THE ROLE OF ENDOTHELIN-1 CONCENTRATION IN ARTERIAL ESSENTIAL HYPERTENSION

Germaine Săvoiu1, Carmen Cristescu2, Doina Verdeș3, Claudia Borza4, Corina Șerban4, Camelia Costea4, Mihaela Andoni1, Lavinia Noveanu5, Rodica Mateescu5, Georgeta Mihalas5

1UNIVERSITY OF MEDICINE AND PHARMACY “VICTOR BABEȘ” TIMISOARA: 1ANATOMY, PHYSIOLOGY AND PATHOPHYSIOLOGY DEPARTMENT; 2CLINICAL PHARMACY DEPARTMENT; 3CELLULAR BIOLOGY DEPARTMENT; 4PATHOPHYSIOLOGY DEPARTMENT; 5PHYSIOLOGY DEPARTMENT.

Summary

The aim of this study was to investigate endothelin-1 (ET-1) plasma concentration in patients with essential hypertension, atherosclerotic dyslipidemia, and with coronary artery disease confirmed by coronary angiography. The study comprised 32 patients with coronary artery disease (mean age 50 ± 3.15 years, 71% males and 29% females) (BCV group), 12 hypertensive patients (HTN group) (mean age 55 ± 4.75 years, 60% males and 40% females) and 12 patients with atherosclerotic dyslipidemia (DYS group) (mean age 53 ± 5.68 years). The control group (CON group) consisted of 12 control subjects (mean age 57 ± 4.25 years). Antihypertensive medication was interrupted for at least two weeks before the study. The concentration of ET-1 was measured by Elisa. ET-1 plasma concentration was significantly higher (p < 0.001) in coronary artery disease group (25 ± 5.42 pg/ml) comparative with atherosclerotic dyslipidemia group (19 ± 5.63 pg/ml), with hypertensive group (16.8 ± 5.16 pg/ml) and with the control group (7.2 ± 2.53 pg/ml). There was a significant positive correlation between ET-1 and systolic arterial hypertension in control group (r = 0.77, p < 0.001) and in hypertensive group (r = 0.71, p < 0.001) and between ET-1 and diastolic arterial hypertension in hypertensive group (r = 0.80, p < 0.001). These results may suggest a role of ET-1 in the development and maintenance of elevated blood pressure in patients with arterial hypertension.

Key words: hypertension, endothelin-1, dyslipidemia savoiugema@yahoo.com

Introduction

Endothelial cells are able to produce both vasoconstrictive and vasodilating substances. The most important endothelium-derived relaxing factors are nitric oxide (NO), prostacyclin, and endothelium-derived hyperpolarizing factor. Endothelial cells produce also vasoconstrictive substances, like prostaglandin endoperoxides and the peptides angiotensin II and endothelin-1 (ET-1) (Iglarz et al., 2007).

Endothelin (ET), discovered in 1988 (Yanagisawa et al., 1988), is the most potent vasoconstrictor known today. The endothelin system is activated in several cardiovascular disease states associated with functional and structural vascular changes, including hypertension, coronary artery disease, and heart failure (Ergul et al., 2002).

Endothelin ET-1 has been associated with the development of atherosclerosis via its actions on all cells of the vasculature particularly vascular smooth muscle cells.

Endothelin-1 is the endothelin generated in the endothelium, where it acts in a paracrine or autocrine manner on ETA and ETB receptors on adjacent endothelial or smooth muscle cells. The effects of
THE ROLE OF ENDOTHELIN-1 CONCENTRATION IN ARTERIAL ESSENTIAL HYPERTENSION

Germaine Săvoiu¹, Carmen Cristescu², Doina Verdeș³, Claudia Borza⁴, Corina Șerban⁴, Camelia Costea⁴, Mihaïela Andoni¹, Lavinia Noveanu⁵, Rodica Mateescu⁵, Georgeta Mihalas⁵

¹UNIVERSITY OF MEDICINE AND PHARMACY “VICTOR BABES” TIMISOARA: ¹ANATOMY, PHYSIOLOGY AND PATHOPHYSIOLOGY DEPARTMENT; ²CLINICAL PHARMACY DEPARTMENT; ³CELLULAR BIOLOGY DEPARTMENT; ⁴PATHOPHYSIOLOGY DEPARTMENT; ⁵PHYSIOLOGY DEPARTMENT.

Summary

The aim of this study was to investigate endothelin-1 (ET-1) plasma concentration in patients with essential hypertension, atherogenic dyslipidemia, and with coronary artery disease confirmed by coronaryography. The study comprised 32 patients with coronary artery disease (mean age 50 ± 3.15 years, 71% males and 29% females) (BCV group), 12 hypertensive patients (HTN group) (mean age 55 ± 4.75 years, 60% males and 40% females) and 12 patients with atherogenic dyslipidemia (DYS group) (mean age 53 ± 5.68 years). The control group (CON group) consisted of 12 control subjects (mean age 57 ± 4.25 years). Antihypertensive medication was interrupted for at least two weeks before the study. The concentration of ET-1 was measured by Elisa. ET-1 plasma concentration was significantly higher (p < 0.001) in coronary artery disease group (25 ± 5.42 pg/ml) comparative with atherogenic dyslipidemia group (19 ± 5.63 pg/ml), with hypertensive group (16.8 ± 5.16 pg/ml) and with the control group (7.2 ± 2.53 pg/ml). There was a significant positive correlation between ET-1 and systolic arterial hypertension in control group (r = 0.77, p < 0.001) and in hypertensive group (r = 0.71, p < 0.001) and between ET-1 and diastolic arterial hypertension in hypertensive group (r = 0.80, p < 0.001). These results may suggest a role of ET-1 in the development and maintenance of elevated blood pressure in patients with arterial hypertension.

Key words: hypertension, endothelin-1, dyslipidemia

savoiugema@yahoo.com

Introduction

Endothelial cells are able to produce both vasoconstrictive and vasodilating substances. The most important endothelium-derived relaxing factors are nitric oxide (NO), prostacyclin, and endothelium-derived hyperpolarizing factor. Endothelial cells produce also vasoconstrictive substances, like prostaglandin endoperoxides and the peptides angiotensin II and endothelin-1 (ET-1) (Iglarz et al., 2007).

Endothelin (ET), discovered in 1988 (Yanagisawa et al., 1988), is the most potent vasoconstrictor known today. The endothelin system is activated in several cardiovascular disease states associated with functional and structural vascular changes, including hypertension, coronary artery disease, and heart failure (Ergul et al., 2002).

Endothelin ET-1 has been associated with the development of atherosclerosis via its actions on all cells of the vasculature particularly vascular smooth muscle cells.

Endothelin-1 is the endothelin generated in the endothelium, where it acts in a paracrine or autocrine manner on ETA and ETB receptors on adjacent endothelial or smooth muscle cells. The effects of
endothelin-1 include cell proliferation, migration and contraction, and the induction of extracellular matrix components and growth factors (Ivey, 2008).

The aim of our study was to determine the levels of ET-1 and to evaluate the correlations of ET-1 with systolic arterial hypertension and with diastolic arterial hypertension in all groups of patients.

**Material and method**

Four groups of age- and sex-matched subjects (age range 50 to 60 years) were included in the study after informed consent was obtained: normal subjects (CON group); coronary artery disease angiographically confirmed group (BCV group); essential hypertension group (HTN group); atherogenic dyslipidemia group (DYS group).

The subjects in the control group had no history of heart or systemic disease; they had normal blood pressure levels, physical examination findings, electrocardiogram, echocardiogram, chest radiogram, and laboratory test results (including urinalysis, levels of serum cholesterol, triglycerides, electrolytes, creatinine, and creatinine clearance), fundus oculi.

Clinical evaluation included blood pressure measurement, physical examination, chest radiograph, 12-lead electrocardiogram.

**Blood pressure measurements**

Blood pressure was measured by a trained nurse with a mercury sphygmomanometer with subjects in a sitting posture, after resting for ≥ 5 minutes with the cuff placed on the arm. In obese arms a larger cuff was used. Diastolic blood pressure was defined as the disappearance of Korotkoff sounds (phase V). In each subject the mean of 2 readings taken at intervals of ≥ 2 minutes was used in the study.

Arterial hypertension was diagnosed after ESC/ESH 2007 guidelines (ESC/ESH, 2007).

**Plasma lipids**

Total cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured enzymatically (Hitachi 717 analyzer).

Low-density lipoprotein cholesterol was calculated according to the Friedewald’s formula (Friedewald, 1972).

**ET-1 radioimmunoassay**

For the biochemical measurements, blood samples variation were obtained by standard venipuncture after a 12-h fast from all subjects.

Blood samples were collected in chilled tubes containing protease inhibitors and centrifuged at 1000 x g for 30 min at 4°C. Plasma was immediately frozen at -20°C until assayed. Plasma ET-1 concentrations were determined by RIA as described by De Juan in 1993.

**Statistical analysis**

Continuous variables were expressed as means ± SD. Means were compared using analysis of variance or the Student t-test. Pearson’s correlation was used to test bivariate correlations and results were verified using the non-parametric Spearman’s rank correlation test.

Statistical significance was defined as two–sided p < 0.05. All statistical analyses were performed using Excell Microsoft Office 2003.

The procedures followed were in accordance with the ethical standards of the Hospital Ethics Committee and with the Helsinki Declaration of 1975, as revised in 2000.

**Results**

**Baseline characteristics**

The characteristics of the subjects and ET-1 values for each group are reported in Table I.
## TABLE I. Baseline characteristics of the patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CON group</th>
<th>BCV group</th>
<th>HTN group</th>
<th>DYS group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>12</td>
<td>32</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Age (y)</td>
<td>57 ± 4.25</td>
<td>50 ± 3.15</td>
<td>55 ± 4.75</td>
<td>53 ± 5.68</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>68</td>
<td>71</td>
<td>60</td>
<td>68</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>114 ± 6.08</td>
<td>149 ± 15.96</td>
<td>147 ± 10.23</td>
<td>120 ± 11.17</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>68 ± 5.84</td>
<td>90 ± 10.23</td>
<td>88 ± 7.78</td>
<td>72 ± 8.88</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>180 ± 11.28</td>
<td>253 ± 19.67</td>
<td>200 ± 12.79</td>
<td>244 ± 21.53</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dL)</td>
<td>110 ± 11.57</td>
<td>177 ± 14.05</td>
<td>115 ± 8.11</td>
<td>152 ± 29.50</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>50 ± 6.40</td>
<td>27 ± 2.05</td>
<td>49 ± 10.74</td>
<td>33 ± 8.90</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>98 ± 23.09</td>
<td>242 ± 69.35</td>
<td>176 ± 74.13</td>
<td>295 ± 92.29</td>
</tr>
<tr>
<td>ET-1 (pg/mL)</td>
<td>7.2 ± 2.53</td>
<td>28 ± 5.42</td>
<td>16.8 ± 5.16</td>
<td>19.7 ± 5.63</td>
</tr>
</tbody>
</table>

Observation: values are presented as mean ± standard deviation

The most elevated concentrations of ET-1 were found in coronary artery disease group (p<0.001), comparative with control, hypertensive and dyslipidemic groups.

It was observed significant statistic differences between the mean values of ET-1 from atherogenic dyslipidemia group comparative with the control group (p < 0.001) and with arterial hypertension group (p < 0.001), and also between arterial hypertension group and the control group (p < 0.001). There was a strong positive correlation between ET-1 and systolic arterial hypertension in the control group (r = 0.77, p < 0.001) and in hypertensive group (r = 0.71, p < 0.001) (figure 1).

We didn’t observed statistically significant correlations between ET-1 and systolic arterial hypertension in the coronary artery group (r = 0.11, p = 0.35) and DYS group (r = 0.18, p = 0.78).

A strong positive correlation between ET-1 and diastolic arterial tension was obtained only in HTN group (r = 0.80, p = 0.001) (figure 2).

A moderate positive correlation was observed between ET-1 and diastolic arterial tension in CON group (r = 0.56, p = 0.03).

---

**Discussion**

Measurements of plasma levels of immunoreactive ET will only provide limited insight into the role of a peptide that is a paracrine tissue hormone rather than an endocrine circulating hormone (Yanagisawa et al., 1988). It has been shown that endothelial cells secrete much more ET-1 towards the adjacent vascular smooth muscle cells than they do luminally.

The mechanism of ET-1-induced hypertension is clearly multifactorial; however, induction of reactive oxygen species production may be involved. ET-1 has been reported to induce oxidative stress through increased NADPH oxidase activity (Pollok et al., 2006).

Other study had found that ET-1 induced oxidative stress, at least in large blood vessels, through a mitochondria-dependent, NADPH oxidase–independent mechanism in rats with deoxycorticosterone acetate-salt hypertension (Callera et al., 2006).

The relationship between ET-1 and reactive oxygen species production and other putative mediators in hypertension is still an opened problem.

Our study demonstrated that patients with coronary artery disease, arterial
RELATIONSHIP BETWEEN BRACHIAL ARTERY FLOW-MEDIATED DILATION AND CAROTID ARTERY INTIMA–MEDIA THICKNESS IN THE MIDDLE-AGED SUBJECTS WITH LOW CARDIOVASCULAR RISK

GERMAINE SĂVOIU*, LAVINIA NOVEANU**, O. FIRA-MLADINESCU*, CORINA GORUN*
SILVIA N. MIRICĂ*, OANA M. DUICU*, SIMONA DRĂGAN***, DANINA MUNTEAN*, GEORGETA MIHALAŞ**

* Department of Pathophysiology, “Victor Babeş” University of Medicine and Pharmacy, Timişoara
** Department of Physiology, “Victor Babeş” University of Medicine and Pharmacy, Timişoara
*** Department of Preventive Cardiology and Rehabilitation, “Victor Babeş” University of Medicine and Pharmacy, Timişoara

Abstract. Endothelial vasodilator dysfunction, assessed by brachial artery flow-mediated dilatation (FMD) and carotid intima-media thickening (IMT), is an indicator of subclinical atherosclerotic disease. We examined their correlation and interaction with traditionally cardiovascular risk factors, in a group of middle-aged subjects with a low total cardiovascular risk (<5%) estimated based on the SCORE (Systematic Coronary Risk Evaluation) system. A number of 74 subjects aged from 45 to 55 years were studied under identical conditions by a single sonograph. The brachial artery was identified at 5 cm proximal to the transient bifurcation by using a 10 MHz ALOKA ProSound SSD 4000 ultrasound system (ALOKA CO., LTD., Tokyo, Japan). After baseline imaging, a right arm cuff was inflated to > 50 mm Hg above systolic blood pressure (SBP), for 5 minutes. After the cuff was deflated ischemia-induced distal hyperemia produced a transient increase of artery diameter. The relative change in mean arterial diameter was calculated as: % Dilation = [Maximum diameter – Baseline diameter] × 100 / Baseline diameter, where maximum diameter was the maximum mean diameter observed at 45 – 60 seconds after cuff release. For carotid ultrasound study, the image was focused on the posterior (far) of the left carotid artery. A minimum of 4 measurements of the common carotid far wall were taken 10 mm proximal to the bifurcation to derive mean carotid IMT. Continuous variables are expressed as means ± SD. Means were compared using analysis of variance or the Student t-test. Our study shows that in a relatively healthy middle-aged subject, there is no significant correlation between carotid IMT and brachial artery FMD. This finding may be related to a temporal dissociation between functional and structural vascular abnormalities in a low risk population.

