Adaptation of vasomotor function of human coronary arterioles to the simultaneous presence of obesity and hypertension

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Acknowledgements

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Diabetes and regulation of human coronary microvessels

DIABETES AND CORONARY DISEASES

- **There is a general agreement that diabetes increases the risk for cardiovascular diseases and its complications, such as coronary heart diseases.**

- **Vasomotor dysfunction of coronary microvessels is one of the early alterations in diabetes, contributing to the dysregulation of coronary blood flow, predisposing patients to myocardial ischemia.**

INTRODUCTION

- Recent studies on animal models of diabetes mellitus have suggested a pivotal role for alterations in cyclooxygenase-2 (COX-2)–dependent synthesis of prostaglandins affecting vasodilator mechanisms.
- In the canine coronary circulation, COX-2–derived prostacyclin contributed to the agonist-induced dilator responses.

HYPOTHESIS OF OUR STUDIES

In coronary arterioles of patients with type 2 diabetes mellitus:

- **Agonist-induced, prostaglandin-mediated vasomotor responses are altered due to**
- **Increased COX-2 expression.**

Patient Characteristics

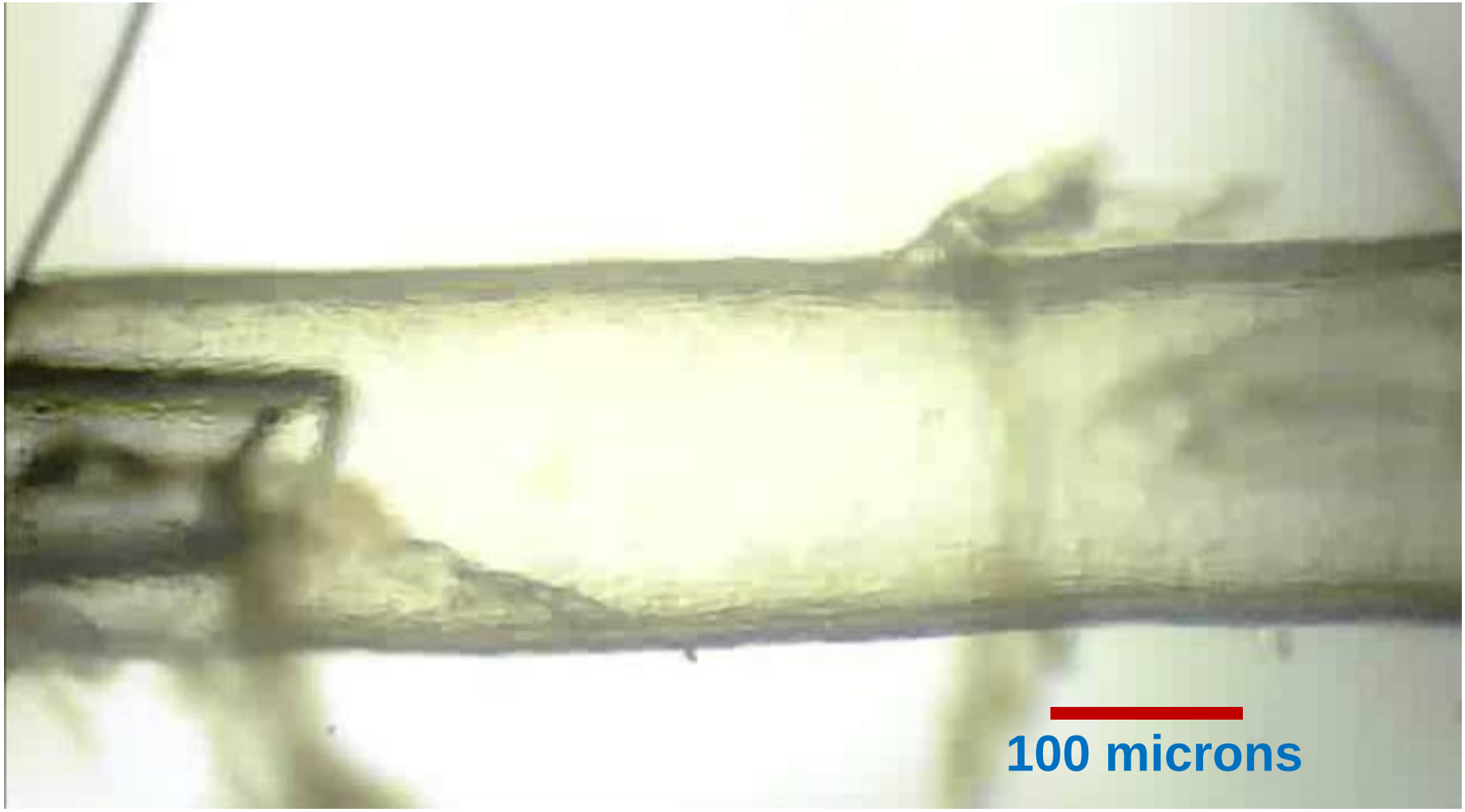
Patients who underwent coronary bypass or valve replacement surgery were chosen. Patients were divided into two groups, with or without documented diabetes mellitus.

All protocols were approved by the Ethical Committee of the University of Debrecen, Medical and Health Science Center. All patients were given written information about the experimental use of human specimen.

Isolation of Coronary Arterioles

- Coronary arteriole (~1 mm in length) from the right atrial appendage was isolated and cannulated and the intraluminal pressure was set to 80 mm Hg.
- Changes in arteriolar diameter were continuously recorded with a digital camera, connected to a microscope.
- Immunohistochemistry: atrial appendages from DM(–) and DM(+) patients were embedded and frozen in OCT compound (Tissue Tek, Electron Microscopy Sciences) and immunolabeled with a polyclonal anti–COX-2 primary antibody (dilution 1:100; Cayman Chemicals).

