

Role of Impaired Lower-Limb Venous Innervation in the Pathogenesis of the Chronic Fatigue Syndrome

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ABSTRACT: *Background:* In patients with acute orthostatic hypotension, there is excessive pooling of blood in the legs, which may result from the strikingly subnormal compliance that is demonstrable in the pedal veins during norepinephrine infusion. The common occurrence of delayed orthostatic hypotension and/or tachycardia in the chronic fatigue syndrome (CFS) led to the present studies of foot vein compliance in CFS patients with a linear variable differential transformer. *Methods:* Seven patients with CFS were compared with 7 age- and gender matched healthy control subjects in their blood pressure, heart-rate, and plasma norepinephrine responses to prolonged standing and in measurements of their foot vein contractile responses to intravenous norepinephrine infusions with the linear variable differential transformer. *Results:* Excessive, delayed (usually after 10 min) orthostatic reductions in systolic and diastolic blood pressure ($P < 0.01$) and inconsistently excessive increases in heart rate were found in the CFS

patients, in whom venous compliance in response to infused norepinephrine was significantly reduced ($P < 0.05$). *Conclusions:* In these patients with CFS, delayed orthostatic hypotension was clearly demonstrable, and, as in previously reported patients with orthostatic hypotension of acute onset, this was associated with reduced pedal vein compliance during norepinephrine infusion, implying impaired sympathetic innervation of foot veins. The rapid symptomatic improvement demonstrated in previous studies of CFS patients during correction of orthostatic venous pooling by inflation of military antishock trousers (MAST) to 35 mm Hg may suggest that excessive lower body venous pooling, perhaps by reducing cerebral perfusion, is involved in the orthostatic component of fatigue in these patients. **KEY INDEXING TERMS:** Chronic fatigue syndrome (CFS); Venous tone; Pedal venous compliance; Pedal venous contractility. [Am J Med Sci 2001;321(3):163–167.]

Delayed active orthostatic hypotension and/or tachycardia, usually obvious only after at least 10 minutes of standing, are sometimes associated with severe fatigue¹ and may be involved in the pathogenesis of the chronic fatigue syndrome (CFS).² Similarly, head-up tilting frequently induces passive orthostatic hypotension, initially associated with tachycardia, in patients with the CFS.^{3–8} In healthy subjects, the upright posture is associated with translocation of about 800 mL of blood from the thorax to the lower body.⁹ When such gravitational pooling of blood in the lower limbs is excessive, therefore, it might be ex-

pected to result in orthostatic hypotension. This has been shown to be the case in many patients by successive measurements in the standing posture of γ -irradiation emanating from the legs of patients after ^{99m}Tc-labeling and reinjection of autologous erythrocytes.^{10,11} The postulated role of excessive orthostatic blood pooling in lower body veins as an important mechanism involved in the pathogenesis of orthostatic hypotension of all types has been strongly supported by the repeated demonstration that prevention of such venous pooling by external lower-body compression at 45 mm Hg with military antishock trousers (ie, a MAST suit; David Clark Co, Worcester, MA) restores the excessive orthostatic changes in blood pressure and heart rate into the normal range of these changes.^{2,5,10,11} In patients with CFS, MAST suit compression not only corrects the orthostatic hypotension and tachycardia but also seems to rapidly reduce orthostatic fatigue and other symptoms, perhaps even cognitive dysfunction, in some of these patients.²

A large increase in the sensitivity of contractile responsiveness to norepinephrine infused into veins of the feet compared with that of veins on the dor-

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sum of the hand in the same persons has been found in patients with orthostatic hypotension but not in healthy subjects.¹²

Because these findings are very common in patients with hyperadrenergic orthostatic hypotension⁵ not always associated with fatigue, the contractile responses of foot veins have been measured in the present study of 7 patients with the CFS and are here reported.

Methods

Subjects

Seven patients whose symptoms satisfied the diagnostic criteria for the CFS were included:¹³ 5 women and 2 men, aged 21 to 51 (mean age, 31) years. It should be mentioned that none of them complained of sore throat, tender lymph nodes, unrefreshing sleep, or multiple joint pains before or during our studies. However, severe and usually incapacitating fatigue had been present for more than 6 months, usually with fibromyalgic pains, postexercise malaise, impaired memory and concentration, as well as cognitive damage. Some degree of depression was present, not surprisingly, but no patient had been treated with antidepressants for at least a month before our studies. The findings have been compared with those in 7 healthy volunteers; 5 women and 2 men, aged 20 to 35 (mean age, 27) years. History and physical examination revealed no evidence of excessive fluid losses, dehydration, or other recognizable, potential causes of orthostatic disorders in the patients or the control subjects.

