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Original Article

RBC volume deficiency in patients with excessive orthostatic decrease in cerebral blood flow velocity

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Abstract

Background: Orthostatic intolerance (OI) is common but heterogeneous. There is a subgroup of OI patients who have excessive decrease in cerebral blood flow velocity (CBFV) of bilateral middle cerebral arteries (MCAs) during head-up tilt without systemic blood pressure change. This study evaluated the role of blood volume reduction in such patients.

Methods: Patients with idiopathic OI who had excessive orthostatic decrease (>20% of the supine level) in mean CBFV of bilateral MCAs and who also received blood volume determination were collected. The chromium (^{51}Cr) dilution method was used for red blood cell (RBC) volume determination in these patients. The blood volume was expressed as a percentage of the expected volume. These patients were further divided into two groups, those with postural tachycardia syndrome (POTS group) and those without (non-POTS group). The data of RBC volume were compared between the two groups. Besides, we used multivariate linear regression to evaluate the factors that predict RBC volume.

Results: Twenty-five patients (13 females, median age = 28 years) were enrolled in this study. Nine of these patients had POTS (5 females, median age = 26 years) and 16 did not (8 females, median age = 29.5 years). Compared with the expected volume, the RBC volume was significantly reduced in all patients (median = 82% of the expected volume). Moreover, the RBC volume was significantly lower in the POTS group than that in the non-POTS group (78% vs. 85% of the expected volume, $p = 0.013$). The orthostatic decrease of MCA flow velocity was 28.3% in the POTS group and 32.5% in the non-POTS group ($p = 0.140$). The orthostatic pulsatility index increment was 15.4% in the POTS group and 20.5% in the non-POTS group ($p = 0.438$). Moreover, basic demography and hemoglobin levels were not different between the two groups. After multivariate linear regression (dependent variables including age, sex, body surface, and groups), only the presence of POTS significantly predicted the RBC volume ($p = 0.006$).

Conclusion: The results of our study indicated that low RBC volume may play an important role in the pathophysiology of OI in this group of patients. Moreover, its role seems even more relevant in patients with POTS than in those without. Further studies for mechanistic evaluation are needed in the future.

Keywords: blood volume determination; orthostatic intolerance (OI); postural tachycardia syndrome (POTS); transcranial Doppler (TCD)

1. Introduction

Orthostatic intolerance (OI) is a group of heterogeneous disorders. Associated symptoms include dizziness, exercise intolerance, impaired concentration, and recurrent syncope, most of which are reversible on lying supine. The aforementioned symptoms may also be present in patients with postural hypotension, postural tachycardia syndrome (POTS), cerebral

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syncope, and primary cerebrovascular dysautoregulation syndrome.[1,2] Also, similar symptoms are often demonstrable in chronic fatigue syndrome.[3] Individuals affected by idiopathic OI are usually young (15–45 years old), with female predominance (male/female = 1:5), and the symptoms are suggested to be related to diffuse cerebral hypoperfusion during upright posture.[1]

On transcranial Doppler (TCD) studies, a subgroup of OI patients were found to have significant decrement in mean middle cerebral artery flow velocity (MCAFV) during head-up tilt (HUT) without concomitant drop in systemic arterial blood pressure.[4] The orthostatic decrease of MCAFV was reported to be as high as 30% from baseline in a case series.[5] However, an international consensus for diagnosing this group of patients is still not available. Draffertshofer et al defined primary cerebrovascular dysautoregulation syndrome as an excessive decrease in TCD-derived MCAFV of more than 20% compared with the supine level during orthostasis without orthostatic hypotension, which is also adopted by our laboratory as the cut-off value.[6] The mechanisms of excessive orthostatic decrease in MCAFV still remain controversial. In this study, we attempted to decipher the role of blood volume in this group of OI patients with or without POTS. We hypothesized that orthostatic tachycardia may be associated with a more extensive decrement of red blood cell (RBC) volume in POTS patients than in those without POTS among patients with excessive orthostatic CBFV decrease.

