Pol J Aviat Med Psychol 2013; 19(1): 49-54

REVIEW PAPER

USE OF LBNP MODEL FOR ASSESSMENT OF HUMAN ADAPTATION MECHANISMS WITH REGARD TO +GZ TOLERANCE

Bronisław TURSKI
Military Institute of Aviation Medicine, Warsaw, Poland

Source of support: Own sources

Author's address: B. Turski, Military Institute of Aviation Medicine, Krasińskiego 54/56 Street, 01-755 Warsaw, Poland, e-mail: bronislaw.turski@wiml.waw.pl

Background: Based on literature data and own experiences the author discussed selected hemodynamic reactions that take place in response to +Gz acceleration and application of lower body negative pressure (LBNP) through use of a vacuum capsule. Results of this research justify a thesis that circulatory system adaptive mechanisms taking place during +Gz acceleration are similar to those obtained during LBNP application.

Keywords: +Gz acceleration, lower body negative pressure (LBNP), adaptive mechanisms of circulatory system in response to a G-force stimulus

BACKGROUND

Negative effects of acceleration, particularly the centripetal forces acting in the head-lower limb axis, are some of the greatest problems of modern military aviation. Despite the use of various protective devices reducing the effects of G-force on a human body, it is an unavoidable factor that is present during each flight. Developments in aviation technology made it possible for modern airplanes to acquire accelerations that exceed the borders of human tolerance. Therefore, it is crucial to determine pilot's adaptation abilities with regard to G-tolerance and to recognize all possible physiological mechanisms that govern these reactions. One of the methods includes use of lower body negative pressure (LBNP) as a simulation of an orthostatic test. It enables precise observation of reactions that influence body's orthostatic tolerance. The difference of pressures acting on upper and lower parts of the body creates hemodynamic conditions that trigger various reactions constituting an integrated bodily response to a given stimulus. These reactions lead to, i.a. redis-

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tribution of certain amount of blood to the lower parts of the body as during acceleration. Volume of redistributed blood depends on the value of applied negative pressure. In order to assess these reactions a vacuum capsule with a regulated tilt table was designed and constructed in the Military Institute of Aviation Medicine [19]. Figure 1 presents the scheme of a vacuum capsule.

Military Institute of Aviation Medicine [11] allowed for concluding that orthostatic tests reflect the capability to maintain proper cardiac output and functioning of peripheral circulation, enabling the assessment of compensatory responses in the presence of +Gz-forces. It should be noted that the intensity of a reaction is different in case of a tilt test, during which volume of redistributed blood equals the value of hydrostatic blood pressure, while in the presence of G-force there is additionally the physical impact of acceleration itself. Yet another mechanism will be in place when a subject placed in a supine position will be subjected to negative pressure around the lower body using airtight capsule separating the upper part of the body from its lower part.

A pressure gradient between upper and lower body created during LBNP causes blood to relocate from higher-pressure region to the lower-pressure region according to the laws of physics, while supine position eliminates the hydrostatic blood pressure factor. Use of lower body negative pressure may be treated a simulation of an orthostatic test, during which adaptive bodily responses may be carefully studied, both with regard to hemodynamic as well as hormonal changes (19,20).

The degree of hemodynamic response during LBNP is greatly influenced by the renin-angiotensin-aldosterone system, which regulates blood pressure and has an effect on antidiuretic hormone – vasopressin (ADH) that until recently was ascribed a leading role in blood pressure regulation [6,22]. Conducted research led to a great breakthrough in the view of the role of systemic humoral factors in blood pressure regulation. This breakthrough involved discovery of atrial natriuretic peptide (ANP), a hormone isolated from cardiac atria characterized by hypotensive and natriuretic action [18]. Determination of ANP amino acid components allowed for producing specific antibodies for immunohistochemical localization of this peptide and its receptors in various organs. Finding ANP in periventricular regions of the central nervous system proved important for the regulation of circulation and water-electrolyte balance. Presence of ANP in the anteroventral area of the third ventricle and periventricular nucleus of the thalamus has a direct impact on proper

