

## سازوکارهای فعالیت، زیست مکانیک و تنظیم موضعی سیاهرگها

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### چکیده:

- بسیاری از فعالیت‌های سیاهرگی از طبیعتی زیست مکانیکی برخوردار بوده و یا خیلی وابسته به نیروهای زیست مکانیکی (همودینامیکی) هستند. این موارد عبارتند از
- ۱- کانال خونی و جمع‌کننده‌هایی با دریچه‌های یکسوکننده جریان
  - ۲- ثابت نگه‌داشتن فشار پرشدگی قلب راست با وجود تفاوت‌های بزرگ در برون‌ده قلبی، بوسیله تنظیم بازگشت وریدی، قدرت بافری فشار سرخرگی
  - ۳- عملکرد ذخیره‌ای، توزیع مجدد حجم خون
  - ۴- مقاومت بعد مویرگی
  - ۵- تبادل بین مویرگی مواد، سد انتخابی
  - ۶- انتقال از طریق دیواره رگها
  - ۷- رگ‌سازی
  - ۸- ساخت مواد بیولوژیک فعال توسط آندوتلیوم، عضله صاف و *Pericytes* (برای مثال: *EDNO*، آندوتلین، ایکوزانوئیدها، فاکتورهای رشد، مواد ماتریکس و غیره).
  - ۹- همکاری بین آندوتلیوم وریدها و *PMNL-s* (حاشیه‌نشینی و *Rolling*)
  - ۱۰- مهار واکنش‌های تورم‌مبواًمبولیک
  - ۱۱- حفظ تحمل وضعیت ایستاده
  - ۱۲- سیستمی مؤثر در سازگاری و تطبیق با حالت‌های چالش‌زای بدن (برای مثال تمرینات فیزیکی، تنظیم حرارت)
  - ۱۳- فعالیت‌های موضعی اختصاصی (برای مثال: ونول‌های پس از آندوتلیال، *homing* سیاهرگ صورت، تنظیم حرارت جمجمه‌ای، گرفتگی هیجانی).
- سازوکارهای موضعی که زیست مکانیک سیاهرگ‌ها را تحت کنترل دارند عبارتند از:
- الف- مکانیکی      ب- هورمونی      ج- یونی      د- متابولیکی      ه- فرآیندهای عصبی
- نشان داده شده‌است که رفتارهای بیومکانیکی وریدها در پاسخ به چندین فاکتور فیزیولوژیک و شرایطی از قبیل درجه حرارت محیط، حاملگی، سن، اندازه بدن، افزایش مزمن بار گرانشی و تمرینات طولانی‌مدت فیزیکی و حتی در برخی شرایط پاتوفیزیولوژیک (برای مثال بیماری فشار خون تجربی و انسانی) بطور سازگارانه‌ای تغییر می‌کند.
- کلید واژه‌ها: ۱- فعالیت وریدها      ۲- زیست مکانیک  
۳- خودتنظیمی      ۴- گردش خون

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## INTRODUCTION

In the human organism, about 65-75% of the total blood volume is localized within the highly distensible, low pressure venous vessel network of approximately 450-500 Km length. About 25-50% of this blood volume is distributed in small veins and venules<sup>(48,49)</sup>, Therefore, it is obvious that elucidation of the biomechanical behavior and physiological control of the veins of different types is essential for understanding their functions under normal and pathological conditions<sup>(37)</sup>.

Recently, clinical practice also stimulates the research in this field for several reasons. For example, healthy vein segments are frequently used as arterial prostheses (aorto-coronary and femoro-popliteal bypasses, etc.). The hemodynamic functioning and patency rate of these vein segments depend significantly on their passive and active biomechanical properties<sup>(6,39,59)</sup>. The incidence of vein diseases - varicosity, superficial thrombophlebitis, primary deep vein incompetence or obstruction, deep vein thrombosis, venous ulceration, phlebosclerosis, venous injuries, orthostatic intolerance, etc. - is extremely high, in many countries it exceeds that of the arterial morbidity by an order of magnitude. In Hungary, the mortality rate due to venous pathology have shown a dangerously increasing tendency during the last two decades: it has doubled since 1970<sup>(35)</sup>. Data

of the literature indicate that different biomechanical anomalies of the venous wall are addition, certain biomechanical malfunctions of the veins may contribute even to arterial diseases, like development and maintenance of arterial hypertension<sup>(50,52,53)</sup>

### Physiological functions of the veins

Many of the venous functions are biomechanical in their nature and/or related closely to biomchanical (hemodynamic) forces<sup>(38)</sup>. The proven and assumed physiological functions of the venous system at different organization - organismic, organ, tissue, vascular wall, and cellular - levels are as follows:

