The Effects of Arterial Blood Pressure Reduction on Endocan and Soluble Endothelial Cell Adhesion Molecules (CAMs) and CAMs Ligands Expression in Hypertensive Patients on Ca-Channel Blocker Therapy

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Key Words
sCAMs • CD11a/LFA-1 • CD15 • Hypertension • Endocan

Abstract
Background/Aims: To determine the effect of arterial blood pressure (BP) reduction on endocan and soluble cell adhesion molecules’ (sCAM) plasma concentration and expression of their ligands on circulatory leukocyte subpopulations. Methods: 24 hypertensive subjects of both sexes (age: 53±8 yrs) were treated with Ca-channel blocker, amlodipin (5-10 mg/day for 8 weeks; to reach BP≤139/89mmHg). The serum sCAMs and endocan concentrations were determined by ELISA kits. Level of ICAM/VCAM ligands on leukocytes was assessed by flow cytometry. Paired t-test, or t-test were used as appropriate, with Pearson’s correlation calculated; p<0.05 was considered significant (SigmaPlot v.11). Results: sICAM-1 and sVCAM-1 were decreased (p≤0.001 and p=0.002, respectively), while E-selectin concentration was increased after amlodipin treatment (P=0.014). CD11a/LFA-1 (ICAM-1 and endocan ligand) was significantly increased in all three cell types with BP decrease. CD15 and CD49d/VLA-4 (VCAM-1 ligand) did not change after the treatment. There was significant positive correlation of systolic and diastolic BP with ICAM-1 and VCAM-1, and significant negative correlation of systolic BP with CD11a/LFA-1. Endocan significantly positively correlated with
ICAM-1. **Conclusions:** The increased expression of ICAM/VACM ligands, together with decrease of sCAMs and endocan suggests the de-activation of endothelium with reduction in BP, decreasing the adherence of circulatory leukocytes to endothelium; subsequently decreasing the risk for development of atherosclerosis.

**Introduction**

Hypertension, diabetes mellitus, obesity, lipid metabolism dysregulation, smoking and manifested cardiovascular diseases (heart failure, myocardial ischemia) are condition with underlying endothelial dysfunction, increased oxidative stress and development of vascular complications [1-5]. Perturbation of endothelial function underlies the atherosclerotic process [6, 7]. Endothelial adherence and migration of leukocytes into tissue is mediated by different sets of adhesion molecules expressed on activated endothelial cells and their complementary ligands on leukocytes, such as ICAM-1:LFA1 pair; or VCAM-1:VLA4 pair [8]. The expression of these sets might not only preselect the types of leukocytes that enter the inflammatory sites, but also activate these leukocytes, induce adherence to epithelial cells, and cause the release of cytokines, which lead to inflammatory response and endothelial damage, such as in atherosclerosis [7], lung diseases [9] and diabetes mellitus [10]. In atherosclerosis, ICAM-1 is up-regulated in sites prone to atherosclerosis development [11, 12], basically due to endothelium activation and inflammatory response. This is necessary step for recruitment of inflammatory cells, release of cytokines and adsorbance of the lipids into the atherosclerotic plaque [8]. When over-expressed on the activated endothelial cells, ICAM-1 and VCAM-1, among others, undergo shedding and their soluble forms, sICAM-1 and sVCAM-1 respectively, are detectable in serum and considered to be markers of endothelial cell activity or injury [13]. Leukocyte ligands for ICAM-1 and VCAM-1 are Lymphocyte Function-associated Antigen-1 (CD11a/CD18, alphaL/beta2 integrin; LFA-1) and Very Late Antigen-4 (CD49d/CD29, alpha4/beta1 integrin; VLA-4) respectively and they participate in cell recruitment to sites of inflammation, as well as in multiple immune cell interactions. Integrin-dependent cell adhesion can be rapidly and reversibly modulated in response to cell signaling [14]. Newly emerging data demonstrated that in responses to turbulent flow, dyslipidemia or some other stimuli (such as increase in intraluminal pressure [15, 16]), endothelial cells over-express adhesion molecules. In addition, in subjects newly diagnosed with hypertension with no secondary cause, serum concentration of sE-selectin, sP-selectin and sICAM-1 and some other markers of inflammation are significantly elevated compared to normotensive subjects [17, 18].

