

Review of Cardiovascular Disorders in Populations with Prolonged Exhaustion and Inadequate Food

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Abstract

The cases were observed from two populations, chiefly laborers in a labor farm, 1958 - 1962 and secondarily farmers in the suburban area of Tianjin, 1966 - 1977. Based on clinical observation, parenteral thiamin was used as the major therapeutic measure because it helps body energy generation. The clinical conclusions obtained from the studied subjects were something different from tradition texts including chronic disorder, such as hypertension, and acute disorder including myocardial infarction. Since they were studied only clinically without required laboratory aids and controls, therapeutic effect was confirmed only with repeated cases. In this review, these clinical phenomena are discussed without elucidating their mechanisms in detail.

Keywords: *Angioplasty Stent; Apoplexy; Arrhythmia; Atrial Fibrillation; Bradycardia; Coronary Heart Disease; Dysautonomia; Hypertension; Micro-Aneurysm; Myocardial Infarction; Postpartum Atonic Uterine Hemorrhage; Premature Heartbeat; Tachycardia; Ventricular Fibrillation*

Introduction

Cardiovascular disorders constitute the major part of clinical medicine especially in people with intensive physical activity. Some of them may be life threatening, such as myocardial infarction or coronary heart disease. Some of them may be insignificant and often neglected such as premature heartbeats, blood pressure change, and vascular abnormalities.

Arrhythmias

Arrhythmias of all types were frequent phenomena among the malnourished; however, their nutritional etiology is often neglected or ruled out in current literature. For example, complex ventricular arrhythmias were often reported to be caused by underlying myocardial infarction, myocarditis, metabolic disorders, and some drugs but excluding nutritional deficiency [1].

Premature heartbeats

Premature ventricular heartbeat was not only a common but also often a severe clinical problem among the arduously hard laborers and the poor peasants. Singular or multiple ventricular premature heartbeats often occurred during rest period after arduous physical labor or after dinner. The severe form, trigeminy or bigeminy, was often encountered when death became imminent such as in cases with massive diarrhea of beef-washing-like watery excretion, fatal fever, or fully bloated abdomen due to gastrointestinal paralysis. They were

also observed in full-term delivering women. Trigeminy or bigeminy disappeared immediately after prompt intramuscular or intravenous thiamin HCl. The common occurrence and dramatic response or life saving effect indicated that thiamin deficiency should be one of the major etiologies for ventricular premature complex.

Severe arrhythmia after electric injury

A middle aged electrician fell in coma immediately after high-voltage electricity injury in August 1976, shortly after Tangshan earth quack. He was rushed to a university hospital in Tianjin for emergent rescue. After regular examination and treatment, the doctors suggested his family to bring the patient home because his heart was fatally injured and incurable.

About 20 hours after the accident, the patient returned home and was examined to be semi-conscious and poor in communication. It was night. Blood pressure was 60/? mm Hg, the heart rate varied between 30 - 40 per minute, and rhythm was severely irregular. Each heart beat was very heavy and loud. It was very forcible as if two ventricular premature heartbeats combined together. Several irregular heartbeats were grouped into a cluster, which was followed by an intermittent cardiac arrest for about 5 seconds. Regretfully, no electrocardiography was available in that village.

Thiamin HCl 200 mg was promptly injected. The alternative occurrence of irregular heartbeat cluster and cardiac arrest still persisted for about one hour. Then the same dose was repeated. After injecting for 3 times, patient became mentally clear and intermittent cardiac arrest disappeared. The clusters of irregular heartbeats converted into normal rhythm but associated with a series of ventricular premature beats after a total dose of thiamin of 1,000 mg at that night. From the second day, the followings were intramuscularly injected three times a day for 10 days: thiamin 100 mg, ATP 20 mg, vitamin B complex (containing VB1 10 mg, VB2 2 mg, niacinamide 30 mg, VB6 2 mg, Folic acid 2 mg, pantothenic acid 1 mg) 2 ampules, and ascorbic acid 100 mg. Ordinary dose of cytochrome C in 5% glucose was intravenously dripped for one time but discontinued owing to its hyperthermal reaction. Heart rate, rhythm, blood pressure, mental status restored normal after the second day of multiple medicine therapy. No more premature heartbeat appeared. Ten days later, only thiamin 100 mg was injected daily. He returned to his job 50 days later and no cardiac complication was found after 32 year until 2008.