1. Blood collector (conduit) with flow -rectifying valves;
2. Maintenance of filling pressure for the right heart by controlling venous return in the face of widely varying cardiac output;
3. Buffering the arterial pressure;
4. Regulated capacity function: distribution of circulating blood volume reserve;
5. Supporting the orthostatic tolerance of the organism via venous muscle pumps, pressure dependent myogenic tone, veniarteriolar and segmental neural reflexes, etc;
6. Adaptation to whole body challen -ges as an effector system (e.g. physical exercise,

stress);

7. Contribution of the rich subcutaneous venous plexus to the thermoregulation of the organism via a countercurrent heat-exchanger mechanism;

8. Control of hydrostatic pressure in the exchange vessels with the venular postcapillary resistance function;

9. Venular contribution to transcapillary exchange of materials (reabsorption);

10. Formation of a selective barrier between intra- and extravascular compartments;

11. Transmural transport of materials;

12. Angiogenesis in the venular section of the microcirculation;

13. Synthesis of biologically active substances by the endothelium, smooth muscle cells and pericytes (e.g. NO, endothelium derived hyperpolarizing factor, endothelin, eicosanoids including the products of cyclooxygenase, lipoxygenase, and cytochrome monooxygenase pathways, adrenomedullin, plasminogen activators and inhibitors, growth factors, platelet-activating factor, matrix materials including collagen, elastin, glycoproteins, proteoglycans, etc.);

14. Cooperation between venous endothelium and polymorphonuclear leukocytes (margination and rolling);

15. Controlling thromboembolic reactions on the endothelial surface e.g. by inhibiting platelet aggregation, or by

accelerating thrombus formation after damages of the vascular wall;

16. Immune functions (e.g. homing: organ specific distribution of circulating effector lymphocytes via the high endothelial venules in the secondary lymphoid organs);

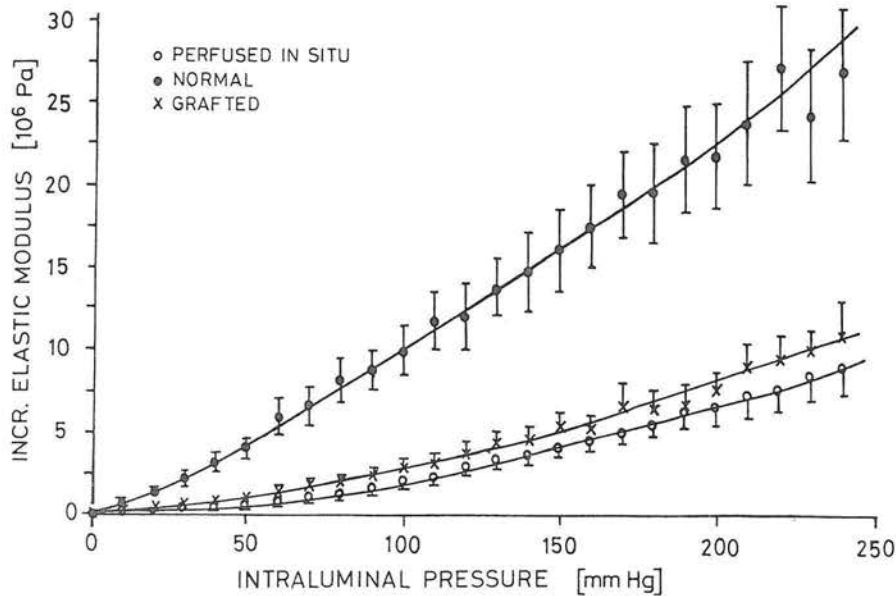
17. Special regional functions (e.g. possible contribution of the facial vein myogenicity to cranial thermoregulation or/and to emotional flushing, portal venous functions in the hepatic, hypothalamo hypophyseal, and other local circulations, ectopic pacemaker activity of the media of caval and pulmonary veins, antisiphonage function of the jugular vein).

### Basic characteristics of venous biomechanics

The shape of the pressure-diameter curves and the derived mechanical stress-strain functions of veins differ substantially from those obtained in arteries of the same order<sup>(13,36)</sup>. Due to the much larger radius/wall thickness ratio (i.e. thinner wall and larger radius), and to the higher incremental distensibility in the low transmural pressure range (1-50 mmHg), the mean tangential stress and elastic modulus (normalized stiffness) values of normal healthy veins greatly exceed the stresses and moduli determined for the arteries at the same transmural pressure levels<sup>(1,39)</sup>. It is noteworthy that in the vein

segments grafted into arteries, long-term exposure to the high pressure loads significantly reduces the above mentioned differences in the isobaric biomechanical parameters (Fig. 1). because the radius/wall

thickness ratio in the vein graft decreases substantially and rearrangement of the viscoelastic structures occurs within 1-2 weeks (39,40,46).



