Original Article

Increased Baroreflex Sensitivity and Reduced Cardiovascular Reactivity in Individuals with Chronic Low Blood Pressure

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This study investigated aberrations in baroreflex function and cardiovascular reactivity related to the condition of chronic low blood pressure. In 40 hypotensive and 40 normotensive control subjects, blood pressures were continuously recorded at rest and during mental stress. Baroreflex sensitivity was determined in the time domain using sequence analysis. Beat-to-beat hemodynamic indices were estimated from the blood pressure waveforms by means of Modelflow analysis. In the hypotensive sample, a higher baroreflex sensitivity was observed under both conditions. Furthermore, this group experienced a less pronounced increase of blood pressure and stroke volume under stress. The findings underline the involvement of the baroreflex in the long-term setting of tonic blood pressure and suggest its relevance in the etiology of chronic hypotension. In addition, this study documents reduced cardiovascular reactivity and thus deficient hemodynamic adjustment to situational requirements in chronic low blood pressure. (*Hypertens Res* 2008; 31: 1873–1878)

***Key Words*: hypotension, blood pressure, baroreflex, cardiac output, mental stress**

Introduction

Chronic low blood pressure is relatively widespread; it affects approximately 3% of the general population (*1*). It is typically accompanied by symptoms such as fatigue, reduced drive, faintness, dizziness, headaches, cold limbs, and reduced cognitive performance, which can have a considerable impact on subjective well-being and quality of life (*1–3*). According to the WHO (*4*), the diagnostic criterion for hypotension is systolic blood pressure below 100 mmHg in women and 110 mmHg in men. The condition of chronic ("essential") hypotension must be distinguished from secondary hypotension (*e.g.*, due to blood loss or medication) as well as from the orthostatic form, in which the individual experiences circulatory problems when assuming an upright position (*5*).

The cardiac baroreflex has been considered to be involved in the etiology of chronic hypotension (*1*, *6*). This regulatory system consists of a negative feedback loop in which changes in the firing rate of the arterial baroreceptors lead to compensatory alterations of heart rate, cardiac contractility, and vasomotor activity (*7*, *8*). The sensitivity of the baroreflex can be quantified reliably by analyzing the spontaneous covariation of the systolic blood pressure and pulse interval ("sequence analysis") (*9*, *10*).

Cardiovascular conditions such as cardiac arrhythmias, coronary artery disease, and cardiac infarction are accompanied by alterations in baroreflex function (*11–13*). It is also well established that the baroreflex is inhibited in chronically elevated blood pressure (*14*, *15*). Therefore, it has been sug-

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gested that the reflex is involved not only in the buffering of transient changes in arterial pressure but also in the long-term setting of blood pressure, and thus in the origin of essential hypertension (*16*, *17*). On account of this, one may predict an increased reflex function in chronic low blood pressure. It has been speculated that in hypotension elevated baroreflex sensitivity results in overcompensation of phasic blood pressure increases, thus stabilizing blood pressure at a lower level (*6*).

Besides baroreflex function, the present study aimed to investigate cardiovascular reactivity in chronic low blood pressure. Based on former findings (*18*, *19*), hemodynamic adjustment to acute stress was hypothesized to be reduced.

Methods

Participants

Forty hypotensive and 40 normotensive control subjects participated in the study. Individuals with relevant physical or mental diseases were excluded. Health status was assessed by means of an anamnestic interview and a questionnaire covering diseases of the cardiovascular, respiratory, gastro-intestinal and uro-genital systems, the thyroid, and the liver, as well as metabolic diseases, psychiatric disorders, and chronic pain. None of the participants used any kind of medication that affected the cardiovascular or central/peripheral nervous system. All subjects were right-handed according to the Edinburgh Handedness Inventory (*20*).

The hypotensive and the control groups were matched according to age and gender. Each sample consisted of 32 female and 8 male subjects. Information about blood pressure, as recorded just before the experimental procedure, age, and body mass index (BMI) in the sample is given in Table 1. Sixty-three of the participants were university students (31 in the hypotensive sample, 32 in the control group). Ten of the remaining subjects were employees, 4 were self-employed and 3 were unemployed.

