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ORIGINAL ARTICLE

Relationship between non-osmotic arginine vasopressin secretion and hemoglobin A1c levels in adult patients with congenital heart disease

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Abstract
Arginine vasopressin (AVP), which induces vasoconstriction and conserves solute–free water when released during high plasma osmolality, is secreted through 2 mechanisms: osmoregulation and baroregulation. This study aims to clarify the mechanisms and influencing factors for non-osmotic AVP secretion in adult patients with congenital heart disease (CHD). AVP levels were measured in 74 adults with CHD. Non-osmotic AVP secretion was defined as excessive AVP secretion relative to the AVP level inferred from plasma osmolality. Accordingly, 10 patients (13.5%) demonstrated non-osmotic AVP secretion, with AVP levels higher than those in patients without non-osmotic AVP secretion (6.4 ± 3.1 vs. 1.6 ± 0.9 pg/ml; $p < 0.0001$). Non-osmotic AVP secretion was significantly correlated with diuretic use [odds ratio (OR) 7.227; confidence interval (CI) 1.743–29.962; $p = 0.0006$], HbA1c level (OR 11.812; CI 1.732–80.548; $p = 0.012$), and B-type natriuretic peptide (BNP) level (OR 1.007; CI 1.001–1.012; $p = 0.022$). Multiple logistic regression analysis revealed that there was a significant association between non-osmotic AVP secretion and HbA1c level (OR 9.958; 1.127–87.979; $p = 0.0039$), and a nearly significant relationship between non-osmotic AVP secretion and BNP (OR 1.006; CI 1.000–1.012; $p = 0.056$). In conclusion, this study showed that 13.5% of adult patients with CHD demonstrated non-osmotic AVP secretion, which could be correlated with heart failure and insulin resistance. The AVP system might be one of the mechanisms linking heart failure and the onset of type 2 diabetes mellitus in adults with CHD.

Keywords Arginine vasopressin · Chronic heart failure · Hemoglobin A1c · Neurohormonal activation

Introduction

Arginine vasopressin (AVP) is a vasoactive hormone that induces vasoconstriction and conserves solute–free water when released during high plasma osmolality [1, 2]. Given that plasma levels of AVP are elevated in adults with chronic congestive heart failure [3, 4], the AVP system has been considered as one of the compensatory mechanisms for maintaining systemic perfusion during low output conditions. Although many systems exist to preserve systemic perfusion (sympathetic nerve system, renin–angiotensin–aldosterone system, etc.), knowledge regarding the relationship between the AVP system and hemodynamics during chronic heart failure is limited, especially in adult patients with congenital heart disease (CHD).

Two mechanisms for AVP secretion have been suggested, namely, osmoregulation and baroregulation, the latter being considered as the mechanism through which changes in hemodynamics could influence AVP secretion [1, 2]. The osmotic secretion of AVP can be estimated using plasma osmolality. Therefore, excessive AVP secretion relative to the calculated AVP level using plasma osmolality reflects a hemodynamic influence on AVP secretion.

This study therefore aims to clarify the mechanisms and influencing factors for non-osmotic AVP secretion in adult patients with CHD.

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Materials and methods

The present study enrolled 74 consecutive subjects aged 20 years or above (46 males, mean age 33.0 ± 12.3 years, range 20–70 years) who visited the Department of Adult Congenital Heart Disease, Chiba Cardiovascular Center. Exclusion criteria included a history of cardiac surgery within 6 months and a previous diagnosis of diabetes mellitus. This study was conducted in accordance with the principles of the Declaration of Helsinki. All subjects provided informed consent, and the study protocol was approved by the Ethics Committee of Chiba Cardiovascular Center.

For the assessment of basic CHDs and comorbidities, data regarding CHD diagnosis, surgical history, NYHA class, presence of cyanosis ($SpO_2 < 90\%$), cardiothoracic ratio on chest X-ray, medications, height, and body weight were obtained from medical records.