Key words: flow mediated dilatation, intima-media thickening, atherosclerosis, cardiovascular risk factors. 

Received: March 2008; in final form May 2008.
RELATIONSHIP BETWEEN BRACHIAL ARTERY FLOW-MEDIATED DILATION AND CAROTID ARTERY INTIMA–MEDIA THICKNESS IN THE MIDDLE-AGED SUBJECTS WITH LOW CARDIOVASCULAR RISK

GERMAINE SĂVOIU*, LAVINIA NOVEANU**, O. FIRA-MLADINESCU*, CORINA GORUN*, SILVIA N. MIRICĂ*, OANA M. DUICU*, SIMONA DRĂGAN***, DANINA MUNTEAN*, GEORGETA MIHALAŞ**

* Department of Pathophysiology, “Victor Babeş” University of Medicine and Pharmacy, Timişoara
** Department of Physiology, “Victor Babeş” University of Medicine and Pharmacy, Timişoara
*** Department of Preventive Cardiology and Rehabilitation, “Victor Babeş” University of Medicine and Pharmacy, Timişoara

Abstract. Endothelial vasodilator dysfunction, assessed by brachial artery flow-mediated dilatation (FMD) and carotid intima-media thickening (IMT), is an indicator of subclinical atherosclerotic disease. We examined their correlation and interaction with traditionally cardiovascular risk factors, in a group of middle-aged subjects with a low total cardiovascular risk (<5%) estimated based on the SCORE (Systematic Coronary Risk Evaluation) system. A number of 74 subjects aged from 45 to 55 years were studied under identical conditions by a single sonograph. The brachial artery was identified at 5 cm proximal to the transient bifurcation by using a 10 MHz ALOKA ProSound SSD 4000 ultrasound system (ALOKA CO., LTD., Tokyo, Japan). After baseline imaging, a right arm cuff was inflated to > 50 mm Hg above systolic blood pressure (SBP), for 5 minutes. After the cuff was deflated ischemia-induced distal hyperemia produced a transient increase of artery diameter. The relative change in mean arterial diameter was calculated as: % Dilation = [(Maximum diameter – Baseline diameter) × 100 / Baseline diameter], where maximum diameter was the maximum mean diameter observed at 45 – 60 seconds after cuff release. For carotid ultrasound study, the image was focused on the posterior (far) of the left carotid artery. A minimum of 4 measurements of the common carotid far wall were taken 10 mm proximal to the bifurcation to derive mean carotid IMT. Continuous variables are expressed as means ± SD. Means were compared using analysis of variance or the Student t-test. Our study shows that in a relatively healthy middle-aged subject, there is no significant correlation between carotid IMT and brachial artery FMD. This finding may be related to a temporal dissociation between functional and structural vascular abnormalities in a low risk population.

Key words: flow mediated dilation, intima-media thickening, atherosclerosis, cardiovascular risk factors.

Received: March 2008;
in final form May 2008.

[Maximum diameter – Baseline diameter] × 100 / Baseline diameter, where the maximum diameter was the maximum mean diameter observed at 45 – 60 seconds after cuff release.

For carotid ultrasound study, the image was focused on the posterior (far) of the left carotid artery. A minimum of 4 measurements of the common carotid far wall were taken 10 mm proximal to the bifurcation to derive mean carotid IMT.

Continuous variables are expressed as means ± SD. Means were compared using analysis of variance or the Student t-test. Pearson’s correlation was used to test bivariate correlations and results were verified using the non-parametric Spearman’s rank correlation test. Multivariate linear regression analysis was used to determine the independent predictors of carotid IMT and brachial FMD and to test the relationship between IMT and brachial FMD, in models including classical risk factors. The relationship between carotid IMT and brachial FMD was tested for entire group and in subgroups defined by traditional risk factors (Pearsons’s and Spearman’s rank bivariate correlation tests were performed). Statistical significance was defined as two-sided \( p < 0.05 \). All statistical analyses were performed using Excell Microsoft Office 2003.

RESULTS

Demographic data, traditional CV risk factors, carotid IMT, and brachial FMD measurement are shown in Table 1. The subjects were predominantly male and were commonly overweight. Many subjects reported current smoking and a history of mild hypertension. Few study subjects had diabetes.

Table 1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>52 (70.27)</td>
</tr>
<tr>
<td>Female gender</td>
<td>22 (29.73)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>47 (63.51)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (2.70)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>58 (78.37)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>59.37 ± 9.92</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>145.15 ± 14.67</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>91.64 ± 12.67</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.48 ± 4.56</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>223.12 ± 26.78</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>156.94 ± 87.66</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>126.89 ± 33.56</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>38.45 ± 10.89</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>96.10 ± 13.67</td>
</tr>
<tr>
<td>Total cardiovascular risk (%)</td>
<td>4.22 ± 0.87</td>
</tr>
<tr>
<td>Mean carotid IMT (mm)</td>
<td>0.70 ± 0.19</td>
</tr>
<tr>
<td>Brachial artery FMD (%)</td>
<td>11.78 ± 4.06</td>
</tr>
</tbody>
</table>
[Maximum diameter – Baseline diameter] × 100 / Baseline diameter, where the maximum diameter was the maximum mean diameter observed at 45 – 60 seconds after cuff release.

For carotid ultrasound study, the image was focused on the posterior (far) of the left carotid artery. A minimum of 4 measurements of the common carotid far wall were taken 10 mm proximal to the bifurcation to derive mean carotid IMT.

Continuous variables are expressed as means ± SD. Means were compared using analysis of variance or the Student t-test. Pearson’s correlation was used to test bivariate correlations and results were verified using the non-parametric Spearman’s rank correlation test. Multivariate linear regression analysis was used to determine the independent predictors of carotid IMT and brachial FMD and to test the relationship between IMT and brachial FMD, in models including classical risk factors. The relationship between carotid IMT and brachial FMD was tested for entire group and in subgroups defined by traditional risk factors (Pearson’s and Spearman’s rank bivariate correlation tests were performed). Statistical significance was defined as two-sided \( p < 0.05 \). All statistical analyses were performed using Excell Microsoft Office 2003.

RESULT

Demographic data, traditional CV risk factors, carotid IMT, and brachial FMD measurement are shown in Table 1. The subjects were predominantly male and were commonly overweight. Many subjects reported current smoking and a history of mild hypertension. Few study subjects had diabetes.

Table 1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>52 (70.27)</td>
</tr>
<tr>
<td>Female gender</td>
<td>22 (29.73)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>47 (63.51)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (2.70)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>58 (78.37)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>59.37 ± 9.92</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>145.15 ± 14.67</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>91.64 ± 12.67</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.48 ± 4.56</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>223.12 ± 26.78</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>156.94 ± 87.66</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>126.89 ± 33.56</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>38.45 ± 10.89</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>96.10 ± 13.67</td>
</tr>
<tr>
<td>Total cardiovascular risk (%)</td>
<td>4.22 ± 0.87</td>
</tr>
<tr>
<td>Mean carotid IMT (mm)</td>
<td>0.70 ± 0.19</td>
</tr>
<tr>
<td>Brachial artery FMD (%)</td>
<td>11.78 ± 4.06</td>
</tr>
</tbody>
</table>
meta-analyzed studies was only 20 subjects, that many of the smaller studies recruited highly selected individuals rather than population-based samples, and that the resulting analysis will necessarily reflect the findings of the largest studies included, as well as being potentially confounded by publication bias and the combination of results from studies which used very different methodologies for the measurement of FMD. Thus, such findings could best be regarded as hypothesis-generating, rather than a definitive indication that FMD is best suited to risk stratification in low-risk populations [9].

The main finding of our study was the moderate correlation between measurements of carotid IMT and brachial artery FMD in a group of middle age adults without CVD and with relatively few risk factors. Our data from 74 subjects thus confirm observations from previous small-scale studies that have suggested an inverse relation between brachial FMD response and carotid IMT [3, 8].

Our data also indicate that young adults presenting with low cardiovascular risk have a moderate risk to develop thickened carotid IMTs, but when they have evidence of endothelial dysfunction, the risk of development thickened IMTs increase significantly. Our results are in concordance with the concepts that endothelial dysfunction is an early event in atherosclerosis. Thus, in addition to the evaluation of conventional cardiovascular risk factors, noninvasive evaluation of endothelial dysfunction might be helpful to discriminate individuals at risk for atherosclerosis [5].

CONCLUSION

Our findings support the conclusion that in apparently healthy individuals with relatively few risk factors, carotid IMT and brachial artery FMD provide distinct, independent informations about the complex atherosclerotic process.

These findings may be related to a temporal dissociation between functional and structural vascular abnormalities in a low risk population. Therefore, these non-invasive measures of early structural subclinical atherosclerosis may provide complementary information about vascular health.

This study encourages the use of both FMD and IMT for the identification of asymptomatic individuals with low cardiovascular risk.

REFERENCES

Mechanisms of ET-1-induced Endothelial Dysfunction

Marc Iglarz, PhD and Martine Clozel, MD

Abstract: There is now increasing evidence that endothelial dysfunction is an early event in the pathophysiology of cardiovascular diseases and can be corrected with certain therapies such as angiotensin converting enzyme inhibitors angiotensin type I receptor antagonists and statins independently of blood pressure lowering effects. Restoring endothelial function appears to be a crucial target since endothelial dysfunction predicts cardiovascular events in various situations such as coronary artery disease peripheral artery disease, or hypertension and in patients undergoing vascular surgery. Preclinical and clinical data strongly support that endothelin receptor antagonists belong to this restricted class of pharmacological agents able to act on the endothelium, and offer a potential therapeutic approach for numerous diseases associated with endothelial dysfunction. The purpose of this review will be therefore, 1) to propose mechanisms by which ET-1 can cause endothelial dysfunction; 2) to provide an overview of pathological situations associated with endothelial dysfunction related to ET-1; and 3) to assemble evidence on efficacy of ET receptor antagonists for improvement of endothelial function.

Key Words: endothelin-1, endothelium, nitric oxide, endothelin receptor antagonists, hypertension, oxidative stress, caveolae, inflammation

INTRODUCTION

Localized at the interface between the vessel wall and circulating blood, the endothelium controls several major functions in cardiovascular homeostasis such as hemostasis, vascular permeability, and blood pressure. The discovery in 1980 of the endothelium’s ability to elicit vasodilation led to a revolution in vascular biology. Endothelial cells are able to produce both vasoconstrictive and vasodilating substances. The main endothelium-derived relaxing factors are nitric oxide (NO), prostacyclin, and endothelin-derived hyperpolarizing factor. They can also present other properties; NO in particular inhibits inflammation, vascular smooth muscle cell proliferation, platelet adhesion, and tissue factor release. Endothelial cells produce vasoconstrictive substances as well, such as prostaglandin endoperoxides and the peptides angiotensin II and endothelin-1 (ET-1). ET-1 is synthesized from a larger preproET-1 precursor that is cleaved into an inactive 38-amino-acid peptide and further processed into the 21-amino-acid active ET-1. ET-1 is described as the most potent vasoconstrictor known and acts mainly in a paracrine manner by binding to 2 G-protein coupled receptors, ETA and ETB, which are located on endothelial cells (ETB), vascular smooth muscle cells, and fibroblasts (ETA and ETB). Endothelial ETB receptors can elicit endothelium-dependent relaxation by inducing NO release, whereas ETA and ETB receptors located on smooth muscle cells and fibroblasts trigger vasoconstriction, cell proliferation, inflammation, and fibrosis. Importantly, ET receptor distribution has been shown to be modified in pathological conditions.

Endothelial dysfunction is defined by an impaired vascular reactivity, but it also refers to a proinflammatory and prothrombotic state. Endothelial dysfunction has been described in many cardiovascular and metabolic disorders such as hypertension, coronary heart disease, dyslipidemia, and type I and II diabetes. Endothelial dysfunction appears to precede the clinical manifestations of many of these cardiovascular disorders, hypertension for example, and also atherosclerosis, where abnormal vasoconstriction can be observed at the future site of plaque development. Thus, endothelial dysfunction is one of the earliest hallmarks of vascular abnormality.

Classically, endothelial dysfunction has been considered to be the result of a decrease in NO. The question now arises whether the decrease in NO is not secondary to an increase in ET-1. Indeed, in addition to being a potent endothelial-derived constrictor of vascular smooth muscle, ET-1 may induce endothelial dysfunction by decreasing NO bioavailability. Indeed, recent data show that endothelium-restricted overexpression of ET-1 causes endothelial dysfunction and a decrease in NO. Furthermore, both preclinical and clinical data suggest that selective (ETA) and that dual (ETA + ETB) receptor antagonists improve NO bioavailability and endothelial function in pathological situations. Taken together with the fact that ET-1 production by endothelial cells can be enhanced by a variety of endogenous and exogenous factors, these observations raise the possibility that ET-1, beyond its vasoconstrictive properties, plays a key role in the development of endothelial dysfunction.

The purpose of this review is to (1) propose mechanisms by which ET-1 can cause endothelial dysfunction; (2) provide an overview of pathological situations associated with endothelial dysfunction related to ET-1; (3) assemble evidence on efficacy of ET receptor antagonists for improvement of endothelial function.
Mechanisms of ET-1-induced Endothelial Dysfunction

Marc Iglarz, PhD and Martine Clozel, MD

Abstract: There is now increasing evidence that endothelial dysfunction is an early event in the pathophysiology of cardiovascular diseases and can be corrected with certain therapies such as angiotensin converting enzyme inhibitors angiotensin type I receptor antagonists and stains independently of blood pressure lowering effects. Restoring endothelial function appears to be a crucial target since endothelial dysfunction predicts cardiovascular events in various situations such as coronary artery disease peripheral artery disease, or hypertension and in patients undergoing vascular surgery. Preclinical and clinical data strongly support that endothelin receptor antagonists belong to this restricted class of pharmacological agents able to act on the endothelium, and offer a potential therapeutic approach for numerous diseases associated with endothelial dysfunction. The purpose of this review will be therefore, 1) to propose mechanisms by which ET-1 can cause endothelial dysfunction; 2) to provide an overview of pathological situations associated with endothelial dysfunction related to ET-1; and 3) to assemble evidence on efficacy of endothelin receptor antagonists for improvement of endothelial function.

