Circulating Blood Volume in Chronic Fatigue Syndrome

David H.P. Streeten, MB, DPhil, FRCP, FACP
David S. Bell, MD, FAAP

Journal of Chronic Fatigue Syndrome, Vol. 4 (1), 1998, 3-11

ABSTRACT

Chronic Fatigue Syndrome (CFS) is an illness associated with severe activity limitation and a characteristic pattern of symptoms despite a relatively normal physical examination and routine laboratory evaluation. The recent description of delayed orthostatic hypotension in patients with CFS, and previous findings of reduced red blood cell (RBC) mass in other patients with orthostatic hypotension not known to have CFS, led us to measure RBC mass and plasma volume in 19 individuals (15 female, four male) with well characterized, severe CFS. RBC mass was found to be significantly reduced (p less than 0.001) below the published normal range in the women, being subnormal in 15 (93,8%) of them as well as in two of the four men. Plasma volume was subnormal in 10 (52,6%) patients and total blood volume was below normal in 12 (63,2%). The high prevalence and frequent severity of the low RBC mass suggest that this abnormality might contribute to the symptoms of CFS by reducing the oxygen-carrying power of the blood reaching the brain in many of these patients.

INTRODUCTION

Chronic Fatigue Syndrome (CFS) is an illness of unknown etiology, characterized by profound exhaustion, orthostatic intolerance, and numerous somatic complaints. The illness is characterized by a severe activity restriction despite normal or relatively minor abnormalities on physical examination and routine laboratory studies. CFS occurs in both children and adults (1-5), may be sudden or gradual in onset (6,7), and follows a variety of initiating insults (2,8,9).

Recent observations have linked CFS with neurally mediated hypotension (10,11) and delayed orthostatic intolerance (12). Previous studies of the pathogenesis of both hyperadrenergic and hypoadrenergic orthostatic hypotension have shown that, in addition to the almost invariable finding of excessive orthostatic blood pooling in the lower limbs (13,14) attributable to subnormal venous constriction of the legs (15), reduction of red blood cell (RBC) mass is frequently present (13,16). For this reason we have explored the prevalence of abnormalities in the total circulating volumes of RBC´s, plasma, and whole blood in a series of nineteen patiens with well documented CFS.

METHODS

The 19 patients included in this paper are drawn from the clinical practice of one of the investigators (DSB) and most had been followed clinically for many years. Nine patients underwent autonomic nervous system testing in Syracuse, the results which will be reported separately. Subjects were selected sequentially if they met the 1994 Center for Disease Control (CDC) diagnostic criteria for CFS (17), met the severity criteria of less than five hours of upright activity daily, and wished to participate in the study.

Severity instruments used at the time of the blood volume studies included (1) sum of the visual analog scores for 12 prominent symptoms seen in CFS (7);(2) a modified Karnofsky score (7);(3), estimation of total activity (7);(4) and the Fisk Fatigue Impact Scale score (18). These four rating scales had been taken on numerous occasions on the majority of the patients reported in the present paper and have been remarkably consistent over a period of years despite a variety of therapeutic trials in which the patients participated (data not shown). While many of the patients in this study have experienced episodes of depression in the past, none was considered to have emotional factors as the cause of his or her illness. None of the patients in this study were taking mineralocortocoids, diuretics, or other medications known to influence circulating blood volume at the time of the study. One patient had type II diabetes mellitus with blood sugar in the normal range with oral hypoglycemic medication. The demographics and severity ratings of the patient population are presented in Table 1.

RBC mass and plasma volume were determined with standard methods, using 51Cr-labeled autologous red blood cells (19) and I25I-labeled human serum albumin (19), respectively, in five university affiliated radiology departments. Normative data was taken from published studies (20), and no healthy controls were evaluated at the time of this study.

Blood pressure measurements (Table 2) were the average of pressures taken during office visits, in the course of routine follow up of their illness. The peripheral hematocrit (Table 2) was the average of peripheral hematocrits recorded in the patient´s chart during the illness. There was no unusual variation between the average hematocrit and the hematocrit taken nearest to the blood volume studies (data not shown). Whole body hematocrit was calculated from the circulating blood volume data (RBC mass/total blood volume).