Peripheral blood was drawn in a fasting state for analysis of plasma osmolality, AVP, B-type natriuretic peptide (BNP), hemoglobin, total protein, albumin, blood urea nitrogen, creatinine, uric acid, sodium, potassium, blood sugar, and HbA1c levels. AVP levels were measured using radioimmunoassay.

Estimated AVP levels according to plasma osmolality were calculated using the following formula [5]:

$$\text{Estimated AVP} = 0.43 \times (\text{plasma osmolality} - 284).$$

In this study, non-osmotic secretion of AVP was defined as excessive AVP secretion relative to the estimated AVP level calculated from plasma osmolality. Various parameters were compared between patients with and without non-osmotic AVP secretion.

Quantitative variables are presented as mean ± standard deviation. Several clinical variables were compared between patients with and without non-osmotic AVP secretion to identify association with non-osmotic AVP secretion. To compare patients' characteristics, the Mann–Whitney test and Chi-square analysis were used for quantitative and qualitative valuables, respectively. Logistic regression analysis was performed to assess the association with non-osmotic AVP secretion using various clinical variables. Variables with p value <0.05 during univariate analysis for non-osmotic AVP secretion were then included in the multivariate analysis. All statistical analyzes were performed using SPSS16.0J for Macintosh software program (SPSS Inc., Chicago, IL, USA).

Table 1 Diagnosis of the patients

Tetralogy of Fallot	23
Ventricular septal defect	8
Transposition of the great arteries	7
Single right ventricle	5
Coarctation of aorta/interruption of the aortic arch	5
Tricuspid valve atresia	4
Congenitally corrected transposition of the great arteries	4
Ebstein anomaly	4
Atrioventricular septal defect	3
Atrial septal defect	3
Others	8

Results

Table 1 shows the patients' diagnosis of CHD, while Table 2 presents the demographic and laboratory data. The NYHA class was distributed as follows: I, 46; II, 21; III, 7; and IV, 0. A total of 17 patients suffered from cyanosis. BNP level, plasma AVP level, and plasma osmolality were 81.4 ± 174 pg/ml, 2.3 ± 2.1 pg/ml, and 291.9 ± 3.6 mOsm/l, respectively. Diuretic drug was medicated to 17 patients and all prescribed diuretics were loop diuretics.

Non-osmotic AVP secretion was observed in 10 patients (13.5%), and the mean AVP level was significantly higher in the patients with non-osmotic AVP secretion than that in the patients without non-osmotic AVP secretion (6.4 ± 3.1 vs. 1.6 ± 0.9 pg/ml; $p < 0.0001$). Moreover, patients with non-osmotic AVP secretion had lower plasma osmolality than those without the condition, although the results were not statistically significant (289.4 ± 4.7 vs. 292.3 ± 3.3 mOsm/l; ns). The basic CHD in patients with non-osmotic AVP secretion included tetralogy of Fallot (4), single right ventricle (2), aortic coarctation (1), congenitally corrected transposition of the great arteries (1), Ebstein anomaly (1), and aortic regurgitation (1). Patients with non-osmotic AVP secretion had higher diuretic use (6/10 vs. 10/64; $p = 0.0077$) and HbA1c levels (5.4 ± 0.5 vs. 5.1 ± 0.3%; $p = 0.0237$) than those without the condition. No differences in sodium, potassium, blood sugar, and blood urea nitrogen level were found between both groups.

Table 3 shows the results of the univariate analysis for factors associated with non-osmotic AVP secretion. Diuretic use [odds ratio (OR) 7.227; confidence interval (CI) 1.743–29.962; $p = 0.0006$], HbA1c level (OR 11.812; CI 1.732–80.548; $p = 0.012$), and BNP level (OR 1.007; CI 1.001–1.012; $p = 0.022$) were found to have p values < 0.05. Multiple logistic regression analysis (Table 4) revealed that there was a significant association between