Key Words: endothelin-1, endothelium, nitric oxide, endothelin receptor antagonists, hypertension, oxidative stress, caveolae, inflammation

(J Cardiovasc Pharmacol™ 2007;50:621–628)

INTRODUCTION

Localized at the interface between the vessel wall and circulating blood, the endothelium controls several major functions in cardiovascular homeostasis such as hemostasis, vascular permeability, and blood pressure. The discovery in 1980 of the endothelium’s ability to elicit vasodilation led to a revolution in vascular biology.1 Endothelial cells are able to produce both vasoconstrictive and vasodilating substances. The main endothelium-derived relaxing factors are nitric oxide (NO), prostacyclin, and endothelium-derived hyperpolarizing factor. They can also present other properties; NO in particular inhibits inflammation, vascular smooth muscle cell proliferation,2 platelet adhesion,3 and tissue factor release.4 Endothelial cells produce vasoconstrictive substances as well, such as prostaglandin endoperoxides and the peptides angiotensin II and endothelin-1 (ET-1). ET-1 is synthesized from a larger preproET-1 precursor that is cleaved into an inactive 38-amino-acid peptide and further processed into the 21-amino acid active ET-1. ET-1 is described as the most potent vasoconstrictor known5 and acts mainly in a paracrine manner by binding to 2 G-protein coupled receptors, ETA and ETB, which are located on endothelial cells (ETB), vascular smooth muscle cells, and fibroblasts (ETA and ETB). Endothelial ETB receptors can elicit endothelium-dependent relaxation by inducing NO release, whereas ETA and ETB receptors located on smooth muscle cells and fibroblasts trigger vasoconstriction, cell proliferation, inflammation, and fibrosis. Importantly, ET receptor distribution has been shown to be modified in pathological conditions.6

Endothelial dysfunction is defined by an impaired vascular reactivity, but it also refers to a proinflammatory and prothrombotic state. Endothelial dysfunction has been described in many cardiovascular and metabolic disorders such as hypertension,7 coronary heart disease,8 dyslipidemia,9 and type I and II diabetes.10 Endothelial dysfunction appears to precede the clinical manifestations of many of these cardiovascular disorders, hypertension for example,11 and also atherosclerosis, where abnormal vasoconstriction can be observed at the future site of plaque development.12 Thus, endothelial dysfunction is one of the earliest hallmarks of vascular abnormality.

Classically, endothelial dysfunction has been considered to be the result of a decrease in NO. The question now arises whether the decrease in NO is not secondary to an increase in ET-1. Indeed, in addition to being a potent endothelial-derived constrictor of vascular smooth muscle, ET-1 may induce endothelial dysfunction by decreasing NO bioavailability. Indeed, recent data show that endothelium-restricted overexpression of ET-1 causes endothelial dysfunction and a decrease in NO.13 Furthermore, both preclinical and clinical data suggest that selective (ETA) and that dual (ETA + ETB) receptor antagonists improve NO bioavailability and endothelial function in pathological situations. Taken together with the fact that ET-1 production by endothelial cells can be enhanced by a variety of endogenous and exogenous factors,6 these observations raise the possibility that ET-1, beyond its vasoconstrictive properties, plays a key role in the development of endothelial dysfunction.

The purpose of this review is to (1) propose mechanisms by which ET-1 can cause endothelial dysfunction; (2) provide an overview of pathological situations associated with endothelial dysfunction related to ET-1; (3) assemble evidence on efficacy of ET receptor antagonists for improvement of endothelial function.
Effect of amloidipine on blood and aortic tissue concentration of endothelin in male rabbits receiving atherogenic diet

**Author:** Mohammadi, M; Mirzaei, F; Badalzadeh, Reza

**Abstract:** Background: Different factors are involved in the induction and progress of atherosclerosis. One of these factors is endothelin-1. Since, in atherosclerotic vessels, there are certain obvious changes, with abnormality in the transfer of calcium ions, some researchers have suggested that calcium channel blockers can slow down the process of atherosclerosis. In this study, we evaluated the effects of amloidipine and/or a high cholesterol diet on the blood and aortic concentration of endothelin in rabbits. Materials and Methods: Thirty-six male New Zealand white rabbits were divided into four groups: the normal control group, normal diet plus amloidipine group, high-cholesterol diet group, and high-cholesterol diet plus amloidipine group. After 8 weeks all animals were anesthetized and blood or tissue samples were collected. Results and Conclusions: Eight weeks of amloidipine treatment significantly reduced total cholesterol, low density lipoproteins (LDL), and triglycerides (TG) in the hypercholesterolemic diet group. Although amloidipine treatment tended to enhance HDL/LDL and HDL/cholesterol ratios in the mentioned group, these effects were not statistically significant. The observed significant increase in plasma high density lipoprotein cholesterol (HDL-C) and decrease in TG is considered to be the main effect of amloidipine treatment on the serum lipid profile in the control group. The plasma level of endothelin-1 in the atherosclerotic model group was significantly increased as compared to the control group (P <0.01). After treatment with amloidipine, the ET-1 level reduced significantly in the control and high-cholesterol diet rabbits (P <0.01). A high-cholesterol diet induced atherosclerotic lesions and thickening of the intima in the thoracic aorta. Amlodipine consumption reduced atherotic injuries in high-cholesterol diet rabbits. There were no lesions in the normal diet groups or the normal diet with amloidipine group. High cholesterol causes increase in plasma and tissue endothelin. Amlodipine treatment reduced the levels of total cholesterol, LDL, and TG and, in a high lipid intake situation reduced endothelin levels in plasma and aortic tissue. Our data shows that amloidipine treatment may be considered as one of the important interventions for prevention and regression of atherosclerosis.

**Links:** Check for full text via 360 Link

**Full text:** Atherosclerosis is a leading cause of mortality and morbidity in the developed world and most of the developing countries. [1] Atherosclerosis is a complex process and is possibly caused by a high-fat diet and a sedentary lifestyle. [2] Hypercholesterolemia is one of the most important risk factors for atherosclerosis, which promotes functional and structural vascular injury. [3] Atherosclerosis is a progressive and systemic vascular disorder that initiates molecular and cellular events that are triggered by endothelial dysfunction, resulting in decreased nitric oxide production, increased ET-1 production and cyclooxygenase activity, and inflammation. [4],[5] The 21-amino acid peptide endothelin-1 (ET-1) is produced by vascular endothelial cells from the 38-amino acid precursor peptide, big ET-1, by the action of endothelin converting enzyme (ECE). [6] ET-1 may contribute to the progression of several cardiovascular disorders such as congestive heart failure, hypertension, and ischemic heart disease. [6] It has also been speculated that ET-1 is important in atherosclerosis. [7] Besides its vasoconstrictor effects ET-1 also contributes to cell proliferation, thereby promoting vascular growth and atherogenesis. [6] The expression of ET-1 is enhanced in smooth muscle cellular macrophages of human atherosclerotic plaques. [8] Many components of human atherosclerosis lesions, such as endothelial cells, macrophages, and smooth muscle cells, express ET-1. These findings indicate that ET-1 may be involved in the
total cholesterol, LDL-C, HDL-C, and TG. These observations indicate that atherogenic diets induce hypercholesterolemia in the experimental New Zealand rabbit model. Although amlodipine treatment enhanced HDL/LDL and HDL/cholesterol ratios in this group, these effects were not statistically significant. The observed significant increase in plasma HDL-C and decrease in TG is considered to be the main effect of amlodipine treatment on the serum lipid profile in the control group [Table 1].

ET-1 level
The plasma level of ET-1 in the atherosclerotic model group was significantly increased as compared with the control group (P P P P P Histological findings
Eight weeks of a 2% high-cholesterol diet induced atherosclerotic lesions and thickening of the intima in the thoracic aorta of all the animals in the HC group. The internal layer was increased and the cells appeared yellowish-white due to the accumulation of lipids. Hypertrophy of endothelial cells and accumulation of lipids in the endothelial layers, with calcification in the media, indicates induction of atheroma. Amlodipine consumption reduced atherotic injuries in high-cholesterol diet rabbits. There were no lesions in the normal diet group or the normal diet with amlodipine group [Figure 1],[Figure 2],[Figure 3].

Discussion
Our results indicate that 8 weeks of a 2% high-cholesterol diet increased all lipid fractions and induced formation of atherosclerotic lesions, including thickening of the intima and/or macrophage foam cell formation, in the thoracic aorta. Because excessive cell calcium transport contributes to many cellular changes in atherogenesis, it has been proposed that the pharmacologic calcium blocker, amlodipine, may be effective in slowing the progression of atherosclerosis. [17] The key finding of this study was that the second generation dihydropyridine, amlodipine, is able to inhibit progression of preexisting atherosclerotic plaque; the formation of ET-1 was also significantly higher in atherosclerotic rabbits. These changes with amlodipine are similar to those reported in rabbits, swine, monkeys, and humans. [18] Based upon these studies, it appeared that CCBs would be most effective if administered concomitantly with the atherogenic stimuli (i.e., cholesterol). Since amlodipine is highly lipophilic, the drug can be rapidly absorbed in the atheroma of atherosclerotic lesions; it accumulates locally and acts more effectively in the atheromatous artery. If the lesions have already begun to form, CCBs usually showed little or no effect. [8] Because of marked increase in calcium permeability in SMC during the development of atherosclerotic lesions, a role for CCBs in the prevention of these lesions would seem reasonable. However, many reports failed to confirm this effect and the role of CCBs in atheroprotection was not established. [19]

The search for a CCB that might inhibit atherogenesis revealed a variety of interesting actions of the second generation dihydropyridine, amlodipine. Because excessive cell calcium transport contributes to many cellular changes in atherogenesis, it has been proposed that antagonists may be effective in slowing the progression of atherosclerosis and heart diseases. [17] Although how amlodipine improves atherosclerosis is still unclear, several possible mechanisms for the anti-atherogenesis (i.e., effects of amlodipine) have been proposed: recruitment of macrophages, lipid oxidation, and proliferation of SMC that are calcium dependent and may be influenced by amlodipine. [17]

ET-1 contributes to vasoconstriction and cell proliferation, thereby promoting vascular growth and atherogenesis. [20] ET-1 may be an early marker and mediator of endothelial dysfunction, leading to enhanced vasoconstrictor responses and contributing to the development of atherosclerotic lesions. [21] Several observations have linked hypercholesterolemia with the endothelin system and progression of atherosclerosis. [22] Increased ET-1 level due to a high-cholesterol diet may be attributed to high levels of lipids and some lipoproteins (LDL) produced by high-cholesterol diets. Recently, it has been reported that oxidized lipids can also induce endothelin converting enzyme-1 expression in human endothelial cells. [3] In our study, hypercholesterolemia produced by a high-cholesterol diet might have contributed to enhanced ET-1 formation via increase of lipids and LDL.
Relationship between brachial flow-mediated dilation and carotid intima-media thickness in an elderly cohort: The Cardiovascular Health Study☆

Joseph Yeboah a,b,*, Gregory L. Burke a,b, John R. Crouse a,b, David M. Herrington a,b

a Department of Internal Medicine/Cardiology, Wake Forest University School of Medicine, Winston-Salem, NC, United States
b Department of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, NC, United States

Received 8 June 2007; received in revised form 14 July 2007; accepted 27 July 2007
Available online 4 September 2007

Abstract

Objective: The aim of this study was to determine the relationship between brachial flow-mediated dilation (FMD) and carotid intima-media thickness (IMT) in a large multi-ethnic elderly cohort.

Background: Brachial flow-mediated dilation (FMD) is a physiologic measure and carotid IMT is an anatomic structural measure of subclinical atherosclerosis. Both brachial FMD and carotid IMT have been associated with cardiovascular risk factors and cardiovascular events. The relationship between brachial FMD and carotid IMT is less clear especially in older adults.

Methods: Brachial FMD, carotid IMT and traditional cardiovascular risk factors were measured in 2338 adults, age 72–98 years who were participants in the Cardiovascular Health Study. The relationship between FMD and IMT was assessed both unadjusted and also after adjusting for age, gender and race/ethnicity, BMI, HDL, LDL, systolic and diastolic blood pressure, serum creatinine, current smoking, diabetes mellitus, hormone therapy and prior CVD.

Results: Both brachial FMD and carotid IMT correlated significantly with age, HDL levels, waist/hip ratio, serum cholesterol and number of CV risk factors. Brachial FMD was not associated with CCA IMT in this elderly cohort (Pearson partial correlation coefficient = −0.0252, \( p = 0.222 \)). In the adjusted linear regression model with CCA IMT as the dependent variable, brachial FMD was also not associated with CCA IMT (beta coefficient = −0.006, \( p = 0.470 \)).

Conclusion: Brachial FMD and CCA IMT are not related in population-based older adults. Brachial FMD and CCA IMT may be distinct and independent stages in the complex atherosclerotic process.

© 2007 Elsevier Ireland Ltd. All rights reserved.

Keywords: Brachial flow-mediated dilation; Carotid intima-media thickness; Endothelial function; Atherosclerosis; Elderly

1. Introduction

Subclinical cardiovascular disease (CVD) has both physiologic and anatomic components. Non-invasive measurement techniques allow for the characterization of both physiologic as well as anatomic structural changes in the arterial wall due to cardiovascular disease. Brachial flow-mediated dilation (FMD) is a validated non-invasive physiologic measure of endothelial dysfunction (a marker of subclinical CVD) [1]. Carotid intima-media thickness (IMT) however, is a non-invasive anatomic structural measure of subclinical CVD [2].
Relationship between brachial flow-mediated dilation and carotid intima-media thickness in an elderly cohort: The Cardiovascular Health Study

Joseph Yeboah a,b,*, Gregory L. Burke a,b, John R. Crouse a,b, David M. Herrington a,b

a Department of Internal Medicine/Cardiology, Wake Forest University School of Medicine, Winston-Salem, NC, United States
b Department of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, NC, United States

Received 8 June 2007; received in revised form 14 July 2007; accepted 27 July 2007
Available online 4 September 2007

Abstract

Objective: The aim of this study was to determine the relationship between brachial flow-mediated dilation (FMD) and carotid intima-media thickness (IMT) in a large multi-ethnic elderly cohort.

Background: Brachial flow-mediated dilation (FMD) is a physiologic measure and carotid IMT is an anatomic structural measure of subclinical atherosclerosis. Both brachial FMD and carotid IMT have been associated with cardiovascular risk factors and cardiovascular events. The relationship between brachial FMD and carotid IMT is less clear especially in older adults.

Methods: Brachial FMD, carotid IMT and traditional cardiovascular risk factors were measured in 2338 adults, age 72–98 years who were participants in the Cardiovascular Health Study. The relationship between FMD and IMT was assessed both unadjusted and also after adjusting for age, gender and race/ethnicity, BMI, HDL, LDL, systolic and diastolic blood pressure, serum creatinine, current smoking, diabetes mellitus, hormone therapy and prior CVD.

Results: Both brachial FMD and carotid IMT correlated significantly with age, HDL levels, waist/hip ratio, serum cholesterol and number of CV risk factors. Brachial FMD was not associated with CCA IMT in this elderly cohort (Pearson partial correlation coefficient = −0.0252, \( p = 0.222 \)). In the adjusted linear regression model with CCA IMT as the dependent variable, brachial FMD was also not associated with CCA IMT (beta coefficient = −0.006, \( p = 0.470 \)).

Conclusion: Brachial FMD and CCA IMT are not related in population-based older adults. Brachial FMD and CCA IMT may be distinct and independent stages in the complex atherosclerotic process.

© 2007 Elsevier Ireland Ltd. All rights reserved.