Fifteen of the women in the hypotensive group and 20 of the women in the control group were using oral contraceptives (U=432.0, p=0.23). Five hypotensive and 3 control subjects reported that they had their period on the day of the experiment (U=415.5, p=0.39). The average time interval from the end of the latest period did not differ significantly between the remaining women in the hypotensive and control groups (hypotensives: 13.45±5.78 days [mean±SD]; controls: 13.07±7.16 days; t=0.26, p=0.80).

Recording of Hemodynamic Data

Blood pressure was monitored continuously using a Finometer device (Model-2; Finapres Medical Systems, Amsterdam, The Netherlands). The cuff of the Finometer was applied to the mid-phalanx of the third finger of the right hand. In order to control for the influence of hydrostatic level errors, the height-correction unit integrated in the device was used. For periodic recalibration, the Physiocal feature (*21*) was in operation. The signal was digitized at a sample rate of 200 Hz.

Table 1. Systolic Blood Pressure, Diastolic Blood Pressure, Age, and Body Mass Index in Both Samples

	Hypotensive group	Control group
Systolic blood pressure (mmHg)	96.5±4.8	121.8±5.3
Diastolic blood pressure (mmHg)	57.7±4.5	77.2±5.9
Age (years)	27.7±5.7	27.8±5.4
Body mass index (kg/m^2)	20.2±2.0	22.5±3.4

Data are means±SD.

Procedure

Assignment of subjects to the two study groups was carried out on the basis of blood pressure readings taken in a screening session conducted at least 1 week prior to the main experiment and again at the beginning of the experimental session. After a rest period of 10 min, three sphygmomanometric blood pressure measurements were taken in a sitting position. For this purpose an automatic inflation blood pressure monitor (MIT, TYP M CR15; Omron, Bannockburn, USA) was used. Readings were separated by 5 min rest intervals. Women whose mean systolic blood pressure was less than 100 mmHg and men whose mean systolic blood pressure was below 110 mmHg were assigned to the hypotensive group. The inclusion criterion for the control group was systolic blood pressure between 115 and 140 mmHg. The criteria had to be fulfilled at both the screening and experimental sessions. Subjects were requested not to smoke or drink alcohol or beverages containing caffeine for 3 h prior to both sessions.

In the experimental session, measures of baroreflex sensitivity and hemodynamics were obtained at rest and during mental stress induced by a serial subtraction task. During the 5 min resting phase, participants were asked to sit still, without speaking, and to relax with their eyes open. The subtraction task included a 3 min interval during which subjects had to count down from 700, subtracting 17 each time. They were asked to perform the task as quickly and as accurately as possible.

Data Analysis

In the first step of data processing, the blood pressure data were resampled at 1,000 Hz by means of spline interpolation using MATLAB software (The MathWorks, Inc., South Asheboro, USA). Baroreflex function was quantified employing a software program developed by Reyes del Paso (*22*). The program locates sequences of three to six consecutive heart cycles in which systolic blood pressure increases are accompanied by increases in pulse interval and those in which blood pressure decreases are accompanied by decreases in