An isolated small artery



BRADYKININ

BRADYKININ

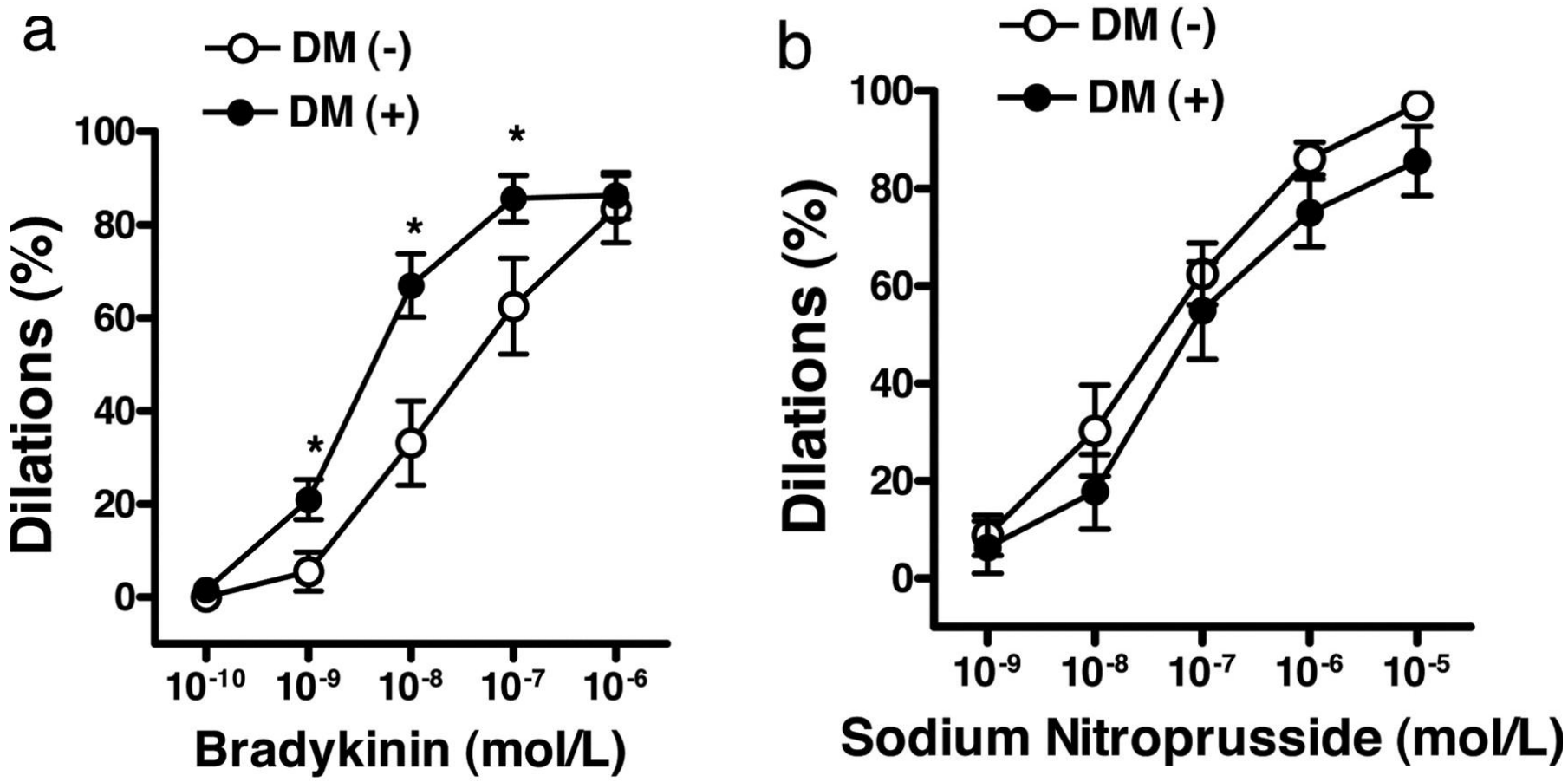
Nitric oxide, Prostaglandins, EDHF, ROS

- **Miura H, Liu Y, Gutterman DD. Human coronary arteriolar dilation to bradykinin depends on membrane hyperpolarization: contribution of nitric oxide and Ca2-activated K channels. *Circulation*. 1999;99:3132–3138.**

  Gutterman DD, Miura H, Liu Y. Redox modulation of vascular tone: focus of potassium channel mechanisms of dilation. *Arterioscler Thromb Vasc Biol*. 2005;25:671–678.

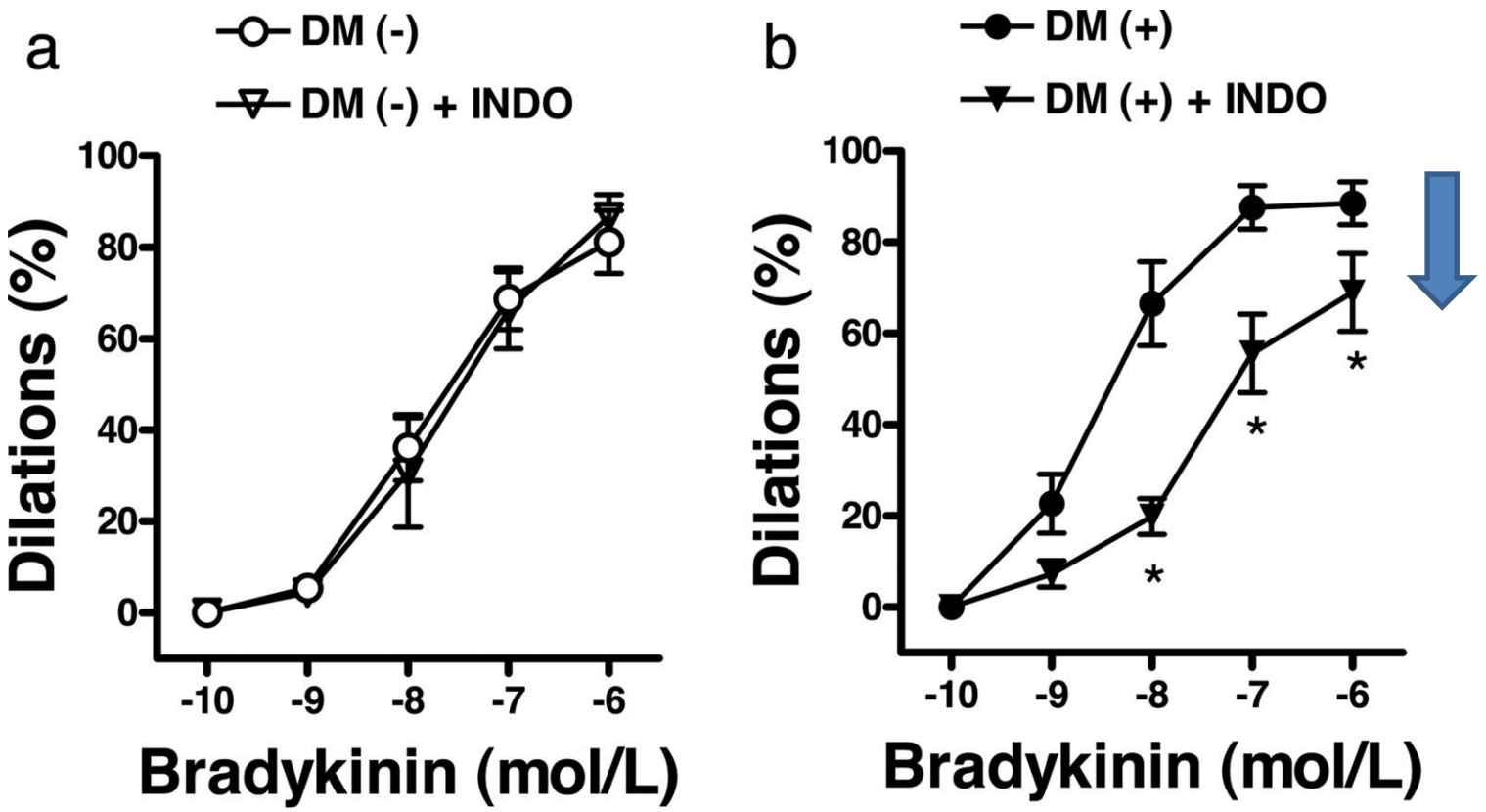
RESULTS

Changes in diameter of coronary arterioles isolated of right atrial appendage from non-diabetic (DM(−), n=13) and diabetic patients (DM(+), n=12) in response to bradykinin and SNP.



