digitalis seems to have variable effects, producing a favorable response in some patients and no effect in others suggests that there may be more than one mechanism involved in the myocardial failure.

One of the more striking clinical features in our patient was the development of severe lactic acidosis. Elevation of both lactate and pyruvate are characteristic of the metabolic defect in beriberi. Goldsmith noted a disproportionate rise in pyruvate in excess of lactate in beriberi, although both are usually significantly elevated. Jeffrey and Abelmann proposed the mechanism of regional hypoxia, with secondary elevation of lactate due to ischemia, as a major contributor factor to the lactic acidosis. Certainly, as noted earlier, there is evidence of regional perfusion inequalities. Although regional lactate production has not been measured, one might reasonably expect excess lactate production by skeletal muscle, skin, kidneys and possibly myocardium. The clinical observation that the severe acidosis in our patient was difficult to control with bicarbonate alone for 18 hours until thiamin was begun supports the concept that thiamine deficiency was important in the generation and the maintenance of the lactic acidosis.

The role of nutrition in the development of beriberi heart disease has been recognized since the original clinical description by Keefer and Aalsmeer. Early studies from the far east found the disease had its highest prevalence among patients whose diet consisted primarily of milled rice. More recent studies in western literature have described beriberi almost exclusively occurring in alcoholics with poor nutritional habits.

Diagnostic and Therapeutic Implications

Blankenhorst proposed seven diagnostic criteria for beriberi heart disease: 1) enlarged heart with normal sinus rhythm, 2) edema and elevated venous pressure, 3) peripheral neuritis or pellagra, 4) non-specific ST-T changes, 5) no other evident cause, 6) history of dietary deficiency, and 7) response to thiamine or autopsy evidence.

Several additional comments concerning diagnosis and treatment appear appropriate. First, beriberi need not always occur with high output failure, as is commonly believed. The hemodynamic profile of low systemic vascular resistance, peripheral arteriovenous shunting with narrow AV oxygen difference, and biventricular failure is helpful but not necessary for the diagnosis. Beriberi can occur, especially terminally, with fulminant vascular collapse, hypotension, and low cardiac output. Second, lactic acidosis plays a major role in the clinical presentation of Shoshin beriberi. We believe that this may be a major clue in less obvious cases of beriberi and that beriberi should be considered in the differential diagnosis of an alcoholic patient who develops metabolic acidosis of unexplained etiology. Third, the hyperkinetic circulatory state in beriberi often has striking physical findings. The physical findings of hyperkinetic circulation with a widened pulse pressure, in combination with unexplained distal cyanosis, is strongly suggestive of beriberi.

Treatment of Shoshin beriberi must be along two main lines: correcting the underlying defect and treating the clinical manifestations. Obviously, thiamine replacement is the cornerstone of therapy. Treatment of the acidosis with bicarbonate is necessary in critical cases, but it may have only limited success until thiamine replacement is given. There is experimental evidence that magnesium may be necessary in critical cases, but it may have only limited success until thiamine replacement is given. There is also experimental evidence that magnesium may be necessary for complete thiamine utilization. Since magnesium deficiency co-exists in many alcoholics (our patient had borderline low Mg++,), magnesium replacement should probably be administered with thiamine. Heart failure must be treated with oxygen, diuretics, rest, and salt restriction. Treatment with digitalis, although debatable, is probably acutely justified to prevent rapid development of low output failure and sudden death. After the acute phase has been treated successfully, if there is no evidence of underlying myocardial disease, digitalis may be discontinued. Our patient has now been observed for four months, while on thiamine therapy alone, without evidence of recurring heart disease.

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References

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