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Electrical and Mechanical Abnormalities in the Heart of a Schizophrenic Patient With Hyponatremia Derived From Water Intoxication

Nobuhito YANAGI, MD
Toru MARUYAMA, MD
Shigeyuki UEHATA, MD*1
Yasura WAKIMOTO, MD*1
Yunoshin SASAKI, MD*1
Makoto ARITA, MD*2

Abstract

Electrical and mechanical abnormalities were studied in the heart of a schizophrenic male patient with severe hyponatremia and concomitant low plasma osmolarity induced by excessive water intake (so-called "water intoxication syndrome") by recording electrocardiography and echocardiography.

There was a significant positive correlation between the plasma osmolarity and serum sodium concentration. The QRS duration of electrocardiography, an index of the ventricular electrical conduction velocity, tended to be prolonged and the left ventricular ejection fraction calculated by echocardiography decreased in proportion to the reduction of the serum sodium concentration. Lowering extracellular sodium concentration theoretically slows electrical conduction velocity, and was observed in this patient. On the other hand, low external sodium concentration should increase cardiac contractility via suppression of the forward mode operation of the sodium-calcium exchange mechanism, thereby increasing the intracellular free calcium concentration. However, this was not the case in our patient, because ejection fraction was not increased but rather significantly decreased with the lowering of serum sodium concentration.

We speculate that in patients with water intoxication, the negative inotropism of the heart caused by low plasma osmolarity prevails over the positive inotropism caused by low serum sodium concentration.

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Key Words

■ **Echocardiography** ■ **Electrocardiography** ■ **Sodium (hyponatremia)**
■ **Water intoxication**

INTRODUCTION

Since Barahal[1] described a female patient who developed dementia after excessive intake of water, quite a few cases of the so-called "water intoxication syndrome" have been reported in psychiatry. The inappropriate secretion of antidiuretic hormone (ADH) and malfunction of the central nervous system regulating water homeostasis are proposed to be the mechanisms of polydipsia. The signs of water intoxication essentially stem from the hyponatremia caused by excessive intake of water.

九州大学医学部 第一内科：〒812–8582 福岡市東区馬出3–1–1；*1恵愛会福間病院，福岡；*2大分医科大学 第二生理学，大分
The First Department of Internal Medicine, Faculty of Medicine, Kyushu University, Fukuoka; *1Keiaikai-Fukuma Hospital, Fukuoka; *2The Second Department of Pathology, Ohita Medical University, Ohita
Address for reprints: YANAGI N, MD, The First Department of Internal Medicine, Faculty of Medicine, Kyushu University, Maidashi 3–1–1, Higashi-ku, Fukuoka 812–8582
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The typical symptoms include nausea, vomiting, diarrhea, confusion, seizures and coma[2]. The serum sodium level is often found to be less than 120 mEq/*l*, and the neurological abnormalities observed in this condition are explained by brain edema, presumably caused by hyponatremia-mediated occurrence of hypo-osmolarity. Since some cases are lethal, this syndrome is thought to be a serious problem in the field of psychiatric patient care[3]. However, the cardiac complication associated with this disorder has not yet been described.

We investigated the electrical and mechanical functions of the heart in a schizophrenic patient with the signs of water intoxication and resulting hyponatremia, and describe the serial changes in electrical and mechanical parameters with special reference to the changes in serum sodium concentration.

CASE

The patient was a 45-year-old man who was initially diagnosed as schizophrenic in 1977 at the age of 25 years. He has been admitted to Keiaikai-Fukuma Hospital for 20 years. He has been treated with 300 mg of chlorpromazine, 30 mg of haloperidol (which is equivalent to 1,500 mg of chlorpromazine), and 50 mg of zotepine (equivalent to 100 mg of chlorpromazine) for more than 5 years, and schizophrenic breakdown has not occurred for several years although he exhibited frequent episodes of polydipsia, which usually occurred suddenly with an incidence of about once every few months. During the episode, his body weight usually gained by 3 to 5 kg due to the excessive intake of water that was the most and essential favorite for him to ease his severe feeling of polydipsia. Although vomiting and polyuria are associated with polydipsia, the neurological signs and symptoms are scarcely recognized even when the serum sodium concentration attains 120 mEq/*l* or even less. He did not have any other complications or previous disease.