Szerafin T et al. Circulation Research 2006;99:e12-317

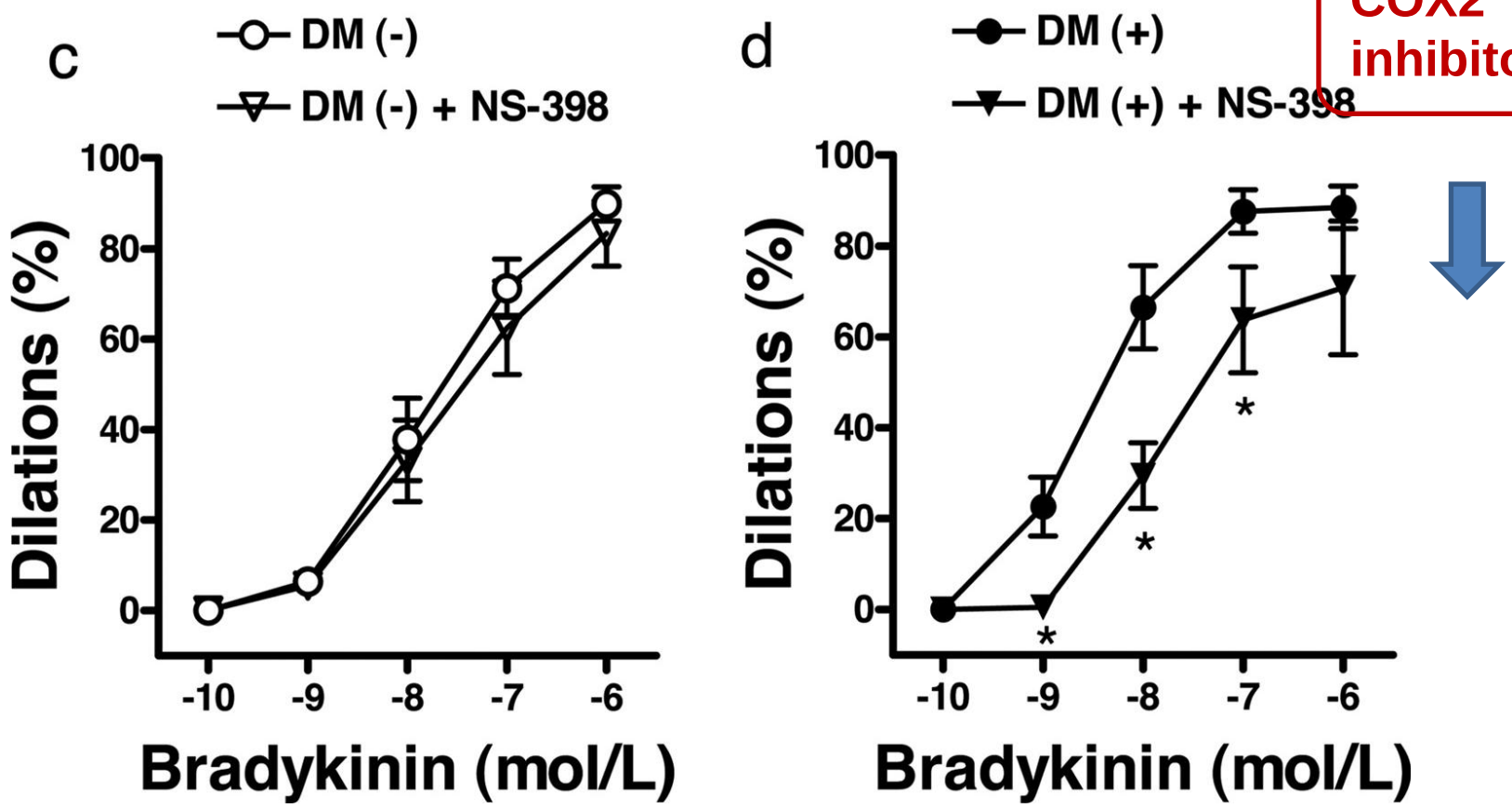
Changes in diameter of coronary arterioles isolated from non-diabetic (DM(−), n=5 to 6) and diabetic patients (DM(+), n=5 to 6) in response to cumulative doses of bradykinin, before and after incubation with indomethacin (a and b).



Szerafin T et al. Circulation Research 2006;99:e12-317

Changes in diameter of coronary arterioles isolated from nondiabetic (DM(−), n=5 to 6) and diabetic patients (DM(+), n=5 to 6) in response to cumulative doses of bradykinin, before and after incubation with indomethacin (a and b) or NS-398 (c and d).

COX2 inhibitor



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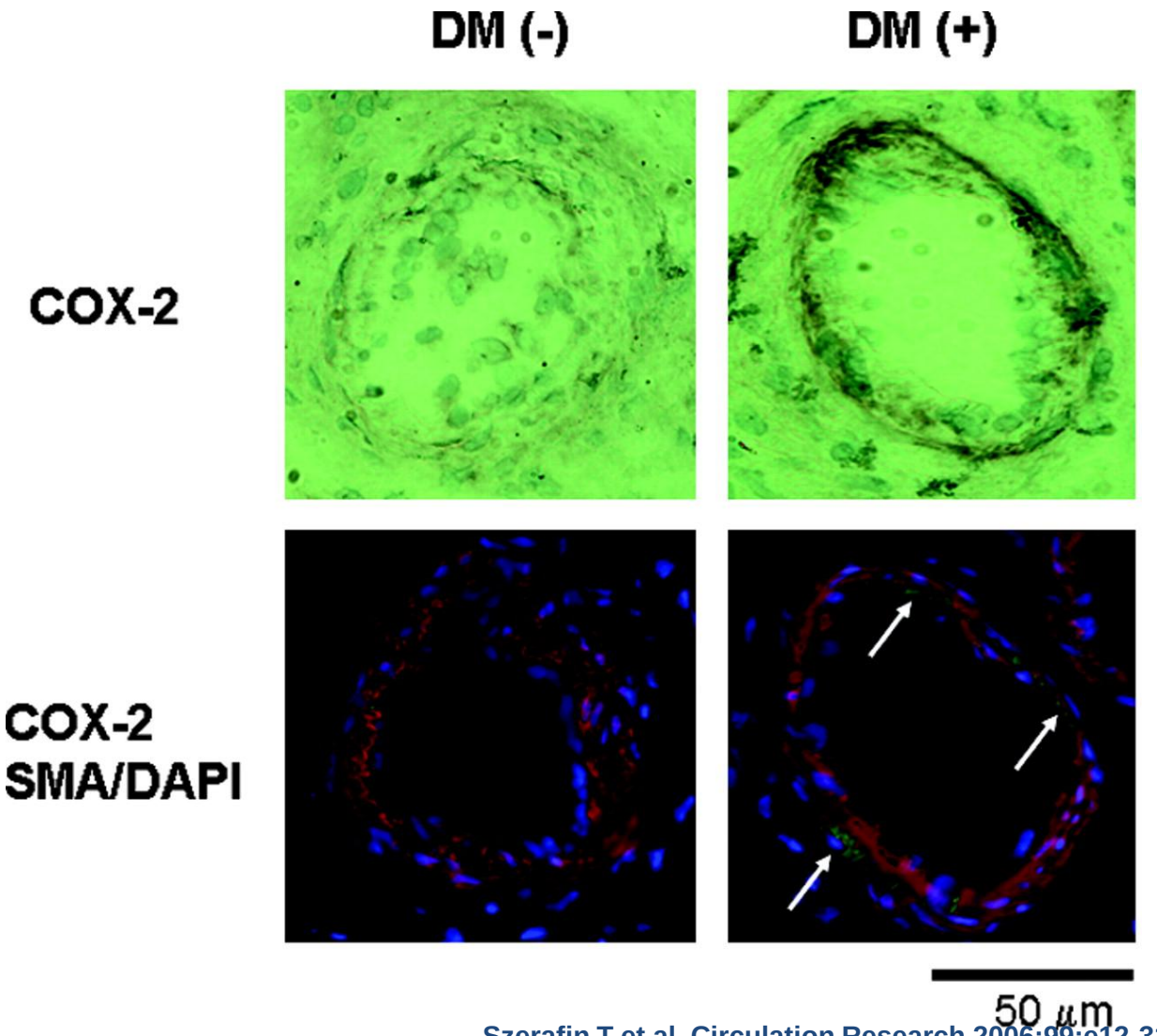
Representative pictures of immunohistochemical staining of COX-2 in coronary arterioles from non-diabetic (DM(−), left) and diabetic patients (DM(+), right).



primarily in the endothelial layer

Szerafin T et al. Circulation Research 2006;99:e12-317

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CONCLUSIONS

- In coronary arterioles of diabetic patients bradykinin induces enhanced COX-2–derived prostaglandin-mediated dilation, due to increased COX-2 expression (in the endothelium),
- which may serve to increase dilator capacity and represent a compensatory mechanism aiming to maintain an appropriate blood supply of the myocardium.