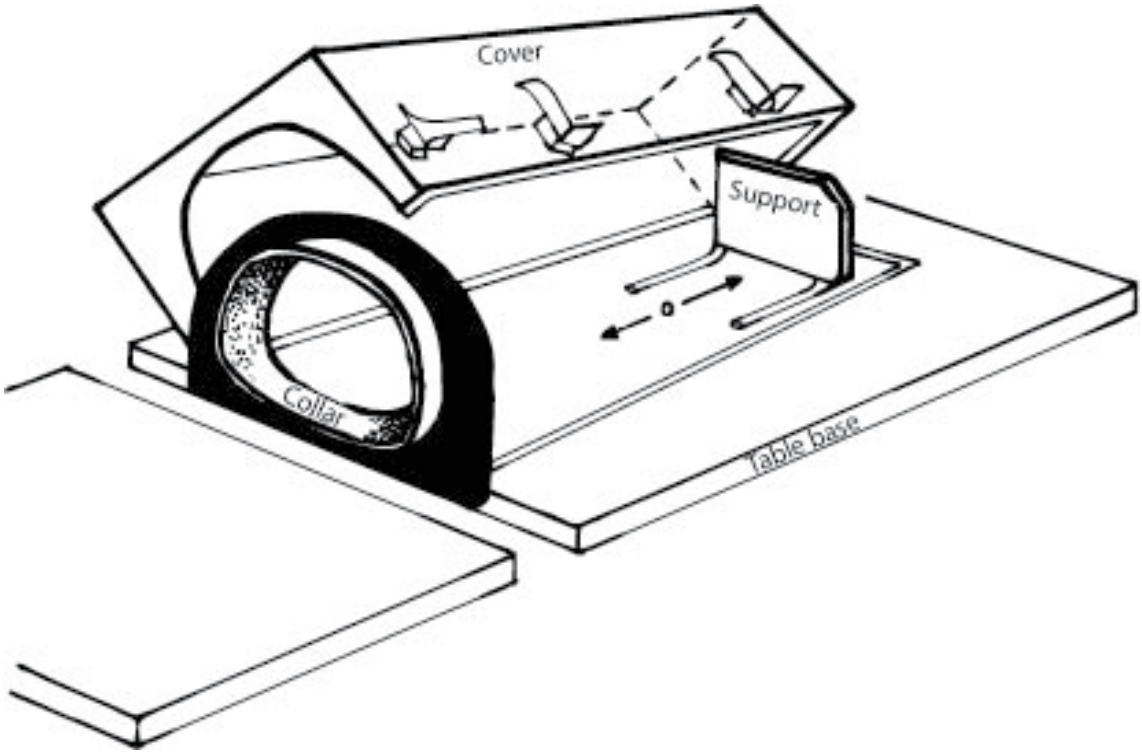

Fig. 1. The scheme of a vacuum capsule.

functioning of autonomic nervous system and vasopressin release [19], exhibiting a dominating role in blood pressure regulation. Mechanical stretching of atrial walls mostly due to increased venous return is the greatest stimulus for ANP release. This increased inflow of venous blood into the heart occurs, among other things, in the state of weightlessness during space flights and during prolonged hypodynamia. Hypogravity and hypodynamia facilitate increased blood flow in the central thoracic vessels stimulating increased ANP release, which has a crucial, immediate impact on blood pressure reduction through, i.a. massive diuresis and natriuresis, as well as dilatation of peripheral vessels [5]. Careful analysis of experimental data raises two observations: elevated pressure in heart atria is the main stimulus for increased ANP release, while infusion of exogenic ANP reduces this pressure. This suggests the presence of a feedback system within the heart regulating ventricular filling pressures through ANP, modeling vascular impedance and intracellular fluid volume. Lowering of atrial filling pressures by ANP leads to reduction in stroke volume (SV) and blood pressure via Frank-Starling mechanism [23]. It has been proposed that measuring ANP levels might serve as a sensitive method for determination of cardiovascular system function. Some authors believe that the main ANP action involves an increase in glomerular filtration rate, even in a presence of significantly reduced systemic blood pressure and decreased blood flow through the skin, which is always observed during intravenous infusion of this peptide. It appears that discovery of ANP significantly broadened the scope of knowledge on the activation of cardiac volume receptors reflected through changes in the volume and composition of excreted urine [18].