Table 2 Patients' characteristics

	Total	Non-osmotic AVP secretion (+)	Non-osmotic AVP secretion (−)	*p* value
n	74	10	64	
Male	46 (62%)	7 (70%)	39 (61%)	0.733
Age (years)	33.0 ± 12.3	35.6 ± 14.8	32.6 ± 11.9	0.6985
Height (cm)	163.0 ± 9.9	161.6 ± 8.9	163.3 ± 10.1	0.5638
Weight (kg)	59.1 ± 12.8	57.9 ± 14.5	59.3 ± 12.6	0.6184
BMI	22.2 ± 4.4	22.0 ± 4.5	22.2 ± 4.4	0.7881
CTR (%)	52.8 ± 7.1	54.9 ± 9.8	52.5 ± 6.7	0.7141
NYHA	1.5 ± 0.7	1.6 ± 0.5	1.5 ± 0.7	0.3334
SBP (mmHg)	110.9 ± 12.3	105.2 ± 14.3	111.8 ± 11.8	0.0766
Cyanosis	17 (23%)	4 (40%)	13 (21%)	0.224
Fontan	14 (19%)	2 (20%)	12 (19%)	0.9546
ACEI/ARB	23 (6%)	3 (30%)	20 (31%)	1
Diuretics	16 (22%)	6 (60%)	10 (16%)	0.0077
AVP (pg/ml)	2.3 ± 2.1	6.4 ± 3.1	1.6 ± 0.9	< 0.0001
Osmolality (mOsm/kg)	291.9 ± 3.6	289.4 ± 4.7	292.3 ± 3.3	0.0985
Serum sodium (mEq/l)	140.7 ± 1.9	139.6 ± 2.6	140.9 ± 1.8	0.1453
Serum potassium (mEq/l)	4.3 ± 0.4	4.4 ± 0.5	4.3 ± 0.4	0.788
Blood sugar (mg/dl)	98.5 ± 18.9	99.0 ± 15.5	98.4 ± 19.4	0.7942
HbA1c (%)	5.1 ± 0.4	5.4 ± 0.5	5.1 ± 0.3	0.0237
BUN (mg/dl)	14.1 ± 4.7	13.2 ± 3.6	14.3 ± 4.9	0.5637
Serum creatinine (mg/dl)	0.75 ± 0.15	0.79 ± 0.16	0.75 ± 0.15	0.2823
Uric acid (mg/dl)	6.2 ± 1.8	7.1 ± 3.1	6.0 ± 1.5	0.327
Total protein (g/dl)	7.3 ± 0.5	7.2 ± 0.4	7.3 ± 0.5	0.4292
Serum albumin (g/dl)	4.6 ± 0.6	4.5 ± 0.4	4.6 ± 0.6	0.1973
Hemoglobin (g/dl)	15.8 ± 2.5	15.2 ± 2.4	15.9 ± 2.5	0.2859
BNP (pg/ml)	81.4 ± 173.9	282.8 ± 413.6	50.0 ± 56.3	0.1232

Data are expressed as mean ± SD, or number

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *AVP* arginine vasopressin, *BMI* body mass index, *BNP* B-type natriuretic peptide, *BUN*, blood urea nitrogen, *CTR* cardiothoracic ratio, *HbA1c* hemoglobin A1c, *SBP* systolic blood pressure

non-osmotic AVP secretion and HbA1c level (OR 9.958; 1.127–87.979; $p = 0.0039$), and a nearly significant relationship between non-osmotic AVP secretion and BNP (OR 1.006; CI 1.000–1.012; $p = 0.056$). Figure 1 shows the relationship between non-osmotic AVP secretion and HbA1c level. It demonstrates a weak correlation, although it is not significant ($r = 0.2447$, $p = 0.4956$).

Discussion

The current study demonstrated that 13.5% of adult patients with CHD showed AVP levels that were excessive with respect to plasma osmolality. Moreover, HbA1c and BNP levels were determined to be a significant and nearly significant associated factor of non-osmotic AVP secretion, respectively.