MECHANISMS

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MECHANISMS

Cosentino F, Eto M, De Paolis P, van der Loo B, Bachschmid M, Ullrich V, Kouroedov A, Delli Gatti C, Joch H, Volpe M, Luscher TF.

High Glucose Causes Upregulation of cyclooxygenase-2 and alters prostanoid profile in human endothelial cells: role of protein kinase C and reactive oxygen species.

***Circulation*. 2003;107:1017–1023.**

Clinical Relevance of Upregulated COX-2 in Coronary Arterioles

- **In humans, endogenous release of basal- and flow-stimulated bradykinin contributes substantially to the dilator responses of coronary vessels.**
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- **The beneficial effect of angiotensin converting enzyme (ACE) inhibitors is, in part, ascribed to the enhanced levels of bradykinin in the vasculature.**

Clinical Relevance of Upregulated COX-2 in Coronary Arterioles

- **On the other hand, recent studies on patients with cardiovascular risk factors reported controversial findings regarding the safety of use of non-steroid anti-inflammatory drugs, including selective COX-2 inhibitors.**
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- Antman EM, DeMets D, Loscalzo J. Cyclooxygenase inhibition and cardiovascular risk. *Circulation*. 2005;112:759 –770.
- **These findings have drawn a great attention to prostaglandins produced by the vascular endothelium.**

Obesity and Hypertension

Barrett-Connor E, Khaw KT.
Is hypertension more benign when associated with obesity?
***Circulation* 72: 53–60, 1985.**

OBESITY AND CORONARY DISEASES

- **Studies have shown that any increase in body mass requires higher cardiac output and consequently increased coronary blood flow.**

- **Given that, an impairment coronary vasomotor function is likely to be more detrimental on myocardial perfusion in obese subjects.**

ADAPTATION?

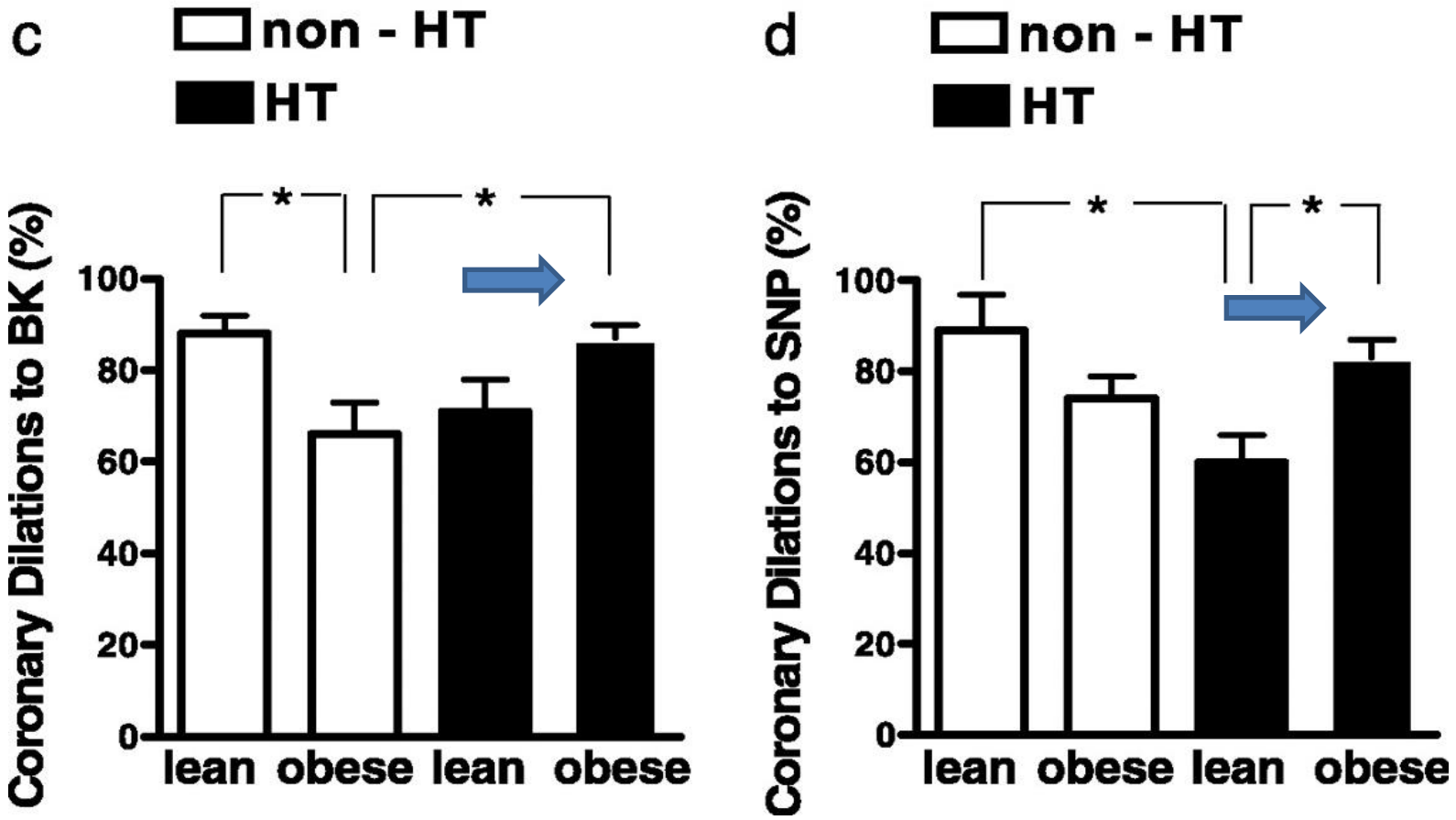
- It has been proposed that obesity, in some cases, may protect patients from the deleterious vascular effect of hypertension by decreasing hypertensive target organ damage.
- Thus it is likely that a functional adaptation of the vascular system develops in obesity

  (at least in the early phase).

HYPOTHESIS

- We hypothesized that hypertension and obesity may not simply have an additive deleterious effect….**rather:**
- Adaptive mechanisms intrinsic to vascular wall are activated in obesity aiming to maintain or enhance the dilator function of coronary arterioles.

Bradykinin (BK) and sodium-nitroprusside (SNP)-induced dilations of coronary arterioles of normotensive (non-HT) and hypertensive (HT) patients.