According to numerous research studies, vascular endothelium is not only a semipermeable membrane that maintains proper plasma oncotic pressure and prevents clotting, but most of all is an important endocrine organ actively taking part in vascular metabolism and blood pressure regulation. This system takes action in at least three areas – blood pressure regulation, extracellular fluid homeostasis and direct impact on the endocrine system [4]. Regulatory role of vascular endothelium has been confirmed by various studies, which demonstrated the presence of a vasoconstricting peptide in endothelial cell cultures.

Endothelin is a 21-amino-acid peptide with four cysteine residues forming a double disulfide bond. Area of action of endothelin receptors encompasses atrial smooth muscles. Endothelin receptor is located near voltage-dependent calcium channels. Endothelin is considered one of the strongest endothelium-derived factors for blood pressure elevation. It is the strongest- and longest-acting vasoconstricting factor discovered so far. This thesis is confirmed by studies showing constant level of endothelin in human blood and increase of its concentrations in arterial hypertension of various etiologies.

Sympathetic activation of renin-angiotensin-aldosterone system appears with prolonged exposition to negative pressure around the lower body [2,7]. Measurements of plasma renin activity showed a 3-7-fold increase in this activity compared to resting state, which indicates significant postural impact on adrenergic system activation [7]. Similar changes [2,4] were found with prolonged exposition to lower body negative pressure (LBNP). These changes [15] were demonstrated with negative pressures of -5 mmHg. Since an increase in LBNP to -10 mmHg does not evoke evident changes in high-pressure baroreceptor activity, vasoconstriction is ascribed to a small drop in central venous pressure that decreases the activity of vagal efferent fibers. Research studies demonstrated that resistance vessels in the calf do not constrict to the same extent as those in a forearm up to the point where the amount of blood in the lower body is sufficient to reduce activity of both low- and high-pressure baroreceptors. Such diversity of responses with low levels of LBNP may be associated with either decreased activity of efferent sympathetic fibers in resistance vessels of crural skeletal muscles or less pronounced synaptic reaction in the calf [7,8,9]. With further reduction of blood volume within thoracic cavity and decreased activity of low-pressure baroreceptors resistance vessels of the forearm and calf will constrict equally. Application of negative pressure ranging from -5 to -15 mmHg does not produce significant changes in blood pressure and heart rate, but only a gradual decrease in central venous pressure, which is related to increased activity of sympathetic innervation in the right calf [5]. A conclusion arises that low levels of negative pressure constitute a strong stimulus for the activity of sympathetic nerve fibers innervating muscles of both upper and lower limbs. Constriction of muscular vessels reaches maximum with -20 mmHg and further increase in negative pressure is of no significance. However, application of -50 mmHg of LBNP causes an increase in heart rate from 55 to 90 beats per minute, reduction of mean blood pressure from 94 to 81 mmHg, decrease in central

venous pressure from 7 to -3 mmHg and cardiac output from 6.1 to 3.7 l/min [7,18,19].

Studies conducted by many authors showed that carotid sinus baroreceptors do not participate notably in a vasoconstriction reflex of forearm vessels even at -40 mmHg [4,5]. Research conducted by various investigators demonstrated that using progressively increasing negative pressure stimulus and its gradual decrease at the same time intervals evokes a hemodynamic response that forms a closed loop on a graph and is known as hysteresis [16].

Both fluid volume redistribution and adaptation of cardiovascular system to LBNP conditions substantiate the presence of hysteresis phenomenon when simulated orthostatic stress proceeds gradually, rising and falling. Volumes of fluid in the lower part of the body are assessed based on a percentage change in calf volume on each LBNP level and were always higher at the rise of negative pressure than during its decline. On the contrary, changes in upper body volumes assessed on the basis of thoracic impedance became reduced as LBNP increased and grew as LBNP returned to resting values. Thoracic blood volume reduction in the course of negative pressure built-up is also reflected by a decrease in stroke volume and cardiac output as well as cardiac ejection time, suggesting that venous return decreases during prolonged, simulated orthostatic test. Total peripheral resistance also displays the hysteresis phenomenon expressed through a reflex reaction and aimed at maintenance of blood pressure in the presence of decreased cardiac output. Reduction of end-diastolic volume leads to lengthening of pre-ejection period (PEP). On the other hand, decrease in stroke volume (SV) leads to reduction of left ventricular ejection time (LVET). Echocardiographic measurements of end-diastolic and end-systolic volumes conducted at rest and in the presence of negative pressures imply that moderate levels of orthostatic stress evoke a reaction, which cannot be explained with Frank-Starling mechanisms [1].