From May 1996 to April 1997, we weighed him twice every day (9 am and 5 pm) and plasma osmolarity was measured by the cryoscopy method. Plasma levels of sodium, potassium and chloride were measured by the electrode method. Laboratory data including levels of human atrial natriuretic peptide (hANP), antidiuretic hormone and catecholamines were measured once a month; plasma renin activity (PRA) was also determined.

Selected abbreviations and acronyms

hANP = human atrial natriuretic peptide
PRA = plasma renin activity

Electrocardiography (ECG) and echocardiography were recorded on the same day as the routine examination. These cardiac examinations were performed 15 min after bed rest. ECG was recorded using dual leads of II and V_5, with the standard paper speed of 25 mm/sec and when necessary, at the speed of 100 mm/sec, *e.g.*, to measure the QRS duration. Echocardiography used the parasternal and apical views, with which the left atrial dimension, left ventricular end-systolic and end-diastolic dimensions and posterior left ventricular wall thickness were evaluated. The left ventricular ejection fraction was calculated according to the methods introduced by Teichholz *et al.*[4] Doppler techniques were applied to evaluate the left ventricular inflow velocity of 2 components: The first component occurred in the early diastole (E) and the second component followed the atrial systole (A), and the ratio of A to E (A/E) was calculated[5]. The diagnosis of water intoxication was made by observation of the patient showing the behavior of frequent water drinking and by the gain of body weight more than 3 kg within a day. Those examinations were repeated within a day when the signs of water intoxication emerged.

Written informed consent for participation in this study was obtained from the patient. Linear regression analysis used the least-square-method and a p value of less than 0.05 was considered as statistically significant.

RESULTS

The treatment was not changed and schizophrenic breakdown did not occur during the investigation period. Water intoxication occurred twice, first in October 1996 when his body weight increased by 5 kg at 5 pm as compared to that measured at 9 am, and the second in February 1997 when the gain of body weight was 4 kg. The serum sodium concentration was 120 and 119 mEq/*l* at the first and second episodes, respectively.

A typical ECG recorded as a control and during water intoxication are shown in **Fig. 1**. PQ interval, QRS duration and QT interval were prolonged during water intoxication in the 2 leads of II and V_5.

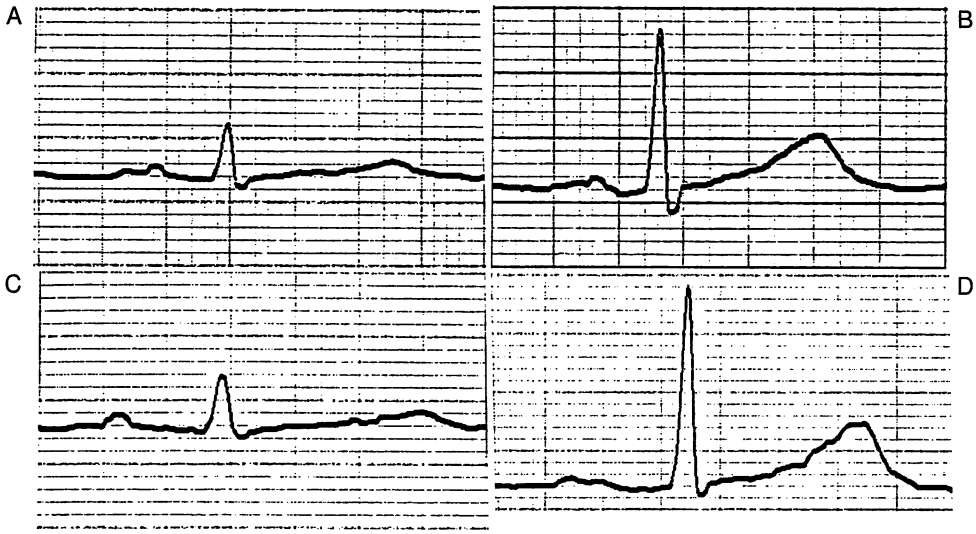

Fig. 1 Electrocardiographic recordings in the control period and during water intoxication
Leads II (*A*) and V_5 (*B*) in the control period and the corresponding 2 leads (*C, D*) during water intoxication.