Table 1 (Demographic Data)
Table 2 (Blood Volume Determination)

RESULTS

Table 1 shows that the patients included 15 women and 4 men, aged 14-50 years, whose ability to perform normal upright activity had been reduced to between one and four hours a day, estimated at 20% to 30% of their previous capacity. The sum of visual analog scores and Fisk Fatigue Impact Scale scores indicate the degree of their incapacitation.

RBC Mass, Plasma Volume and Whole Blood Volume Measurements

The data in table 2 show that RBC mass was below the normal range (25-30 mL/Kg) in 14 of 15 female patients and in 2 of 4 males. In the 15 female patients, the RBC mass (Mean 18.8, SD 3.1 mL/Kg) was significantly lower than the 20 normal female subjects reported by Huff and Feller (20), viz. 24.4 / 2.6 mL/Kg (p less than 0.001), as displayed in Table 3. The small number (4) of male patients precluded determination of statistical significance of the differences between their data and those of normal subjects reported by Huff and Feller.

Plasma volume was quite variable in our patients, being below the normal range in 10, normal in 4 and elevated in 2 of the 15 female subjects (Table 2). The mean plasma volume in these 15 individuals (38.7 / 19.5 mL/Kg) was not significantly different from the mean of normal female subjects, 34.8 / 3.2 mL/Kg (18).

Similarly, the total blood volume in our 15 female subjects (Mean 57.49, SD 20.47) was not significantly different from the values found in the same 20 normal females (58.9 / 4.9 mL/Kg).

It is evident from Table 2 that the peripheral hematocrit was below 37% in only 4 of our patients. In fact, mean peripheral hematocrit was significantly higher (p more than 0.01) than whole body hematocrit in our patient group. Blood pressures, measured in the sitting position, were normal (95-140/60-90) in all but one subject whose blood pressure was 150/87.

Table 3. Mean (SD) Blood volume results in female patients.

	Patients	Normal Controls	p Value
	n=15	n=20	-
RBC mass (mL/Kg)	18.8 / 3.1	24.4 / 2.6	less than 0.001
Plasma volume (mL/Kg)	38.8 / 19.5	34.8 / 3.2	N.S.
Total blood volume	57.5 / 20.5	59.2 / 4.9	N.S.
Total blood volume	57.5 / 20.5	59.2 / 4.9	N.S.

DISCUSSION

The characteristic elements which compromise the chronic fatigue syndrome (CFS) are asthenia, fatigue, orthostatic intolerance, and numerous somatic complaints. The lack of detectable tissue damage in routine laboratory testing has led to assumptions that CFS may by either a trivial illness, a psychosomatic disorder, or a variant of depression. Blood volume measurements have traditionally been used in the management of polycythemia but not in te evaluation of CFS until recently (12).

Of the 19 patients reported here, abnormalities in blood volume were very common. The most common, found in 16 of 19 patients, was a reduction in red blood cell mass. Eleven subjects had low plasma volumes, and total circulating blood volume was subnormal in 12 of 19 subjects. In some individuals this abnormality was strikingly severe. Patient #15, for example, had an RBC mass of 12.9 mL/Kg, which is 46% of the expected normal, and a total blood volume of 35.8 mL/Kg, which represents 49.7% of the expected normal value (21).

Her peripheral hematocrit was not impressively low at 33.8%, presumably because of the symmetrical reduction of both RBC mass and plasma volume. In other patients the plasma volume was normal or even elevated in the face of a low RBC mass, and in none of these patients was the RBC mass abnormality detected by conventional interpretation of the peripheral hematocrit.

All of the subjects in this study had symptoms of orthostatic intolerance which probably contributed to their activity restriction, but tilt table and autonomic nervous system testing was not carried out systematically in these individuals. Normal sitting blood pressures were recorded in all patients under office visit circumstances, except for relatively low values in three and a mildly elevated blood pressure in one. Some of these patients have been tested subsequently and found to have delayed orthostatic hypotension (12), which may be characteristic for CFS (11,12). In general, blood pressure measurements were not predictive of the results of circulating blood volume measurements.