Keywords: Brachial flow-mediated dilation; Carotid intima-media thickness; Endothelial function; Atherosclerosis; Elderly

1. Introduction

Subclinical cardiovascular disease (CVD) has both physiologic and anatomic components. Non-invasive measurement techniques allow for the characterization of both physiologic as well as anatomic structural changes in the arterial wall due to cardiovascular disease. Brachial flow-mediated dilation (FMD) is a validated non-invasive physiologic measure of endothelial dysfunction (a marker of subclinical CVD) [1]. Carotid intima-media thickness (IMT) however, is a non-invasive anatomic structural measure of subclinical CVD [2].
Oral Magnesium Therapy Improves Endothelial Function in Patients With Coronary Artery Disease

Michael Shechter, MD, MA; Michael Sharir, MD; Maura J. Paul Labrador, MPH; James Forrester, MD; Burton Silver, PhD; C. Noel Bairey Merz, MD

Methods and Results—In a randomized, double-blind, placebo-controlled trial, 50 stable CAD patients (41 men and 9 women, mean±SD age 67±11 years, age range 42 to 82 years) were randomized to receive either magnesium (n=25) (30 mmol/d Magnosolv-Granulat; Asta Medica Company, Inc) or placebo (n=25) for 6 months. Before and after 6 months, endothelium-dependent brachial artery flow-mediated vasodilation (FMD) and endothelium-independent NTG-mediated vasodilation were assessed with high-resolution (10-MHz) ultrasound. Exercise stress testing was performed with use of the Bruce protocol. Intracellular magnesium concentrations ([Mg²⁺]) were assessed from sublingual cells through x-ray dispersion (EXA) (normal mean±SD values 37.9±4.0 mEq/L). The magnesium therapy significantly increased postintervention ([Mg²⁺]), versus placebo (36.2±5.0 versus 32.7±2.7 mEq/L, P<0.02). There was a significant correlation in the total population between baseline [Mg²⁺], and baseline FMD (r=0.48, P<0.01). The magnesium intervention resulted in a significant improvement in postintervention FMD (15.5±12.0%, P=0.02 compared with baseline), which was not evident with placebo (4.4±2.5%, P=0.78 compared with baseline). There was better exercise tolerance (9.3±2.0 versus 7.3±3.1 minutes, P=0.05) and less ischemic ST-segment changes (4 versus 10 patients, P=0.05) in the magnesium versus placebo groups, respectively.

Conclusions—Oral magnesium therapy in CAD patients is associated with significant improvement in brachial artery endothelial function and exercise tolerance, suggesting a potential mechanism by which magnesium could beneficially alter outcomes in CAD patients. (Circulation. 2000;102:2353-2358.)

Key Words: magnesium ■ lipoproteins ■ endothelium ■ coronary disease

Magnesium blocks many of the physiological actions of calcium. Epidemiological evidence that links magnesium deficiency to coronary artery disease (CAD) has been investigated for >3 decades. In the Atherosclerosis Risk in Communities (ARIC) Study, the relation of serum and dietary magnesium and CAD incidence during 4 to 7 years of follow-up was examined in a sample of 13 922 middle-aged adults free of baseline CAD from 4 US communities. After adjustment for traditional risk factors, the relative risk of CAD across quartiles of serum magnesium was 1.00, 0.92, 0.48, and 0.44 (P for trend=0.009), suggesting that low magnesium may be involved in the pathogenesis of CAD.

It is known that the vascular endothelium plays a key role in circulatory homeostasis through its ability to regulate the vascular milieu via the synthesis and release of biologically active substances, such as endothelium-derived relaxing factor (EDRF). The endothelium influences not only vascular tone but also vascular remodeling, as well as hemostasis and thrombosis, through platelet, coagulant, and fibrin effects. In atherosclerotic arteries, these functions of the endothelium are impaired and potentiate an adverse pathophysiology through increased vasoconstriction (ie, paradoxical vasoconstriction) and thrombosis. It has been suggested that by reducing cardiovascular risk factors, the modification or reversal of endothelial dysfunction may be of significant therapeutic benefit in the treatment of CAD.

The present study was designed to compare the effect of an oral magnesium intervention versus placebo on brachial artery endothelial function and exercise tolerance in patients with stable CAD.

Methods

Study Design and Population

The study design was a randomized, prospective, double-blind, placebo-controlled trial. Patients were recruited consecutively from a
supervised cardiac exercise and rehabilitation program at Cedars-Sinai Medical Center. Inclusion criteria included men and women aged >20 years, with CAD documented through prior myocardial infarction, CABC, or coronary angiography or angioplasty. Exclusion criteria included unstable angina, congestive heart failure of higher than New York Heart Association functional class III, chronic diarrhea, renal failure (serum creatinine $>$3 mg/dL), acute myocardial infarction within the preceding 3 months, hyperthyroidism/hypothyroidism, type 1 (insulin-dependent) diabetes mellitus, peripheral vascular disease, history of drug or alcohol abuse, chronic liver disease, or refusal to sign the informed consent. The study was approved by the institutional review board, and all participants gave written informed consent.

**Study Protocol**

The patients were randomized through a computerized randomization program (Rancode-Plus, Version 3.1; IDV Data Analysis) to receive either 15 mmol Magnosolv-Granulat PO BID (Asta Medical Company, Inc) or placebo for 6 months. Each pouch of Magnosolv-Granulat contains 15 mmol Mg$^{2+}$, 365 mg total magnesium (342 mg magnesium oxide, 670 mg carbonicum). The patients were instructed to continue taking their other regular medications and to maintain their usual diet during the study. Before and after 6 months, the patients underwent after an overnight fast, a physical examination, brachial reactivity testing, treadmill exercise testing, and blood tests (after an overnight fast, a physical examination, brachial reactivity testing, treadmill exercise testing, and blood tests for the measurement of lipids, blood cell count, electrolytes, and sublingual intracellular magnesium levels. Compliance of study medication was assessed at 1, 3, and 6 months on the basis of pill count.

**Vascular Function Protocol**

Endothelial function in the form of endothelium-dependent brachial artery flow-mediated vasodilation (FMD) was measured as previously described.

Briefly, FMD was assessed in the right arm of the subject in the recumbent position in a temperature-controlled room (22°C) after a 10-minute equilibration period by a single ultrasonographer blinded to treatment assignment. With a 10-MHz linear array (CL 10-5; ATL) ultrasound (HDI 3000cv system; ATL), the brachial artery was longitudinally imaged $\sim$5 cm proximal to the antecubital crease, where the clearest image was obtained. When a reasonable image was obtained, the surface of the skin was marked, and the arm was kept in the same position throughout the study. The ultrasound probe was kept at the same position by the ultrasonographer during the entire study. ECG was monitored continuously, and blood pressure was monitored in the left arm every minute during the study.

**Study Phases**

**Endothelium-Dependent FMD**

After a 2-minute baseline period, a frozen longitudinal image of 3 cm of vessel without color flow was obtained and frozen for 5 seconds. The image was then unfrozen and switched to pulsed-wave Doppler for 5 seconds at a sweep speed at 50 mm/s. A pneumatic tourniquet placed around the forearm proximal to the target artery was inflated after the baseline phase to a pressure of 50 mm Hg above the subject’s systolic blood pressure (or until no blood flow was detected through the brachial artery with the Doppler probe), and this pressure was held for 3 minutes. Increased flow was then induced with sudden cuff deflation. A continuous scan was performed at deflation and 60 and 90 seconds after cuff deflation with frozen and Doppler measurements recorded at similar intervals to the baseline phase.

**Nitroglycerin-Induced (Non–Endothelium-Dependent) Vasodilatation**

At 13 minutes after cuff deflation, a second 2-minute baseline resting scan was recorded to confirm the vessel recovery. A sublingual nitroglycerin (NTG) tablet (0.4 mg Nitrostat; Parke-Davis) was then administered, and scanning was performed continuously for 5 minutes after the NTG.

**Data Analysis**

The ultrasound images were recorded on S-VHS videotape with an SLV-RS7 videocassette recorder (SONY). The diameter of the brachial artery was measured from the anterior to the posterior interface between the media and adventitia (“m line” at a fixed distance). The mean diameter was calculated from 4 cardiac cycles synchronized with the R-wave peaks on the ECG. All measurements were made at end diastole to avoid possible errors resulting from variable arterial compliance.

Internal diameter was calculated with PC Prosound software (USC) with an Horita Data Translation Image Processing board (DT2862; 60 Hz). The diameter changes caused by endothelium-dependent flow-mediated vasodilatation (percent FMD) and endothelium-independent NTG-mediated vasodilatation (percent NTG) were expressed as the percent changes relative to those at the initial resting scan. The intraobserver variability for repeated measurements is 0.0 $\pm$0.07 mm in our laboratory.

**Treadmill Exercise Testing**

After an overnight fast, a maximum symptom-limited exercise treadmill test (Bruce protocol) was performed on all patients. We recorded blood pressure and heart rate at each exercise stage and at peak exercise, time to onset of angina, and 1-mm ST-segment depression; ST-segment depression at peak exercise; maximal ST-segment depression; presence of cardiac arrhythmias; metabolic equivalents (METs) and double-product (heart rate in bpm $\times$ systolic blood pressure in mm Hg) achieved; and total exercise duration. Myocardial ischemia was defined as the presence of $\geq$0.1-mV horizontal or downsloping ST-segment depression 80 ms after the J-point during exercise or recovery. Cardiac arrhythmias were defined as ventricular premature beats of Lown grade II or higher.

**Intracellular Magnesium Measurement**

Tissue magnesium concentration ([Mg$^{2+}$]) was measured in sublingual epithelial cells scraped from the mucosa adjacent to the frenulum and immediately fixed on a carbon slide with cytology fixative. The slides were examined with a scanning electron microscope (Philips), and suitable cells were identified. [Mg$^{2+}$] was measured with radiographic analysis of individual epithelial cells (EXA; Intracellular Diagnostics, Inc) (normal values 37.9 $\pm$4.0 mEq/L). Reported values are the mean of 5 to 10 cells per patient; a specimen was rejected if variance exceeded 2%. Sublingual epithelial cell [Mg$^{2+}$] correlates well with human atrial [Mg$^{2+}$]. This method is used to assess total cellular magnesium and cannot differentiate free Mg$^{2+}$ from bound species.

**Lipid Determination**

Fasting blood samples were analyzed for total cholesterol, HDL cholesterol (HDL-C), VLDL cholesterol, and triglyceride concentrations with an Hitachi 747 autoanalyzer. LDL cholesterol (LDL-C) was calculated with the Friedwald formula. No patients had a triglyceride level of $\geq$350 mg/dL (4 mmol/L).
ENDOTHELIAL DYSFUNCTION IN SYSTEMIC LUPUS ERYTHEMATOSUS

A. CARABĂ*, GERMAINE SĂVOIU**, VIORICA CRIŞAN***, CORINA GORUN**, IULIANA ZVARICI*, I. ROMOŞAN*

*Department of Internal Medicine, **Department of Pathophysiology, ***Department of Rheumatology, “Victor Babeş” University of Medicine and Pharmaceutics, Timişoara

Abstract. Systemic lupus erythematosus (SLE) is associated with an increased risk of atherosclerosis; endothelial dysfunction representing the first step in its pathogenesis. The aim of this study is represented by the assessment of the endothelial dysfunction in SLE and the characterization of SLE specific factors which contribute to its appearance. The study was done on 24 subjects, divided into two groups: group A (12 patients with SLE without renal involvement) and group B (12 healthy sex and age-matched controls). Total cholesterol, triglycerides, antinuclear antibodies, anti dsDNA antibodies, C3, circulating immune complexes were determined in all patients. SLE activity was assessed using SLE Disease Activity Index (SLEDAI). Endothelial function was assessed by means of flow mediated dilation (FMD) on brachial artery, using B-mode ultrasonography. The statistical analysis was done using Pearson’s test and Student’s t-test. p < 0.05 was considered statistically significant. The group of SLE patients was formed of 12 females, with the mean age of 37.16 ± 9.69 years. The values of SLE specific tests and SLEDAI were represented by: anti dsDNA antibodies 1/682 ± 1/914, C3 68.91 ± 11.91 mg/dL, circulating immune complexes 10.03 ± 2.85 µEq/mL, total cholesterol 208.66 ± 49.63 mg/dL, triglycerides 153.41 ± 46.26 mg/dL, SLEDAI 11.66 ± 3.70. The values of FMD were 8.85 ± 2.02% (group A) and 20.33 ± 6.19% (group B), p < 0.001. The statistical analysis showed a strong inverse correlation between FMD and SLEDAI, a strong correlation between FMD and C3, respectively anti dsDNA antibodies, a moderate inverse correlation between FMD and circulating immune complexes, total cholesterol, systolic and diastolic blood pressure. Endothelial dysfunction is present in SLE patients even in the absence of traditional cardiovascular risk factors, due to disease activity.

Key words: endothelial dysfunction, systemic lupus erythematosus.

INTRODUCTION

Systemic lupus erythematosus (SLE) represents the autoimmune disease, with a wide range of clinical and biological manifestations [8]. Despite the improvement of therapeutic regimes, the morbidity and mortality associated with SLE remained at high levels. In 1976, Urowitz et al. [18] postulated a bimodal...
Total cholesterol (Abbott photometry), triglycerides (Abbott reactive), antinuclear antibodies (immunofluorescence on Hep-2 cells), anti dsDNA antibodies (immunofluorescence on Crithidia luciliae), C3 (Roche immunoturbidimetry), circulating immune complexes (EIA method) were determined in all patients.

The SLE activity was assessed using SLE Disease Activity Index (SLEDAI).

Endothelial function was assessed by means of flow-mediated vasodilation on brachial artery, using B-mode ultrasonography (ALOKA ProSound 4000, with linear transducer of 7.5 MHz). Before the test, the patient was relaxed in a stable room temperature between 20 – 25 ºC; the smoking was prohibited. The diameter of brachial artery was measured incident with the R wave of the electrocardiograph trace (Di). Then, ischemia was induced by inflating the pneumatic cuff to a pressure 50 mmHg above systolic one, in order to obliterate the brachial artery and induce ischemia. After 5 minutes, the cuff was deflated and the diameter was measured after 60 seconds post-deflation (Df). FMD was calculated with the formula:

\[
FMD = \frac{(D_f - D_i)}{D_i} \times 100
\]

All the values were presented as mean ± standard deviation. The statistical analysis was done using Pearson’s test (for correlation) and Student’s t-test (for comparing of FMD between the two groups). \( p < 0.05 \) was considered statistically significant.