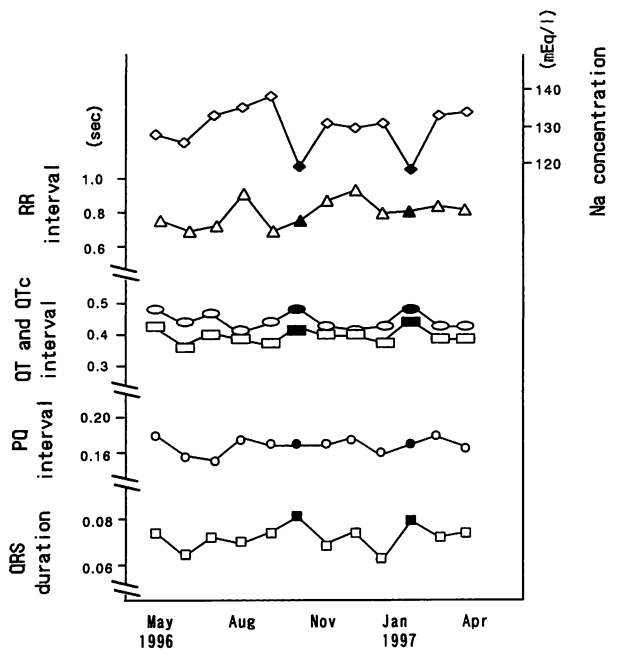

Fig. 2 Serial changes in the serum sodium concentration (◇), the PQ interval (○), QRS duration (□), QT interval (□), QTc interval (○) and RR interval (△) on the electrocardiogram
Closed symbols indicate water intoxication (Oct., 1996 and Feb., 1997).

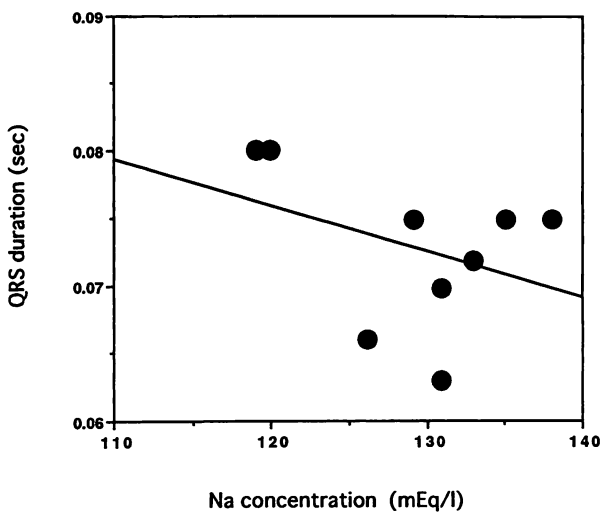

Fig. 3 Relationship between QRS duration on the electrocardiogram and serum sodium concentration ($r^2 = 0.141$, $p = 0.11$)

The serial changes in these ECG parameters are shown in **Fig. 2**. Corrected QT interval was calculated by Bazett's formula[6]. Only QRS duration was inversely correlated with the serum sodium concentration. When PQ interval, QRS duration and QT as well as corrected QT intervals were plotted as a function of serum sodium concentration, QRS duration tended to be prolonged in proportion to the fall in serum sodium concentration, although statistical significance was not attained ($r^2 = 0.141$, $p = 0.11$; **Fig. 3**).

Echocardiography revealed various abnormalities, depending on the changes in serum sodium concentration. Left atrial dimension was 3.7 and