**Figure.1** Incremental elastic moduli (mean  $\pm$  SEM) of normal, grafted, and in situ perfused canine vein segments. Both the autolog grafted (end-to-end) and the in situ perfused veins (end-to-side arterial anastomoses) were maintained in the arterial circulation for several weeks before excision. Quasi-static large-deformation mechanical test was applied in order to determine biomechanical properties of the vessels in vitro.

Presumably, developing in the grafted vein wall reflects the operation of a physiological adaptation mechanism which tends to normalize the extremely high tangential stress under arterial pressure loading. This assumption is supported also by some experimental evidence, showing that certain morphological and biochemical alterations of the grafted veins are of reversible character (11).

The propagation velocity of pressure

waves along the large veins takes approximately 2 m/sec at physiological mean venous pressure level, and shows marked local variability as compared to the arteries (34,45). This is due to the highly non-linear nature of the incremental distensibility of these veins. Furthermore, the local pressure fluctuations and the pressure differences between anatomically closely related regions are relatively high in the large veins even under physiological

conditions. Viscoelastic properties of consecutive sections of the veins in certain regions also exhibit substantial differences. For example, elastic stiffness of the perivalvular regions of the saphenous vein wall is approximately 50% lower than that calculated for other segments of the same vein<sup>(47)</sup>.

Recent studies on isolated cylindrical vein segments indicate that biomechanical properties of the passive connective tissue components (collagen, elastin, intercellular matrix) of the vascular wall, its instantaneous smooth muscle tone, and the axial extension ratio of these segments greatly influence the pressure-volume characteristics, while contribution of the endothelium to the passive wall mechanics seems to be negligible<sup>(29)</sup>. At normal physiological conditions, when the smooth muscle tone is present, the role of adventitial collagen is probably negligible in hemodynamic stress bearing function of the vein wall compared to the role of elastin and the vascular smooth muscle itself. The significance of the longitudinal extension ratio of the veins in affecting their active tangential stress-strain characteristics has also been demonstrated recently<sup>(43)</sup>. Apart from the extrinsic neurogenic and humoral tone, certain veins also exhibit pronounced intrinsic tone, which can be substantially affected by acute and chronic hemodynamic loads on the vessel wall<sup>(2,9,10,37,41,42)</sup>. Consequently,

stress-strain or pressure-volume relationships of the vein wall can not be appropriately characterized, neither *in vivo*, nor *in vitro*, without defining the contractile state present in the vascular smooth muscle.

Active change in venous capacitance is obviously one of the important mechanisms which influence the venous return. The maximum systemic reflex response of the venous capacitance is estimated as about 5 ml/kg in humans<sup>(23)</sup>. Skeletal muscle veins might play only a minor role in the reflex regulation of vascular capacitance<sup>(24,32,33)</sup>, their sympathetic noradrenergic contractile response is relatively low<sup>(3,33)</sup>. In contrast to the above observations on the veins of the extremities, the mesenteric venous circulation seems to have a key function in the reflex control of the vascular capacity (i.e., it contains at least 25% of the total blood volume). Compliance and capacity characteristics of the intestinal venules (at least in rats) are primarily controlled by the sympathetic nervous activity<sup>(51)</sup>. This observation is supported by baroreflex studies performed in dogs<sup>(7)</sup>. Activation of the baroreceptor reflex elicits contraction of the intestinal venules, which is responsible for about 80% of the blood volume shift in the intestinal vascular bed<sup>(22)</sup>. Hemorrhage induces a substantial venoconstriction of hepatic capacitance vessels probably via multiple arterial and venous mechanoreceptors and chemoreceptors in Cats<sup>(19,20)</sup>.

Hormones (e.g. vasopressin) are also known to cause significant changes in the capacitance of the splanchnic vessels<sup>(57)</sup>