Although extensively investigated in inflammation and tumorigenesis [12, 14, 19], as well as in atherosclerosis [6-8, 11], almost none is known about the circulatory leukocytes interaction with endothelial cells in essential hypertension. Rare studies such as study by Ianone et al [13], in patients with autoimmune disease systemic sclerosis (SSc) having pulmonary hypertension (PAH) have demonstrated that peripheral blood T-cells expressing LFA-1 were significantly higher in patients with pulmonary hypertension (SSc-PAH) compared to patients with SSc without PAH. The proportion of T cells bearing VLA-4 antigen was significantly reduced in the SSc-PAH group compared to healthy controls and compared to patients with SSc without pulmonary hypertension. Expression of L-selectin on T cells was significantly lower in patients with SSc-PAH than in the healthy control group or in patients with SSc without PAH [13]. In addition, in patients with SSc-PAH, serum soluble ICAM-1, VCAM-1, P-selectin and PECAM-1 levels were higher than in healthy controls. All together, this study suggests that changes in the T cell/endothelium interplay take place in pulmonary hypertension in patients with systemic sclerosis, at least.

Endocan (ESM-1, the proteoglycan), is secreted by endothelial cells [20]. It has been shown to compete with ICAM-1 for LFA-1 [21]. Endocan circulates in plasma of healthy subjects and is increased in acute and severe inflammation [20], while endocan concentration is decreased in obese persons [6]. Thus, endocan can be considered as a marker of endothelial
activation and its interaction with LFA-1 could be important in leukocyte adhesion and interaction with activated endothelium. Whether endocan is enhancing or preventing that interaction remains to be clarified.

The hypothesis of this study was that increased blood pressure is associated with higher serum sCAMs concentration and fewer free accessible circulatory leukocyte ligands for CAMs, since the adhesion of leukocytes and initiation of inflammatory process involves interaction of CAMs with their complementary ligands at leukocytes. Additional hypothesis is that this molecular interaction might involve endocan-mediated pathway, which is also a marker of endothelial activation. Therefore, normalization of blood pressure de-activates the endothelium, alleviates the inflammation process and changes the CAMs-ligands interaction. Subsequently, this could decrease the risk for development of atherosclerosis.

The aim of this study was to determine the effect of arterial blood pressure (BP) reduction on soluble cell adhesion molecules' (sICAM-1, VCAM-1 and E-selectin) and endocan plasma concentration; and the expression of their respective ligands (CD11a/LFA-1, CD15/VLA-4 and CD49d) on circulatory leukocyte subpopulations in newly discovered hypertensive patients.

Materials and Methods

Subjects

Twenty four newly discovered hypertensive subjects of both sexes (age: 53±8 yrs) were recruited from people who underwent health-screening examinations at Gesundheitszentrum Lange Reihe Dr. Tadzic und Kollegen, Hamburg, Germany. The inclusion criteria were patients with essential hypertension (systolic BP≥140 mmHg, and diastolic BP≥90 mmHg). The exclusion criteria were: secondary forms of hypertension, autoimmune disease, angina pectoris, coronary heart disease, myocardial infarction, cerebrovascular disease, haemoragic stroke, ischaemic stroke including transient ischemic attack and renal and liver disease.

After initial clinical assessment (below), blood pressure measurement and blood sampling, patients were administered Ca-channel blocker, amlodipin (5-10 mg/day for 8 weeks; dose to reach BP≤139/89 mmHg). Peripheral blood samples were taken prior of administration of the antihypertensive drug and again after 8 weeks of continuous therapy. Age, sex, body weight, body mass index (BMI), blood pressure measurement, waist and hip circumference (to calculate waist to hip ratio), and laboratory parameters (fasting glycaemia, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, triglycerides, plasma renin activity (PRA), aldosterone, and urinary sodium, potassium, creatinine and urea concentration, were recorded for each patient at the first visit before of starting the therapy and 8 weeks after the therapy. The results are presented in Table 1. The study was approved by the Ethical Committees of the University Josip Juraj Strossmayer Osijek, Faculty of Medicine and by the Ethical Committee of the Gesundheitszentrum Lange Reihe Dr. Tadzic und Kollegen. All patients voluntary participated in the study and provided written informed consent.