2. Methods

2.1. Study population

We retrospectively reviewed all patients with chronic orthostatic intolerance (>6 months) in our cerebral hemodynamic laboratory who also received blood volume determination from August 2001 to October 2011. Only those with excessive decrement in the mean MCAFV (more than 20% in the first 5 minutes) during a 70° HUT and of age less than 50 years were included in this study. The exclusion criteria included orthostatic hypotension [systolic or diastolic blood pressure (BP) drop ≥20 mmHg and 10 mmHg during the first 5 minutes of HUT, respectively], carotid stenosis greater than 30%, anemia (<130 g/L for males and <120 g/L for females), use of α and/or β adrenergic blockers, neurally mediated syncope (vasovagal syncope), chronic heart failure, cardiac arrhythmia, valvular or ischemic heart disease, epilepsy, history of vertebrobasilar insufficiency, stroke, electrolyte imbalance, hyperventilation syndrome or panic disorders, and other diseases that may adversely affect the autonomic nervous systems, including chronic kidney disease (expected glomerular filtration rate < 60 mL/minute), diabetes mellitus, peripheral neuropathy, familial pandysautonomia, multiple system atrophy, and amyloidosis. A total of 47 patients were reviewed, and 25 patients met all the inclusion and exclusion criteria. All of these participants had received complete physical and neurological examinations, dizziness and autonomic questionnaire, complete blood count, and serum biochemistry tests based on the protocol of our laboratory. All of these patients also underwent brain magnetic resonance angiogram and electroencephalogram.

This case review study was approved by the internal review board of Taipei Veterans General Hospital (201208011BC).

2.2. TCD monitoring during HUT

HUT examination required that each participant lie on a motorized tilt table with foot board support. Real time beat-to-beat arterial blood pressure and heart rate were recorded noninvasively by an infrared finger plethysmography (Portapres-Model 2; FMS, Amsterdam, The Netherlands) fixed to the middle finger of the left hand.

A transcranial Doppler ultrasonographic monitor (Multi-Dop X/TCD7; DWL, Sipplingen, Germany) was used to detect MCAFV bilaterally. The transducer was fixed in place and the flow continuously monitored at the point of optimum signal. Each participant remained in the supine position for 10 minutes prior to tilting head-up to 70° for 30 minutes or until syncopal symptoms developed. The mean MCAFV decrease within the first 5 minutes after tilting from supine to upright was presented as percentage. The pulsatility index (PI) was measured and calculated by the equation:

PI = (systolic velocity − diastolic velocity)/mean velocity.

PI level was measured in supine and upright positions, respectively. The orthostatic PI change was presented as a ratio of upright/supine.

2.3. RBC volume determination

RBCs are labeled with ^{51}Cr (Sodium Chromate-^{51}Cr Injection, Fujifilm, Tokyo, Japan). The procedure was as follows: (1) approximately 25 mL of blood was obtained via vein puncture and labeled with 100 μCi (3.7 MBq) of $Na_2^{51}CrO_4$ for 30 minutes; (2) 20 mL of the tagged blood was reinjected into each patient's circulation; (3) 20 mL of blood sample was drawn for determination of radioactivity, from the opposite arm at 30 minutes post-injection; (4) radioactive assays were carried out on samples in the liquid state, with a conventional well-type scintillation counter.

The blood volume determination was based on a dilution technique: volume = (quantity injected)/(concentration of diluted tracer). The method for determining the RBC volume has been described in previous communications and was widely adopted with minor modifications.[7,8] The expected RBC volume was calculated according to previous literature as 1.1 × body surface area in males and 0.84 × body surface area in females.[9] The individual data for every participant were expressed as a percentage of each expected volume, respectively. The group data were expressed as the median (interquartile range).

2.4. Statistical analysis

The Wilcoxon rank sum test was used for group comparisons of all parameters except Fisher's exact test for sex ratio.

For multivariate linear regression, age, body surface area, and group were set as independent variables. The RBC volume was set as the dependent variable. Data were analyzed using the SPSS software package (version 17; SPSS, Inc., Chicago, IL, USA). Statistical significance was set at $p < 0.05$.