A subnormal RBC mass and/or decreased circulating blood volume may well result in diminished cerebral blood flow with subnormal oxygen-carrying capacity (22). These abnormalities, by reducing cerebral oxygenation, might well be important factors in the pathogenesis of chronic fatigue and deserve further evaluation. It is important to note, however, that 3 of 19 patients in this study had normal RBC mass and plasma volume, and thus a deficiency of circulating blood volume could not account for their symptomatology.

Clinically, there was no obvious difference in the degree of fatigue, orthostatic intolerance, or somatic symptoms in these patients as compared with those whose RBC mass was reduced (Table 1).

The high prevalence of reduced RBC mass in our patients with severe CFS suggests that this abnormality may well be important to the pathogenesis of their persisting symptoms, though not necessarily in that of the initiating event. While most frequently seen after a viral infection and with no obvious precipitating cause (1), CFS has also developed after ciguatera poisoning (23), head injury (personal observation), and lead poisoning (personal observation). Post-polio fatigue bears striking resemblance to CFS (24,25). Hereditary factors may also play a role, perhaps through effects on autonomic nervous system function. Thus, whatever its initiating cause, CFS may be perpetuated, at least in part, by low RBC mass in many patients.

In this study, matched control subjects were not assessed for circulating blood volume, and thus the data presented here should be considered a preliminary report. Since significant reduction of RBC and whole blood volume may be among the few objectively demonstrable laboratory abnormalities in the majority of patients during the chronic stages of CFS, we beleive that further studies of these changes would be worthwile.

TABLE 1.

Demographic Data

Patient	Age	Sex	Years Ill	Hrs/day*	Act+	VAS±	Fisk§
1.	31	F	13	1	20%	109	157
2.	38	F	11	3	20%	72	130
3.	44	F	12	1	20%	79	132
4.	33	F	8	2	25%	90	
5.	38	F	3,4	2	30%	40	105
6.	34	F	10	2	20%	37	85
7.	49	F	11	3,5	30%	49	99
8.	47	F	2,4	1	20%	43	60
9.	34	F	14	4	30%	105	140
10.	50	F	2,5	1	20%	66	112
11.	14	F	4	3	20%	70	138
12.	39	F	4,1	3	30%	82	111
13.	41	F	26	2	20%	78	113
14.	40	F	3	1	20%	92	155
15.	53	F	10	1	20%	110	152
16.	38	M	9,7	2	30%	95	118
17.	33	M	3,3	1	30%	52	110
18.	14	M	2	4	50%	62	108
19.	35	M	8	2	20%	57	93

TABLE 2.

Blood Volume Determination

Patient	BP*	Hct§	WBHct¥	RBC mass	PV	TBV
Normal	-	-	-	25-30 ml/kg	39-49 ml/kg	64-79 ml/kg
1.	126/85	42,3	37,4	17,7	29,6	47,3
2.	101/65	41,2	29,1	19,9	48,5	68,4
3.	136/76	36,9	15,3	17,7	98,0	115,0
4.	122/76	47,3	53,0	19,4	21,9	41,3
5.	95/56	35,7	31,9	21,5	45,8	67,1
6.	117/75	39,7	34,5	25,4	48,3	73,7
7.	140/82	41,3	40,0	16,8	21,1	37,7
8.	108/79	40,0	31,2	17,4	37,4	54,8
9.	125/73	41,6	39,3	21,4	35,9	57,3
10.	97/63	40,0	29,3	22,0	53,0	75,0
11.	147/66	45,9	46,0	19,8	23,2	43,0
12.	130/76	37,5	30,4	16,8	38,5	55,3
13.	142/83	38,8	38,1	18,9	30,7	19,6
14.	100/64	36,3	36,0	14,8	26,3	41,1
15.	150/87	39,8	35,5	12,9	23,4	35,8
16.	124/77	42,8	39,3	27,5	42,5	70,0
17.	137/81	44,0	34,4	28,5	54,3	82,8
18.	98/67	40,3	32,9	19,6	39,9	59,5
19.	137/90	43,7	38,2	21,3	34,4	55,8