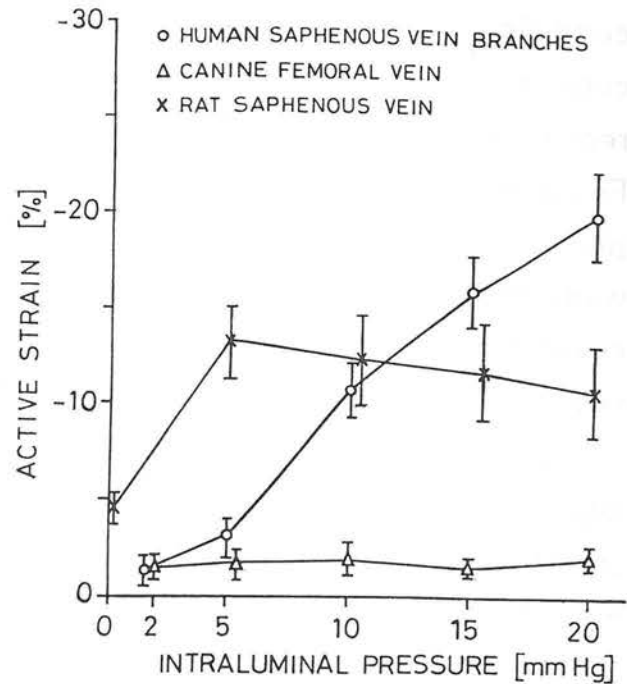
### Local control mechanisms of the venous tone

Local mechanisms controlling venous biomechanics may include processes<sup>(37,38)</sup>. The detailed discussion of the last four aspects is out of the scope of this paper.

Using a special glass microelectrode set-up and computer aided videomicroangiometry, both in vivo and in vitro studies indicate that a sudden intraluminal pressure increase in the physiological range may induce a substantial depolarization of the smooth muscle membrane and an endothelium independent active tone (Fig.2.) in certain veins of human and animal extremities<sup>(2,37,41)</sup>.

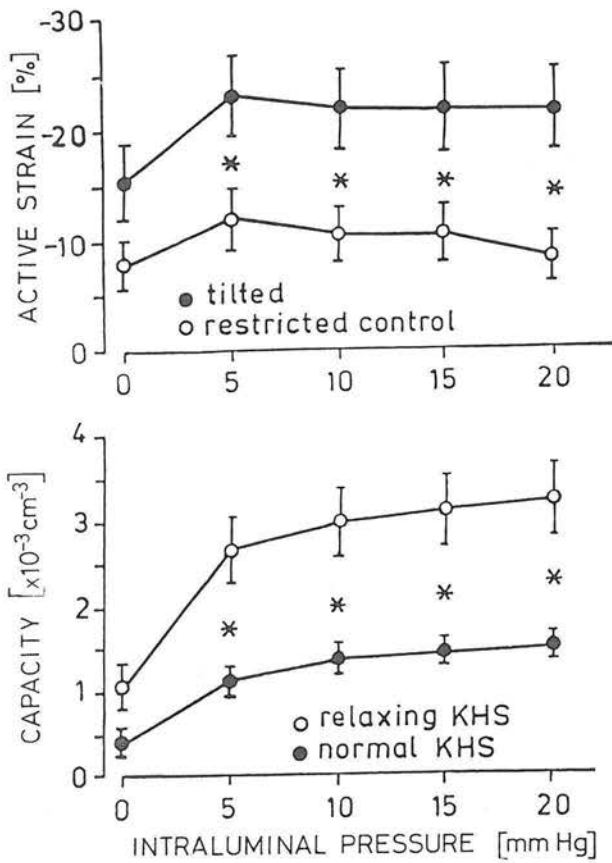
Norepinephrine and the endothelium may modulate substantially the venular myogenic response<sup>(10)</sup>. These observations provide evidence for the existence of a pressure induced myogenic capacity autoregulation in the venous system.

Long-term elevation of the venous pressure in the physiological range, induced by sustained "head-up" tilting of rats (Fig.3.), significantly enhances the acute pressure induced myogenic contractile responses of saphenous vein segments<sup>(42)</sup>.



*Figure.2 Pressure induced myogenic response of perfused and superfused isolated segments of human saphenous vein branches, as well as canine femoral and rat saphenous vein branches, as well as canine femoral and rat saphenous veins. The myogenic tone is quantitated in isobaric active tangential strain (mean  $\pm$  SEM). Endothelial damage with air bubble did not influence the response of the human vein branches significantly (not shown).*

This adaptive myogenic mechanism may increase substantially the orthostatic tolerance of the body, exposed to sustained erect position. Chronic gravitational increases in venous pressure may also cause a remodelling of the microcirculation: capillary rarefaction was found in oxydative hind limb muscles of rats tilted head-up in long tube-like cages for three weeks<sup>(27)</sup>.



**Figure .3 Pressure induced myogenic response(top) and the concomitant change in lumen capacity (bottom) of saphenous vein segments from rats maintained 45 °C head-up in special tilt cages for two weeks. Similarly to Fig. 2., the myogenic tone is given in isobaric active tangential strain.**

Long-term (30 days) "head down tilt, simulating certain aspects of microgravity, induced an increase of the venous capacity in the lower limbs of human subjects. This change is probably due to a decrease in tone of the vascular smooth muscle and of the adjacent skeletal muscle, which observation is in line with those made in human subjects during space flight<sup>(30)</sup>.