Routine Laboratory Screening Procedures

Including blood count, concentration of serum electrolytes and creatinine, and other measurements included in a 24-component multiphasic examination, routine laboratory tests revealed only mildly subnormal hematocrits (0.32–0.37) in 4 of the female patients.

Blood Pressure Study

During recumbency for 30 min, and while standing for 10 to 30 minutes or until presyncopal symptoms occurred, blood pressure (BP) and heart rate (HR) were measured every minute with a Dinamap (Critikon Co., Tampa, FL).

Plasma Norepinephrine Concentrations

Heparinized blood samples (5- to 10-mL) were drawn through a cannula previously placed in a forearm vein before the beginning of the BP measurements and drawn after recumbency for 30 minutes and again after standing for 10 min. The blood samples were immediately placed on ice, and plasma was separated in a refrigerated centrifuge and frozen for norepinephrine determinations by high-performance liquid chromatography within 2 weeks.

Norepinephrine Infusion Studies

Between 8:30 AM and 11:30 AM, a 25-gauge "butterfly" needle was inserted into a vein on the anterior surface of 1 foot or ankle and kept patent with 0.9% saline. Venous contractile responses were measured with a linear variable differential transformer (LVDT) as described elsewhere^{14,15} during the intermittent infusion at a constant rate (0.1 mL/min) into this vein of a 5% dextrose/0.9% saline solution alone, followed by increasing concentrations of norepinephrine, which had been added to the vehicle immediately before the infusions.

The infused limb was supported during the infusions on an inclining surface to empty the vein, which was intermittently distended by inflation to 45 mm Hg of a sphygmomanometer cuff above the ankle. Distension of the vein resulted in upward displacement of the light, central core of the LVDT, which had been

positioned on the skin overlying the infused vein. The magnitude of this displacement, recorded as an upward stroke of the tracing on the recorder, was calibrated so that a 0.1-inch upward deflection of the record resulted from a 0.01-mm increase in diameter of the infused vein. Each rate of norepinephrine infusion continued for 5 minutes before and during the 2-minute cuff inflations, and responses to each successive rate of norepinephrine infusion were recorded at least twice. The studies were performed with the patients recumbent in a quiet, single room at a temperature of 22 to 23°C.

Calculation of Responses

Blood Pressure and Heart Rate Measurements. BP and HR were averaged in each subject during successive 10-minute periods in the recumbent and standing postures. The mean values during the third 10-minute period in recumbency were compared with the mean in each of the 10-minute periods of standing or, when the BP fell rapidly as presyncopal signs developed, with the final orthostatic readings.

Changes in Venous Distensibility. Changes in venous distensibility, reflecting changes in venous compliance in response to successively increasing rates of norepinephrine infusion, were expressed as the percentage reduction of the venous diameter by the infusions during distension of the vein at 45 mm Hg. The regression of the successive changes in venous diameter, at each rate of norepinephrine infusion (expressed logarithmically), was computed from the data on each person and used to calculate the rate of norepinephrine infusion that would be expected to induce 50 and 80% reductions in venous diameter (ED₅₀ and ED₈₀) in each subject.

Statistical Analysis

Student *t* test and both 95 and 99% confidence intervals¹⁶ of the orthostatic changes in BP, HR, and norepinephrine-induced ED₅₀ were measured in the control subjects and the patients with CFS. Significance was attributed to *P* values < 0.05.

Results

Blood Pressure and Heart Rate Changes. The mean results of the BP and HR measurements in the healthy subjects and the patients with CFS during the last 10 minutes in recumbency and the successive 10-minute periods of standing are shown in Table 1. The table also indicates the changes from the recumbent to the final orthostatic measurements made at 60 minutes in the control subjects and during the last 10 minutes of orthostasis or at presyncope when this occurred in the patients.

The 99% confidence intervals of the orthostatic changes in systolic and diastolic BP in control subjects and patients did not overlap (*P* < 0.01) but the orthostatic changes in HR were not significantly different in the 2 groups of subjects.