Atrial fibrillation

About 3% of laborers developed atrial fibrillation, which could persist life long even after releasing from the labor farm. It was often asymptomatic. Auscultation was characteristically diagnostic. In a few cases treated with parenteral thiamin 50 mg daily for a few weeks, the result was very good. Atrial fibrillation disappeared and never returned and therefore its etiology of thiamin deficiency was confirmed. However, the majority of cases were not treated because of its chronicity, non-life threatening, and medicine destitution. When they were released from prolonged arduous hard labor and inadequate food, atrial fibrillation often finished without therapy.

Ventricular fibrillation

It was suspected in a terminal case. Shortly after drastic reduction of food in December 1960, the beginning of the Holocaust Nationwide Starvation, a laborer suddenly fell in coma. His pulse, blood pressure, heart sound, and breath became undetectable. However, he continued slurring to eat Peking duck, a famous delicious food, for 2 hours. Then, his slur became faint, fainter, until silent. The silence was followed by an immediate generalized spasmodic fibrilliform contraction of the entire facial expression muscles before his death. Ventricular fibrillation had to be suspected; otherwise, it would be impossible for a corpse to slur. The fibrilliform spasmodic contraction of the entire facial expression muscles was another very unique phenomenon, perhaps, had never been described. The very fine wrinkles formed by the fibrilliform contraction made a very horrible picture as if the entire face were totally skinned. Unfortunately, no way and no thing were available for saving his life.

Tachycardia and bradycardia

Tachycardia in beriberi has been well documented. The heart rate could be 160 to 220 beats per minutes. Its response to parenteral thiamin was dramatic. However, it was rare in the camp probably due to the co-existence of protein/calorie deficiency. On the other hand, bradycardia, 40 - 60 beats per minute, was very common among the laborers chiefly due to associated semi-starvation.

In a case, Mr. Wang 47, complaining weakness and coldness daily, the heart rate became 18/minute when he was dragged back to the camp clinic with a sledge from the great wildness in the winter of 1959. Death was imminent but thiamin injection was not available. Fortunately, there was an empty thiamin ampule just finished before its disposal; it was obliged to rinse the residue with 10 ml of saline and promptly intravenously injected. About 5 mg of thiamin residue saved his life as judged from his heart rate 50/min within an hour. If adrenalin were used, he would definitely die because of extreme exhaustion of his cardiac muscle. Similarly, if 50% glucose alone were injected without simultaneous parenteral thiamin, he would be also definitely die. Intravenous 50% glucose alone might cause arrhythmias in patients with thiamin deficiency as observed in the farm. His pulse and blood pressure restored to normal after full rest, multiple oral thiamin, and yeast for several weeks. A full rest in bed was a very powerful therapeutic measure for the arduous hard laborers.

Blood Pressure

Hypotension and paroxysmal hypertension

In a large survey in the labor camp, blood pressure was measured 90/60 mm Hg or lower in the majority of the inmates. Essentially, every laborer was hypotensive chiefly due to associated protein/calorie deficiency.

In a case with headache, his blood pressure fluctuated paroxysmally between normal and 180-200/80-110 mm Hg, mimicking pheochromocytoma. It was cured with parenteral thiamin. The mechanism could be due to functional failure of the autonomic nervous system. In severe thiamin deficiency, this system is apt in trouble causing different life-threatening syndromes with different clinical patterns, which were manifested according to statistical random combinations of multiple severe or fatal signs from many organs and systems grouped together. It made clinical diagnosis interpretation very difficult, therefore, usually defined as vegetative system crisis [2] or dys-autonomia [3]. This case was very mild and simple form of the syndrome.

Apoplexy prevention

In the village during the Cultural Revolution 1966 - 1977, peasants from each family were ordered to dig canal in the winter regardless their healthy condition. Patients with blood pressure over 160 - 170/100 mm Hg often developed cerebral stroke in the evening after strenuous physical labor. On the contrary, a few patients with the same degrees of blood pressure and labor intensity were stroke free because each was promptly injected with thiamin HCl 100 mg immediately after labor. An injection of thiamin HCl 100 mg could reduce systolic blood pressure by 20 mm Hg for several hours to 1 - 2 days in the hypertensives but no effect in normotensive persons. It was also proved to be effective for stroke prevention in eminent cases with hypertensive episode, such as after arduous physical exercise, severe eclampsia in the late pregnancy, malignant hypertension, and hypertension crisis. The following is a case successfully protected from cerebral stroke.