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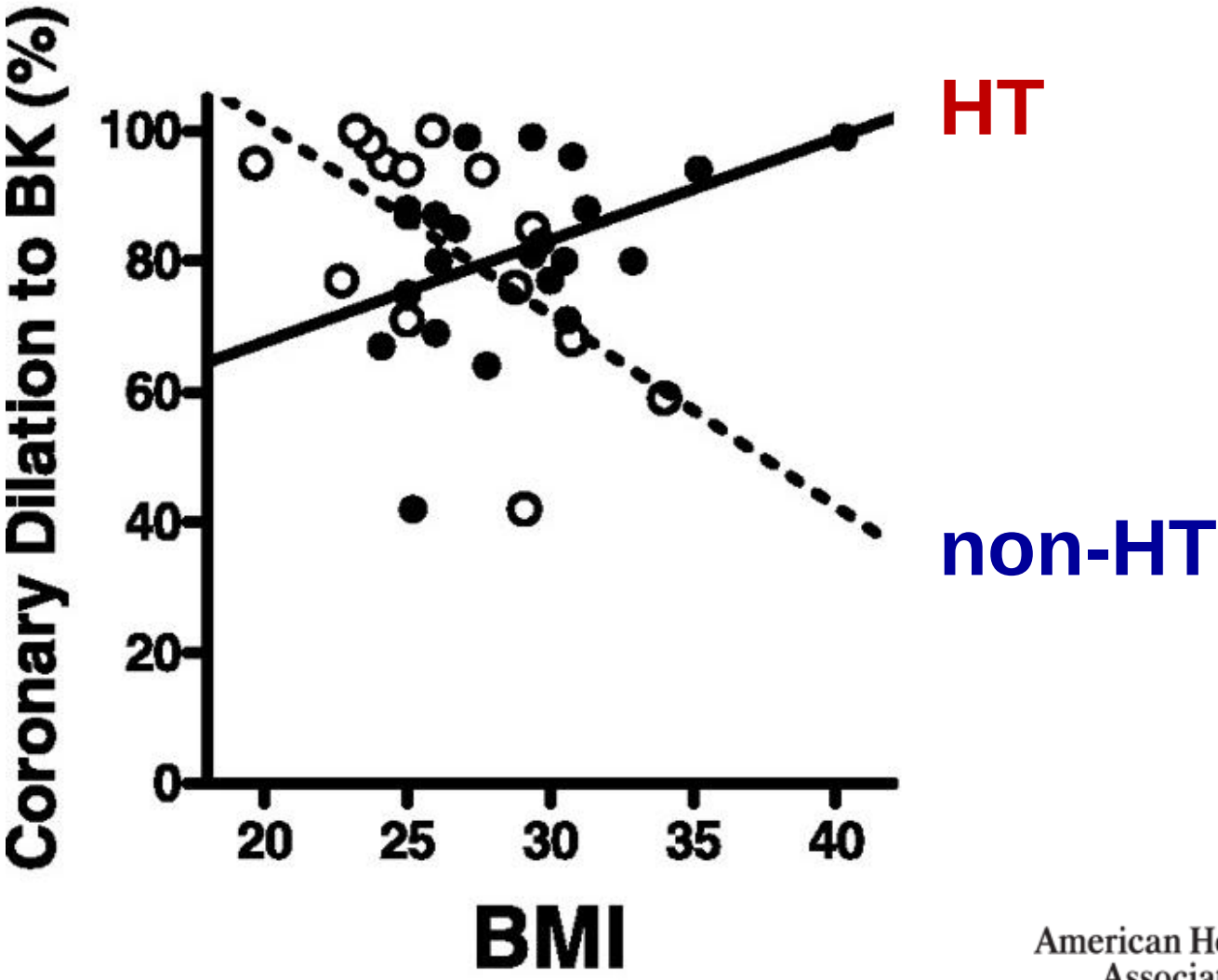
Pearson correlations between BK-induced dilations and BMI, both in normotensive (non-HT, empty symbols) and hypertensive (HT, filled symbols) patients.



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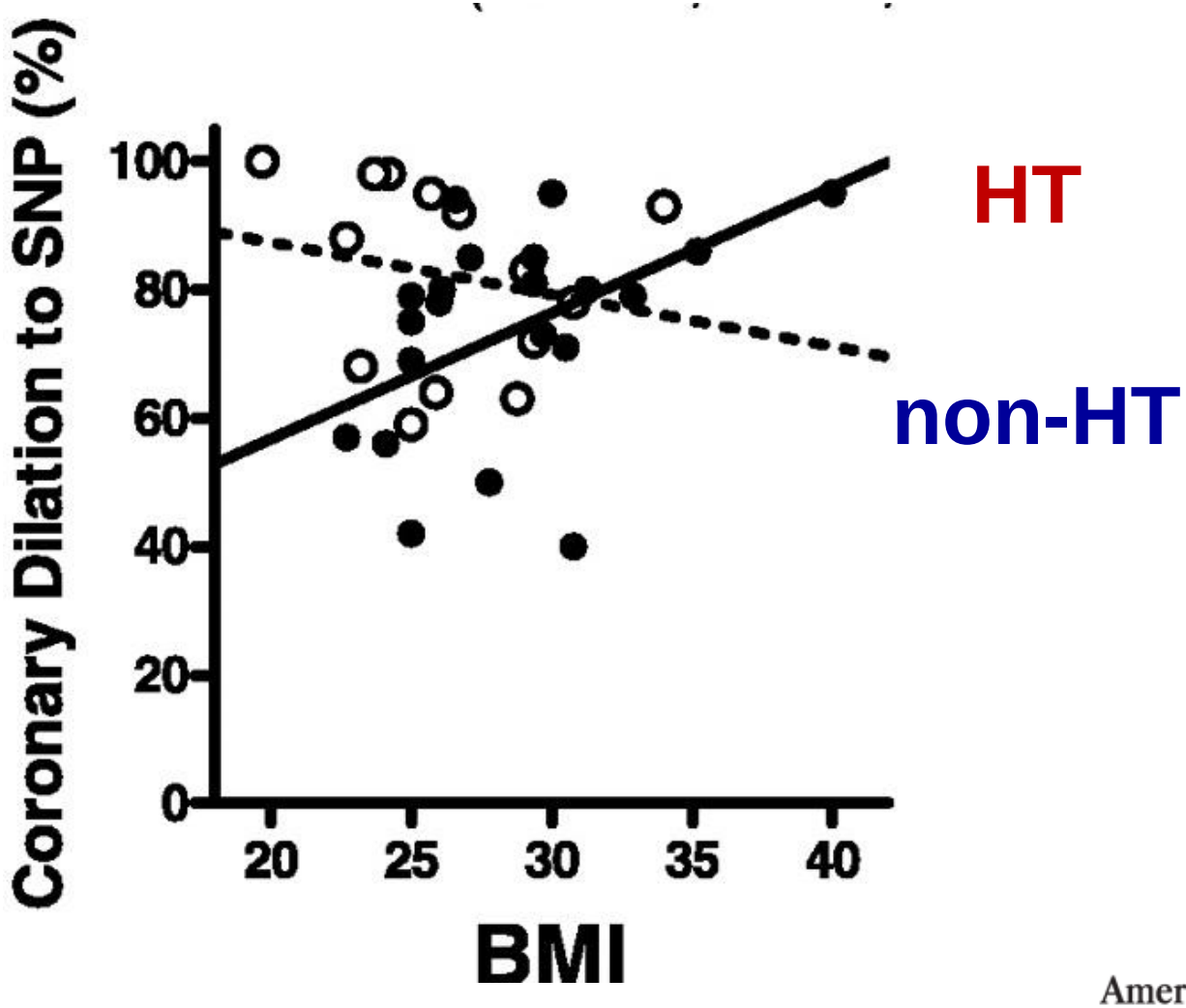
Pearson correlations between SNP-induced dilations and BMI, both in normotensive (non-HT, empty symbols) and hypertensive (HT, filled symbols) patients.