3. Results

The demographic data, hemoglobin, hematocrit, orthostatic PI change, and MCAFV decrease during HUT are demonstrated in Table 1. Tilt table TCD monitoring showed mild PI increase and significant mean MCAFV decrease in bilateral MCA during HUT in all patients. The RBC volume was significantly reduced compared with the expected value (82% of the expected volume). We further analyzed the data between non-POTS and POTS groups. The decreased RBC volume was significantly more severe in the POTS group (78% of the expected volume) than that in the non-POTS group (85% of the expected volume; $p = 0.013$; Fig. 1). The age of the non-POTS group was slightly but not significantly older than that of the POTS group. Meanwhile, the hemoglobin, hematocrit, orthostatic PI change, and MCAFV drop between the two groups were not significantly different. In multivariate linear regression, patients with POTS significantly predicted a smaller RBC volumes ($p = 0.006$). Age, sex, and body surface area were not significant predictors of RBC volume (Table 2).

4. Discussion

In this study, we observed a significant reduction of RBC volume in a group of OI patients with excessive orthostatic decrement in MCAFV without concomitant systemic BP change. We further demonstrated among these patients that after controlling for age, sex, and body surface area, those with POTS suffered from a more severe decrease in RBC volume than did those without.

Table 1
Basic characteristics and orthostatic TCD data.

	All ($n = 25$)	Non-POTS ($n = 16$)	POTS ($n = 9$)	p
Age (y)	28 (20–34)	29.5 (21.5–43.5)	26 (17.5–34.5)	0.240
Surface area (m^2)	1.61 (1.53–1.74)	1.61 (1.54–1.74)	1.59 (1.53–1.65)	0.350
Sex (M/F)	12:13	8:8	4:5	0.677
Hgb (g/L)	141 (131–149)	141 (134–148)	138 (128–156)	0.377
Hct	40.9 (38.9–43.8)	41.3 (39.4–43.4)	40.2 (37.7–44.7)	0.497
PI increment	18.1 (2.3–29.2)	20.5 (6.1–30.3)	15.4 (9.4–28.5)	0.438
MCAFV drop	32.0 (27.5–35.5)	32.5 (30.6–35.8)	28.3 (26.2–33.2)	0.140

Data are presented as % unless otherwise indicated.
Hct = hematocrit; Hgb = hemoglobin; MCAFV = middle cerebral artery flow velocity; PI = pulsatility index; POTS = postural orthostatic tachycardia syndrome.

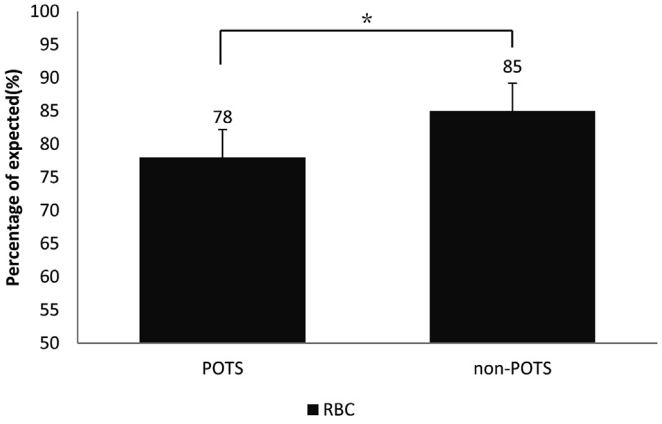

Fig. 1. RBC volume is decreased in all patients. The RBC deficiency is significantly more severe in POTS than in non-POTS. * $p = 0.013$.
POTS = postural orthostatic tachycardia syndrome; RBC = red blood cell.

OI patients can be very disabled by many nonspecific symptoms, including fatigue, palpitation, and shortness of breath upon standing upright.[10,11] POTS may be one of the most common conditions of it. There is heterogeneity in POTS, which includes partial dysautonomia and hyperadrenergic state as two of the major forms.[12] In the former form, symptoms derive from compensatory increase of heart rate and myocardial contractility during upright induced blood pooling. In the latter form, elevated norepinephrine level on standing results in orthostatic tachycardia. In these patients, excessive decrease in MCAFV during HUT was frequently found.[2,13] However, the mechanisms of abnormal orthostatic MCAFV change have not yet been fully clarified. The postulated hypotheses include cerebral vasoconstriction[14] with sympathetic supersensitivity, hypocapnea-associated vasoconstriction,[15,16] impaired cerebral autoregulation,[4,17] excessive venous pooling, decreased stroke volume related to tachycardia, and decreased blood volume. Cerebral vasoconstriction with an increase in PI during HUT is also shown in our study.