Plasma norepinephrine concentrations were 242 ± 30 pg/mL (mean ± SEM) after recumbency for 30 minutes and 565 ± 44 pg/mL after standing for 10 minutes in the CFS patients, and 221 ± 18 pg/mL (not significant) after recumbency and 408 ± 25 pg/mL after standing (*P* < 0.02) in the healthy control subjects.

Venous Contractile Responses to Infused Norepinephrine. In 1 of the patients (patient 6 in Table 1), the contractile responses to norepinephrine were compared in a hand vein and a foot vein. This

Table 1. Orthostatic BP and HR Changes in Healthy Control Subjects and CFS Patients

Pt	Blood Pressures in Healthy Subjects						Blood Pressures in CFS Patients							
	Lying	Standing				Final Orthostatic Δ SBP/ Δ DBP	P	Final Orthostatic Δ SBP/ Δ DBP	Lying	Standing				
		1-10'	11-20'	21-30'	31-40'					1-10'	11-20'	21-30'	31-40'	
1	114/68	108/75	116/78	118/77	113/75	-1/+7		-56 /-18	138/86	126/82	82/68			
2	149/71	134/82	149/73	151/78	147/72	-2 /+1		-33 /-8	119/65	102/52	86/57			
3	135/87	131/96	137/80	136/91	136/97	+1 /+10		-15 /-6	101/64	102/60	101/60	95/60	86/58	
4	104/60	112/57	111/62	109/72		+5 /+12		-22 /-12	115/81	109/84	108/75	103/72	93/69	
5	128/77	117/79	122/74	110/73	122/71	-6 /-6		-35 /-16	134/73	99/57				
6	116/59	137/67	141/73	135/68	137/64	+21 /+5		-24 /-10	126/90	106/82	110/86	102/80		
7	121/63	120/80	135/82	134/80	123/69	+2 /+6		-31 /-8	140/76	116/94	109/68			
Mean	124/69	123/77	130/75	129/77	128/74	+8.9 /+5.0		-30.9 /-11.1	125/76	109/73	99/69	100/71	90/64	
SEM	6.0/4.0	6.5/4.9	5.6/2.6	6.8/3.0	6.7/5.3	3.6 /2.4		5.4 /1.8	5.7/4.1	3.9/6.6	5.5/4.7	3.1/7.2	3.5/5.6	
99% CIs of Δ SBP/ Δ DBP														
						-4.4 to +22.2	<0.01	-10.9 to -50.9						
						-3.9 to +13.9	<0.01	-4.4 to -17.8						

Pt	Heart Rates in Healthy Subjects					Final Orthostatic Δ HR	P	Final Orthostatic Δ HR	Heart Rates in CFS Patients							
	Lying	Standing							Final Orthostatic Δ HR	P	Final Orthostatic Δ HR	Lying	Standing			
		1-10'	11-20'	21-30'	31-40'								1-10'	11-20'	21-30'	31-40'
1	69	95	90	85	90	+21		+92	68	156	160					
2	63	65	65	72		+9		+20	63	81	83					
3	95	111	107	100	100	+5		+7	58	63	64	65	65			
4	75	80	82			+7		+32	64	87	99	98	96			
5	65	64	65	78	78	+13		+22	82	104						
6	73	81	90	80	75	+2		+12	108	120	120					
7	73	86	89	82	84	+11		+50	67	89	101	117				
Mean	73.3	84.6	84.0	81.7	83.2	+9.7		+33.6	72.9	100	102.5	93.3	80.5			
SEM	4.2	7.0	6.0	5.1	4.7	2.5		12.0	7.0	12.4	15.0	18.8	15.7			
95% CIs of Δ HR																
						+3.7 to +16.0	NS	+2.6 to +64.4								

Pt, Patient; Δ SBP, change in systolic BP; Δ DBP, change in diastolic BP; Δ HR, change in heart rate.

revealed an entirely normal response of the dorsal hand vein and a strikingly increased response in her foot vein, reflected by ED₅₀ values of 12.5 ng/min in the hand vein and 0.47 ng/min in the foot vein, a 27-fold increase in sensitivity to norepinephrine in the foot vein (Figure 1)

The dose-related reductions in venous compliances induced by logarithmically increasing rates of norepinephrine infusion in the patients with CFS are compared in Figure 2, with the individual results and the 95% confidence limits of these relationships in the 7 control subjects. It is evident that there was a clear increase in the sensitivity of the venous contractile responses to norepinephrine in 6 of the 7 patients (numbered in the figure) compared with the responses of the healthy subjects. The differences in the reductions in venous compliance in the 2 groups induced by NE infusion were significant at the 1 ng/min ($P < 0.05$) and 4 ng/min ($P < 0.01$) infusion rates.

