Research article/Raziskovalni prispevek

CENTRAL AND LOCAL MICROVASCULAR REACTIVITY IN NORMOTENSIVE SUBJECTS WITH A FAMILY HISTORY OF HYPERTENSION

CENTRALNI IN LOKALNI VPLIVI NA ODZIVNOST DROBNEGA ŽILJA PRI NORMOTONIKIH, DRUŽINSKO OBREMENJENIH S HIPERTENZIJO

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Key words: *hypertension; cutaneous microcirculation; vasomotion; laser-Doppler flowmetry; heart rate variability*

Abstract – Background. *Using the laser-Doppler method we measured blood flow on the nailfold skin to compare the reactivity of cutaneous microcirculation between normotensive subjects with a familial predisposition to hypertension and normotensive subjects without a familial predisposition to hypertension.*

Methods. *Three groups of normotensive subjects were included in the study: 11 subjects with a familial predisposition to hypertension without a previous record of high blood pressure, six predisposed subjects with a previous record of high blood pressure and 13 subjects with no predisposition to hypertension. The flow was measured after direct and indirect skin cooling and heating and during postocclusive reactive hyperemia (PRH) after a ten-minute occlusion of digital arteries. The frequency of flow oscillations in the second part of the PRH was established. Heart rate spectral analysis was performed based on the monitoring of the peripheral pulse frequency by means of the finapres device.*

Results. *In comparison to the other two groups of subjects, the group with a predisposition and a previous record of high blood pressure displayed a larger surface area in the low frequency band (0.05 to 0.15 Hz) of the heart rate variability power spectrum (the Bonferroni test, $p < 0.05$). As compared to subjects without predisposition, both groups of predisposed subjects exhibit higher frequency of flow oscillations in the second part of the PRH (the Bonferroni test, $p < 0.05$).*

Conclusions. *We conclude that there is a change in cutaneous microvascular reactivity of local (most probably myogenic) origin in normotensive subjects with a predisposition to hypertension, whereas normotensives with a predisposition and a previous record of high blood pressure exhibit also different cutaneous microvascular reactivity of central (non-vascular) origin.*

Ključne besede: *hipertenzija; kožna mikrocirkulacija; vazomocija; lasersko-doplersko merjenje pretoka; variabilnost srčne frekvence*

Izvleček – Izhodišča. *Z lasersko-doplersko metodo merjenja pretoka smo primerjali odzivnost drobnega žilja kože med normotoniki, ki so družinsko obremenjeni s hipertenzijo, in normotenzivnimi preiskovanci brez take obremenitve.*

Metode. *V študijo smo vključili tri skupine normotenzivnih preiskovancev: v prvi skupini je bilo 11 normotonikov, družinsko obremenjenih s hipertenzijo, ki jim doslej še niso namerili povišane vrednosti krvnega tlaka, v drugi skupini je bilo 6 družinsko obremenjenih normotonikov, ki so jim v preteklosti že izmerili povišano vrednost krvnega tlaka, v tretji skupini pa je bilo 13 normotonikov brez družinske obremenitve s hipertenzijo. Morebitno prisotnost strukturnih sprememb drobnega žilja smo ocenili z merjenjem pretoka po lokalnem gretju kože do 40°C, in največjega pretoka v prvem delu pookluzivne reaktivne hiperemije (PRH) po deset minut trajajočem arterijskem zažemu. Za proučitev centralnih vplivov na odzivnost drobnega žilja smo merili kožni pretok po sistemskem ohlajanju in gretju ter opravili spektralno analizo variabilnosti srčne frekvence, določene s spremljanjem frekvence perifernega pulza s finapres aparatom. S Fourierjevo frekvenčno analizo 50 sekund dolgih zapisov pretoka smo določili prevladujočo frekvenco nihanj pretoka v drugem delu PRH, ki nam je služila kot indikator lokalnih (miogenih) vplivov na odzivnost drobnega žilja.*

Rezultati. *Pretok po lokalnem gretju kože in največji pretok v prvem delu PRH se med skupinami nista statistično pomembno razlikovala. Obremenjeni preiskovanci z že izmerjeno povišano vrednostjo tlaka so kazali značilno večjo vrednost površine v nizkofrekventnem delu močnostnega spektra variabilnosti frekvence srca (Bonferroni test, $p < 0,05$) in pomembno večjo frekvenco nihanj pretoka v drugem delu PRH (Bonferroni test, $p < 0,05$) v primerjavi z ostalimi preiskovanci.*

Zaključki. *Sklepamo, da pri normotonikih, družinsko obremenjenih s hipertenzijo, strukturne spremembe drobnih žil še niso prisotne. Dokazali pa smo spremenjeno odzivnost drobnih žil kože miogenega in izvenžilnega (centralnega) izvora pri normotonikih, družinsko obremenjenih s hipertenzijo, ki*

so jim v preteklosti že izmerili povišane vrednosti krvnega tlaka. Ti izsledki govorijo v prid prizadetosti v žilni steni in izven nje (centralno) že pri obremenjenih normotonikih, ki so jim že izmerili povišane vrednosti krvnega tlaka.