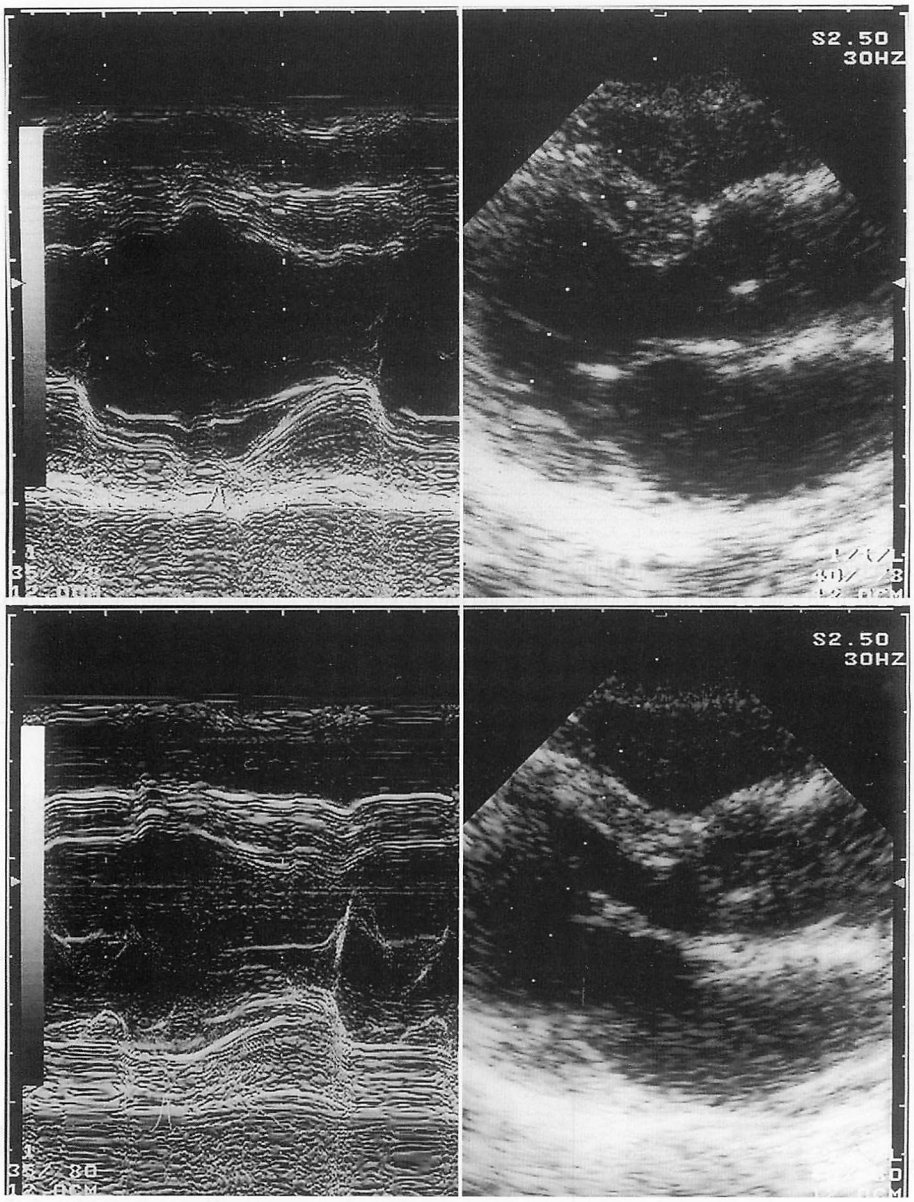

Fig. 4 M-mode (*left*) and two-dimensional (*right*) echocardiograms
Upper: In the control period.
Lowrer: During water intoxication.

3.3 cm corresponding to the serum sodium concentrations of 120 and 135 mEq/*l*, respectively. Similarly, the respective values of A/E evaluated by the Doppler technique were 1.19 and 0.91. Ultrasonic echocardiographic findings are indicated in **Fig. 4**. Posterior left ventricular wall thickness was 1.0 and 0.8 cm corresponding to the serum sodium concentration of 120 and 135 mEq/*l*, respectively. Left ventricular end-diastolic dimension was estimated to be 4.9 and 5.2 cm, and left ventricular end-systolic dimension was 3.3 and 3.0 cm, respectively. Ejection fraction calculated at the serum sodium concentration of 120 and 135 mEq/*l* were 60% and 72%, respectively. **Fig. 5** shows the correlation between the serum sodium concentration and the ejection fraction. Ejection fraction declined in proportion to the fall in serum sodium concentration with a significant positive correlation ($r^2 = 0.444$, $p < 0.05$).

The levels of osmolarity, electrolytes and humoral factors such as hANP, ADH, PRA and catecholamines are summarized in **Table 1**.

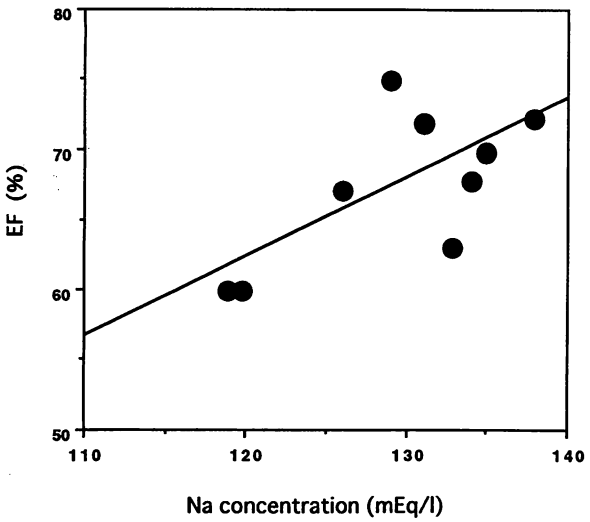

Fig. 5 Relationship between left ventricular ejection fraction (EF) obtained by echocardiography and serum sodium concentration
There is a significant positive correlation between these 2 parameters ($r^2 = 0.444$, $p < 0.05$).