Recently, neurohormonal activation in patients with chronic heart failure has been receiving increased attention in the management of heart failure [6, 7]. Several systems have been found to sustain systemic perfusion with a failing heart, e.g., the sympathetic nervous system, and the renin–angiotensin–aldosterone system, among others. Although such compensatory mechanisms are useful in maintaining systemic perfusion, the AVP system being one of them, prolonged compensatory systems activation is disadvantageous for individuals. Although high AVP levels have been associated with chronic heart failure [3, 4], little is known regarding the adverse outcomes of a prolonged increase of AVP levels.

AVP secretion is regulated by 2 mechanisms: osmoregulation and baroregulation [1, 2]. In this study, non-osmotic AVP secretion was defined as excessive AVP secretion relative to that determined using plasma osmolality. Therefore, we intended to select patients whose hemodynamics promoted AVP secretion. The fact that a high BNP level was a nearly significant associated factor of non-osmotic AVP secretion in this study suggests that AVP secretion takes

Table 3 Univariate analysis of the factors associated with the non-osmotic AVP secretion

	Odds ratio	95% CI	*p* value
Male	1.496	(0.353–6.330)	0.584
Age (years)	1.018	(0.969–1.070)	0.477
Height (cm)	0.982	(0.916–1.053)	0.618
Weight (kg)	0.991	(0.940–1.045)	0.74
BMI	0.991	(0.849–1.156)	0.906
CTR (%)	1.007	(0.956–1.148)	0.321
NYHA	1.366	(0.532–3.504)	0.517
SBP (mmHg)	0.953	(0.897–1.012)	0.118
Cyanosis	2.615	(0.642–10.649)	0.18
Fontan	1.083	(0.204–5.765)	0.925
ACEI/ARB	0.943	(0.221–4.028)	0.937
Diuretics	7.227	(1.743–29.962)	0.0006
Serum sodium (mEq/l)	0.734	(0.528–1.020)	0.066
Serum potassium (mEq/l)	1.208	(0.234–6.230)	0.822
Blood Sugar (g/dl)	1.002	(0.968–1.037)	0.926
HbA1c (%)	11.812	(1.732–80.548)	0.012
BUN (mg/dl)	0.945	(0.796–1.121)	0.513
Serum creatinine (mg/dl)	6.67	(0.079–561.054)	0.401
Uric acid (mg/dl)	1.349	(0.940–1.937)	0.105
Total protein (g/dl)	0.676	(0.168–2.728)	0.583
Serum albumin (g/dl)	0.682	(0.243–1.911)	0.682
Hemoglobin (g/dl)	0.886	(0.674–1.166)	0.388
BNP (pg/ml)	1.007	(1.001–1.012)	0.022

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *AVP* arginine vasopressin, *BMI* body mass index, *BNP* B-type natriuretic peptide, *BUN* blood urea nitrogen, *CTR* cardiothoracic ratio, *HbA1c* hemoglobin A1c, *SBP* systolic blood pressure

Table 4 Multivariate analysis of the factors associated with the non-osmotic AVP secretion

	Odds ratio	95% CI	*p* value
HbA1c (%)	9.958	(1.127–87.979)	0.0039
BNP (pg/ml)	1.006	(1.000–1.012)	0.056

AVP arginine vasopressin, *BNP* B-type natriuretic peptide, *HbA1c* hemoglobin A1c

part in the maintenance of systemic perfusion among adult patients with CHD.

Although no difference in the fasting plasma glucose level was observed, the HbA1c level had a significant association with non-osmotic AVP secretion. Considering the half-life of erythrocytes, the percentage of hemoglobin represented by HbA1c provides an index of the average plasma glucose concentration during the previous 2–3 months [8]. In adults without diabetes, the glycated hemoglobin level is similarly associated with a risk for diabetes and more strongly

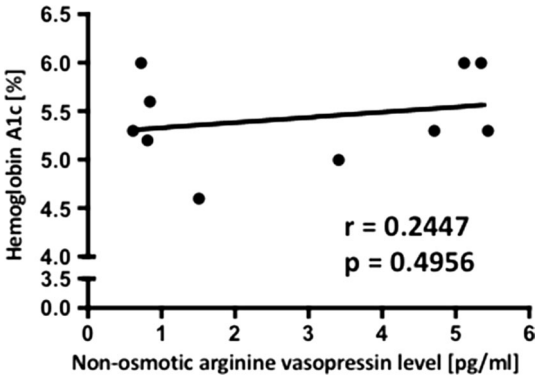

Fig. 1 The relationship between non-osmotic arginine vasopressin secretion and HbA1c level

associated with risks for cardiovascular disease and death from any cause compared to the fasting glucose level [9].