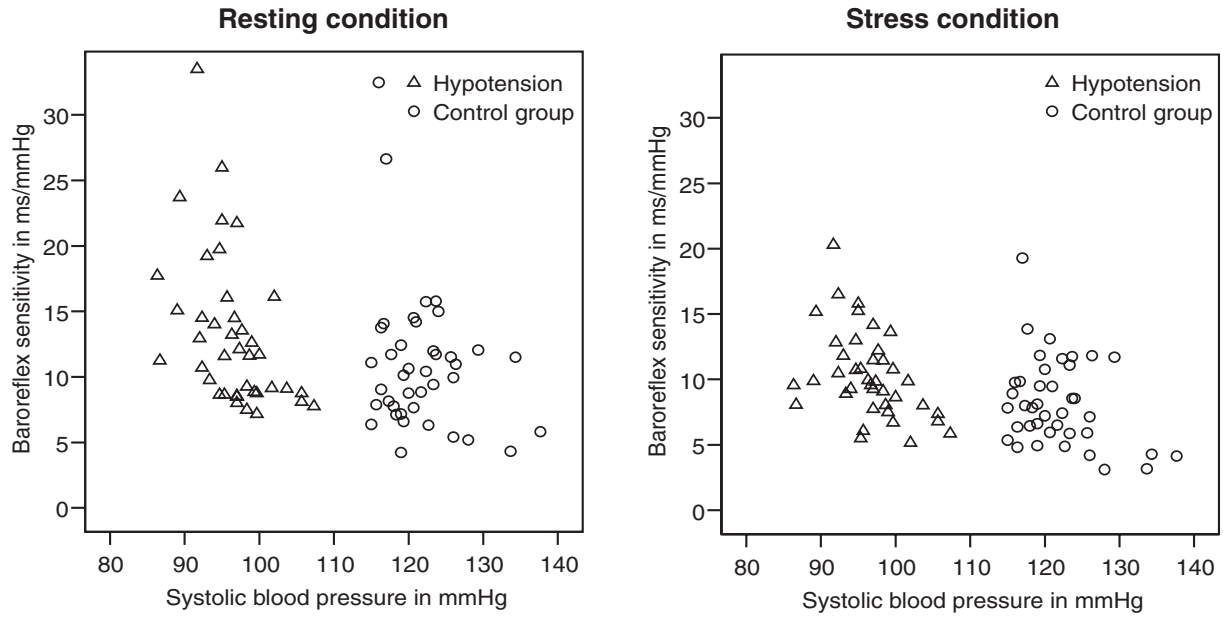

Fig. 1. *Scatter plots for the relationships between systolic blood pressure and baroreflex sensitivity at rest and during stress across both experimental groups.*

pulse interval. Baroreflex sensitivity was expressed as the change in pulse interval (in ms) per mmHg blood pressure change within these sequences, measured by the slope of the regression line (*10*, *23*). (The validity of this index has been well documented (*10*, *22*, *23*). However, although sequence analysis yields accurate measures of baroreflex function close to the operating point, *i.e.*, in the habitual blood pressure range, this technique, in contrast to invasive techniques, does not enable analysis of the baroreflex curve in the full blood pressure range (*10*).)

Hemodynamic parameters were determined based on the Modelflow method (*24*) using the software Beatscope 1.1a (Finapres Medical Systems). Therefore, the raw data recorded at 200 Hz were used. The Modelflow technique makes it possible to model blood flow from arterial pressure by computing a flow wave that is integrated to obtain beat-to-beat stroke volume (in mL). The method has proved to be particularly reliable in quantifying within-subject changes in stroke-volume (*25*). Blood pressure (in mmHg), heart rate (in beats/min), cardiac output (in L/min), and total peripheral resistance (in MU) were also included in the analysis.

All indices obtained were averaged over the time intervals of the resting and stress conditions. The data on baroreflex sensitivity was analyzed using an analysis of variance (ANOVA) for repeated measures. Blood pressure group (hypotensive *vs*. control group) was applied as a between-subjects factor and experimental condition (rest *vs*. stress) was applied as a within-subjects factor. Cardiovascular reactivity was quantified by computing relative (%) changes in the hemodynamic parameters between both experimental conditions. The revealed indices were compared between the blood pressure groups using *t*-tests (one-tailed testing).

Results

Baroreflex sensitivity under resting conditions and during mental stress was higher in the hypotensive than in the control group, with reflex sensitivity (ms/mmHg) generally being lower under stress (rest: hypotension, 13.23±5.85 [mean±SD], control group, 11.16±5.95; stress: hypotension, 10.32±3.31, control group, 8.19±3.35). The ANOVA revealed significant main effects of the factors group ($F[1,78]=5.36$, $p=0.023$) and experimental condition ($F[1,78]=29.46$, $p<0.01$). Figure 1 displays the scatter plots for the relationships between systolic blood pressure and baroreflex sensitivity at rest and during stress across both experimental groups (rest: $r=0.29$, $p<0.01$; stress: $r=0.42$, $p<0.01$).

All hemodynamic parameters increased under the stress condition. With respect to systolic and diastolic blood pressure, as well as cardiac output, the magnitude of the increase was significantly lower in the hypotensive than in the control group (Fig. 2).