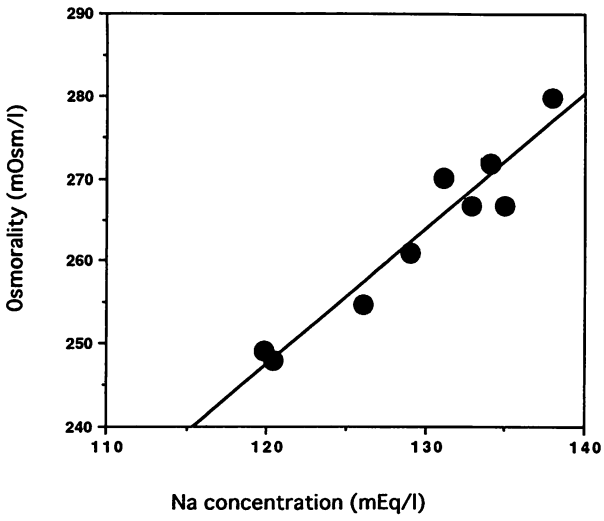

Fig. 6 Relationship between plasma osmolarity and serum sodium concentration
Note that there is a highly significant positive correlation between these 2 parameters ($r^2 = 0.897$, $p < 0.01$).

Table 1 Serial changes in electrolytes, osmolarity and various humoral factors

	1996 May	Oct.	Dec.	1997 Feb.	Apr.	Normal value
Na^+ (mEq/*l*)	128	120	130	119	134	134–145
K^+ (mEq/*l*)	3.9	3.9	3.8	4.2	3.7	3.5–5.0
Cl^- (mEq/*l*)	93	85	92	94	88	98–108
Osmolarity (mOsm/*l*)	267	249	280	245	282	275–290
hANP (pg/*l*)	35.0	32.6	30.0	32.2	23.9	<43
ADH (pg/*l*)	0.7	0.3	1.0	0.8	0.8	0.3–4.2
PRA (pg/*l*)	2.1	4.5	5.4	3.5	5.2	3.6–63.7
Epinephrine (μg/*l*)	0.05	0.10	0.06	0.08	0.06	<0.12
Norepinephrine (μg/*l*)	0.60	0.75	0.59	0.65	0.58	0.10–0.41

ADH = antidiuretic hormone.

Hyponatremia was noted during water intoxication, but other electrolytes remained constant. Plasma osmolarity varied in parallel with serum sodium concentration. **Fig. 6** shows the relationship between the plasma osmolarity and the serum sodium concentration recorded during the 2 successive episodes of intoxication, which indicates a highly significant, positive linear correlation ($r^2 = 0.897$, $p < 0.01$) between these 2 parameters, thereby suggesting that the level of plasma osmolarity is proportional to the sodium concentration. This finding suggests that the plasma osmolarity could not be compensated in our patient with water intoxication.

The level of hANP ranged between 18 and 35 pg/ml, and that of ADH was between 0.3 and 1.0 pg/ml, which was close to the lower margin of the normal range. The range of PRA was also on the lower margin. The plasma concentration of catecholamines showed considerable variation. Plasma epinephrine and norepinephrine concentrations ranged from 0.05 to 0.15 μg/ml and 0.55 to 1.11 μg/ml, respectively. These indicate a trend toward enhanced sympathetic activity in this patient. However, the concentrations of all these humoral factors including the plasma catecholamines did not significantly correlate with the levels of the serum

sodium concentration (not shown), suggesting that the enhanced sympathetic function might have been secondary to the altered psychiatric condition and not to the severity of water intoxication.

DISCUSSION

The present clinical investigation assessed the electrical and mechanical abnormalities of the heart under the conditions of so-called "water intoxication syndrome". Polydipsia to such an extent that body weight increased by more than 5 kg within a day is supposed to be associated with an increase in extracellular fluid volume. This consideration is supported by the dilutional hyponatremia associated with low plasma osmolarity and an increase in the left atrial dimension which was shown by echocardiography. The cardiac performance in such circumstances is thought to be determined by the interaction of complex factors, *e.g.*, changes of electrolytes, osmolarity and blood volume.