Calculation of the ED₅₀ and ED₈₀ of the venous responses to norepinephrine (Figure 3) revealed a significant increase in contractile sensitivity to norepinephrine in the patients compared with the 7 healthy subjects ($P < 0.05$) and with a larger group of healthy control subjects studied previously ($P < 0.001$; not shown).

Discussion

The occurrence of a significantly excessive, orthostatic fall in systolic and diastolic BP and at least an

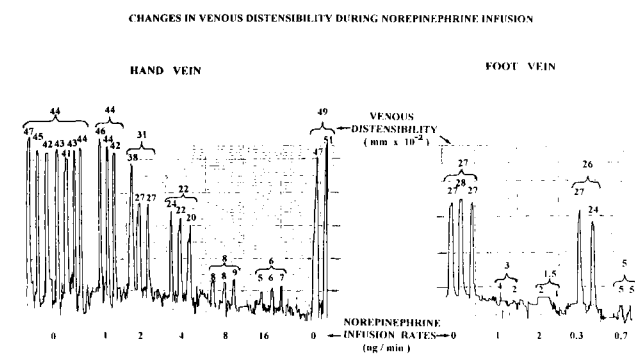


Figure 1. LVDT record of the effects in a patient (#6) of increasing rates of norepinephrine (NE) infusion on distensibility of hand and foot vein during each 1 minute inflation of a sphygmomanometer cuff on the leg to 45 mm Hg. It is evident that the venoconstriction induced by increasing rates of NE infusion resulted in steadily reduced venous distensibility and that distensibility of 0.06 mm occurred at a NE infusion rate of 16 ng/min in the hand vein while approximately similar distensibility (0.05 mm) occurred when NE was infused at 0.7 ng/min into the foot vein.

Impaired Venous Tone in Chronic Fatigue Syndrome

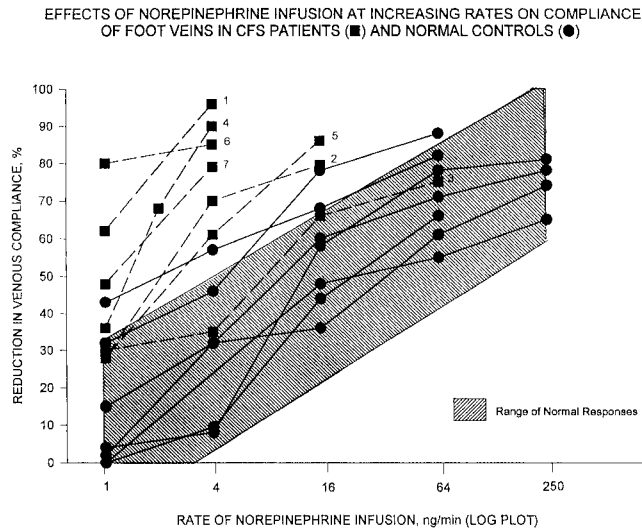


Figure 2. Effects of norepinephrine (NE) infusions at increasing rates on compliance of foot veins in CFS patients (■) and control subjects (●). The percentage reductions in venous compliance induced by NE infused at 4 ng/min exceed the 95% confidence limits and, in all but patient 3, the individual reductions in the control subjects. The responses to NE infusion are significantly increased in the CFS patients compared with the controls both at NE infusion rates of 1 ($P < 0.05$) and 4 ($P < 0.01$) ng/min.

initially excessive orthostatic rise in HR has been observed in all but 1 of the reports we can find of studies in which these measurements were continued for more than 10 minutes in groups of patients with the CFS.^{2-5,11,12,17} The 1 exception that I know of¹⁸ has been challenged.¹⁹ When several orthostatic measurements of BP and HR before syncope or presyncope have been reported,² the gradually pro-