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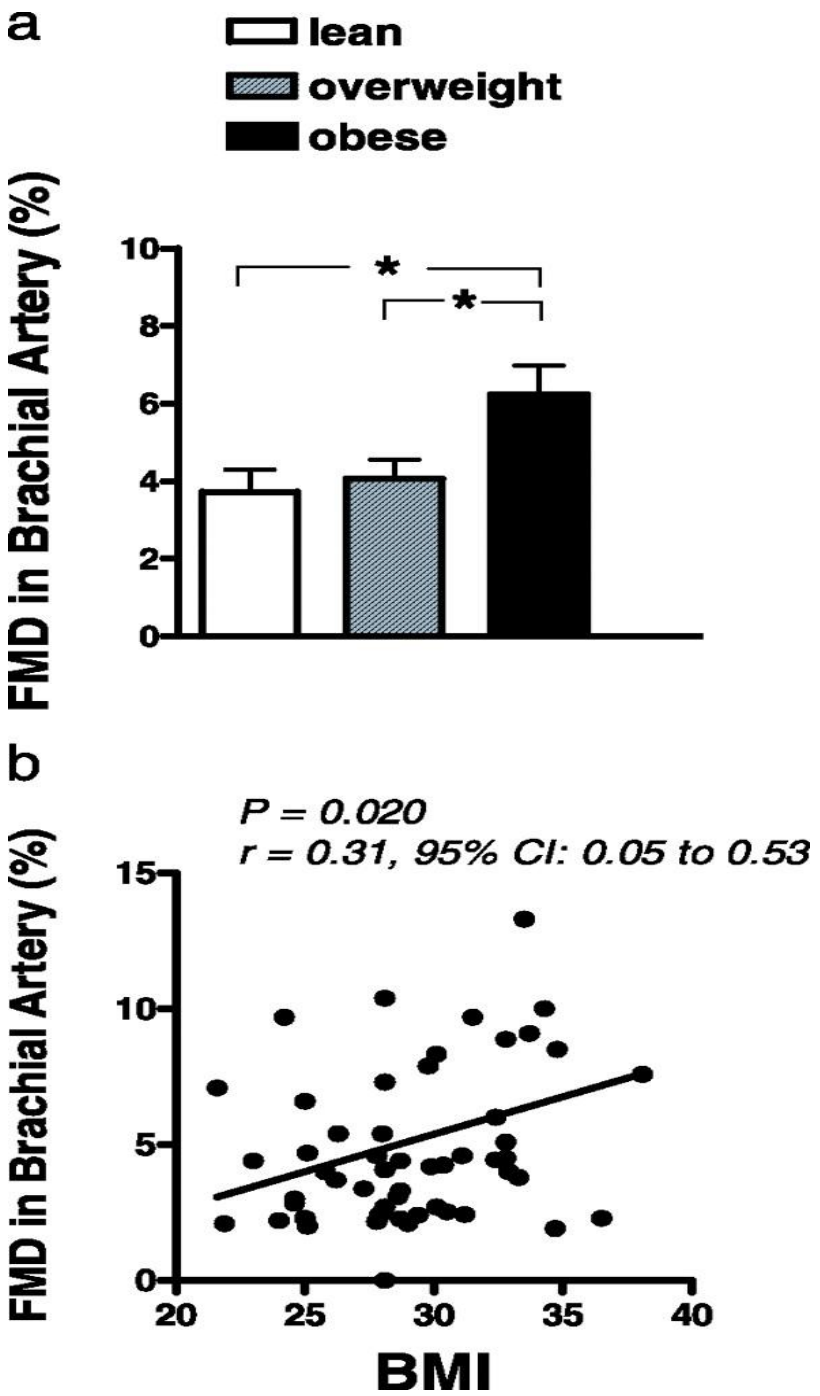
Flow-mediated dilation (FMD) of the brachial artery in lean, overweight and obese patients with hypertension.



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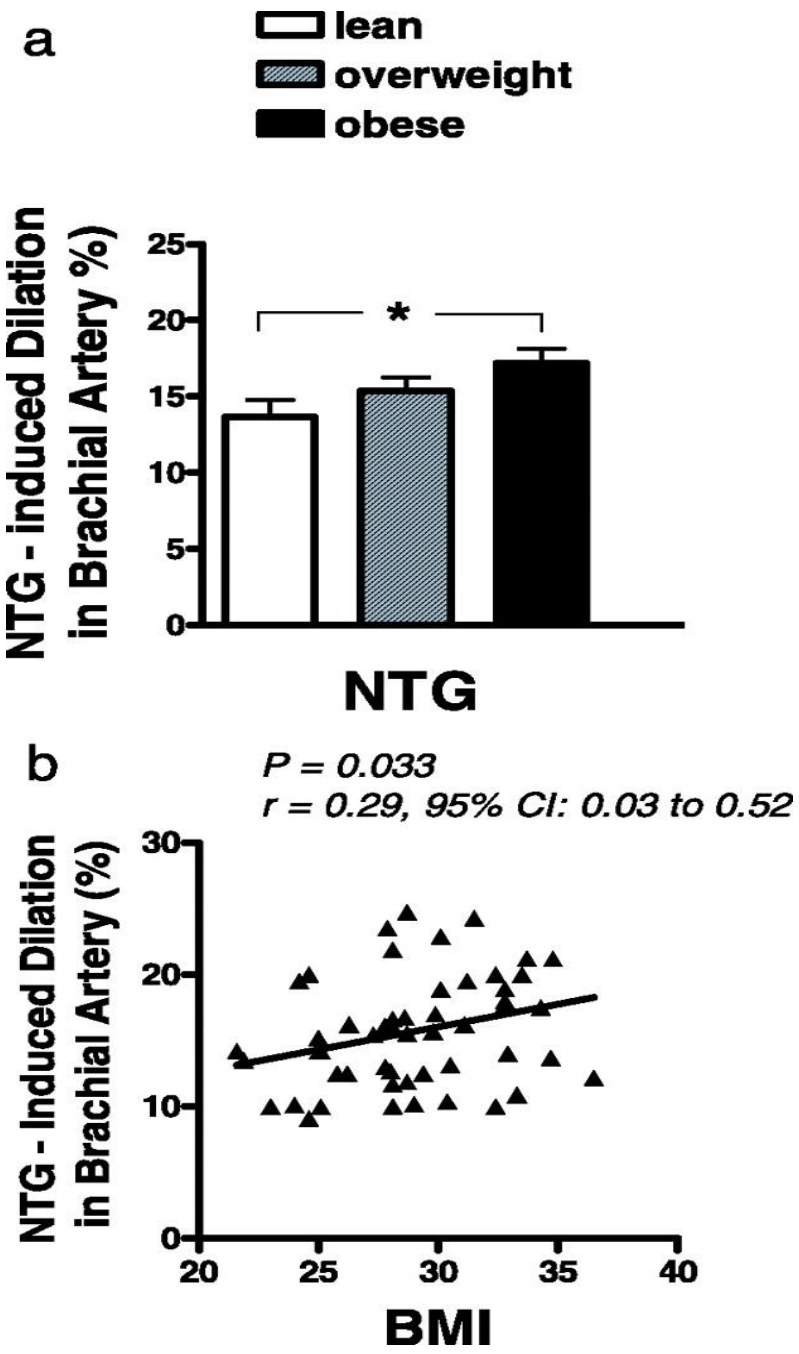
Nitroglycerin (NTG)-induced brachial artery dilations in lean, overweight and obese patients with hypertension.