The conduction velocity of ventricular electrical propagation can be indirectly evaluated by QRS duration, provided that the QRS configuration and hence the ventricular activation sequence are not altered. Lowering the external sodium concentration results in the slowing of conduction in the heart of animal models. Buchanan *et al.*[7] reported that the conduction slows in proportion to the reduction of external sodium concentration in the ventricular papillary muscle of guinea pigs, and explained this finding by a fall of the rapid sodium inward current, the most important determinant for electrical propagation in the cable theory. Our results are in good agreement with their experimental finding. However, if the serum potassium concentration was altered during the episode of water intoxication, the problem would be more complicated. Although the conduction velocity of the electrical impulse is most likely to be influenced by potassium as well as sodium concentrations in the blood[8], we found no significant change in the serum potassium concentration in the present case; ventricular arrhythmias were also not documented.

Mechanical cardiac performance observed in patients with hyponatremia or in water intoxication is a matter of some interest. Ben-Haim *et al.*[9] conducted experiments using isolated working rat hearts subjected to hyponatremic conditions, with a constant osmolarity of the perfusing solution. In their study, cardiac output was increased when decreasing the sodium concentration from 136 to 96 mEq/*l*. They attributed the positive inotropism seen under low external sodium conditions to the suppression of the forward operation of sodium-calcium exchange mechanism in the sarcolemma. Sodium-calcium exchange is important in regulating intracellular free calcium concentration and hence the cardiac contractility. This exchange normally extrudes the internal calcium by virtue of the transsarcolemmal sodium gradient[10] (forward mode operation). Since the reduction of external sodium decreases the transsarcolemmal gradient of sodium concentration, this maneuver should lead to the accumulation of internal free calcium and increase the contractile tension, provided that the perfusate osmolarity is kept constant[11]. In our patient the plasma osmolarity was altered concomitantly with the serum sodium concentration, so the clinical situation is more complicated. Lado *et al.*[12] investigated cardiac contractility *in vivo* under a variety of changes in osmolarity. Reduction of the osmolarity from 298 to 228 mOsm/*l* caused negative inotropism with presumed myocyte swelling, which suggests that increased cellular volume (*i.e.*, diluted intracellular electrolytes concentration) decreased the intracellular free calcium concentration and thus contraction. In addition, chronic myocardial swelling is reported to produce cellular damage and lead to interstitial fibrosis[13]. Our data showed a parallel change of plasma osmolarity with the serum sodium concentration (**Fig. 6**), indicating that osmolar homeostasis was not attained, if not zero, in this patient. Lowered osmolarity and lowered sodium concentration underlie water intoxication and these 2 physiological factors might have exerted opposing effects on the cardiac contractility. Our data showed that in the setting of water intoxication, reduced osmolarity, rather than hyponatremia, is predominant in regulating cardiac contractility.

Myocardial edema induced by various clinical settings (including low osmolar condition) has attracted increasing attention. This pathological situation is frequently encountered during myocardial infarction[14,15] and the following reperfusion[16] and can be diagnosed by cardiac imaging, especially with the use of nuclear magnetic resonance imaging[17]. In our present study, the presence of myocardial edema was suggested by echocardiographic findings including thickening of the left ventricular wall and the increased A/E, implicat-

ing impaired left ventricular compliance, a finding frequently recognized in myocardial edema[13,18].

In our schizophrenic patient with hyponatremia derived from repetitive and reversible water intoxication, the reduction of ejection fraction (detected by echocardiography) and the trend toward QRS widening (detected by ECG) were associated with a proportional decrease in the serum sodium concentration. Although these changes might have been modified by the concomitant changes in plasma osmolarity and intravascular blood volume, these observations are indicative of the cardiac manifestations in water intoxication syndrome.