Introduction

The etiology of essential hypertension is still not completely clear. The proponents of central hypothesis claim that primary disturbance lies within central regulation of haemodynamics. On the other hand some other studies have shown that microcirculation might be of primary importance in essential hypertension development.

In agreement with central explanation of hypertension development are some studies on spectral analysis of heart rate variability. These studies are based on fact, that the heart rate variability is significantly influenced by the autonomic nervous system activity (1). The low frequency band of the heart rate variability power spectrum (0.05 to 0.15 Hz) is under combined control of sympathetic and parasympathetic parts of autonomic nervous system. On the other hand in the high frequency band (0.15 to 0.4 Hz) the parasympathetic part plays the predominant role. In young hypertensive subjects the balance of sympathetic versus parasympathetic activity, as assessed by heart rate variability, has been shown to be shifted in favor of the former (2). It might be possible that more pronounced microvascular reactivity in hypertension is caused by increased sympathetic activity (3, 4). Thermoregulation response is important predominantly as a tool of studying structural and functional local (microvascular) changes in hypertension (5). Local skin heating causes cutaneous vasodilatation, which is most pronounced at skin temperature of about 40° C. Skin heating above this temperature does not cause any further increase in skin blood flow. Therefore, reduced maximal skin blood flow is used as an indicator of structural microvascular changes in established hypertension.

Postocclusive reactive hyperemia (PRH) is a transient increase in blood flow after the release of arterial occlusion. PRH is a local phenomenon (6) and could be divided into two different parts (Fig. 1). Using arm vein occlusive plethismography the reduced peak blood flow in the first part of the PRH in hypertensives was proved, what has been ascribed to the structural vascular changes (7, 8). Other researchers also agree, that developed hypertension is characterized by structural microvascular changes. On the other hand there is still no agreement about the existence of eventual structural microvascular changes in pre-hypertensive stage of hypertension development. On the contrary to the plethismography more accurate laser-Doppler flow measurement did not show any difference in the peak skin blood flow of the first part of the PRH between borderline hypertensives and normotensive subjects (9).

The majority of studies proved increased microvascular reactivity at the initial stages of hypertension development. Local skin cooling provoked more pronounced vasoconstriction in hypertensives at the beginning of the disease as compared to normotensives (10). Increased reactivity of vascular smooth muscles could also be the consequence of their different intrinsic properties. The most important might be the pronounced myogenic mechanism of flow autoregulation (11, 12). It was show by our previous study on healthy volunteers using laser-Doppler flow measurement that stronger myogenic stimulus provoked flow oscillations with higher frequency in the second part of the PRH (13). Therefore, it is our opinion, that the frequency of the flow oscillations in the second part of the PRH is an indicator of myogenic microvascular reactivity.

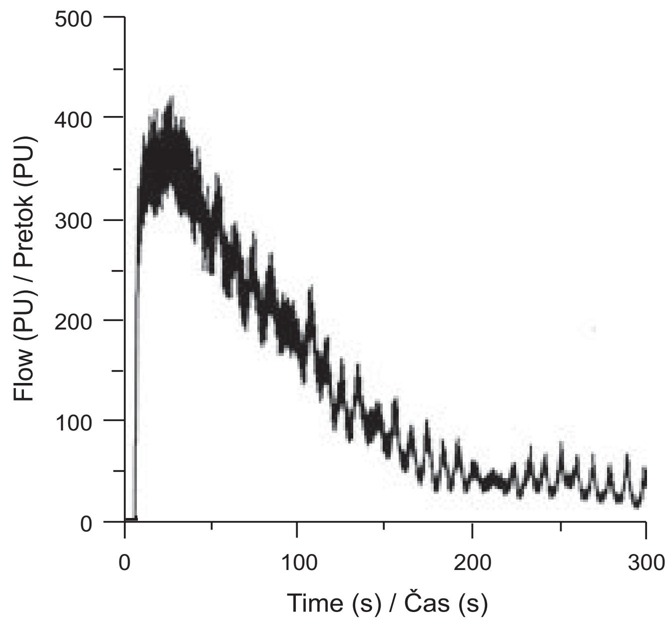

Fig. 1. *Example of the laser-Doppler flow recording obtained after a ten-minute occlusion of digital arteries. Two parts of the postocclusive reactive hyperemia (PRH) are readily distinguishable: the first part is characterized by the peak flow and the second part by the occurrence of the periodic flow oscillations.*