Discussion

As a main result, the study revealed markedly higher sensitivity of the cardiac baroreflex in individuals with chronic low blood pressure at rest as well as under conditions of mental stress. This may indicate resetting of the operating point of

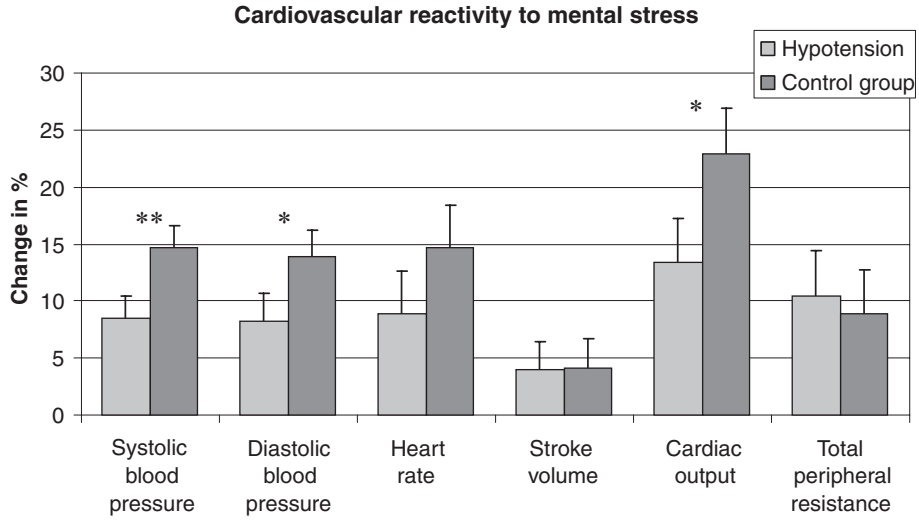

Fig. 2. *Relative changes in the hemodynamic parameters between resting and stress conditions. *p < 0.05, **p < 0.01; bars represent SEM.*

the reflex to lower blood pressure values. The baroreflex system is commonly viewed as the main mechanism for short-term stabilization of blood pressure (*7*, *8*). More recently, however, its importance for setting the long-term level of blood pressure has been taken into account (*15–17*). This idea had been challenged in the past, mainly because the baroreceptor system shows a certain degree of habituation ("resetting") to altered tonic blood pressure levels (*26*, *27*). Observations in animals, however, have suggested that the baroreceptors do not completely reset and that the activity of the afferent branch of the baroreflex remains elevated in hypertension (*28*). Moreover, in animals, surgical baroreceptor denervation led to a sustained blood pressure increase (*29*, *30*), whereas prolonged stimulation of the baroreceptor afferents produced a sustained blood pressure decline (*16*).

Data from humans also support the role of the baroreflex in the long-term regulation of blood pressure. In addition to the well-known baroreflex-hyposensitivity in chronically elevated blood pressure (*14*, *15*), there is evidence of an inverse relationship between baroreflex sensitivity and tonic blood pressure in healthy normotensive subjects (*17*, *31*). In a recent longitudinal study, reduced baroreflex sensitivity predicted a 5-year rise in blood pressure (*32*). Clinical observations showed that patients with complete denervation of the carotid baroreceptors experience severe labile hypertension (*33*, *34*). This is also consistent with studies demonstrating that an increase of baroreflex sensitivity by means of biofeedback is followed by blood pressure attrition (*35*). Taken together, these findings suggest that inter-individual differences in baroreflex sensitivity are not merely epiphenomena of varying tonic blood pressure levels, but that the baroreflex is causally involved in setting tonic blood pressure. Thus, on account of the present data, it seems justified to regard hypersensitivity of the baroreflex as a relevant factor in the origin of chronic hypotension.

The significant decrease in baroreflex sensitivity during mental load that was observed in both study groups most likely resulted from stress-related autonomic modulation. Given the evidence linking baroreflex sensitivity with parasympathetic tone (*36*, *37*), the attrition may reflect vagal withdrawal induced by mental activity. The reduction of baroreflex sensitivity under such conditions attenuates the buffering effect of the reflex, thereby facilitating a stress-induced increase in blood pressure. This may be regarded as part of an adaptive mechanism enabling improvement of energetic and metabolic supply during acute stress (*38*).

The rise of the hemodynamic parameters during mental load can be attributed to stress-related elevation of general cardiac arousal, mediated by autonomic nervous and hormonal pathways (*39*). In hypotensives, the increase in blood pressure and cardiac output was significantly smaller than in the control group. This finding is in accordance with previous studies reporting reduced cardiovascular reactivity to mental and physical stress in individuals with chronic low blood pressure (*18*, *19*, *40*). One may hypothesize that this reflects reduced hemodynamic adjustment to current requirements, resulting in deficient organ perfusion, which in turn may contribute to the development of hypotensive symptoms. This is also in line with the previously documented deficits in cerebral blood flow regulation in low blood pressure (*1*, *41*). These aberrances include reduced adjustment of brain perfusion to mental activity, which was shown to be relevant for the genesis of hypotension-related cognitive deficits (*19*, *42*).