In contrast to the depolarizing effect of tangential stretch due to increased transmural pressure, a larger than 20% local stepwise longitudinal hyperpolarization of the smooth muscle cell membrane and a decrease in the vascular tone in vivo. The same applies to the artery. Local endothelium damage with air bubble reverses this response to depolarization and to an increase in vascular tone<sup>(37,43)</sup>. This mechanism which is probably activated by increased shear stress via the endothelium may provide protection against vasospasm when the vessels are locally overstretched. (Laser-doppler flow measurements proved that the in vivo extension of a vessel segment results in an increase of local linear blood flow velocity, certainly due to the elevated pressure gradient - a Pitot-tube phenomenon.) There is evidence revealing that changes in blood flow velocity may affect local venular tone independently of the pressure<sup>(9,21)</sup>.

Biomechanical properties and local control processes of the veins may change in an adaptive manner in different physiological conditions.

Ambient temperature affects significantly the in vivo distensibility of the veins: at lower temperature (24 °C) the distensibility of human forearm veins was only one-half of that measured at high temperature (35 °C) using single-strand mercury-in-silastic plethysmograph. The difference can be explained by changes in the vascular smooth

muscle tone develops sustained myogenic tone which is very sensitive to small changes of the temperature in the range of 33-44 °C. This vein may function as a temperature sensitive sphincter which distributes cooled nasal venous blood head, aiding cerebral thermoregulation<sup>(58)</sup>.

In pregnancy the compliance of the small mesenteric veins of the rat decreases by 40% and their unloaded lumen volume doubles in comparison with those from non-pregnant females<sup>(26)</sup>. Data of noninvasive studies, employing three different methods (ultrasonography, venous - occlusion -plethysmography, and light- reflexion -rheography) indicate that distensibility of the lower extremity veins is somewhat higher in multipara than in primipara women<sup>(28)</sup>. A cause - effect relationship between higher vein distensibility, the frequently occurring secondary valvular insufficiency, and resulting varicosity is assumed<sup>(18)</sup>. Others, however, prefer to accept the view that decreased elasticity of the veins is involved in the development of the varicosity prior to valvular incompetence<sup>(5)</sup>. Biochemical and functional anomalies of the vein wall may contribute to the development of varicosity as well<sup>(31)</sup>.

The biomechanical properties of the vein wall also depend on the age newborn lambs significantly increases during the first month after birth<sup>(56)</sup>. In adult rats (30 month old vs. 10 months old), the total "baselinë venous

compliance (mean circula- tory filling pressure determinations at different blood of the forearm veins in elderly patients, however, is significantly lower than that of young individuals<sup>(14)</sup>. The circumferential tensile strength of isolated vein wall samples obtained from adult humans is also related to age<sup>(8)</sup>. The physiology of vascular aging, including systemic vein and blood volume data, has been reviewed recently<sup>(12)</sup>.

The size of the body also affects the caliber of the veins: data of femoral vein in healthy adults shows closer correlation with body size, than that of the jugular vein<sup>(44)</sup>. These studies, however, failed to reveal any correlation between in vivo vein distensibility on the one hand (15 degree acute tilt tests), and the type of the vessel, the sex, or the age on the other hand.

An increased gravitational load induced by 45 degree "head up" tilt, doubles the veous pressure in the lower extremities of rats; in two weeks the passive lumen volume of the saphenous vein increases by approximately 60% (the wall thickness does not change substantially), while the incremental distensibility decreases in the 5-10 mmHg intraluminal pressure range<sup>(42)</sup>.

Long-term strenuous physical exercise which is known to increase blood volume markedly enhances the passive lumen volume of the large abdominal visceral veins in dogs, whilst the changes in other passive

mechanical parameters are negligible. Biomechanics of the arteries and head veins are not affected significantly<sup>(54)</sup>. Using venous occlusion plethysmography with radionuclide, correlation was found between the specific compliance of human forearm veins - used as an estimate of systemic venous compliance - and the work tolerance<sup>(55)</sup>.

### GENERAL CONCLUSION

During the last few years valuable information has been progressively accumulated in relation to the biomechanical properties, functions and physiological control of the veins. A large number of excellent and stimulating data was published in this field of research. We have good reasons to believe that the fast accumulation of reliable experimental and clinical data about this very important topic reaches soon a new critical level, and then, even a more effective integration of our knowledge will be possible than at present.

### ACKNOWLEDGEMENT

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