Sl. 1. *Primer lasersko-doplerskega vzorca pretoka po sprostitvi desetminutnega arterijskega zažema. Vidna sta dva dela pookluzijske reaktivne hiperemije (PRH): za prvi del je značilen največji pretok, za drugi del pa periodična nihanja pretoka.*

Methods

Three groups of normotensive subjects were included in the study: in the group A there were 13 normotensives without a family history of hypertension, in the group B there were 11 normotensives with a family history of hypertension without any known previous record of blood pressure above 140/90 mm Hg, and in the group C there were 6 familial predisposed normotensives in which blood pressure exceeding 140/90 mm Hg had been recorded at least twice in the past. A positive familial predisposition for hypertension was considered when at least one of the subject's parents took antihypertensive drugs starting at the age of 55 years or erlier. Informed consent was obtained from each subject. The investigation conforms with the principles outlined in the Declaration of Helsinki.

To measure cutaneous microcirculation flow on the nailfold skin of the right-hand index finger the laser-Doppler (LD) flowmeter (Periflux PF3, Ohmeda, Stockholm, Sweden) was used. A digital thermometer measured skin temperature on the right-hand index finger. Blood pressure of the upper arm was measured with a mercury sphygmomanometer. To occlude digital arteries on the index finger a 2 cm cuff was applied. We performed direct and indirect skin cooling and heating, respectively, by water, which had been previously cooled to 15°

C and heated to 42° C, respectively. For a continuous measurement of systolic, diastolic and mean arterial pressure on digital arteries as well as the heart rate a finapres device (The Ohmeda 2300 Finapres Blood Pressure Monitor, Ohmeda, Stockholm, Sweden) was used.

Using the computer program written by ing. Dane Peterec from Institute of Physiology the PRH curve was drawn and the peak flow in the first part of the PRH was determined. After a program filtering in the frequency band between 0.05 and 0.3 Hz the frequency of oscillations in the second part of the PRH was defined from this curve as the number of peaks in a 50-second interval.

The heart rate variability power spectrum was drawn by the finapres software (Neurocard program). Spectral areas in the low frequency and the high frequency bands of the spectrum were calculated.

Statistical analyses were performed by the SPSS statistical package. Mean values for the resting flow, flows after direct heating and cooling as well as after indirect skin heating and cooling, the peak flow after the release of the occlusion and the frequency of oscillations in the second part of the PRH were calculated for each group of subjects. By means of the Bonferroni test allowing multiple comparisons we looked for a significant difference with a 95% confidence interval for the aforementioned parameters among the three groups of subjects. When the parameter distribution was not normal, data were evaluated for statistical analysis after natural logarithmic transformation or the nonparametric test for multiple comparisons (Kruskal-Wallis test) was used.

Results

General data on subjects. Table 1 shows that there were significantly higher values of systolic and diastolic blood pressure measured on the upper arm by mercury sphygmomanometer in group C as compared to the other two groups of subjects, even though both systolic and diastolic pressures were still in normotensive range in all groups. No significant differences in the heart rate and the resting blood flow were found among the three groups of subjects.

Tab. 1. *General data on subjects.*

Tab. 1. *Splošni podatki o preiskovancih.*

	Group A Skupina A	Group B Skupina B	Group C Skupina C	Significance Signifikantnost
Age (years) Starost (leta)	26.83 ± 1.33	26.27 ± 3.07	27.85 ± 3.60	ns
Skin temp. (°C) Temperatura kože (° C)	30.09 ± 3.56	30.06 ± 2.92	30.55 ± 3.43	ns
Pd-upper arm (mm Hg) Diastolični tlak – roka (mm Hg)	77.23 ± 7.80	77.91 ± 8.03	84.00 ± 5.59	C:B*, C:A*
Ps-upper arm (mm Hg) Sistolični tlak – roka (mm Hg)	114.69 ± 11.78	118.45 ± 10.34	129.17 ± 8.99	C:B*, C:A*
Heart rate (min^{-1}) Pulz (min^{-1})	72.50 ± 11.33	63.20 ± 10.55	67.60 ± 7.57	ns
Resting LD flow (PU) Pretok krvi v mirovanju	45.05 ± 29.12	67.98 ± 49.01	40.03 ± 22.26	ns

All values shown are mean values ± standard deviation. * – significant difference between the relevant two groups, ns – statistically nonsignificant, ps – systolic blood pressure, pd – diastolic blood pressure, PU – perfusion unit.