The serum soluble cell adhesion molecules (sCAMs) ICAM-1, VCAM-1, E-selectin and endocan concentrations measurement

As endothelial activation markers, serum concentration of soluble vascular cell adhesion molecule (sVCAM)-1, soluble intercellular adhesion molecule (sICAM)-1 and sE-selectin were assessed by commercially available ELISA kit (eBioscience, Platinum ELISA, Austria), while endocan (ESM1) plasma concentration was assessed by ESM1 ELISA kit (USCN, Life Science Inc., China). Normal serum values from healthy controls determined by the manufacturers are as follows: sVCAM-1 772.4±207.2 (range 400.6 – 1340.8 ng/ml), sICAM-1 504±171 ng/ml (range 302 – 1115 ng/ml), sE-selectin 66.5±34.8 (range 21.0 – 186.0 ng/ml). Data for endocan were no available. Leukocyte activation markers and soluble endothelial markers were assessed at baseline and 8 weeks after the antihypertensive therapy with Ca-channel blocker amlodipin (5-10 mg/day for 8 weeks; dose to reach BP≤139/89 mmHg).
Basic blood analysis

Patients’ blood was sent to the routine diagnostic laboratory at Dres, Ennen und Gebauer, Hamburg (Germany) immediately after sampling. Serum levels of HDL, LDL, total cholesterol, triglycerides, glucose, creatinine, sodium and potassium were determined by Abbott architect c16000 blood analysis instrument. Levels of aldosterone and renin were determined by RIA (Siemens, Los Angeles, USA).

Assessment of CD11a/LFA-1, CD15 and CD49d expression on blood circulatory leukocytes

Antibodies and reagents. The human sE–selectin Platinum Elisa (BMS 205 / BMS205TEN, the human sVCAM-1 BMS232/BMS232TEN, the human sCD105 BMS2105INST and the human sICAM-1 BMS201/BMS201 TEN) were obtained from eBioscience (Vienna, Austria). Endocan (endothelial-cell specific molecule - 1 (ESM1-1) antibodies were obtained from USCNK Life Science Inc. The antibodies used for flow cytometry were phycoerythrin conjugates purchased from eBioscience, as follows: anti-CD11a (clone HI111); anti-CD15 (clone HI98) and antiCD49d (clone 9F10).

Blood collection and processing for flow cytometry. Patients’ blood was collected into tubes containing EDTA (Becton Dickinson, San Diego, CA). 100 μl of whole blood was added to FACS tube and stained according to the manufacturers protocol (eBioscience, Protocol B: Human Lysed Whole Blood). In short, the cells were incubated with phycoerythrin (PE) - conjugated primary antibodies (anti-CD11a, anti-CD15 or antiCD49d) or their appropriate isotype controls at 1:100 dilution for 20 minutes on RT in the dark. The erythrocytes were lysed by using 1xRBC lysing buffer (eBioscience).

Flow cytometry data analysis. Dead cells were excluded based on their light scattering properties. At least 20,000 live cells were collected by a BD FACS calibur cytometer and analyzed using the WinMDI software. Monocytes, granulocytes and lymphocyte were identified and gated on the sideward versus forward scatter plot and further analyzed for CD11a, CD15 and CD49d expression on a histogram. Expression data are presented as the geometric mean of fluorescence intensity determined by subtracting geometric mean fluorescence intensity of the isotype control from geometric mean fluorescence intensity of the specific mAb.

Statistical analysis

The sample size required to show a significant effect on sCAMs in hypertensive patients, was calculated based on preliminary data in 10 patients with alpha=0.05 and a statistical power of 80% for t-test and ANOVA showing a needed sample size of 17 patients for sCAMs and other biochemical parameters, while for leukocyte ligands, the sample size was determined as 10 patients. Shapiro Wilk test was used to test the data distribution. For normally distributed data, dependant variables were compared by paired t-test, independent variables by Student’s t-test and the difference between leukocyte ligands expression among the cell subpopulations by One-way ANOVA followed by Tukey post-hoc test. In the case of abnormal data distribution Mann-Whitney U-test, Wilcoxon’s test, and Kruskal-Wallis analysis of variance test followed by
Dunn’s post-hoc test were employed. In addition, Pearson’s and Sperman’s correlation were calculated in the case of normally and abnormally distributed data, respectively. All calculations were performed with software SigmaPlot v.11. All data are presented as mean±SD. p≤0.05 was considered significant.