Fulop T et al. Arterioscler Thromb Vasc Biol 2007;27:2348-2354

MECHANISMS

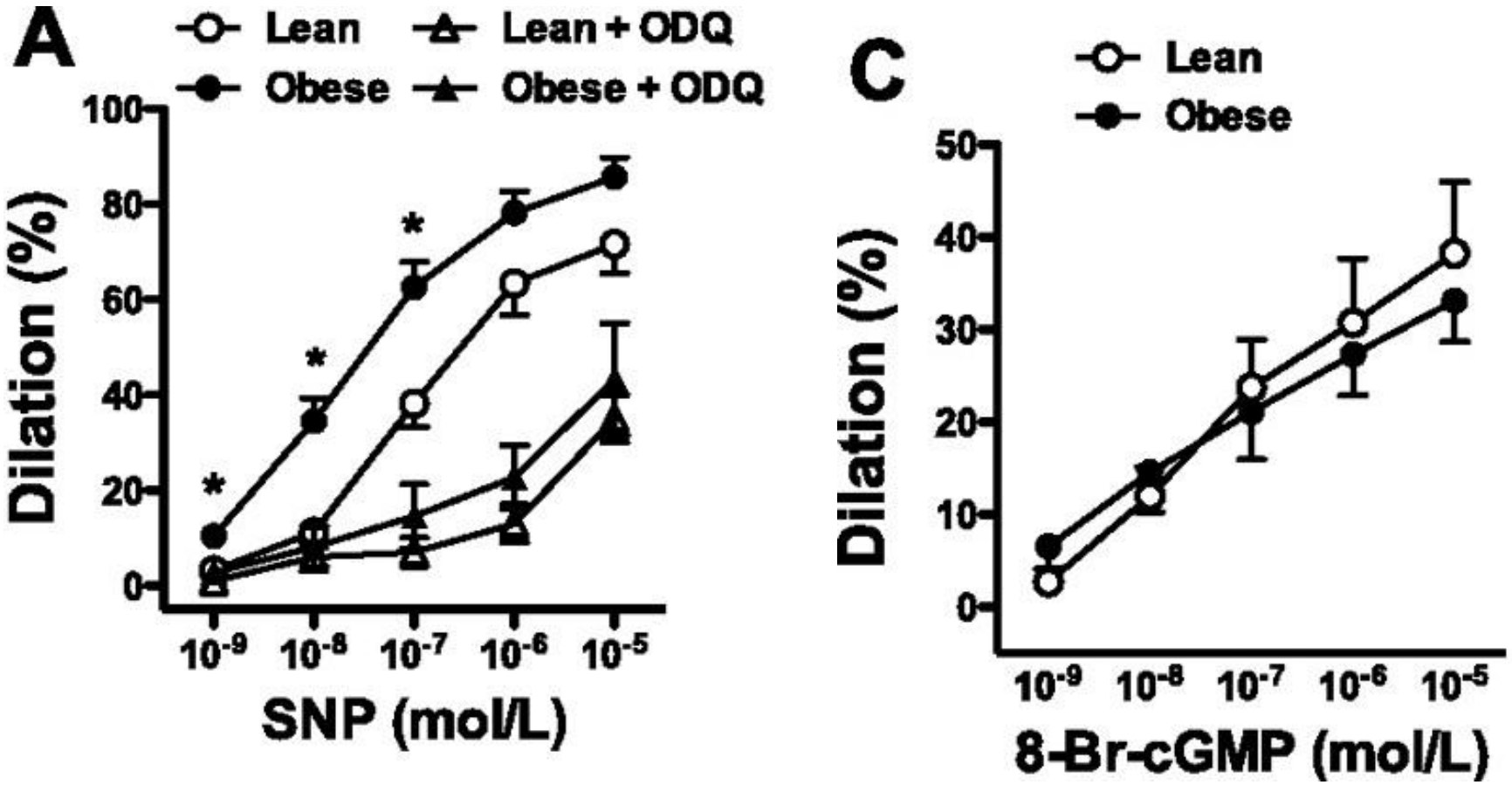
Jebelovszki E, Kiraly C, Erdei N, Feher A, Pasztor ET, Rutkai I, Forster T, Edes I, Koller A, Bagi Z.

High-fat diet-induced obesity leads to increased NO sensitivity of rat coronary arterioles: role of soluble guanylate cyclase activation.

***Am J Physiol Heart Circ Physiol* 294: H2558–H2564, 2008.**

sGC

Changes in diameter of coronary arterioles isolated from lean and high-fat diet-induced obese rats in response to cumulative concentrations of sodium nitroprusside (SNP) and 8 Br-cGMP.



Jebelovszki E et al. Am J Physiol Heart Circ Physiol 2008;294:H2558-H2564

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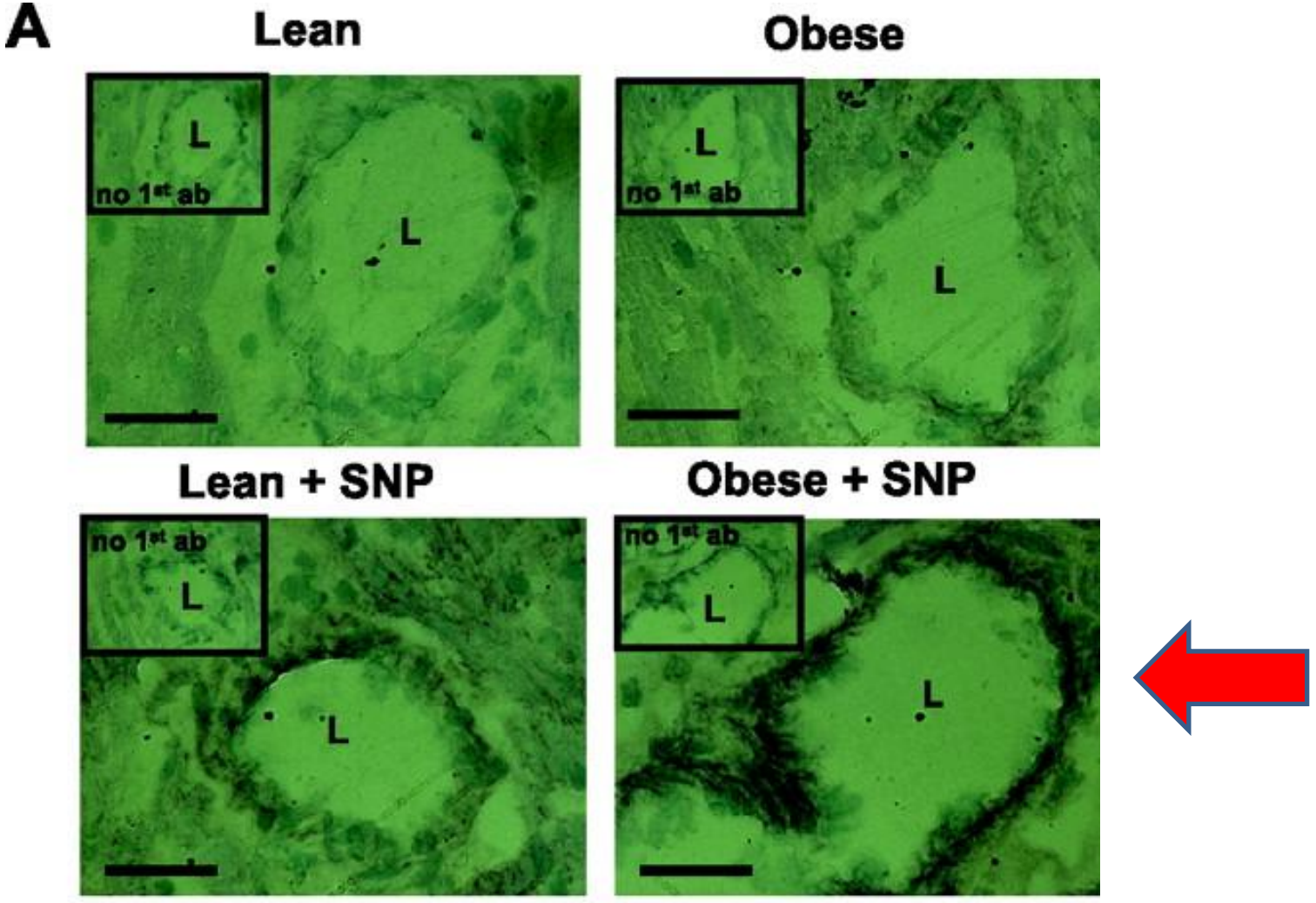
Representative photomicrographs of immuncytochemistry (A) showing cGMP immunoreactivity (indicated by the brown product) in the coronary arteriolar wall of lean and obese rats.