A typical case was Ms Wang 56, a patient with hypertension 170/100 mm Hg and on daily hypotensives for 3 years in Tianjin west. At Jan 15, 2019, she became headache after household exhaustion and common cold. The headache involved the whole head with increasing in intensity as if explosive and intolerable with BP 180/120 mm Hg. The headache was so severe that many kinds of analgesics failed. Thiamin 300 mg injection was suggested. It relieved her headache quickly but briefly. Therefore, daily injections of two or three time was held and then finally 4 times for 4 days with a total of 10 days of thiamin therapy. Headache disappeared completely and blood pressure reduced and maintained 120/80 mm Hg and never higher than 130/80 thereafter. The possible cerebral stroke thus avoided.

The heart

Myocardial infarction

A peasant woman of 60 years old suffered from severe chest pain with typical electrocardiography of acute myocardial infarction and audible front cardiac wall friction. Her severe chest pain and multiple premature heartbeats were relieved promptly for about 1 - 2 hours after each intramuscular thiamin when required. She was cured with parenteral vitamin therapy including thiamin, vitamin B complex, and ascorbic acid without regular pharmaceuticals.

Parenteral thiamin should be essential in cardiac stroke and 200 - 300 mg of thiamin must be injected imminently and followed by continuous injections of 200 mg every 1 - 3 hours or dripping until clinical condition became stable. Regular rescue procedures such as oxygen may be used but no intervention, narcotics or steroids. More cases should be tried to establish thiamin therapy for cardiac stroke.

Angioplasty stent in coronary insufficiency

Although angioplasty stent can dilate the narrowed vessels to some degree; however, it is an invasion of an artificial item with limited effective duration, daily medication of multiple drugs and potential multiple stents requirement. Thus, it becomes a great health and financial burden to the patient and should be replaced with a metabolic procedure. Parenteral thiamin 200 - 300 mg twice or thrice a day could preliminary relief signs and symptoms sluggishly within a few weeks or months. Once an interval was found, the signs and symptoms would be improved gradually or dramatically until signs free if continued for further few months. Thirty-three patients in Tianjin west of China were successfully tried regardless with stent or not. Their associated abnormalities were also cured, including nail-layering phenomena for 64 years, kidney cyst and Parkinson syndrome. Another case with daily tachycardia after by-pass surgery for 10 years also restored normal rate under parenteral thiamin therapy [4].

If re-stenosis occurred, "refuel" with parenteral thiamin would be useful. When injection becomes impossible, mega dose of oral benfotiamine may be used. However, it seemed less effective as compared this few cases with the majority of thiamin injected patients. Another worry may be the metabolic fate of the complete benzene ring on benfotiamine molecule.

The blood vessels

Micro-aneurysms of arterioles

Among the prolonged arduous laborers, tiny red spots on the skin were common findings in the extremities or the trunk without local abnormal sensation and likely to be overlooked. They were few in number, no more than 10 spots in an extremity or trunk, and small in size, 1 - 2 mm in diameter. It was red and turned black within 3 - 5 days before disappearance. When pressing with the head of a clothespin, the red spot did not disappear as seen in a liver spider. It did not rise above the surrounding skin and not swell as in insect bite. However, its color change attracted medical attention. This red spot was proved to be a micro-aneurysm of an arteriole by checking the perineal side of the dilated scrotum where arterioles were visible to the naked eyes. A red berry spot could be seen crossing over the red line of an arteriole, just like a city crossing on the highway lines in a geographic map. It turned black within 3 - 5 days. No local bleeding was observed during or after blackening. The distal portion of the arteriole diminished and left a dead end, which became invisible later. When the spot was freshly red it could be corrected. Prompt local subcutaneous infusing 10 mg of thiamin HCl in 2 cases and 1 ml of vitamin B complex in 1 case restored the red line. This micro-aneurysm itself had minimal clinical significance. However, it indicated that development or rupture of aneurysm in small or larger arteries in severe malnutrition would be likely. The following phenomena may be caused:

1. Nosebleed or epistaxia from Kiesselbach's plexus or Little's area: This plexus may have the similar pathology as micro-aneurysm. It often involves the aged who were in uncomfortable status, such as severe fatigue, or poor sleep, especially after a few days with excessive catarrh drops from the nose. Although bleeding is very alarming, however, it could be stopped by pressing the bleeding

nostril and/or inserting a small tissue roller and wait for 10 - 20 minutes for coagulation. If it was still refractory, intramuscular thiamin HCl 200 - 300 mg would solve the problem immediately because the Klesselbach's plexus might be thiamin deficient causing micro-aneurysm as reported [5].