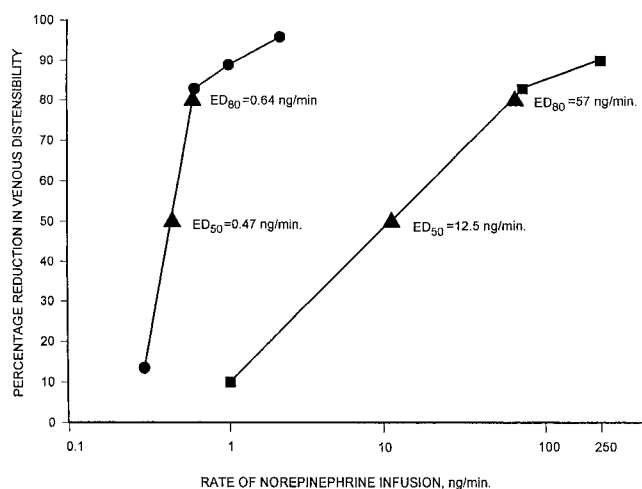


Figure 3. Comparison of the mean percentage reductions in venous compliance of foot veins induced by norepinephrine infusions in patients with chronic fatigue syndrome (●) and healthy control subjects (■). The ED₅₀ and ED₈₀ of the changes in venous compliance of the foot veins of the patients were significantly greater ($P < 0.05$) than these values in the healthy subjects.

gressive fall in BP and rise in HR during continued orthostasis, found in the present measurements, have also been observed. A sudden, terminal fall in HR, which was measured only once every minute in the patients described herein, was not seen in these patients at presyncope; in the continuous, beat-to-beat measurements of HR reported by Bou-Holaigah et al⁴, however, this presumably vagally-induced bradycardia occurred in all of the patients whose head-up tilt resulted in syncope and in 6 of the 9 patients who experienced presyncope.

The plasma norepinephrine concentrations in the CFS patients were normal in recumbency, and their significant elevation after orthostasis for 10 minutes is consistent with the initial orthostatic tachycardia in indicating that the orthostatic hypotension was hyperadrenergic in these patients.

Pooling of blood in the legs during standing has been shown to be excessive in various types of orthostatic hypotension^{10,11} and is probably an important component of the pathogenesis of orthostatic hypotension and tachycardia. Its prevention by external compression at 45 mm Hg virtually invariably restores excessive orthostatic BP and HR changes into the normal ranges.^{1,2,5,10} That these changes in BP and HR are progressive in patients with CFS and rapidly correctable with the MAST suit probably imply, therefore, that there is gradually increasing sequestration of blood in the lower body during orthostasis in patients with CFS.

The present results have shown that in 6 of the 7 patients with CFS whom we studied, there was strikingly increased venous contractile sensitivity to infused norepinephrine. If the increased sensitivity is measured by calculation of the ED₅₀ of norepinephrine infusion rate, the mean change in this measurement in the foot veins of our 7 patients may be calculated to be an 11-fold increase compared with measurements in a large group of healthy subjects. On the other hand, it is evident from Figure 1 that there was a greater contractile effect of norepinephrine infused at 0.7 ng/min on the foot vein of 1 of our patients than the effect of the infusion at 250 ng/min into the dorsal hand vein of the same subject: a > 350-fold increase in sensitivity. Such differences are severely pathological judging from the only previous comparison of hand- and foot-vein responsiveness to norepinephrine reported in healthy subjects,¹² which recorded no significant difference.

Persistent reduction in the concentration of a ligand commonly induces up-regulation of its receptors in responsive tissues, as has been shown in the regulation of human vascular α -adrenoceptors.²⁰ Perhaps it is reasonable to postulate, therefore, subject to future confirmation or refutation, that a common primary mechanism of the CFS and other disorders, when associated with orthostatic hypotension, may be impairment of the normal orthostatic increase in norepinephrine release at the terminals of the sym-

pathetic nerves innervating leg veins, with consequent up-regulation of α -adrenoceptors in these veins and perhaps at other venous sites in the lower body of human subjects. Regrettably, we can find no reports in the literature on the anatomical and functional integrity of the foot vein innervation in abnormal human subjects. The long-known inability of many vertebrates to tolerate a head-up/feet-down posture because of profound hypotension in this posture²¹ probably implies that only human subjects or apes could be used to provide direct confirmation of the conclusions drawn from the venous contractile responses to orthostasis reported herein.