Reduction of the circulating blood volume is ascribed to its accumulation in the venous system [9] or shifting of some of intravascular plasma water into the interstitial space.

Rise of transmural pressure in the lower part of the body is the direct cause of LBNP action, which is accompanied by venous congestion and reflex constriction of lower body arteries. This reaction is quite rapid and reversible. Final point of homeostatic equilibrium corresponding to a given level of negative pressure may only be reached when so-called "fast" and "slow" mechanisms reach a state of dynamic balance. Moreover, level of preceding simulated orthostatic stress may influence the time needed to attain the new balance, as the degree of extravascular fluid volume sequestration during LBNP is related to the previous state of fluid distribution.

Established evidence of rapidly- and slowly-escalating fluid redistribution during orthostatic stress allows for building a complex scheme of cardiovascular reactions and fluid distribution during exposition to LBNP [16]. Figure 2 presents a scheme of cardiovascular responses to LBNP according to Tomaselli [16].

Our own research comparing the centripetal +Gz-tolerance with LBNP test produced encouraging results that provide evidence for cardiovascular interrelationships in response to both of these stimuli. These studies showed two types of reactions depending on the magnitude of negative pressure stimulus, which differ both with regard to the speed as well as the intensity of central and peripheral circulatory system response.

Use of lower body negative pressure (LBNP) as a simulated orthostatic test for physiological studies introduced a new quality to the assessment of cardiovascular regulatory mechanisms. Studies conducted using LBNP in a supine position do not include the hydrostatic blood pressure factor, which plays an important role in determining the intensity of cardiovascular changes that occur following forced redistribution of certain blood volume to the lower limbs [21].

LBNP constitutes a valuable research model for the analysis of adaptive and compensatory mechanisms of both central and peripheral circulation. Under properly isolated, static conditions, freely controlling the size of the stimulus, one may evoke significant cardiovascular changes, which are completely and immediately reversible provided that adequate study regime, compensated by the system, is upheld. This is why cardiology and cardiosurgery clinics (examinations after coronary artery bypass procedures and other types of heart surgery) as well as physiological and neurophysiological research facilities use this device so readily. Aside from using LBNP in space, it is also utilized under earthly conditions, e.g. for the therapy of diabetic angiopathy in order to restore the patency of small vessels pathologically changed by the disease.

Taking into consideration the results of research conducted by many authors as well as own experience, a thesis may be put forth that use of lower body negative pressure is an excellent method for assessment of systemic physiological reactions