One limitation of the present study results from the focus on chronic hypotension. Keeping in mind that orthostatic hypotension is also a highly relevant and prevalent disorder

(*5*), it may also be worthwhile to conduct orthostatic testing in future studies. It would also be of interest to assess subjective hypotensive symptoms and relate these to baroreflex function and cardiovascular reactivity, which may yield further information about the clinical relevance of aberrant cardiovascular regulation.

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References

1. Duschek S, Schandry R: Reduced brain perfusion and cognitive performance due to essential hypotension. *Clin Auton Res* 2007; **17**: 69–76.
2. Rosengren A, Tibblin G, Wilhelmsen L: Low systolic blood pressure and self perceived wellbeing in middle aged men. *BMJ* 1993; **306**: 243–246.
3. Wessely S, Nickson J, Cox B: Symptoms of low blood pressure: a population study. *BMJ* 1990; **301**: 362–365.
4. WHO: Arterial Hypertension: Technical Report Series No. 628. Genova, World Health Organization, 1978.
5. Novak V, Novak P, Spies JM, Low PA: Autoregulation of cerebral blood flow in orthostatic hypotension. *Stroke* 1998; **29**: 104–111.
6. Weisz N, Schandry R, Jacobs A, Mialet J, Duschek S: Early contingent negative variation of the EEG and attentional flexibility are reduced in hypotension. *Int J Psychophysiol* 2002; **45** (Suppl 3): 253–260.
7. Dembowsky K, Seller H: Arterial baroreceptor reflexes, in Vaitl D, Schandry R (eds): From the Heart to the Brain: The Psychophysiology of Circulation-Brain Interaction. Frankfurt a.M., Europäischer Verlag der Wissenschaften, 1995, pp 35–60.
8. Levy MN, Pappano AJ: Cardiovascular Physiology. Philadelphia, Mosby Elsevier, 2007.
9. Steptoe A, Vögele C: Cardiac baroreceptor reflex function during postural change assessed using non-invasive spontaneous sequence analysis in young men. *Cardiovasc Res* 1990; **24**: 627–632.
10. Parati G, di Rienzo M, Mancia G: How to measure baroreflex sensitivity: from the cardiovascular laboratory to daily life. *J Hypertens* 2000; **18**: 7–19.
11. La Rovere MT, Specchia G, Mortara A, Schwartz PJ: Baroreflex sensitivity, clinical correlates, and cardiovascular mortality among patients with a first myocardial infarction. A prospective study. *Circulation* 1988; **78**: 816–824.
12. Osculati G, Grassi G, Giannattasio C, *et al*: Early alterations of the baroreflex control of heart rate in patients with acute myocardial infarction. *Circulation* 1990; **81**: 939–948.
13. Katsube Y, Sato H, Naka M, Kim BH, Kinoshita N, Hori M: Decreased baroreflex sesnsitivity in patients with stable coronary heart disease is correlated with the severity of coronary narrowing. *Am J Cardiol* 1996; **78**: 1007–1010.
14. Bertinieri G, di Rienzo M, Parati B, *et al*: Baroreceptor-heart rate reflex studied in normotensives and essential hypertensives by beat-to-beat analysis of 24-hour blood pressure and heart rate. *J Hypertens* 1987; **5**: 5333–5335.
15. Biaggioni I: Sympathetic control of the circulation in hypertension: lessons from autonomic disorders. *Curr Opin Nephrol Hypertens* 2003; **12**: 175–180.
16. Lohmeier TE, Irwin ED, Rossing MA, Serdar DJ, Kieval RS: Prolonged activation of the baroreflex produces sustained hypotension. *Hypertension* 2004; **43**: 306–311.
17. Hesse C, Charkoudian N, Liu Z, Joyner MJ, Eisenach JH: Baroreflex sensitivity inversely correlates with ambulatory blood pressure in healthy normotensive humans. *Hypertension* 2007; **50**: 41–46.
18. Duschek S, Matthias E, Schandry R: Essential hypotension is accompanied by deficits in attention and working memory. *Behav Med* 2005; **30**: 149–158.
19. Duschek S, Schandry R: Deficient adjustment of cerebral blood flow to cognitive activity due to chronically low blood pressure. *Biol Psychol* 2006; **72**: 311–317.
20. Oldfield RC: The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 1971; **9**: 97–113.
21. Wesseling KH, De Wit B, Van der Hoeven GMA, Van Goudoever J, Settels JJ: Physiocal, calibrating finger vascular physiology for Finapres. *Homeostasis* 1995; **36**: 67–82.
22. Reyes del Paso GA: A program to assess baroreceptor cardiac reflex function. *Behav Res Meth Instrum* 1994; **26**: 62–64.
23. Parlow J, Viale JP, Annat G, Hughson R, Quintin L: Spontaneous cardiac baroreflex in humans: comparison with drugs-induced responses. *Hypertension* 1995; **25**: 1058–1068.
24. Wesseling KH, Jansen JR, Settels JJ, Schreuder JJ: Computation of aortic flow from pressure in humans using a nonlinear, three-element model. *J Appl Physiol* 1993; **74**: 2566–2573.
25. Bogert LWJ, Lieshout JJ: Non-invasive arterial pressure and stroke volume changes from the human finger. *Exp Physiol* 2005; **90**: 437–446.
26. Rau H, Elbert T: Psychophysiology of arterial baroreceptors and the etiology of hypertension. *Biol Psychol* 2001; **57**: 179–201.
27. McCubbin JW, Green JH, Page IH: Baroreceptor function in renal hypertension. *Circ Res* 1956; **4**: 205–210.
28. Lohmeier TE: The sympathetic nervous system and long-term blood pressure regulation. *Am J Hypertens* 2001; **14**: 147S–154S.
29. Cowley AW, Quillen EW, Barber BJ: Further evidence for lack of baroreceptor control of long-term level of arterial pressure, in Sleight P (ed): Arterial Baroreceptors in Hypertension. Oxford, Oxford University Press, 1980, pp 391–399.
30. Persson PB: Interaction of arterial and cardiopulmonary reflexes, in Persson PB, Kirchheim HR (eds): Baroreceptor Reflexes. Berlin, Springer, 1991, pp 126–153.
31. Duschek S, Reyes del Paso G: Quantification of cardiac baroreflex function at rest and during autonomic stimulation. *J Physiol Sci* 2007; **57**: 259–268.
32. Ducher M, Fauvel JP, Cerrutti C: Risk profile in hypertension genesis: a five-year follow-up study. *Am J Hypertens*