Vrednosti so podane kot srednja vrednost ± standardna deviacija. * – statistično značilna razlika med določenima skupinama preiskovancev, ns – statistično neznačilno, ps – sistolični tlak, pd – diastolični tlak, PU – perfuzijska enota.

Assessment of extra-vascular (central) factors (Tab. 2). The surface area in the low frequency band of the heart rate variability power spectrum was significantly higher in group C as compared to the other two groups, but there were no significant differences in the surface area in the high frequency band among the three groups of subjects. There were also no differences in cutaneous blood flow after indirect skin heating and cooling.

Assessment of local factors (Tab. 3). Cutaneous flow after direct skin heating and cooling did not differ significantly among the three groups of subjects. The peak flow in the first part of the PRH did not show any significant difference among the three groups of subjects either. By comparing frequency of oscillations in the second part of the PRH we found a significantly higher value in group C as compared to group B and in group B in comparison with group A.

Discussion

The results of our study based on the laser-Doppler flowmetry showed no significant difference in the dilatation capacity of microcirculation among normotensive subjects with a predisposition to hypertension, subjects with no such predisposition and normotensives with a previous record of high blood pressure. However, the results show a significantly larger surface area in the low frequency band of the heart rate variability power spectrum in subjects with a predisposition and a previous record of high blood pressure. We have also shown a higher frequency of the flow oscillations in the second part of the PRH in the subjects with a predisposition to hypertension.

It is generally acknowledged that structural microcirculatory changes are the basic characteristics of developed hypertension (14). The results of our study correspond to the findings of other studies on borderline hypertensive subjects and normotensives with a family history of hypertension, which did not find any difference in the peak flow during the PRH measured by the laser-Doppler method (9). Our results did not prove structural microvascular changes in normotensive subjects with a family history of hypertension. Our results further support the absence of structural changes at this stage of hypertension development; in local skin heating to 42°C, which causes the maximum thermally induced dilatation of cutaneous vessels, no significant differences in flow were found among the three groups of subjects.

Basic studies on the development of hypertension deal with early functional changes in microcirculation (increased reactivity), which precede structural changes in the vessel wall (3, 4). The cause for increased vessel reactivity may lie in the vessel wall, centrally (in vasomotor center, its afferent and efferent nerves) or it may be a combination of both. Heart rate variability is affected primarily by the activity of autonomic nervous system; therefore, the difference in the surface area of the heart rate variability power spectrum can be evaluated as an indicator of altered activity of the autonomic nervous system. The results of our study showed a larger surface area in the low frequency band in the group with a predisposition to hypertension, which speaks in favor of the increased activity of sympathetic nervous system at the earliest stage of the hypertension development. Similar results can be found in a study on young hypertensive subjects (2). The results of our study also correspond to the Julius' hypothesis on the changed balance between the sympathetic and parasympathetic nervous system at the level of vasomotor center to the advantage of the former (15). However, contrary to the Juli-

Tab. 2. *Mean values of the surface areas in the low and high frequency bands of the heart rate variability power spectrum and mean flow values after indirect skin cooling and heating.*

Tab. 2. *Srednje vrednosti površin v nizkofrekventnem in visokofrekventnem delu močnostnega spektra variabilnosti frekvence srca in srednji pretok po sistemskem hlajenju in gretju.*

	Group A Skupina A	Group B Skupina B	Group C Skupina C	Significance Signifikantnost
Area-LF ([s²/Hz]xHz) Površina ([s²/Hz]xHz)	0.0071 ± 0.0038	0.0054 ± 0.0037	0.0166 ± 0.0157	C:B*, C:A*
Area-HF ([s²/Hz]xHz) Površina ([s²/Hz]xHz)	0.0079 ± 0.0069	0.0076 ± 0.0055	0.0103 ± 0.0097	ns
Flow-IC (PU) Pretok-IC (PU)	42.68 ± 22.71	39.41 ± 16.77	81.41 ± 98.13	ns
Flow-IH (PU) Pretok-IH (PU)	77.66 ± 46.87	101.55 ± 61.80	116.32 ± 90.66	ns

* significant difference between the relevant two groups, ns – statistically nonsignificant, area-LF – the surface area in the low frequency band of the heart rate variability power spectrum, area-HF – the surface area in the high frequency band of the spectrum, flow-IC and flow-IH – the blood flows after indirect skin cooling and heating, respectively, PU – perfusion unit. All values shown are mean values ± standard deviation.