Subject to this proviso, I would suggest that the large variety of disorders that might cause the CFS include (1) reduced orthostatic contractility or tone in the veins (idiopathic, diabetic, toxic, infective, and other autonomic neuropathies) and (2) severe hypercortisolism, which impairs arteriolar and probably venous contractility.^{22,23}

References:

1. **Streeten DHP, Anderson GH Jr.** Delayed orthostatic intolerance. *Arch Intern Med* 1992;152:1066–72.
2. **Streeten DHP, Thomas FD, Bell DS.** The roles of orthostatic hypotension, orthostatic tachycardia, and subnormal erythrocyte volume in the pathogenesis of the chronic fatigue syndrome. *Am J Med Sci* 2000;320:1–8.
3. **Rowe PC, Bou-Holaigah I, Kan S, et al.** Is neurally mediated hypotension an unrecognized cause of chronic fatigue? *Lancet* 1995;345:623–4.
4. **Bou-Holaigah I, Rowe PC, Kan J, et al.** The relationship between neurally mediated hypotension and the chronic fatigue syndrome. *JAMA* 1995;274:961–7.
5. **Streeten DHP, Scullard TF.** Excessive gravitational blood pooling caused by impaired venous tone is the predominant non-cardiac mechanism of orthostatic intolerance. *Clin Sci (Colch)* 1996;90:277–85.
6. **DeLorenzo F, Hargreaves J, Kakkar VV.** Possible relationship between chronic fatigue and postural tachycardia syndromes. *Clin Auton Res* 1996;6:263–4.
7. **Freeman R, Komaroff AL.** Does the chronic fatigue syndrome involve the autonomic nervous system? *Am J Med* 1997;102:357–64.
8. **Stewart J, Weldon A, Arlievsky N, et al.** Neurally mediated hypotension and autonomic dysfunction measured by heart rate variability during head-up tilt testing in children with chronic fatigue syndrome. *Clin Auton Res* 1998;8:221–30.
9. **Blomqvist CG, Stone HL.** Cardiovascular adjustments to gravitational stress. In: Shepard JT, editor. *Handbook of physiology: The cardiovascular system. Peripheral circulation and organ blood flow.* Bethesda: American Physiological Society; 1983. p. 1025–63.
10. **Streeten DHP, Anderson GH Jr, Richardson R, et al.** Abnormal orthostatic changes in blood pressure and heart rate in subjects with intact sympathetic nervous function: evidence for excessive venous pooling. *J Lab Clin Med* 1988;111:326–35.
11. **Streeten DHP.** *Orthostatic disorders of the circulation.* New York: Plenum Press; 1987.
12. **Streeten DHP.** Pathogenesis of hyperadrenergic orthostatic hypotension. Evidence of disordered venous innervation exclusively in the lower limbs. *J Clin Invest* 1990;86:1582–8.
13. **Fukuda K, Straus SE, Hickie I, et al.** The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Ann Intern Med* 1994;121:953–9.
14. **Alradi AO, Carruthers SG.** Evaluation and application of the linear variable differential transformer technique for the assessment of human dorsal hand vein alpha-receptor activity. *Clin Pharmacol Ther* 1985;38:495–502.
15. **Miller JW, Streeten DHP.** Vascular responsiveness to norepinephrine in sympatheticotonic orthostatic hypotension. *J Lab Clin Med* 1990;115:549–58.
16. **Gardner MJ, Altman DG,** editors. *Statistics with confidence: confidence intervals and statistical guidelines.* London: British Medical Journal; 1994.
17. **Schondorf R, Freeman R.** The importance of orthostatic intolerance in the chronic fatigue syndrome. *Am J Med Sci* 1999;317:117–23.
18. **Duprez DA, De Buyzere ML, Drieghe B, et al.** Long-term and short-term blood pressure and RR-interval variability and psychosomatic distress in chronic fatigue syndrome. *Clin Sci (Colch)* 1998;94:57–63.
19. **Streeten DHP, Bell DS.** Long- and short-term blood pressure and RR-interval variability and psychosomatic distress in chronic fatigue syndrome [letter]. *Clin Sci (Colch)* 1999;97:319–22.
20. **Davies IB, Sudera D, Sever PS.** Endogenous agonist regulation of α -adrenoceptors in man. *Clin Sci (Colch)* 1981;61:207S–210S.
21. **Hill L.** The influence of the force of gravity on the circulation of the blood. *J Physiol (Lond)* 1895;21:323–52.
22. **Fritz I, Levine R.** Action of adrenal cortical steroids and norepinephrine on vascular responses of stress in adrenalectomized rats. *Am J Physiol* 1951;165:456–65.
23. **Streeten DHP.** The presentation and diagnosis of primary and secondary cortisol deficiency. *Curr Opin Endocrinol Diabetes* 1995;2:214–221.