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要　約

水中毒症から低ナトリウム血症をきたした精神分裂病患者の心臓における電気的および機械的現象

柳　統仁　丸山　徹　上畠　茂幸

脇元　安　佐々木勇之進　有田　眞

精神科領域においてしばしば遭遇するいわゆる水中毒は，過剰な水摂取による血管内水分量の増加，希釈性低Na血症と低浸透圧血症の3者で特徴付けられる．

我々は今回，ある精神分裂病の男性患者の心電図と心エコー図の観察から，水中毒における心臓の電気的および機械的挙動の経時的な変化を初めて観察した．血漿浸透圧は血清Na濃度に比例した．血清Na濃度の低下に伴って心電図上のQRS幅は延長し，心エコー図上の左室駆出率は低下した．すなわち，血清Na濃度の低下に伴う心室内興奮伝播速度の低下が示唆されたが，これは伝導に関与する速い内向きNa電流の低下で説明された．一方，血清Na濃度の低下はNa−Ca交換機転の抑制を介して細胞内Caの蓄積に伴う陽性変力作用をもたらすことが予想された．これに反して，この症例で陰性変力作用が出現したのは，血漿浸透圧の低下に伴う心筋自体の可逆的変化が，Na−Ca交換機転の抑制により予想される陽性変力作用を凌駕したためと考えられた．

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References

1) Barahal HS: Water intoxication in mental case. Psychiatr Quart 1938; **12**: 767−771
2) Illowsky BP, Kirch DG: Polydipsia and hyponatremia in psychiatric patients. Am J Psychiatry 1988; **145**: 675−683
3) Peh LH, Devan GS, Low BL: A fatal case of water intoxication in a schizophrenic patient. Br J Psychiatry 1990; **156**: 891−894
4) Teichholz LE, Kreulen TH, Herman MV, Gorlin R: Problems in echocardiographic volume determinations: Echocardiographic-angiographic correlations in the presence of absence of asynergy. Am J Cardiol 1976; **37**: 7−11
5) Feigenbaum H: Echocardiography, 4th Ed, Lea and Febiger, Philadelphia, 1986; pp 199−200
6) Bazett HC: An analysis of the time-relations of electrocardiograms. Heart 1920; **7**: 353−370
7) Buchanan JW Jr, Saito T, Gettes LS: The effects of antiarrhythmic drugs, stimulation frequency, and potassium-induced resting membrane potential changes on conduction velocity and dV/dt_{max} in guinea pig myocardium. Circ Res 1985; **56**: 696−703
8) Kagiyama Y, Hill JL, Gettes LS: Interaction of acidosis and increased extracellular potassium on action potential characteristics and conduction in guinea pig ventricular muscle. Circ Res 1982; **51**: 614−623
9) Ben-Haim SA, Edoute Y, Hayam G, Better OS: Sodium modulates inotropic response to hyperosmolarity in isolated working rat heart. Am J Physiol 1992; **263**: H1154−H1160
10) Sheu SS, Fozzard HA: Transmembrane Na^+ and Ca^{2+} electrochemical gradients in cardiac muscle and their relationship to force development. J Gen Physiol 1982; **80**: 326−351
11) Allen DG, Eisner DA, Lab MJ, Orchard CH: The effects of low sodium solutions on intracellular calcium concentration and tension in ferret ventricular muscle. J Physiol (Lond) 1983; **345**: 391−407
12) Lado MG, Sheu SS, Fozzard HA: Effects of tonicity on tension and intracellular sodium and calcium activities in sheep heart. Circ Res 1984; **54**: 576−585
13) Laine GA, Allen SJ: Left ventricular myocardial

edema: Lymph flow, interstitial fibrosis, and cardiac function. Circ Res 1991; **68**: 1713−1721
14) Tranum-Jensen J, Janse MJ, Fiolet JWT, Krieger WJ, D'Alnoncourt CN, Durrer D: Tissue osmolarity, cell swelling, and reperfusion in acute regional myocardial ischemia in the isolated porcine heart. Circ Res 1981; **49**: 364−381
15) Waldenstrom A, Martinussen HJ, Gerdin B, Hallgren R: Accumulation of hyaluronan and tissue edema in experimental myocardial infarction. J Clin Invest 1991; **88**: 1622−1628
16) Garcia-Dorado D, Oliveras J: Myocardial oedema: A preventable cause of reperfusion injury? Cardiovasc Res 1993; **27**: 1555−1563
17) Allen SJ: The pathophysiology of myocardial edema: Principles of myocardial fluid balance. Curr Opin Anaesthesiol 1994; **7**: 12−17
18) Detwiler PW, Nicolosi AC, Weng ZC, Spotnitz HM: Effects of perfusion-induced edema on diastolic stress-strain relation in intact swine papillary muscle. J Thorac Cardiovasc Surg 1994; **108**: 467−476