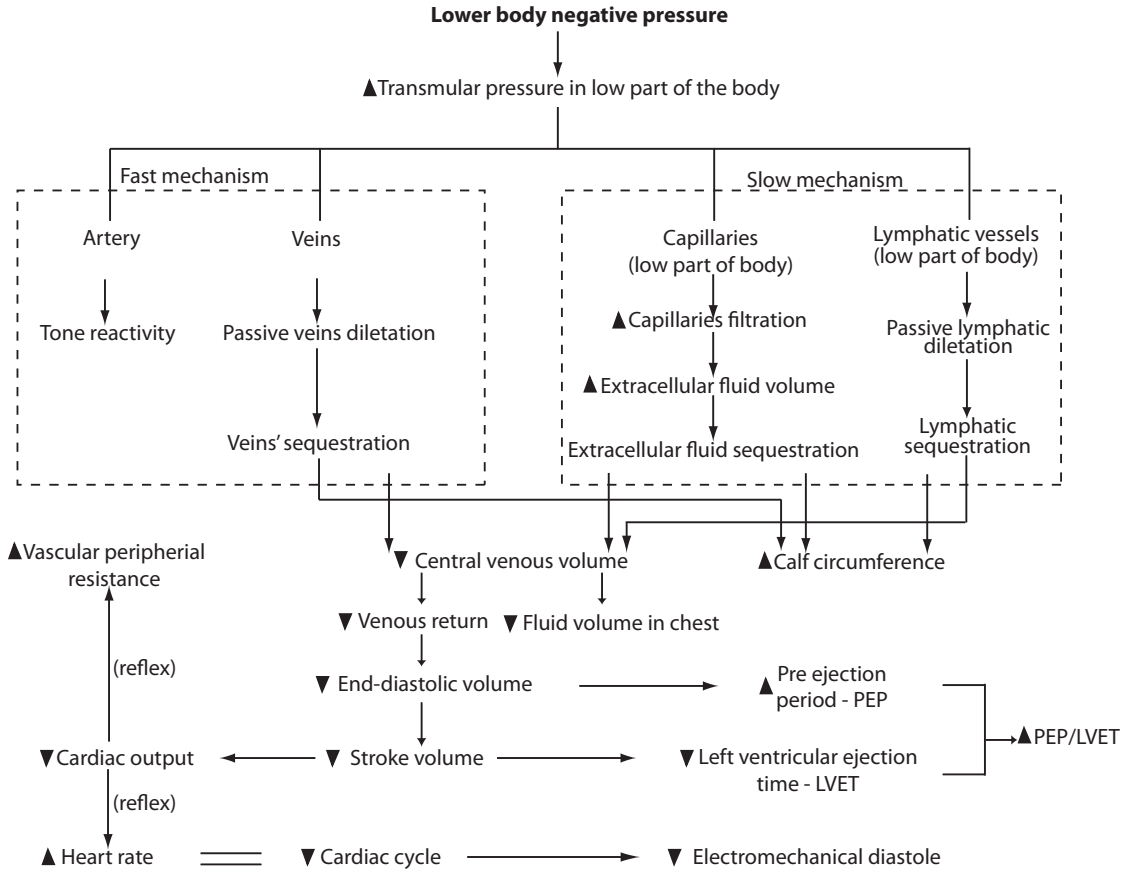

Fig. 2. LBNP according to Tomaselli.

that occur in response to this stimulus. Depending on the level of applied negative pressure we may observe the performance of human adaptation mechanisms, which are also present during +Gz acceleration. Comparison of the responses of those mechanisms revealed many similarities, which require further observations.

A multiple discriminant analysis was conducted due to a high similarity of mechanisms and reactions related to systemic tolerance to +Gz accelerations and to lower body negative pressure. Use of this statistical method allowed for selecting from each indicant measured during a 20-minute-long test those values that significantly differentiated between study groups. The following indicants were measured: arterial blood pressure, heart rate, thoracic impedance reography, non-standard electrocardiographic leads, phonocardiography, air pletysmography conducted on the middle finger of the right hand, percentage changes. Selected parameters acquired from various tests such as: percentage increase in peripheral pulse amplitude as well as percentage increase in pulse wave propagation time, percentage increase in the first derivative curve of the thoracic impedance signal, left ventricular pre-ejection period, left ventricular ejection time and mean arterial blood pressure calculated with Wezler equation.

Values of all variables from various periods of the study combined into a single data set became the starting point for discriminant analysis. Final analysis yielded six parameters that, as a set of variables taken altogether, in a highly significant manner ($P<0.01$) became the basis for the assessment of orthostatic tolerance in studied subjects and corroborated selection of subjects into appropriate groups created depending on +Gz tolerance variability. Accurateness of decision-making process during selection of subjects into appropriate groups based on those six parameters was 82.1%. This high proportion of correlation with classification conducted after centrifuge tests constitutes a proof of appropriate choice of measured physiological indicants for differentiation between groups and confirms the usefulness of LBNP test in the assessment of orthostatic reaction of a human body [17].

AUTHORS' DECLARATION:

Study Design: Bronisław Turski; **Data Collection:** Bronisław Turski; **Statistical Analysis:** Bronisław Turski; **Manuscript Preparation:** Bronisław Turski; **Funds Collection:** Bronisław Turski. The Author declares that there is no conflict of interest.

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Cite this article as: Turski B: Use of LBNP model for assessment of human adaptation mechanisms with regard to +Gz tolerance. Pol J Aviat Med Psychol, 2013; 19(1): 49-54.