Results

Subjects

The anthropometric and laboratory data of patients (N= 24; 13 men and 11 women) that conformed to inclusion and exclusion criteria and successfully participated in the study are presented in the Table 1. The average age of patients was 53±8 yrs. All patients were obese (BMI>30 kg/m²) with hyperlipidemia, hyperglycaemia and hypertension at the time of enrollement. After 8 weeks of amlodipin therapy (dose: 5-10 mg/day for 8 weeks; to reach BP≤139/89 mmHg), there was significant decrease in systolic and diastolic blood pressure, with values bellow 139/89 mmHg. PRA and aldosterone levels significantly increased, while urine sodium concentration significantly increased and urine potassium concentration significantly decreased with the treatment. There were no significant changes in plasma urea and creatinine values (Table 1).

The serum soluble cell adhesion molecules (sCAMs) ICAM-1, VCAM-1, E-selectin and endocan concentrations

Serum levels of sICAM-1 (351.4±111.9 vs. 252.9±83.6; p≤0.001) and sVCAM-1 (706.6±244.5 vs. 535.5±176.8; p=0.002) were significantly decreased after the treatment, compared to control conditions, while E-selectin levels were significantly increased after the amlodipin treatment (34.3±20.56 vs 53.6±26.6, P=0.014) (Figure 1). Endocan levels tended to decrease with BP reduction (p=0.063) (Figure 2A).

CD11a/LFA-1, CD15 and CD49d expression on blood circulatory leukocytes

Expression of CD11a/LFA-1 (ICAM-1 and endocan ligand) was significantly increased in all three cell types with BP decrease (Ly p=0.009, Mo p≤0.001, Gr p=0.005). CD15 (E-selectin ligand) showed weak reactivity on lymphocytes and monocytes, but it was abundant on granulocytes. CD15 and CD49d/VLA-4 (VCAM-1 ligand) did not change significantly after the treatment. All three ligands showed significantly different pattern of expression on various cell types (p≤0.001) (Figures 3C). Gating strategy and representative histograms are shown in Figure 3A and 3B, respectively. There was no significant correlation between any of the CAMs-ligand pair.

Fig. 1. The plasma soluble cell adhesion molecules (sCAMs): ICAM-1 (panel A), E-selectin (panel B) and VCAM-1 (panel C) concentrations before (white bars) and after (gray bars) the normalization of blood pressure with amlodipine therapy. Data are expressed as mean ± SD for N=24 patients; p- value of each relation is expressed at the panels.
However, there was significant positive correlation of systolic and diastolic BP with ICAM-1 and VCAM-1 (Figure 4A and 4B, respectively), and negative correlation of systolic BP with their respective leukocyte ligands, reaching significance for granulocyte and monocyte CD11a/LFA-1 (Figure 5). Endocan significantly positively correlated with ICAM-1 (Figure 2B). In addition, there was no significant correlation between the degree of blood pressure reduction (ΔBP) and the degree of adhesion molecules changes (ΔCAMs) for any of the adhesion molecules, except in the case of ΔsVCAM-1 and Δ diastolic BP, where a significant negative correlation was found (p=0.0339, r=-0.545; Figure 4C).

Discussion

The cell adhesion molecules, such as ICAM-1, VCAM-1 and E-selectin just recently emerged as an important marker of endothelial activation preceding the adhesion of the activated leukocytes and initiating the atherosclerotic lesions. Endothelial dysfunction is in core of hypertension [7, 22, 23], effects of high dietary salt intake [22, 23] and diabetes mellitus [7]. However the understanding of the role of inflammation and endothelial-leukocyte interaction in subsequent vascular damage in these conditions is at its beginnings and mainly investigated in the field of autoimmune diseases [13].

The novelty of this study is the attempt to inter-relate the markers of endothelial cell activation, their corresponding ligands on circulatory leukocytes and blood pressure, and to elucidate the possible contribution of the endocan pathway in development of initial conditions for adherence of activated leukocytes to endothelium in hypertensive patients prior to and after the blood pressure reduction.