* statistično značilna razlika med določenima skupinama preiskovancev, ns – statistično neznačilno, area-LF – površina v nizkofrekventnem delu močnostnega spektra variabilnosti frekvence srca, area-HF – površina v visokofrekventnem delu mocnostnega spektra variabilnosti frekvence srca, flow-IC in flow-IH – pretoki po sistemskem hlajenju oz. gretju, PU – perfuzijska enota. Vrednosti so podane kot srednja vrednost ± standardna deviacija.

Tab. 3. *Mean values of the peak flow in the first part of the postocclusive reactive hyperemia (PRH); mean values of the frequency of oscillations in the second part of the PRH; and mean flow values after direct skin cooling and heating.*

Tab. 3. *Srednje vrednosti največjega pretoka v prvem delu pookluzijske reaktivne hiperemije (PRH); srednje vrednosti frekvence nihanj pretoka v drugem delu PRH; in srednje vrednosti pretoka po lokalnem hlajenju in gretju.*

	Group A Skupina A	Group B Skupina B	Group C Skupina C	Significance Signifikantnost
Flow-peak (PU) Pretok – največji (PU)	276.13 ± 160.68	302.34 ± 157.04	300.74 ± 227.27	ns
Fr (Hz) Frekvenca (Hz)	0.096 ± 0.026	0.181 ± 0.016	0.201 ± 0.027	C:A*, B:A*
Flow-DC (PU) Pretok-DC (PU)	60.82 ± 44.62	52.70 ± 44.31	49.47 ± 30.93	ns
Flow-DH (PU) Pretok-DH (PU)	124.01 ± 80.41	155.94 ± 115.03	97.96 ± 60.10	ns

*significant difference between the relevant two groups, ns – statistically nonsignificant, flow-peak – the peak flow in the first part of the PRH, flow-DC and flow-DH – flows during direct skin cooling and heating, respectively, fr – the frequency of flow oscillations in the second part of the PRH, PU – perfusion unit. All values shown are mean values ± standard deviation.

* statistično značilna razlika med določenima skupinama preiskovancev, ns – statistično neznačilno, flow-peak – največji pretok v prvem delu PRH, flow-DC in flow-DH – pretoki po lokalnem hlajenju oz. gretju, fr – frekvenca nihanj pretoka v drugem delu PRH, PU – perfuzijska enota. Vrednosti so podane kot srednja vrednost ± standardna deviacija.

us we did not find any increased heart rate in the predisposed group.

In our study myogenic microvascular reactivity in normotensives with a family history of hypertension was estimated as well. Several researches agree that the flow oscillations with a frequency between 0.07 and 0.19 Hz in the second part of the PRH represent vasomotion (16). This is a local phenomenon – the origin of these oscillations is attributed to the myocites in the vessel walls of microcirculatory bifurcations. The fundamental characteristic of these specialized myocites is automaticity, which is reminiscent of the automaticity of a heart pace maker. The frequency of flow oscillations increases with the reduced lumen of the vessel where the impulse originated and the amplitude of the oscillations is inversely related to the frequency. The results of our study demonstrated that the frequency of flow oscillations in the second part of the PRH, representing vasomotion, was higher in predisposed normotensives in which high blood pressure had been recorded in the past. Higher frequency of oscillations in the second part of the PRH can be explained by an increased myogenic response of microcirculation in these subjects. This finding of our study agrees with the microcirculation hypothesis of the hypertension development (17) and the findings of the basic studies, discussing the increased myogenic vessel reactivity at an early stage of hypertension development (11, 18).

Conclusion

We can conclude that in predisposed subjects with a previous record of high blood pressure cutaneous microvascular reactivity estimated by laser-Doppler method is different as compared to that of the other subjects. No structural changes in microcirculation have been show in this group of subjects. Higher frequency of the flow oscillations in the second part of the PRH in predisposed subjects speaks in favor of increased myogenic microvascular reactivity in this group. Also, we showed a significant difference in heart rate variability in predisposed subjects with a previous record of high blood pressure, which is explicitly dependent on extra-vascular (central) elements. This leads to an explanation on the presence of alterations on several levels in the cardiovascular system and its regulatory loops (both in the smooth muscle of the vessel wall and centrally) even in normotensive subjects with a familial predisposition to hypertension and a previous record of high blood pressure.

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