**RESULTS**

The demographic, clinical and biological characteristics of the studied groups are shown in Table 1. Diabetes mellitus and chronic renal diseases were absent in all subjects.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SLE group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males/Females</td>
<td>0/12</td>
<td>0/12</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>37.16 ± 9.69</td>
<td>35.02 ± 8.21</td>
</tr>
<tr>
<td>Mean duration of SLE evolution (years)</td>
<td>7.16 ± 3.66</td>
<td>0</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>208.66 ± 49.63</td>
<td>209.25 ± 35.27</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>153.41 ± 46.26</td>
<td>155.71 ± 25.87</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>41.66%</td>
<td>33.33%</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>137.08 ± 19.59/82.91 ± 9.87</td>
<td>135.94 ± 8.99/80.75 ± 9.29</td>
</tr>
</tbody>
</table>
Correlation Between Flow-Mediated Vasodilatation of the Brachial Artery and Intima-Media Thickness in the Carotid Artery in Men

Masayoshi Hashimoto, Masato Eto, Masahiro Akishita, Koichi Kozaki, Junya Ako, Katsuya Iijima, Seungbum Kim, Kenji Toba, Masao Yoshizumi, Yasuyoshi Ouchi

Abstract—Endothelial dysfunction has been reported to be the initial step in atherosclerosis. A noninvasive technique that uses ultrasound to measure the intima-media thickness of the carotid artery has been applied to evaluate localized atherosclerosis. This study was undertaken to elucidate whether endothelial dysfunction in the brachial artery is related to the intima-media thickness of the carotid artery. Thirty-four men with atherosclerosis (mean ± SE age 61 ± 2 years) and 33 age-matched men without clinical atherosclerosis were examined. The intima-media thickness and plaque formation of the common carotid artery were assessed by B-mode ultrasonography. We also noninvasively measured brachial artery diameter by the same ultrasound machine when the subjects were at rest, during reactive hyperemia, which causes endothelium-dependent vasodilatation, and after sublingual administration of nitroglycerin, which causes endothelium-independent vasodilatation. The atherosclerosis group had a significantly greater intima-media thickness of the common carotid artery than did the control group (1.02 ± 0.04 versus 0.91 ± 0.03 mm, P < 0.05). The flow-mediated diameter (FMD) increase (percent FMD = ΔD/D × 100) in the atherosclerosis group was significantly smaller than that in the control group (2.8 ± 0.4% versus 5.1 ± 0.6%, P < 0.01). A significant negative correlation between the intima-media thickness of the carotid artery and percent FMD was found in all of the subjects. On multiple regression analysis, percent FMD showed a significant negative correlation with the intima-media thickness of the common carotid artery. These findings support the concept that endothelial dysfunction is significantly related to atherogenesis.

Key Words: vasodilatation ■ endothelium ■ carotid artery ■ atherosclerosis

Evidence has accumulated that impairment of vascular endothelial function is the initial step in the development of atherosclerosis.1 One important finding is the impaired release of endothelium-dependent relaxing factor, which is now thought to be NO or its related substances, from endothelial cells.1 Flow-mediated dilatation (FMD) induced by reactive hyperemia has been known to be endothelium dependent,2 and this phenomenon can be detected during reactive hyperemia by high-resolution ultrasound in superficial arteries.3-4 Several coronary risk factors such as hypercholesterolemia,5 smoking,6 and hyperhomocysteinemia7 have been reported to be significantly related to decreased FMD. However, no study has been reported to demonstrate an association between increased intima-media thickness (IMT) of the carotid artery and decreased FMD.

A noninvasive technique that uses B-mode ultrasonography can visualize and assess the lumen and vessel wall of the carotid artery. We analyzed IMT of the right common carotid artery by using this method.7 IMT thickening consists of both an intimal atherosclerotic process and medial hypertrophy. Because IMT is increased in subjects with familial hypercholesterolemia8 and shows a progressive reduction with cholesterol-lowering treatment,9,10 IMT seems to be significantly related to the early phase of atherosclerosis.

This study was undertaken to elucidate whether impaired endothelial function in the brachial artery is related to IMT thickening in the common carotid artery. Because of the significant correlation between IMT and coronary or cerebrovascular disease,11-16 we examined the clinical significance of increased IMT in relation to impaired endothelial function in the study subjects.

Methods

Subjects
Thirty-four men with atherosclerosis aged 61.1 ± 2.0 years (mean ± SE) and 33 age-matched men without clinical atherosclerosis (controls) were enrolled in this study. These subjects were recruited from outpatient clinics, inpatient wards, and community volunteers. A history and physical examination were obtained, and laboratory tests were performed in all subjects to exclude diseases other than hypertension, hyperlipidemia, and diabetes mellitus. Exclusion criteria for this study included clinical manifestations of cerebrovascular disease, venous thromboembolism, or liver disor-
Study Design
Each subject made 1 visit to the University of Tokyo Hospital. Blood sampling was performed in the morning of the examination, after a 14-hour overnight fast, to measure the serum lipid profile and other biochemical parameters. Serum total cholesterol and triglyceride concentrations were measured enzymatically, and the serum HDL cholesterol concentration was measured by the heparin–Ca2+/Ni2+ precipitation method.17 Plasma glucose concentration was assayed by the glucose oxidase method, and the hemoglobin A1c level was measured by high-performance liquid chromatography.

Measurement of IMT of the Carotid Artery
Ultrasound measurements of IMT of the common carotid artery were performed by an examiner who was unaware of the subjects’ clinical backgrounds. IMT of the carotid artery was measured from high-resolution, 2-dimensional ultrasound images obtained by an SSA-270A ultrasound machine (Toshiba) with a 7.5-MHz linear-array transducer. The subject reclined on the examination table for 15 minutes before the initial carotid ultrasound scanning. IMT measurement of the carotid artery was performed according to the method of Salonen and Salonen as described previously18–20 in a quiet, temperature-controlled (22°C to 24°C) room. This measurement was applied to the far wall of the right carotid artery. While subjects were in the supine position, a linear-array ultrasound probe (7.5 MHz), which was part of the same ultrasound machine, was applied longitudinally to the surface of the skin on the right side of the neck. Longitudinal scanning was performed from the common carotid artery to the bifurcation of the common carotid artery. Scanning was performed in the optimal position. Blood pressure was monitored in the left arm every 2 minutes during the study by an automated blood pressure recorder. An ECG monitor integrated with the ultrasound machine was also applied. The ultrasound images were recorded on S-VHS videotape with an SLV-RST7 videocassette recorder (Sony). After the bifurcation of the common carotid artery was confirmed, IMT was measured from the B-mode screen with electronic calipers to within 0.2 mm proximal to the bifurcation. Four points were measured in 1 scan, which was synchronized with the R-wave peaks on the ECG to avoid possible errors resulting from variable arterial compliance.22 Maximal vasodilatation was observed 45 to 60 seconds after cuff release.3,21 The mean diameter was calculated from 4 cardiac cycles synchronized with the 10 mm proximal to the bifurcation. Two scans were made for each study subject. The mean IMT was considered statistically significant. Five men without clinical atherosclerosis were taking calcium channel antagonists (CCAs) for clinical reasons. On the other hand, 1 of the 33 subjects without clinical atherosclerosis had been prescribed an NTG product by his family doctor for chest discomfort. The clinical and metabolic characteristics of the 34 men with atherosclerosis and of the 33 men without clinical atherosclerosis (controls) are presented in Table 1. Age, body mass index, and mean blood pressure of the men with atherosclerosis were not statistically different from those of the men without clinical atherosclerosis. Serum total cholesterol, HDL cholesterol, triglyceride, fasting plasma glucose, and hemoglobin A1c levels were similar between the 2 groups. The percent prevalences of hypertension, hyperlipidemia, diabetes mellitus, and current smoking are presented in Table 1, and these were not statistically different between the 2 groups.

Two men without clinical atherosclerosis and 6 men with atherosclerosis were taking 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. Six men without clinical atherosclerosis and 18 men with atherosclerosis were taking diuretics and other cardiovascular medications. The difference in the prevalence of medication use between the 2 groups was significant (P<0.01). Five men without clinical atherosclerosis and 18 men with atherosclerosis were taking antihypertensive medication. The difference in the prevalence of medication use between the 2 groups was also significant (P<0.01). The combination of smoking and alcohol drinking was more prevalent in the atherosclerosis group (17 of 33 subjects) than in the control group (7 of 33 subjects; P<0.01). The clinical and metabolic characteristics of the 34 men with atherosclerosis were not statistically different from those of the men without clinical atherosclerosis. Serum total cholesterol, HDL cholesterol, triglyceride, fasting plasma glucose, and hemoglobin A1c levels were similar between the 2 groups. The percent prevalences of hypertension, hyperlipidemia, diabetes mellitus, and current smoking are presented in Table 1, and these were not statistically different between the 2 groups.

Two men without clinical atherosclerosis and 6 men with atherosclerosis were taking 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. Six men without clinical atherosclerosis and 18 men with atherosclerosis were taking diuretics and other cardiovascular medications. The difference in the prevalence of medication use between the 2 groups was significant (P<0.01). Five men without clinical atherosclerosis and 18 men with atherosclerosis were taking antihypertensive medication. The difference in the prevalence of medication use between the 2 groups was also significant (P<0.01).
The Metabolic Syndrome, LDL Particle Size, and Atherosclerosis

The Atherosclerosis and Insulin Resistance (AIR) Study

Johannes Hulthe, Lena Bokemark, John Wikstrand, Björn Fagerberg

Abstract—An operative definition of the metabolic syndrome has been suggested by a working group associated with the World Health Organization in 1998. The aim of this study was to examine whether small, low density lipoprotein (LDL) particle size was associated with the metabolic syndrome and with subclinical atherosclerosis as measured by ultrasound in the carotid and femoral arteries. The study was performed in a population-based sample of clinically healthy men (N=391), all 58 years old and not undergoing any treatment with cardiovascular drugs. Exclusion criteria were cardiovascular or other clinically overt diseases or continuous medication with cardiovascular drugs. The results showed that subjects characterized by the metabolic syndrome (n=62) had a thicker mean intima-media complex (IMT) in both the carotid and femoral arteries (0.86 versus 0.77 mm, P<0.001, and 1.03 versus 1.00 mm, P=0.022, respectively) and also lower mean values for LDL particle size (25.78 versus 26.80 nm, respectively, P<0.001) compared with subjects with no risk factors (n=77). The group with the metabolic syndrome (n=62) also had higher mean values for serum cholesterol and heart rate. In the whole study group (N=391), there were significant but weak negative relationships between small LDL particle size, increasing IMT, and increasing cross-sectional intima-media area of the carotid and femoral arteries and also negative relationships between LDL particle size and plaque occurrence and size in the carotid and femoral arteries. In summary, this is the first large-scale study to demonstrate a relationship between the clustering of risk factors that constitute the metabolic syndrome and a small LDL particle size pattern and the occurrence of preclinical atherosclerosis in the carotid and femoral arteries, as assessed by the ultrasound technique, in healthy 58-year-old men recruited from the general population. (Arterioscler Thromb Vasc Biol. 2000; 20: 2140-2147.)

Key Words: metabolic syndrome ■ atherosclerosis ■ ultrasound ■ LDL particle size

The observation that insulin resistance is associated with a clustering of risk factors for cardiovascular disease has led to the suggestion of a syndrome, which has been given different names, eg, the metabolic syndrome or the insulin resistance syndrome.1 However, it is still unclear how this proposed syndrome should be delineated and how the underlying mechanisms affect the cardiovascular disease process.1 Central to the hypothesis is the concept that insulin resistance leads to a multitude of perturbations that in the end may cause atherosclerotic disease.1 Also, other risk markers have been associated with the metabolic syndrome, such as heart rate,2,3 which seem to be associated with increased sympathetic nervous activity in combination with decreased vagal tone. Earlier studies have indicated an association between insulin resistance and variables related to atherosclerotic disease among whites.4–6 However, the definition of the metabolic syndrome has not yet been fully clarified. An operative definition of the metabolic syndrome has been suggested by a working group associated with the World Health Organization in 1998.7

The dyslipidemia associated with insulin resistance is characterized by hypertriglyceridemia and a low concentration of serum HDL cholesterol.8–10 The hepatic synthesis of lipoproteins and the degradation of circulating lipoproteins are, to a large extent, dependent on insulin action.11–13 The size and composition of the lipoproteins may consequently be related to insulin resistance. Hence, it is generally believed that small LDL particle size may be associated with insulin resistance.14–17 However, there are also several reports that have failed to confirm a relationship between LDL particle size and insulin resistance.18,19 Small LDL particle size has also been suggested to be associated with the development of atherosclerosis as measured by coronary angiography,20–23 but again, this is not a consistent finding.24–28 Taken together, available data show that it is still unclear whether small LDL particle size is related to the insulin resistance syndrome and to the atherosclerotic disease process.

A negative relationship between LDL particle size and intima-media thickness (IMT) has been found in a previous study by Skoglund-Andersson et al.29 In that study, only
performed in both the right and left carotid arteries. The largest plaque in either artery was used in the present analysis. Reproducibility studies of a blinded rereading of plaque occurrence in 53 male subjects showed that plaque size was assessed in the same way on both occasions in 95% of the cases.

**Measurements**

Established questionnaires were used to evaluate each subject’s history of previous and current disease and smoking. Body weight was measured on a balance scale with the subject dressed in underwear. Measurements of waist and hip ratios were performed while the subjects were in the supine position. Blood pressure was measured twice after the subject had been resting in the supine position for 5 minutes with the use of an appropriate cuff size in relation to arm size. Diastolic blood pressure was determined as Korotkoff phase V. A 12-lead standard ECG was recorded. Heart rate was recorded from the ECG. Blood samples for serum cholesterol, serum triglycerides, and lipoprotein fractions were drawn after a fasting period of 10 to 12 hours and were thereafter frozen in aliquots at −70°C within 4 hours. Twelve-hour urine samples were collected overnight on 2 consecutive occasions. Information on smoking habits was obtained by a self-administered questionnaire. The total number of years of smoking was multiplied by the number of cigarettes smoked daily. The product was called “cigarette-years.” This variable was calculated only for subjects classified as present or past smokers.

**Biochemical Analysis**

Cholesterol and triglyceride levels were determined by fully enzymatic techniques. HDL was determined after precipitation of apo B–containing lipoproteins with MnCl2 and dextran sulfate. LDL cholesterol was calculated as described by Friedewald et al. Apo A-I and apo B concentrations were measured by a rate nephelometric method. Blood glucose was measured with the glucose oxidase technique. Plasma insulin was determined in all subjects with a radioimmunoassay (Pharmacia Insulin RIA, Pharmacia Diagnostics). All lipid analyses were performed at the Wallenberg Laboratory.

**Statistical Analysis**

All statistics were performed by using spss for Windows 7.5 (SPSS, Inc.). Nonparametric Spearman’s rank correlation test was used in the correlation analysis, with the relationship illustrated by Friedewald’s correlation coefficient (r). The Mann-Whitney U test was used when comparing mean values for ultrasound and LDL particle size variables in subjects with the metabolic syndrome and subjects with no risk factors. Furthermore, a t-distributed variable was used to calculate 95% confidence intervals (CIs) for differences. Comparisons between groups for anthropometric data, blood pressure, triglycerides, HDL cholesterol, BMI, blood glucose, and plasma insulin were not formally tested for significance, and comparisons with controls are not presented. Mantel’s test for linear association was used to test the relationship between LDL particle size and plaque occurrence and size in the carotid and femoral arteries. Because of technical reasons there were missing data for IMT in the common carotid artery in 3 subjects and for LDL particle size in 11 subjects. These subjects were not excluded from the results presented in Table 1. P<0.05 (2-sided) was regarded as statistically significant.

**Results**

**Prevalence of Risk Factors in the Study Group**

No subjects had overt diabetes mellitus. A blood glucose value ≥6.1 mmol/L was found in 22 subjects (5.6%). Eighty-one subjects had a fasting blood glucose level ≥5.6 mmol/L and/or insulin resistance (20.7%). There were 96 (25%) subjects who had raised systolic and/or diastolic arterial blood pressure; 127 (33%) subjects had raised triglyceride or low HDL levels; 293 (75%) subjects had central obesity or a raised BMI; and 46 (12%) subjects had microalbuminuria. Sixty-two subjects (16%) fulfilled the criteria for the metabolic syndrome according to the definition given above; 252 (64%) subjects had at least 1 risk factor (but not the full syndrome); and 77 (20%) subjects had no risk factors.