The major findings in this study are the following: a) significantly decreased serum levels of sICAM-1 and sVCAM-1 with arterial blood pressure reduction after amlodipine treatment (Figure 1); b) with decrease in blood pressure, the expression of CD11a/LFA-1 (ICAM-1 and endocan ligand) was significantly increased in all three leukocyte cell types (lymphocytes, monocytes and granulocytes) while CD15 and CD49d/VLA-4 (VCAM-1 ligand) did not change significantly (Figure 3A-C, respectively); c) There was significant positive correlation of systolic and diastolic BP with ICAM-1 and VCAM-1, and negative correlation of systolic BP of
ICAM-1 leukocyte ligands, LFA-1 for granulocytes and monocytes (Figure 4A, 4B and Figure 5 respectively); d) endocan positively correlated with ICAM-1 and tended to decrease with BP reduction (Figure 2B and 2A, respectively).

The adhesion of leukocytes via CAMs and their complementary ligands at leukocytes involves the inflammation mediated by TNF-α signaling pathway, which has been shown to instigate the VCAM-1 and ICAM-1 expression in the endothelium [24]. In atherosclerosis,
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ICAM-1 is up-regulated in sites prone to atherosclerosis development [11, 12]. Our finding that sICAM-1 and sVCAM-1 are significantly decreasing with decrease in blood pressure (endothelial deactivation) is in agreement of previous findings that VCAM-1 is not expressed in intact endothelium; however, its expression is significantly increased in atherosclerosis.
ICAM-1 expression is stimulated with proinflammatory cytokines TNF-α, IL-1β, IL-4 or INFγ [25, 26]. It mediates monocyte infiltration and could be important in proliferation of vascular smooth muscle cells [25-27]. Or vice versa, in hypertension, in SHR rats, there is a significant increase in sICAM-1, sVCAM-1 [18, 27]. Interestingly, sE-selectin showed different pattern of expression in response to changes in blood pressure – it increases with blood pressure reduction. E-selectin is expressed only on cytokines-activated endothelium and facilitates neutrophils' recruitment. Neutrophils' tethering and rolling on E-selectin, upon exiting the microvasculature, down-regulate their surface L-selectin through ectodomain shedding by a disintegrin and metalloprotease 17 (ADAM17) [28]. E-selectin is associated with the development of acute coronary syndrome [29].

Fig. 5. Correlation between CD11a/LFA-1 expression on peripheral blood lymphocytes (A), granulocytes (B) and monocytes (C) with systolic (left panels) and diastolic blood pressures (right panels). There is a significant positive correlation of CD11a with BP; p value of each relation is expressed at the panels; 18 results are plotted at each graph.
activation, E-selectin has been shown to be elevated in hypertension [18]. Rubio-Guerra et al. evaluated the relationship between the levels of circulating soluble CAMsand the degree of atherosclerosis in hypertensive type-2 diabetic patients and found significant correlations between ICAM-1 levels and maximal carotid artery intimal-medial thickness in these patients. No correlation was observed with E-selectin and VCAM-1. These results suggest that ICAM-1, but not E-selectin is associated and correlated with the degree of atherosclerosis in type-2 diabetic hypertensive patients [7]. Interestingly, increased levels of sE-selectin have been found in hypotensive patients with sepsis while other markers of endothelial activation (ICAM-1, VCAM-1) remained unchanged [30]. This is in agreement with E.selectin increase with blood pressure reduction as demonstrated in present study (Figure 1). In addition, CD15 (Sialyl Lewisx, E-selectin ligand) expression did not vary significantly after the treatment. Sialyl Lewisx is constitutively expressed on granulocytes and monocytes and on activated T and B lymphocytes [31]. Taken together, our findings suggest that with decrease in blood pressure, there is a de-activation of the endothelial cells, followed by changes in the adhesion of the circulating leukocytes. ICAM-1 and its ligand LFA-1 is the most prominent pair to mediate the interaction of endothelium with leukocytes while blood pressure is high.

Endocan (ESM-1, the proteoglycan), is secreted by endothelial cells. It has been shown to compete with ICAM-1 for LFA-1 [21] thus possibly inhibiting leukocytes adhesion and transmigration [21]. The results of present study of tendency of endocan concentration to decrease and significant positive correlation of endocan with ICAM-1 (Figure 2B) would be in agreement with study by Bechard et al [21]. Considering the crucial role of the ICAM-1/LFA-1 interactions during firm adhesion of human lymphocytes and monocytes to endothelium [21] endocan may be considered as a protective and limiting in the regulation of monocyte/granulocytes extravasation at the inflammatory sites or at the activated endothelium in preventing exhaustive adhesion of the leukocytes and possible subsequent damage of the endothelium. This potential mechanism is schematically represented and explained in Figure 6.