Orthostasis results in gravitational blood pooling with approximately 600 mL in the lower limbs and sympathetic activation in both OI patients and normal individuals.[18] However, compensation for these dynamic changes occurs much more rapidly in healthy individuals. The plasma volume shift from vascular space to interstitial space is also greatly enhanced in orthostasis of patients with OI.[19] Several studies showed that relative excessive cardiac sympathetic

Table 2
Multivariate linear regression of RBC volumes.

	β	t	Standard error	p
Constant		1.311	0.484	0.205
Age	−0.368	−1.718	0.002	0.101
Sex	0.075	0.247	0.053	0.807
Surface area	0.227	0.707	0.268	0.487
Group (POTS)	−0.580	−3.065	0.034	0.006*

*$p < 0.05$, $R^2 = 0.362$.

activities may explain symptoms such as dyspnea, chest tightness, and tachycardia.[20,21] With a similar mechanism, sympathetic activity-related vasoconstriction may contribute to the excessive cerebral blood flow decrease in the upright posture.[16,22]

In addition to the fluid shift during orthostasis, baseline hypovolemia, especially reduced effective RBC volume, was also reported in orthostatic intolerance. Fouad et al[23] reported that significantly decreased blood volume is common in patients with OI. Streeten et al[3] found that RBC volume was significantly decreased in patients with chronic fatigue syndrome. Raj and Robertson[24] indicated that significantly decreased RBC and plasma volume were also demonstrated in POTS patients compared with the control group. Low levels of plasma renin activity and erythropeitin (EPO) have been hypothesized to play a role in such deficiency.[25] The relatively reduced RBC mass and possible subsequent reduced oxygenation in our patients may further exacerbate orthostatic symptoms during HUT-related sympathetic activation.

Disordered autonomic regulation with normal serum renin and low serum aldosterone levels have been reported in patients with POTS.[26] Differences in severity of decrement in effective RBC volume may also account for differences in orthostatic heart rate between OI patients with POTS and without POTS. This is because a greater reduction in effective RBC volume may contribute to a greater increase in orthostatic heart rate.[26] Therefore, in addition to disordered autonomic regulation, those patients with POTS who have lower effective RBC volume and are less effective in blood volume compensation than those without POTS may respond to orthostatic stress with a greater increase in orthostatic heart rate. There is evidence that perturbation of the renin–angiotensin–aldosterone axis might result from impaired sympathetic innervation of kidneys in POTS, which resulted in hypovolemia being more severe in these patients.[27] Therefore, regardless of documented autonomic dysfunction in orthostatic tachycardia, effective RBC volume deficiency may still play an important role in the underlying pathophysiology. During the past decades, fluid management has been used to treat orthostatic symptoms in POTS patients, with divergent results.[28–30] Erythropeitin was also applied to treat POTS patients, producing some benefits.[31,32] However, data regarding the patients' RBC mass were not considered in these studies. A trial to treat specific OI patients based on RBC volume may provide more precise guidance for clinical management.

To the best of our knowledge, this is the first study focusing on RBC volume to discriminate the specific subgroups of patients with idiopathic OI. Additionally, the Asian data on POTS have been very limited to date. However, this study has some limitations. First, the sample size is rather small because not all of the idiopathic OI patients received the blood volume determination in our laboratory. In addition, this study did not include the autonomic function of these patients, which is often abnormal in patients with idiopathic OI. Because there was a discrepancy in orthostatic heart rate change between the two groups, a more thorough autonomic evaluation may clarify this issue. Lastly, due to ethical concerns, we did not recruit a normal control group for the blood volume determination study. Future prospective research enrolling more patients with improved matching with regard to gender is needed to clarify the role of blood volume in these two groups of patients. In conclusion, excessive decrement in MCAFV during HUT without systemic arterial BP change is an important feature among a subgroup of idiopathic OI patients. In these patients, decreased RBC volume is frequently found. The results of our study suggest that low RBC volume may play an important role in its pathophysiology. Also, those with POTS may suffer more severe deficiency of RBC volume than those without. The pathophysiological mechanisms of RBC volume deficiency deserve further elucidation.

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