In recent years, the relationship between high AVP levels and diabetes mellitus has gained attention [10–15]. Accordingly, the association between high AVP levels and the risk for diabetes was partly mediated by insulin resistance. AVP activates the hypothalamic–pituitary–adrenal axis during chronic stress, which may be one of the mediators of its association with insulin resistance [10]. Moreover, AVP activates V1b receptors in the α-cells of the pancreatic islets to increase the secretion of glucagon and potentiate insulin release from the β-cells of the pancreatic islets [11]. These mechanisms explain how AVP can induce insulin resistance and exhaustion of the β-cells, and lead to diabetes mellitus. Therefore, chronic heart failure, which may induce non-osmotic AVP secretion, may elevate HbA1c levels via the AVP system.

Several studies have reported insulin resistance in patients with congestive heart failure [16–18]. Although one possible mechanism connecting insulin resistance and congestive heart failure could be the sympathetic nervous system [16], this correlation was not confirmed in a large study [17]. Nonetheless, the present study suggests the possible relationship between insulin resistance and AVP secretion during chronic heart failure.

One study has shown that CHD survivors had increased risk for developing type 2 diabetes mellitus after age 30 years [19], while others have reported insulin resistance in patients with CHD [20, 21]. In our previous study, we also reported that HbA1c levels were higher in adult patients with Fontan circulation and cyanosis [22]. Although the reason for the increased risk of type 2 diabetes mellitus in patients with CHD had not been fully elucidated in Madsen's report [19], the current study suggests that non-osmotic AVP secretion due to chronic heart failure can be one of the mechanisms for the onset of diabetes.

Owing to success in pediatric cardiology and pediatric cardiac surgery, most patients with CHD, even complex ones, can be expected to reach adulthood in developed countries [23, 24]. Apart from CHD, acquired general medical comorbidities, similar to those observed seen in the adult population, can also increase mortality [25]. Needless to say, diabetes mellitus is one of the most important risk factors for acquired cardiovascular diseases [26]. Given that increased HbA1c levels suggest higher risks for diabetes and cardiovascular diseases in adults without diabetes [9], non-osmotic AVP secretion possibly due to chronic heart failure in adult patients with CHD should be taken seriously. Recently, the concept of early vascular aging has been attracting a lot of attention [27, 28]. Considering that adult patients with CHD can be candidates for early vascular aging, acquired cardiovascular diseases in both adult and younger patients with CHD should be given proper attention.

We acknowledge some limitations of the present study, which include its small, single-center nature. In estimating the level of osmotic AVP secretion, we calculated it from plasma osmolality using the reported formula [5]. However, there are individual differences in both the osmotic threshold and slope of AVP osmotically stimulated secretion. These individual differences can have an influence on our data. Given that hemodynamics varied among patients with CHD, it was difficult to evaluate the hemodynamic load using BNP alone. Moreover, hemodynamics changed significantly with age, such as closure of the defect, in most of the patients. Lastly, this study did not include sequential data.

The present study has shown that non-osmotic AVP secretion, defined as AVP level higher than that calculated using plasma osmolality, was correlated with elevated HbA1c levels in adult patients with CHD. Moreover, a high BNP level had a nearly significant association with excessive AVP secretion. Therefore, the AVP system could be one of the mechanisms linking heart failure and type 2 diabetes mellitus in adult patients with CHD.

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Compliance with ethical standards

Conflict of interest The authors report no relationships that could be construed as a conflict of interest.

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