VLA-4 and LFA-1 integrins belong to a large family of adhesion receptors widely expressed on immune cells [32, 33]. They participate in cell recruitment to sites of inflammation, as well as multiple immune cell interactions [14]. New emerging studies demonstrated that increase in endothelial NO/cGMP changes, i.g. decreases the affinity of VCAM-1 to VLA-4, having de-adhesive effects [34].

One intriguing finding of this study is the increased expression of leukocyte adhesion ligands with the decrease in blood pressure (Figure 3). The expression of CD11a/LFA-1 (ICAM-1 and endocan ligand) was significantly increased in all three leukocyte cell types (lymphocytes, monocytes and granulocytes) after amlodipin treatment. One possible explanation for that would be that with the blood pressure normalization, endothelial cells deactivate and release previously attached leukocytes. This is in agreement with study by Mills et al [34] that in response to exercise, hypertensive subjects showed significantly greater mean density of CD11a on lymphocytes and on monocytes, two times greater increased in IL-2 and increased adhesion of peripheral blood monocytes to endothelial cell layer compared to normotensive subjects. Furthermore, in normotensive subjects, the adhesion of leukocytes decreased following exercise. Taken together, in hypertension, there is endothelial activation and increased mononuclear cell adhesion to endothelial cells, possibly through cytokine-induced activation of mononuclear cell CD11a. This may be relevant to the increased risk of atherosclerosis in human hypertension [35]. Additional evidence for our hypothesis of de-activation of the endothelium and de-adhesion of leukocytes is finding that infusion of isoprotenerol, non-specific beta-adrenergic agonist increases the number of circulating CD62Llow/CD11ahigh leukocytes more in hypertensive than in normotensive subjects. In addition, in hypertensive subjects the sICAM-1 concentration was elevated compared to normotensive subjects [36].

These findings are further supported by the population study on association of hypertension with inflammation, endothelial dysfunction and abnormal metabolism among Mongolian people in China [18]. Rates of abnormal metabolism, elevated CRP, elevated sICAM-1, elevated S-E-selectin and elevated angiotensin II as well as coexistence of
abnormal metabolism with the elevated biomarkers were all higher in hypertensive than in normotensive subjects indicating that individuals with co-existence of abnormal metabolism with inflammation and endothelial dysfunction had higher risk of prevalent hypertension [18]. The limitation of the present study is our inability to directly measure the adherent leukocytes to endothelium in our patients. For example, intra-vital microscopy is an excellent method to study in vivo leukocyte recruitment and adhesion and has been used in various models of experimental animals and in cell cultures [37, 38]. However, it is not suitable for in vivo studies in humans at all.

Based on the results of the present study, it is possible to propose the potential mechanism of blood pressure reduction on cell adhesion molecules interaction with their ligands on circulatory leukocyte subpopulation, and the potential counter-balancing role of endocan. In hypertension, there is high concentration of ICAM-1 and VCAM-1, with low E-selectin on endothelium, as markers of endothelial cell activation. This is accompanied with high adherence of leukocytes via LFA-1 and VLA-4 interaction with endothelium. Endocan, released by activated endothelium competes with ICAM-1 for LFA-1 thus disturbing the leukocyte adherence (hypothetical protective effect of endocan; left side of the Figure 6). With blood pressure reduction, there is decrease in ICAM-1, VCAM-1 expression and concomitant increase in the expression of their ligands LFA-1 and VLA-4 on possibly detached leukocytes, accompanied by the decrease in endocan secretion (right side of the Figure 6).
Conclusion

In hypertension, endocan could be secreted by activate endothelium and might have protective role by competing with ICAM-1 for their ligand LFA-1 on to-be-adherent leukocytes. The increased expression of sCAMs’ ligands on circulatory leukocytes, together with significant decrease of endothelial CAMs after amlodipin treatment suggests the de-activation of the endothelium with successful reduction in blood pressure. This could subsequently decrease the risk for development of atherosclerotic lesions.

Conflict of Interests

None of the authors has any conflicts in relation to the work presented in this paper.

References

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