2. Aneurysm in the Willis' circle of the brain: It is believed as "congenital", however, such superstition may be proved to be wrong with parenteral thiamin therapy to reject surgical removal.
3. In cases with hemorrhage in subarachnoid space or cerebral arteries, continuing injection of large dose of thiamin may accelerate recovery or life saving by stopping bleeding. It is critically important but based on interrupted clinical observations, therefore, hypothetical.

Varicose arteries

Varicose artery was not too rare although it has been rarely described. It involved bilateral anterior branches of the superficial temporal arteries on the face and thereby obviously visible. The lesion occupied a length of 5 - 7 cm of the artery. Within this range, the normally very tortuous facial artery became conspicuously increased in its tortuosity and caliber. There might be 7 - 10 sharp turns or bents like stretched elastic spring coils. The caliber of the involved portion was slightly thicker than its distal and proximal parts of this artery. To make records for comparison, the varicosis was painted with Chinese brush and ink before covering it with a sheet of moist soft paper. The curvatures of the tortuous and extended temporal arteries could be clearly printed while its caliber could be not.

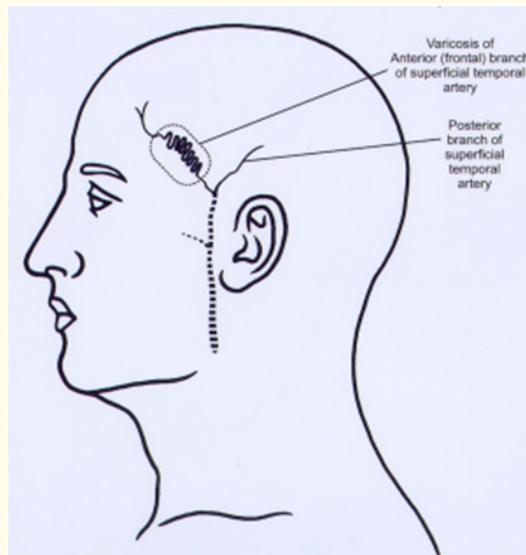


Figure 1: The varicose anterior branch of superficial temporal artery.

Five cases of 30 - 50 year-old inmates without hypertension were observed within 4 years. Two inmates still confined in the cell showed no change in their varicoses either before or after the Holocaust Nationwide Hunger. Three cases were released but continued to work in the camp. Their diets greatly improved with plenty of fishes, eggs and pork. After one year, their first and last sharp turns on both ends of the varicosis became straightened. Six months later, further improvements were observed. Unfortunately, all the improvements restored to their original sizes and shapes 4-7 months after Holocaust Nationwide Starvation in all three cases of the released. No further observation could be done because the author left the camp. It remains only as an hypothesis.

Massive uterine atonic postpartum hemorrhage

Hemorrhage of this kind is not directly related to blood vessel but due to contract failure of atonic postpartum uterine. In a case with full-term labor, the delivery was smooth while hemorrhage continued after placental delivery. Approximately 500 - 1000 ml of blood was lost and the patient became hypotensive. Agrimonin (a hemostat extracted from herbal medicine), and vitamin K were not effective while intramuscular thiamin HCl 100 mg twice promptly and completely stopped the bleeding and initiated the contraction of the dilated uterus. Thus, large dose of parenteral thiamin or oral benfotiamine should be a routine part in managing delivery because thiamin deficiency could cause uterus muscle contraction failure [6].

Discussion

Effect of thiamin deficiency

The above phenomena might be resulted from the deleterious reactions of excessive multiple metabolites produced in thiamin deficiency and exhaustive physical labor, such as free radicals, α -oxoaldehydes, lipid peroxides, advanced glycation end-products (AGEs), etc. For example, exhaustive physical exercise caused excessive generation of free radicals in skeletal muscles [7]. Starvation enhanced hepatic free radical release due to tissue depletion of glutathione [8]. Life-long proteins, such as collagen and elastin, are very sensitive and vulnerable to the cross-linkage reaction of α -oxoglyoxals and AGEs leading to different forms of degradation.

The directly observable micro-aneurysm formation provided evidence for vascular damage in thiamin deficiency. Similar pathology might be the basis of varicosis of the anterior branch of temporal arteries but milder in degree and longer in length. It might be a segment of continuous vascular lesion consisting of degradation of the cellular and/or matrix components, including endothelial dysfunction, smooth muscle cell apoptosis, chronic inflammation, degradation of elastin or collagen fibers, and excessive production of matrix metalloproteinase (MMP) before reaching the extent of aneurysm formation, rupture or thrombosis [9].

Uterine atonic postpartum hemorrhage was different. In addition to smooth muscle contraction failure, depletion of von Willebrand factor in the Weibel-Palade bodies of the dysfunctional endothelium might be responsible [10].