**Anthropometric Data, Blood Pressure, Heart Rate, Serum Lipids and Lipoproteins, and Smoking Habits in Subjects With the Metabolic Syndrome Compared With Subjects With No Risk Factors**

Subjects with the metabolic syndrome had, as expected, higher BMI, blood pressure, serum triglycerides, blood glucose, and plasma insulin and also lower HDL levels compared with subjects with no risk factors (not tested for statistical significance because of the selection criteria; Table 1). Furthermore, subjects with the metabolic syndrome had significantly higher mean values for heart rate, serum total cholesterol, and apo B compared with subjects with no risk factors (Table 1). There were no differences in mean LDL cholesterol concentrations or cigarette-years between the 2 groups.
performed in both the right and left carotid arteries. The largest plaque in either artery was used in the present analysis. Reproducibility studies of a blinded rereading of plaque occurrence in 53 male subjects showed that plaque size was assessed in the same way on both occasions in 95% of the cases.

**Measurements**

Established questionnaires were used to evaluate each subject’s history of previous and current disease and smoking. Body weight was measured on a balance scale with the subject dressed in underwear. Measurements of waist and hip ratios were performed while the subjects were in the supine position. Blood pressure was measured twice after the subject had been resting in the supine position for 5 minutes with the use of an appropriate cuff size in relation to arm size. Diastolic blood pressure was determined as Korotkoff phase V. A 12-lead standard ECG was recorded. Heart rate was recorded from the ECG. Blood samples for serum cholesterol, serum triglycerides, and lipoprotein fractions were drawn after a fasting period of 10 to 12 hours and were thereafter frozen in aliquots at −70°C within 4 hours. Twelve-hour urine samples were collected overnight on 2 consecutive occasions. Information on smoking habits was obtained by a self-administered questionnaire. The total number of years of smoking was multiplied by the number of cigarettes smoked daily. The product was called “cigarette-years.” This variable was calculated only for subjects classified as present or past smokers.

**Biochemical Analysis**

Cholesterol and triglyceride levels were determined by fully enzymatic techniques. HDL was determined after precipitation of apo B–containing lipoproteins with MnCl2 and dextran sulfate. LDL cholesterol was calculated as described by Friedewald et al. Apo A-I and apo B concentrations were measured by a rate nephelometric method. Blood glucose was measured with the glucose oxidase technique. Plasma insulin was determined in all subjects with a radioimmunoassay (Pharmacia Insulin RIA, Pharmacia Diagnostics). All lipid analyses were performed at the Wallenberg Laboratory.

**Statistical Analysis**

All statistics were performed by using spss for Windows 7.5 (SPSS, Inc). Nonparametric Spearman’s rank correlation test was used in the correlation analysis, with the relationship illustrated by the subject’s correlation coefficient ($r$). The Mann-Whitney U test was used when comparing mean values for ultrasound and LDL particle size variables in subjects with the metabolic syndrome and subjects with no risk factors. Furthermore, a $t$-distributed variable was used to calculate 95% confidence intervals (CIs) for differences. Comparisons between groups for anthropometric data, blood pressure, triglycerides, HDL cholesterol, BMI, blood glucose, and plasma insulin were not formally tested for significance, but differences between groups were assessed by using the nonparametric Mann-Whitney U test. A one-tailed test was used when a particular hypothesis was formulated. A $P$ value of less than 0.05 was regarded as statistically significant.

**Results**

**Prevalence of Risk Factors in the Study Group**

No subjects had overt diabetes mellitus. A blood glucose value ≥6.1 mmol/L was found in 22 subjects (5.6%). Eighty-one subjects had a fasting blood glucose level ≥5.6 mmol/L and/or insulin resistance (20.7%). There were 96 (25%) subjects who had raised systolic and/or diastolic arterial blood pressure; 127 (33%) subjects had raised triglyceride or low HDL levels; 293 (75%) subjects had central obesity or a raised BMI; and 46 (12%) subjects had microalbuminuria. Sixty-two subjects (16%) fulfilled the criteria for the metabolic syndrome according to the definition given above; 252 (64%) subjects had at least 1 risk factor (but not the full syndrome); and 77 (20%) subjects had no risk factors.

**Anthropometric Data, Blood Pressure, Heart Rate, Serum Lipids and Lipoproteins, and Smoking Habits in Subjects With the Metabolic Syndrome Compared With Subjects With No Risk Factors**

Subjects with the metabolic syndrome had, as expected, higher BMI, blood pressure, serum triglycerides, blood glucose, and plasma insulin and also lower HDL levels compared with subjects with no risk factors (not tested for statistical significance because of the selection criteria; Table 1). Furthermore, subjects with the metabolic syndrome had significantly higher mean values for heart rate, serum total cholesterol, and apo B compared with subjects with no risk factors (Table 1). There were no differences in mean LDL cholesterol concentrations or cigarette-years between the 2
Hypertension and dyslipidaemia in obesity and insulin resistance: Pathophysiology, impact on atherosclerotic disease and pharmacotherapy

M. John Chapman a,b,⁎, Andrei C. Sposito c

a INSERM (National Institute for Health and Medical Research), Unité 551, Hôpital de la Pitié, Paris, F-75013, France
b Université Pierre et Marie Curie-Paris 6, UMR S551, Paris F-75013, France
c University of Brasilia Medical School, Brasilia, Brazil

Abstract

Hypertension, a prevalent risk factor for cardiovascular disease, frequently occurs in conjunction with metabolic disturbances and in particular with dyslipidaemia; such comorbidity presents in more than one-third of hypertensive patients. Moreover, hypertension and dyslipidaemia often manifest concomitantly in the clinical context of obesity and insulin resistance. In this setting, distinct metabolic anomalies may account for the development of both conditions, and may equally act to exacerbate their effects on vascular dysfunction. Significantly, hypertension and dyslipidaemia are linked mechanistically and may act in synergy at the arterial wall to enhance atherosclerosis. In this review, we identify potential mechanisms underlying the pathophysiological interaction between hypertension and dyslipidaemia at the cellular and molecular levels, and which may underlie elevated cardiovascular risk in obesity and insulin resistance. Finally, the clinical evidence supporting the beneficial effects of an integrated pharmacotherapeutic strategy to the reduction of cardiovascular risk in patients with insulin resistance, type 2 diabetes and the metabolic syndrome is critically discussed.

© 2007 Elsevier Inc. All rights reserved.

Keywords: Hypertension; Dyslipidaemia; Obesity; Insulin resistance; Cardiovascular risk; Atherosclerosis

Abbreviations: ADA, American Diabetes Association; ADMA, asymmetrical dimethylarginine; Ang, angiotensin; apo, apolipoprotein; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; CAFÉ, Conduit Artery Function Evaluation; CAMELOT, Comparison of Amlodipine Versus Enalapril to Limit Occurrences of Thrombosis; CETP, cholesteryl ester transfer protein; CHD, coronary heart disease; CRP, C-reactive protein; CV, cardiovascular; CVD, cardiovascular disease; eNOS, endothelial nitric oxide synthase; ET, endothelin; HDL, high-density lipoprotein; IDF, International Diabetes Federation; IDL, intermediate-density lipoprotein; IL, interleukin; LDL, low-density lipoprotein; LL,A, Lipid-Lowering Arm; NADFJH, nicotinamide adenine dinucleotide phosphate; NCEP ATP, National Cholesterol Education Program Adult Treatment Panel; NO, nitric oxide; NOS, nitric oxide synthase; SREBP, sterol-regulatory element-binding protein; TGRL, triglyceride-rich lipoprotein; TNF, tumour necrosis factor; TNT, Treating to New Targets; VLDL, very low-density lipoprotein; VSMC, vascular smooth muscle cell.

Contents

1. Introduction ............................................ 355
2. Hypertension and dyslipidaemia in obesity and insulin-resistant states ............................................ 357
   2.1. Obesity-related factors as a direct cause of insulin resistance, hypertension and dyslipidaemia . 358
   2.1.1. Inflammation in adipose tissue ......................... 358
   2.1.2. Vasoconstrictive systems and fluid retention .................. 359
   2.1.3. Free fatty acids ............................................. 360

⁎ Corresponding author. National Institute for Health and Medical Research (INSERM), Unité 551, Dyslipoprotéinemies et Athérosclérose: Génétique, Métabolisme et Thérapeutique; Hôpital de la Pitié, 83, Bd de l’Hôpital; Pavillon B. Delessert; 75651-Paris Cedex 13, France. Tel.: +33 1 42 17 78 78; fax: +33 1 45 82 81 98.
E-mail address: chapman@chups.jussieu.fr (M.J. Chapman).

0163-7258/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.pharmthera.2007.10.004
3. Interaction between hypertension and dyslipidaemia in atherosclerosis

In addition to mechanisms that are operative in obesity and insulin-resistant states, and which may lead to the concomitant development of hypertension and dyslipidaemia, coexistence of these conditions may also arise as a result of the direct hypertensive effects of dyslipidaemia. Indeed, a number of studies have revealed that disorders of lipid metabolism may be associated with exaggerated elevations in blood pressure during exercise or mental stress (Kavey et al., 1997; Sung et al., 1997; Brett et al., 2000; Barreto-Filho et al., 2003; Vacanti et al., 2005); such findings provide evidence for a link between a history of hypertension and elevated plasma cholesterol levels (Neutel et al., 1992; Lopes et al., 1997). Consistent with these observations, exaggerations in CV responses and blood pressure elevations induced by systemic hypoxia in normotensive patients with familial hypercholesterolaemia (as compared with normocholesterolaemic patients without the disorder) were normalised by lipid-lowering treatment with statins (Barreto-Filho et al., 2003). Thus, dyslipidaemia may lead to an increased sensitivity to hypertensinogenic stimuli (e.g., high dietary salt intake), or may promote directly the development of hypertension in individuals with a pathophysiological background predisposing them to this condition. Additionally, functional and structural alterations secondary to hypertension, such as the modification of haemodynamic forces at bifurcations in the arterial tree, as well as inflammation and oxidative stress, may magnify the proatherogenic effects of dyslipidaemia. The mechanisms through which hypertension and dyslipidaemia interact and contribute to vascular dysfunction are discussed in the following sections.

3.1. Mechanisms underlying the hypertensive action of dyslipidaemia

3.1.1. Autocrine-paracrine vasoactive systems: nitric oxide, endothelin and the renin-angiotensin system

As discussed above, attenuated NO signalling has been linked to an elevation in blood pressure and to other metabolic changes which are associated with induction of hypertension (Haynes et al., 1993; Castellano et al., 1995; Paniagua et al., 2001).

In endothelial cells, native LDL and oxidised LDL have been shown to reduce the bioavailability of NO by down-regulating the expression of endothelial NOS (eNOS) (Liao et al., 1995; Vidal et al., 1998), and to contribute to eNOS uncoupling (via a nicotinamide adenine dinucleotide phosphate [NAD(P)H] oxidase-dependent mechanism), thereby resulting in the generation of superoxide anion (Vergnani et al., 2000; Mason, 2006). Furthermore, hypercholesterolaemia has been associated with increased endothelial production of oxygen free radicals such as superoxide anion, via activation of NAD(P)H-dependent oxidases (Guzik et al., 2000) (Fig. 6). Superoxide anion may subsequently react directly with NO to form peroxynitrite, a highly reactive radical species.

In a recent study, the risk of hypertension was evaluated in a large population sample of more than 1500 individuals, on the basis of total plasma cholesterol levels and the presence of a dysfunctional polymorphism for eNOS (Pereira et al., 2006). Overall, the risk of hypertension was 2-fold higher for individuals with total cholesterol above 209 mg/dl (5.4 mmol/l) than for those with cholesterol levels below this value. However, the risk of presenting hypertension was 3-times higher for those hypercholesterolaemic patients who were homozygous for the dysfunctional eNOS allele. Interestingly, in patients with total cholesterol below 209 mg/dl (5.4 mmol/l), the risk of hypertension was not affected by the presence of this polymorphism (Pereira et al., 2006). These findings clearly indicate that the role of eNOS in blood pressure regulation is modulated by plasma cholesterol levels.

Hypercholesterolaemia is also associated with increased circulating levels of the endogenous inhibitor of NO synthesis ADMA (Böger et al., 1998) (Fig. 6). Thus, hypercholesterolaemia potentially reduces NO-induced vasodilation via a spectrum of mechanisms involving both reduced production and increased removal of NO.

In addition to an impairment in endothelium-dependent vasodilation, patients with hypercholesterolaemia present an enhanced activation of vasoconstrictive systems (Fig. 4). It has been demonstrated that the activity of the circulating and arterial wall renin–angiotensin system is upregulated in patients with hypercholesterolaemia, and that LDL levels are a powerful independent determinant of response to Ang II (John et al., 1999; Strehlow et al., 2000). Hypercholesterolaemic patients also present increased circulating levels of the vasoconstrictor ET-1 (Haak et al., 1994) and enhanced activity of ET receptors (Cardillo et al., 2000). Furthermore, the reduction of NO bioavailability typical of hypercholesterolaemic patients may upregulate a hypertensive cascade involving both the renin–angiotensin system and the ET-1 pathway, in that NO down-regulates the expression of both ET-1 and angiotensin-converting enzyme (ACE) synthesis (Fig. 4) (Takemoto et al., 1997; Ichiki et al., 1998; Usui et al., 1998; Schiffrin, 1999; Raji, 2001).

Paralleling the action of hypercholesterolaemia on NO, plasma levels of both TGRLs and HDL appear to influence endothelial function. In rats, plasma triglyceride levels are independently associated with endothelial dysfunction, and with the generation of oxygen free radicals, which are in turn associated with a reduction in the bioavailability of NO (Kusterer et al., 1999). Additionally, hypertriglyceridaemia may promote an imbalance in the NO-ET-1 ratio as it is associated with both elevations in plasma concentration of ADMA (Lundman et al., 2001) and with enhanced secretion of ET-1 (Monti et al., 2001). Conversely, HDL particles promote the production of NO by upregulating eNOS activity (Yuhanna et al., 2001), and by enhancing the stability of the eNOS protein (Rämet et al., 2003). Thus, dyslipidaemia affects several of the major mechanisms implicated in blood pressure regulation through autocrine-paracrine signalling; in combination they are likely to favour either the development or the exacerbation of a hypertensive state.