2006; **19**: 775–781.
33. Smit AA, Timmers HJ, Wieling W, *et al*: Long-term effects of carotid sinus denervation on arterial blood pressure in humans. *Circulation* 2002; **105**: 1329–1335.
34. Sharabi Y, Dendi R, Holmes C, Goldstein DS: Baroreflex failure as a late sequela of neck irradiation. *Hypertension* 2003; **42**: 110–116.
35. Reyes del Paso GA, González MI: Modification of baroreceptor cardiac reflex function by biofeedback. *Appl Psychophysiol Biofeedback* 2004; **29**: 197–211.
36. Reyes del Paso GA, Langewitz W, Robles H, Perez N: A between-subjects comparison of respiratory sinus arrythmia and baroreceptor cardiac reflex sensitivity as non-invasive measures of tonic parasympathetic cardiac control. *Int J Psychophysiol* 1996; **22**: 163–171.
37. Sleight P, La Rovere, MT, Mortara A, *et al*: Physiology and pathophysiology of heart rate and blood pressure variability in humans: is power spectral analysis largely an index of baroreceptor gain? *Clin Sci* 1995; **88**: 103–109.
38. Pinel JPJ: Biopsychology. Boston, Pearson Education, 2007.
39. Hugdahl K: Psychophysiology. Cambridge, Harvard University Press, 2001.
40. Cadalbert B: Die Psychophysiologie des niedrigen Blutdrucks: Kreislaufregulation, Lebensgewohnheiten und Beschwerden [The Psychophysiology of Low Blood Pressure: Cardiovascular Regulation, Life Style, and Complaints]. Frankfurt a.M., Peter Lang, 1997.
41. Duschek S, Hadjamu M, Schandry R: Enhancement of cerebral blood flow and cognitive performance due to pharmacological blood pressure elevation in chronic hypotension. *Psychophysiology* 2007; **44**: 145–153.
42. Duschek S, Schandry R: Cognitive performance and cerebral blood flow in essential hypotension. *Psychophysiology* 2004; **41**: 905–913.