Thiamin deficiency and stroke

Nutritional deficiency has never been considered as a possible contributory factor for aneurysm, cardiac or cerebral stroke. However, thiamin administration was effective for prevention of apoplexy in cases with hypertension after arduous physical labor and in the case with obvious myocardial infarction. These were also supported by Gaevyi and Romanova. They reported that single injection of thiamin diphosphate 5 - 10 mg/kg in anaesthetized cats caused a reduction of systemic arterial pressure and PO_2 cerebral tissue. Clinically, one injection of thiamin diphosphate 50 mg causes 2 - 27 mm Hg reduction of systolic pressure in each of 30 hypertensives but no change in 25 normotensive controls [11]. They also reported mild blood pressure reduction up to 9 - 10% within 40 minutes in 33 patients with blood pressure 176 +/- 17.5 mm Hg after intramuscular thiamin bromide 60 mg [12]. The hypotensive effect of thiamin might be resulted from its reaction on the detrimental metabolites, which exert multiple pathogenic effects as follows.

Oxidative stress: According to Vaziri., *et al.* [13], excessive free radicals could elevate blood pressure by:

- i. Diminishing endothelium derived nitric oxide and irreversibly inactivating prostacyclin synthase leading to elevation of systemic vascular resistance.
- ii. Oxidizing free or esterified arachidonic acid within cell membrane and generating isoprostanes that engage vasoconstrictor and prothrombotic mechanisms.
- iii. Causing vasoconstriction directly.
- iv. Causing cellular injury, fibrosis, cellular proliferation, and formation of atherogenic oxidized lipoproteins.

- v. Taking part in lead-induced or chronic renal failure-induced hypertension.

α -oxoaldehydes: As pointed by Brownlee [14], alpha-oxoaldehydes damage the target cells by three mechanisms:

- i. Modify intracellular proteins to have cellular function changed.
- ii. Modify extracellular matrix components, which interact abnormally with other matrix components and with the receptors or for matrix proteins (integrins) on cells.
- iii. Modify plasma proteins, which bind to AGE receptors on vascular endothelial cells, glomerular mesangial cells, and macrophages, including receptor-mediated production of reactive oxygen free radicals.

This AGE receptor ligation activates pleiotropic transcript factor, NF κ B (κ or kappa is a Greek), and causes pathological gene expression. Vasdev, *et al.* [12] fed Wistar Kyoto rats with methylglyoxal for 1 week and caused significant increase of blood pressure. Elevated cellular methylglyoxal has the following effects to increase blood pressure [15]:

- i. Induces structural and functional changes of blood vessels.
- ii. Increases aldehyde conjugates and micro-vascular damage in kidney.
- iii. Gives rise to AGEs.
- iv. Increases oxidative stress.
- v. Activates the nuclear factor NF κ B.

AGEs: AGEs have the following detrimental effects leading to hypertension [16,17]:

- i. Modify proteins and cause sclerosis of renal glomeruli, thickening of the capillary basement membrane, atherosclerosis, aortic stiffness and some other abnormalities.
- ii. Directly damage the structure and metabolism of extracellular matrix.
- iii. Interact with their receptors (RAGE) forming AGE-RAGE complex, which alternates cellular functions, such as activation of nuclear factor NF κ B, stimulation of the transcription of gene for cytokines, growth factors and adhesive molecules, or induction of migration of monocytes.
- iv. Damage low-density lipoprotein particles and accelerate atherosclerosis.
- v. Damage biological membrane and endothelium as in primary hypertension.
- vi. Increase oxidative stress.
- vii. Alternate vascular tone.
- viii. Reduce nitric oxide.

Thiamin is protective against all of these detrimental effects.

Thiamin deficiency and arrhythmias

No relationship between arrhythmia and thiamin deficiency has ever been mentioned, however, parenteral thiamin was dramatically effective in eliminating ventricular premature contractions, either singular or multiple including trigeminy or bigeminy. Its effect for premature beats in myocardial infarction was even more obvious as in the case of peasant woman. Arrhythmia was due to Ca²⁺ overload in damaged cardiac muscle cells [18]. Another interpretation was that arrhythmias, such as atrial fibrillation, resulted from malfunction of myofibrillar proteins after oxidative modification [19,20]. Nothing has ever been mentioned about its relation with thiamin deficiency albeit the therapeutic result was excellent.

Conclusion

Thiamin should be essential in the therapy of the cardiovascular disorders described. Its therapeutic role in myocardial infarction, coronary insufficiency, or hypertension is even more critically important.

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