3.1.2. Sympathetic nervous system

Sympathetic over-activity in hypertensive patients is potentially a result of decreased baroreflex sensitivity, which is
Original Contribution

FLOW-MEDIATED DILATION AND INTIMA-MEDIA THICKNESS OF THE BRACHIAL AND AXILLARY ARTERIES IN INDIVIDUALS WITH AND WITHOUT INDUCIBLE AXILLARY ARTERY COMPRESSION

C. H. STAPLETON,* D. J. GREEN,† N. T. CABLE,* and K. P. GEORGE*

*Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, UK; and † School of Sport Science, Exercise and Health, The University of Western Australia, Perth, Australia

(Received 8 October 2008; revised 25 February 2009; in final form 26 March 2009)

Abstract—The presence of axillary artery aneurysm and/or thrombus in overhead throwing athletes has been linked, theoretically, with the finding of compression by the humeral head induced by a diagnostic arm maneuver. However, whether this intermittent compression is incidental or of pathological significance has yet to be determined. Flow-mediated vasodilation (FMD), intima-media thickness (IMT) and maximum vasodilatory capacity were measured locally (3rd portion of the axillary artery) and downstream (brachial artery) in individuals previously tested for inducible axillary artery compression (compressor group [COMP]: n = 8, mean (SD) age: 23 (4) y; “noncompressor” control group [NONCOMP]: n = 8, 26 (4) y). A high-resolution ultrasound machine recorded arterial diameter and blood flow velocity. A rapid inflation/deflation pneumatic cuff placed distal to the site of measurement induced reactive hyperemia. Custom-designed wall tracking software with synchronized Doppler waveform analysis detected changes in arterial diameter, blood flow velocity and shear rate from baseline to 3 min after cuff deflation. Glyceryl trinitrate and/or ischemic hand grip exercises were administered to induce maximum vasodilation. No significant differences in FMD, IMT or maximum vasodilator capacity were observed between groups at the axillary artery. However, the downstream brachial FMD response was significantly diminished in the COMP group (6.38 [3.28]%) compared with the NONCOMP group (10.38 [2.74]%; p = 0.006) despite a comparable shear rate between groups (COMP: 81.92 (44.55) s⁻¹; NONCOMP: 83.18 (40.02) s⁻¹; p = 0.961). Pooled data revealed a significant negative relationship (r = -0.52, p = 0.038) between the FMD response and degree of arterial compression. These results suggest a chronic change in downstream vascular function in individuals demonstrating clinically significant inducible axillary artery compression. (E-mail: c.stapleton@2005.ljmu.ac.uk)

Key Words: Endothelial function, Doppler echocardiography, vascular compression.

INTRODUCTION AND LITERATURE

Previous research has revealed that between 8 and 20% of healthy, asymptomatic individuals demonstrate clinically significant (>50% diameter reduction) compression of the third portion of the axillary artery, with the arm positioned at 120° abduction, 30° horizontal extension and 90° external rotation (Rohrer et al. 1990; Stapleton et al. 2008). This position is commonly used in diagnostic ultrasound to confirm the presence of a vascular compression syndrome (Thrush 1999). The cause of compression is unclear, but excessive anterior or inferior translation of the humeral head at the glenohumeral joint when the arm is positioned overhead has been proposed (Dijkstra and Westra 1978; Stapleton et al. 2008; Vlychou et al. 2001).

Whether this finding is a normal and innocuous consequence of overhead movement of the upper limb, or represents a process with potential pathological significance, has yet to be ascertained. The overhead arm position simulates the cocking phase of the throwing motion and is performed in many sports. Case reports in overhead throwing athletes have documented a continuum of findings from intermittent compression of the axillary artery and its branches with the arm in an overhead or abducted position, to thrombosis, aneurysm formation and peripheral embolisation (Dijkstra and Westra 1978; Finkelstein and Johnston 1993; Ishitobi et al. 2001; Kee et al. 1995; Redler et al. 1986; Reekers et al. 1993; Schneider et al.)
1999; Todd et al. 1998; Vlychou et al. 2001). The humeral head and/or the pectoralis minor muscle, combined with repetitive overhead arm motion, have been implicated as the cause of transient axillary artery compression, resulting in intimal damage and subsequent thrombus and/or aneurysm formation (Schneider et al. 1999; Vlychou et al. 2001). Despite this conjecture, the consequences of repeated transient compression on upper limb arterial structure and function have not yet been investigated, and currently there is no established link between clinically significant inducible axillary artery compression and vascular health.

Theoretically, clinically significant changes to vessel diameter and peak systolic velocity are likely to alter local and downstream blood flow and shear stress patterns, thereby potentially disrupting endothelial homeostasis. Without such hemodynamic disturbances, normal laminar flow induces sufficient shear stress to align the endothelial cells in the direction of flow and maintain a critical balance between the release of vasodilating agents, such as nitric oxide (NO), and vasoconstrictors like endothelin (ET-1). It has been widely reported that the reciprocal regulation of NO and ET-1 is vital for the maintenance of vascular tone, antithrombotic and antiatherogenic properties of the endothelium, as well as playing a key role in countering inflammatory events (Alam et al. 2005; Deanfield et al. 2005; Maiorana et al. 2003). Therefore, when the endothelium is exposed to abnormally high or low hemodynamic shear forces, a resultant imbalance between vasoconstrictors and vasodilators can occur, and endothelial dysfunction ensues (Deanfield et al. 2005). Endothelial dysfunction resulting from reduced NO bioavailability is reflected by a diminished NO-dependent flow-mediated dilation (FMD) response. Typically, if abnormally high or low grades of shear stress persist, structural adaptations occur at the vessel wall, affecting wall thickness and diameter, which act to return shear stress levels to within a normal range (Papaioannou et al. 2006).

Therefore, the aim of this study was to investigate the effects of clinically significant inducible axillary artery compression on arterial structure and function, assessed using the methods of flow-mediated dilation (FMD), intimal wall thickness (IMT) and assessment of maximal vasodilatory capacity. These measures were assessed locally, at the third portion of the axillary artery, and downstream at the brachial artery, in healthy, active, asymptomatic adults who demonstrate inducible axillary artery compression and noncompressor controls.

It was hypothesized that individuals identified with inducible compression at the axillary artery will demonstrate reduced measures of FMD and IMT, locally, at the axillary artery, but with unknown effect on maximum vasodilatory capacity and measures taken downstream, at the brachial artery.

MATERIALS AND METHODS

Subjects

Ethical approval was granted from the Institutional Review Board. After written and verbal briefing, subjects provided written informed consent. A health screening questionnaire was completed to exclude subjects with factors known to influence the FMD response, e.g., hypertension, diabetes, hypercholesterolemia, smoking, asthma, amenorrhea, recent allergic reactions, infections or injuries and medications or conditions contraindicated for glyceryl trinitrate, e.g., hypotension. In addition, subjects underwent subjective and objective musculoskeletal screening to exclude any past or present musculoskeletal injury affecting anatomical structures running adjacent to the course of the arteries in the shoulder girdle, as well as conditions likely to be exacerbated by the experimental procedure. Eight subjects meeting the criteria for clinically significant arterial compression (see later) formed the “compressor” group (COMP: 2 males, 6 females; mean (SD) age 23 (4) y) and were closely matched for age and sex with a “noncompressor” control group (NONCOMP: 26 (4) y). Pair matching was necessary because some subjects presented with bilateral compression or bilateral noncompression. All subjects were classed as healthy, asymptomatic, moderately active individuals that did not participate in overhead sports or activities. See Table 1 for baseline group characteristics.

Screening for inducible axillary artery compression

After 10 minutes of rest in the supine position to stabilize heart rate and blood flow, the subjects’ dominant arm was passively supported at 60° abduction (baseline)
The relation between coronary flow rate, plasma endothelin-1 concentrations, and clinical characteristics in patients with normal coronary arteries

Huseyin Celebi\textsuperscript{a}, Alp Burak Catakoglu\textsuperscript{a}, Hilal Kurtoglu\textsuperscript{b}, Murat Sener\textsuperscript{b}, Ruken Hanavdelogullarib, Cemsid Demiroglub, Vedat Aytekin\textsuperscript{b}, Saide Aytekin\textsuperscript{b,⁎}

\textsuperscript{a}Department of Cardiology, Florence Nightingale Hospital, Istanbul, Turkey
\textsuperscript{b}Department of Cardiology, Istanbul Bilim University, Florence Nightingale Hospital, Istanbul, Turkey

Received 22 September 2007; received in revised form 31 October 2007; accepted 2 November 2007

Abstract

\textbf{Background:} Coronary slow flow (CSF) is characterized by delayed opacification of epicardial arteries in the absence of occlusive disease. In the present study, we aimed to investigate the relation between coronary flow rate, plasma endothelin-1 (ET-1) concentrations, and clinical characteristics in patients with normal coronary arteries.

\textbf{Methods:} The study population included 77 patients with angiographically normal coronary arteries who underwent coronary angiography on suspicion of ischemic heart disease due to typical chest pain or ischemic findings on treadmill exercise test or myocardial scintigraphy. Based on the Thrombolysis In Myocardial Infarction frame count (TFC), patients were grouped into those with normal coronary flow and those with slow coronary flow.

\textbf{Results:} Forty-eight (61.5%) patients were found to have CSF. Plasma ET-1 concentrations were significantly higher with the presence of CSF ($P=.03$). There were significant differences between plasma ET-1 concentrations, and mean TFC, TFC for left anterior descending coronary artery (LAD), TFC for left circumflex coronary artery (CX), and TFC for right coronary artery separately in patients with and without CSF ($P=.033$, $P<.001$, $P<.001$, and $P<.001$, respectively). Mean TFC, TFC for LAD, and TFC for CX, and ET-1 concentrations were significantly higher in smokers than in nonsmokers ($P<.001$, $P=.004$, and $P=.033$, respectively). However, logistic regression analysis suggested that ET-1 concentration was not an independent determinant of CSF.

\textbf{Conclusions:} Although there is a significant relation between ET-1 concentrations and coronary flow rate, ET-1 concentrations are not sufficient to determine the presence of CSF. Smoking is strongly associated with CSF, TFC, and increased ET-1 concentrations.

© 2008 Published by Elsevier Inc.

Keywords: Slow coronary flow; Smoking; Coronary angiography; Angina pectoris; Normal coronary arteries; Endothelin-1

1. Background

Approximately 10–30% of patients with angina pectoris have normal coronary arteries [1]. The prognosis of these patients is not different from that of the normal population. However, recurrent hospitalizations and repeat coronary angiographies due to chest pain result in discomfort and increase economic costs [2,3]. Coronary slow flow (CSF) is characterized by late opacification of epicardial coronary arteries without occlusive disease, and its exact etiopathogenesis is still unknown. Endothelial and vasomotor dysfunction, microvascular dysfunction,
Table 1
Baseline clinical characteristics

<table>
<thead>
<tr>
<th>Patients with CSF (n=48)</th>
<th>Patients without CSF (n=29)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) [mean±S.D.]</td>
<td>53.4±9.5</td>
<td>53.5±8.5</td>
</tr>
<tr>
<td>Male gender [n (%)]</td>
<td>21 (43.7)</td>
<td>5 (17.2)</td>
</tr>
<tr>
<td>Hypertension [n (%)]</td>
<td>27 (56.3)</td>
<td>16 (55.2)</td>
</tr>
<tr>
<td>Serum low-density lipoprotein cholesterol (mg/dl) [mean±S.D.]</td>
<td>126.4±31.2</td>
<td>135.5±33.6</td>
</tr>
<tr>
<td>Diabetes mellitus [n (%)]</td>
<td>7 (14.6)</td>
<td>6 (20.7)</td>
</tr>
<tr>
<td>Body mass index (kg/m²) [mean±S.D.]</td>
<td>29.2±5.6</td>
<td>28.8±4.4</td>
</tr>
<tr>
<td>Smoking [n (%)]</td>
<td>20 (41.7)</td>
<td>4 (13.8)</td>
</tr>
<tr>
<td>Family history [n (%)]</td>
<td>18 (37.5)</td>
<td>7 (24.1)</td>
</tr>
<tr>
<td>Typical angina pectoris [n (%)]</td>
<td>38 (79.2)</td>
<td>23 (79.3)</td>
</tr>
<tr>
<td>Baseline medications [n (%)]</td>
<td>26 (54.2)</td>
<td>18 (62.1)</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>17 (35.4)</td>
<td>16 (55.2)</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor</td>
<td>6 (12.5)</td>
<td>5 (17.2)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>6 (12.5)</td>
<td>6 (20.7)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>7 (14.6)</td>
<td>6 (20.7)</td>
</tr>
<tr>
<td>Angiotensin II receptor blocker</td>
<td>5 (10.4)</td>
<td>3 (10.3)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>17 (35.4)</td>
<td>15 (51.7)</td>
</tr>
<tr>
<td>Nitrate</td>
<td>4 (8.3)</td>
<td>3 (10.3)</td>
</tr>
<tr>
<td>Statin</td>
<td>14 (29.2)</td>
<td>10 (34.5)</td>
</tr>
</tbody>
</table>

Table 2
ET-1 concentrations and TFCs of patients with and without CSF

<table>
<thead>
<tr>
<th>Patients with CSF (n=48) [mean±S.D.]</th>
<th>Patients without CSF (n=29) [mean±S.D.]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET-1 (pg/ml)</td>
<td>1.59±2.86</td>
<td>0.41±0.43</td>
</tr>
<tr>
<td>Mean TFC (frame)</td>
<td>10.3±1.5</td>
<td>7.7±1.0</td>
</tr>
<tr>
<td>TFC-LAD (frame)</td>
<td>18.1±3.0</td>
<td>13.4±2.2</td>
</tr>
<tr>
<td>TFC-CX (frame)</td>
<td>11.2±2.2</td>
<td>8.8±1.1</td>
</tr>
<tr>
<td>TFC-RCA (frame)</td>
<td>8.9±2.1</td>
<td>6.8±1.4</td>
</tr>
</tbody>
</table>

Table 3
Baseline clinical characteristics, ET-1 concentrations, and TFCs of smokers and nonsmokers

<table>
<thead>
<tr>
<th>Smokers (n=24)</th>
<th>Nonsmokers (n=53)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) [mean±S.D.]</td>
<td>51.2±9.0</td>
<td>54.3±9.0</td>
</tr>
<tr>
<td>Male gender [n (%)]</td>
<td>16 (66.7)</td>
<td>10 (18.9)</td>
</tr>
<tr>
<td>Hypertension [n (%)]</td>
<td>8 (33.3)</td>
<td>35 (66)</td>
</tr>
<tr>
<td>Hypercholesterolemia [n (%)]</td>
<td>12 (60)</td>
<td>33 (68.8)</td>
</tr>
<tr>
<td>Diabetes mellitus [n (%)]</td>
<td>4 (16.7)</td>
<td>9 (17)</td>
</tr>
<tr>
<td>Body mass index (kg/m²) [mean±S.D.]</td>
<td>28.6±4.9</td>
<td>29.3±5.3</td>
</tr>
<tr>
<td>Baseline medications [n (%)]</td>
<td>8 (33.3)</td>
<td>41 (77.4)</td>
</tr>
<tr>
<td>Family history [n (%)]</td>
<td>20 (83.3)</td>
<td>33 (68.8)</td>
</tr>
<tr>
<td>Typical angina pectoris [n (%)]</td>
<td>15 (62.5)</td>
<td>15 (60)</td>
</tr>
</tbody>
</table>

Fig. 1. Comparison of ET-1 levels between patients, by the presence of coronary flow and smoking habits.
Atheromatous plaque from human carotid artery: Potential involvement of the endothelin-1 and their receptors

M. Rosa Bernal-López a,e,*, Ainhoa Rípodas b, Paloma Aragoncillo c, Manuel Gil Aguado d, Francisco Javier Serrano Hernando d, Francisco J. Tinahones a, Ricardo Gómez-Huelgas a, Arturo Fernández-Cruz b

a Research Laboratory, Fundación IMABIS, Hospital Carlos Haya, Málaga, Spain
b Research Laboratory, Internal Medicine III Department, Hospital Clínico San Carlos (HCSC), Madrid, Spain
c Department of Pathology, HCSC, Spain
d Cardiac Surgery Department and Angiology and Vascular Surgery, Cardiovascular Institute, HCSC, Spain
e Ciber Fisiopatología de la Obesidad y Nutrición (CB06/003) Instituto de Salud Carlos III, Spain

1. Introduction

The function of the endothelin system in the development of the vascular wall in atherosclerosis is still not well understood. Endothelial dysfunction plays an important function in the pathogenesis of atherosclerosis and it has demonstrated that endothelin-1 (ET-1) is elevated in atheromatous plaques. Endothelin (ET) is a polypeptide hormone secreted by the endothelial cells in some blood vessels. ET is composed of a family of potent mammalian vasoconstrictor peptides, first isolated from the culture medium of vascular endothelial cells [1]. Genomic DNA analysis revealed the existence of three distinct genes, which encode three isopeptides ET-1, ET-2, and ET-3 [2]. ET-1 is produced by endothelial and epithelial cells, macrophages, fibroblasts, and many other cell types, including cardiac myocytes [3]. The three isoforms of ET are widely distributed and function biologically by interaction with two different endothelin receptors, ET A and ET B, which have been cloned and characterized [4]. These receptor subtypes mediate a wide variety of physiologic actions in several organ systems. ET-1 has been localized to endothelial cells of coronary blood vessels, endocardium and cardiac myofibers [5]. Pharmacological studies on ET-1 have linked it with hypertension, heart attacks, renal failure and inflammation, mainly through ET A receptor-mediated actions. This receptor, found mainly in vascular smooth muscle cells (VSMC), mediates vasoconstriction, growth and inflammation actions [6]. The ET B receptors present on the endothelial cells mediate vasodilation either directly or indirectly via local mediators. On the other hand, ET B expression in the vascular smooth cells may mediate vasoconstriction [7]. Also, this receptor inhibits growth and inflammation through the release of nitric oxide and prostaglandins [2]. Recently, Sutherland et al. [8,9] observed that elevated distribution of collagen, indicative of fibrosis, coupled with increased cell cycling and high levels of ET-1 and ET A expression in the absence of chronic inflammation suggest that altered internal mammary artery (IMA) VSMC regulation is fundamental to the remodeling process. Under the influence of pro-inflammatory mediators, the VSMC can therefore become an important site of ET-1 production [10]. Shirai et al. [11] found that the expression of

...
Atheromatous plaque from human carotid artery: Potential involvement of the endothelin-1 and their receptors


1. Introduction

The function of the endothelin system in the development of the vascular wall in atherosclerosis is still not well understood. Endothelial dysfunction plays an important function in the pathogenesis of atherosclerosis and it has demonstrated that endothelin-1 (ET-1) is elevated in atherosclerotic plaques. Endothelin (ET) is a polypeptide hormone secreted by the endothelial cells in some blood vessels. ET is composed of a family of potent mammalian vasoconstrictor peptides, first isolated from the culture medium of vascular endothelial cells [1]. Genomic DNA analysis revealed the existence of three distinct genes, which encode three isopeptides ET-1, ET-2, and ET-3 [2]. ET-1 is produced by endothelial and epithelial cells, macrophages, fibroblasts, and many other cell types, including cardiac myocytes [3]. The three isoforms of ET are widely distributed and function biologically by interaction with two different endothelin receptors, ET_A and ET_B, which have been cloned and characterized [4]. These receptor subtypes mediate a wide variety of physiologic actions in several organ systems. ET-1 has been localized to endothelial cells of coronary blood vessels, endocardium and cardiac myofibers [5]. Pharmacological studies on ET-1 have linked it with hypertension, heart attacks, renal failure and inflammation, mainly through ET_A receptor-mediated actions. This receptor, found mainly in vascular smooth muscle cells (VSMC), mediates vasoconstriction, growth and inflammation actions [6]. The ET_B receptors present on the endothelial cells mediate vasodilation either directly or indirectly via local mediators. On the other hand, ET_B expression in the vascular smooth cells may mediate vasoconstriction [7]. Also, this receptor inhibits growth and inflammation through the release of nitric oxide and prostaglandins [2]. Recently, Sutherland et al. [8,9] observed that elevated distribution of collagen, indicative of fibrosis, coupled with increased cell cycling and high levels of ET-1 and ET_A expression in the absence of chronic inflammation suggest that altered internal mammary artery (IMA) VSMC regulation is fundamental to the remodeling process. Under the influence of pro-inflammatory mediators, the VSMC can therefore become an important site of ET-1 production [10]. Shirai et al. [11] found that the expression of...
Review

Endothelin-1 signalling in vascular smooth muscle: Pathways controlling cellular functions associated with atherosclerosis

Melanie E. Ivey\textsuperscript{a,b}, Narin Osman\textsuperscript{a,c}, Peter J. Little\textsuperscript{a,b,c,*}

\textsuperscript{a} Cell Biology of Diabetes Laboratory, Baker Heart Research Institute, Melbourne, Victoria, Australia
\textsuperscript{b} The Department of Medicine, Central and Eastern Clinical School, Alfred Hospital, Monash University, Melbourne, Victoria, Australia
\textsuperscript{c} The Department of Immunology, Central and Eastern Clinical School, Alfred Hospital, Monash University, Melbourne, Victoria, Australia

Received 22 October 2007; received in revised form 4 March 2008; accepted 10 March 2008
Available online 16 March 2008

Abstract

Atherosclerosis is the primary ischaemic vascular condition underlying a majority of cardiovascular disease related deaths. Endothelin-1 is a vasoactive peptide agent upregulated in atherosclerosis and in conjunction with its G protein-coupled receptors exerts diverse actions on all cells of the vasculature in particular vascular smooth muscle cells (VSMC). The effects of endothelin-1 include cell proliferation, migration and contraction, and the induction of extracellular matrix components and growth factors. VSMC as the major component of the neointima in atherosclerotic plaques accordingly play a key role in atherogenesis. In this review we examine classic and novel signalling pathways activated by endothelin-1 in VSMC (including phospholipase C, adenylate cyclase, Rho kinase, transactivation of receptor tyrosine kinases, mitogen activated protein kinase cascades and \(\beta\)-arrestin) and their likely impact on the development and progression of atherosclerosis.

© 2008 Elsevier Ireland Ltd. All rights reserved.

Keywords: Endothelin-1; Vascular smooth muscle cell; Cell signalling; Atherosclerosis

Contents

1. Introduction ........................................................................................................ 238
2. Endothelin receptors and G protein coupling ...................................................... 238
3. Cellular signalling pathways activated by ET-1 in VSMC .................................... 239
   3.1. \(G_{\alpha q1}\) mediated activation of phospholipase C ............................................. 239
   3.2. Activation of cAMP and PKA ........................................................................ 240
   3.3. Rho activation of Rho kinase ........................................................................ 241
   3.4. Transactivation of cell membrane tyrosine kinase receptors .............................. 241
   3.5. MAPK signalling .......................................................................................... 242
   3.6. \(\beta\)-Arrestin scaffolding dependent signalling .................................................. 243
4. Conclusion ........................................................................................................ 244
Acknowledgements .............................................................................................. 244
References .......................................................................................................... 244

* Corresponding author at: Cell Biology of Diabetes Laboratory, Division of Vascular Biology, Baker Heart Research Institute, St. Kilda Road Central, PO Box 6492, Melbourne, Victoria 8008, Australia. Tel.: +61 3 8532 1203; fax: +61 3 8532 1100.
E-mail address: peter.little@baker.edu.au (P.J. Little).

0021-9150/$ – see front matter © 2008 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.atherosclerosis.2008.03.006

Review

Endothelin-1 signalling in vascular smooth muscle: Pathways controlling cellular functions associated with atherosclerosis

Melanie E. Iveya, b, Narin Osmana, c, Peter J. Littlea, b, c, *

a Cell Biology of Diabetes Laboratory, Baker Heart Research Institute, Melbourne, Victoria, Australia
b The Department of Medicine, Central and Eastern Clinical School, Alfred Hospital, Monash University, Melbourne, Victoria, Australia
c The Department of Immunology, Central and Eastern Clinical School, Alfred Hospital, Monash University, Melbourne, Victoria, Australia

Received 22 October 2007; received in revised form 4 March 2008; accepted 10 March 2008
Available online 16 March 2008

Abstract

Atherosclerosis is the primary ischaemic vascular condition underlying a majority of cardiovascular disease related deaths. Endothelin-1 is a vasoactive peptide agent upregulated in atherosclerosis and in conjunction with its G protein-coupled receptors exerts diverse actions on all cells of the vasculature in particular vascular smooth muscle cells (VSMC). The effects of endothelin-1 include cell proliferation, migration and contraction, and the induction of extracellular matrix components and growth factors. VSMC as the major component of the neointima in atherosclerotic plaques accordingly play a key role in atherogenesis. In this review we examine classic and novel signalling pathways activated by endothelin-1 in VSMC (including phospholipase C, adenylate cyclase, Rho kinase, transactivation of receptor tyrosine kinases, mitogen activated protein kinase cascades and β-arrestin) and their likely impact on the development and progression of atherosclerosis.

© 2008 Elsevier Ireland Ltd. All rights reserved.

Keywords: Endothelin-1; Vascular smooth muscle cell; Cell signalling; Atherosclerosis

Contents

1. Introduction ................................................................. 238
2. Endothelin receptors and G protein coupling ................................................................. 238
3. Cellular signalling pathways activated by ET-1 in VSMC ......................................................... 239
   3.1. Goq11 mediated activation of phospholipase C ................................................................. 239
   3.2. Activation of cAMP and PKA ......................................................................................... 240
   3.3. Rho activation of Rho kinase ......................................................................................... 241
   3.4. Transactivation of cell membrane tyrosine kinase receptors ................................................. 241
   3.5. MAPK signalling ........................................................................................................... 242
   3.6. β-Arrestin scaffolding dependent signalling ..................................................................... 243
4. Conclusion .............................................................................. 244
Acknowledgements ......................................................................................... 244
References ................................................................................................. 244

* Corresponding author at: Cell Biology of Diabetes Laboratory, Division of Vascular Biology, Baker Heart Research Institute, St. Kilda Road Central, PO Box 6492, Melbourne, Victoria 8008, Australia. Tel.: +61 3 8532 1203; fax: +61 3 8532 1100.
E-mail address: peter.little@baker.edu.au (P.J. Little).

0021-9150/$ – see front matter © 2008 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.atherosclerosis.2008.03.006
Abstract

Endothelins are powerful vasoconstrictor peptides that also play numerous other roles. The endothelin (ET) family consists of three peptides produced by a variety of tissues. Endothelin-1 (ET-1) is the principal isoform produced by the endothelium in the human cardiovascular system, and it exerts its actions through binding to specific receptors, the so-called type A (ET\(_A\)) and type B (ET\(_B\)) receptors. ET-1 is primarily a locally acting paracrine substance that appears to contribute to the maintenance of basal vascular tone. It is also activated in several diseases, including congestive heart failure, arterial hypertension, atherosclerosis, endothelial dysfunction, coronary artery diseases, renal failure, cerebrovascular disease, pulmonary arterial hypertension, and sepsis. Thus, ET-1 antagonists are promising new agents. They have been shown to be effective in the management of primary pulmonary hypertension, but disappointing in heart failure. Clinical trials are needed to determine whether manipulation of the ET system will be beneficial in other diseases.

© 2007 European Federation of Internal Medicine. Published by Elsevier B.V. All rights reserved.

Keywords: Endothelins; Vasoconstriction; Vasoactive agents

Contents

1. Introduction ........................................................... 273
2. History .............................................................. 273
3. Types of endothelin ....................................................... 273
4. Endothelin-1 synthesis ...................................................... 273
5. Plasma concentrations of ET-1 .................................................. 273
6. Clearance of ET-1 ........................................................ 273
7. Endothelin receptors ....................................................... 274
8. Vascular actions of ET-1 ..................................................... 275
9. Association with cardiovascular and non-cardiovascular diseases .................................. 276
   9.1. Heart failure ........................................................ 276
   9.2. Arterial hypertension ................................................... 277
   9.3. Atherosclerosis ...................................................... 277
   9.4. Endothelial dysfunction .................................................. 277
   9.5. Coronary artery diseases ................................................. 278
   9.6. Renal failure ....................................................... 278
   9.7. Cerebrovascular disease .................................................. 278
   9.8. Pulmonary arterial hypertension .............................................. 278
   9.9. Sepsis ........................................................... 279
   9.10. Other diseases ....................................................... 279

* Tel.: +1 617 525 6733; fax: +1 617 582 6027.
E-mail address: rshah@rics.bwh.harvard.edu.
Review article

Endothelins in health and disease

Rahman Shah *

Section of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School,
75 Francis Street, Boston, MA 02115, USA

Received 26 August 2006; received in revised form 3 January 2007

Abstract

Endothelins are powerful vasoconstrictor peptides that also play numerous other roles. The endothelin (ET) family consists of three peptides produced by a variety of tissues. Endothelin-1 (ET-1) is the principal isoform produced by the endothelium in the human cardiovascular system, and it exerts its actions through binding to specific receptors, the so-called type A (ETA) and type B (ETB) receptors. ET-1 is primarily a locally acting paracrine substance that appears to contribute to the maintenance of basal vascular tone. It is also activated in several diseases, including congestive heart failure, arterial hypertension, atherosclerosis, endothelial dysfunction, coronary artery diseases, renal failure, cerebrovascular disease, pulmonary arterial hypertension, and sepsis. Thus, ET-1 antagonists are promising new agents. They have been shown to be effective in the management of primary pulmonary hypertension, but disappointing in heart failure. Clinical trials are needed to determine whether manipulation of the ET system will be beneficial in other diseases.

© 2007 European Federation of Internal Medicine. Published by Elsevier B.V. All rights reserved.

Keywords: Endothelins; Vasoconstriction; Vasoactive agents

Contents

1. Introduction ........................................................... 273
2. History .............................................................. 273
3. Types of endothelin ....................................................... 273
4. Endothelin-1 synthesis ...................................................... 273
5. Plasma concentrations of ET-1 .................................................. 273
6. Clearance of ET-1 ........................................................ 273
7. Endothelin receptors ....................................................... 274
8. Vascular actions of ET-1 ..................................................... 275
9. Association with cardiovascular and non-cardiovascular diseases .................................. 276
   9.1. Heart failure ........................................................ 276
   9.2. Arterial hypertension ................................................... 277
   9.3. Atherosclerosis ...................................................... 277
   9.4. Endothelial dysfunction .................................................. 277
   9.5. Coronary artery diseases ................................................. 278
   9.6. Renal failure ....................................................... 278
   9.7. Cerebrovascular disease .................................................. 278
   9.8. Pulmonary arterial hypertension .............................................. 278
   9.9. Sepsis ........................................................... 279
   9.10. Other diseases ....................................................... 279

* Tel.: +1 617 525 6733; fax: +1 617 582 6027.
E-mail address: rshah@rics.bwh.harvard.edu.

© 2007 European Federation of Internal Medicine. Published by Elsevier B.V. All rights reserved.