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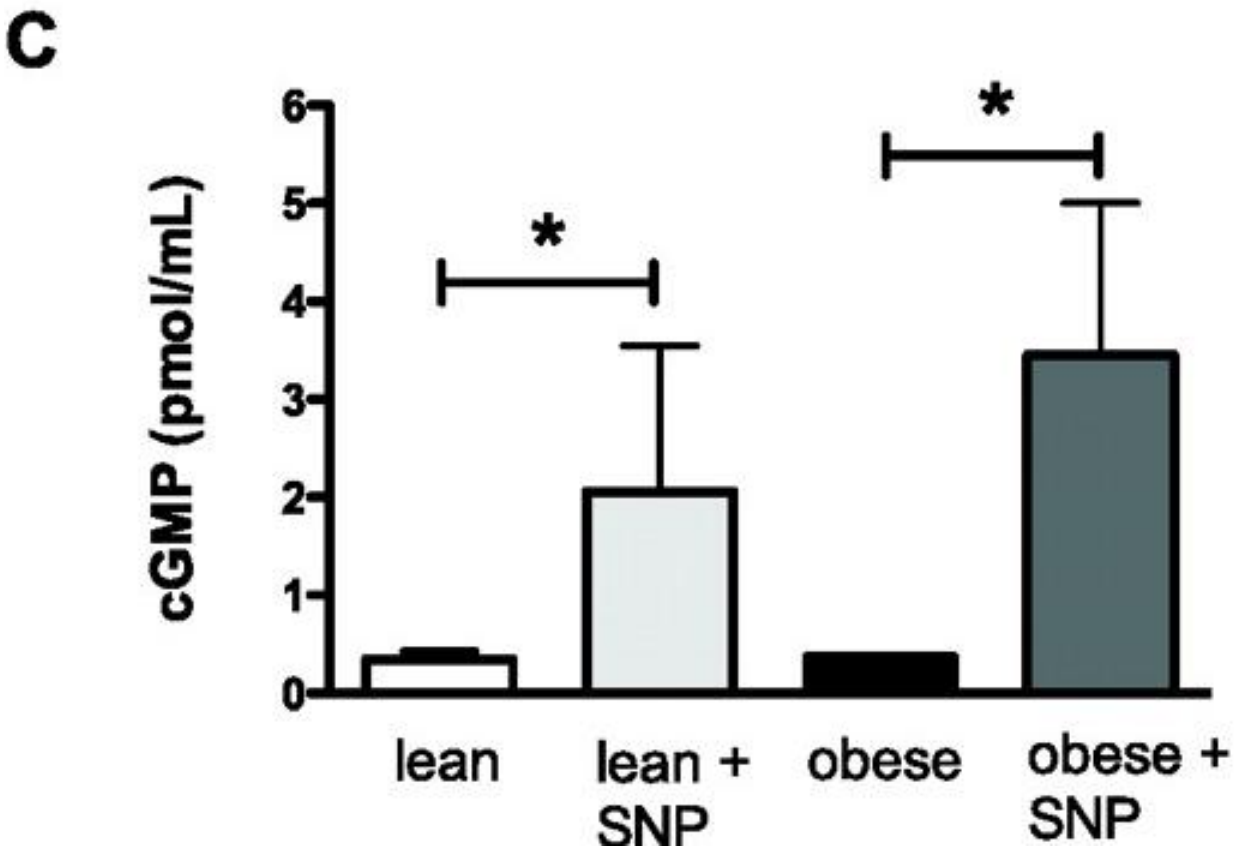
Summarized data of densitometry analysis (B) showing cGMP immunoreactivity (indicated by the brown product) in the coronary arteriolar wall of lean and obese rats



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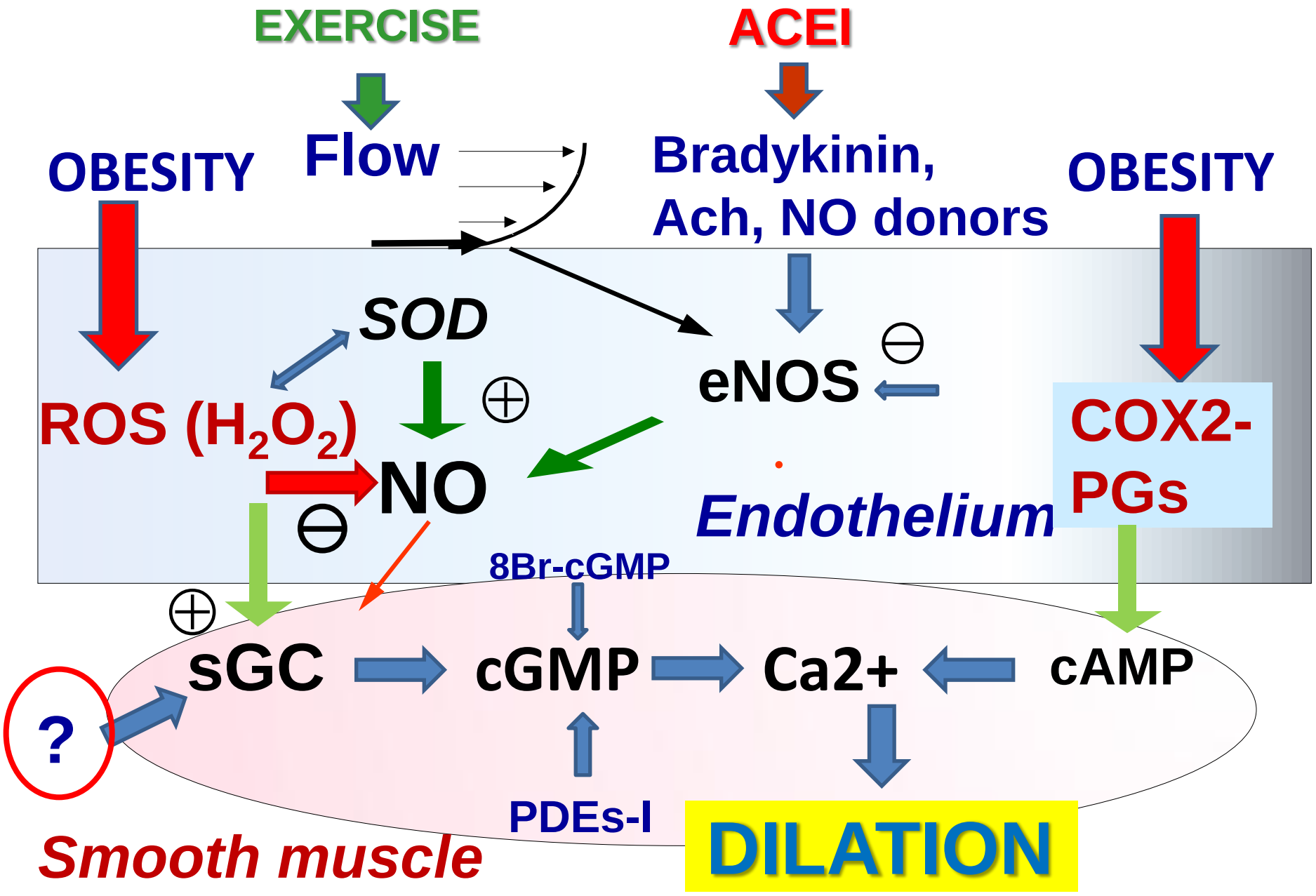
EXERCISE
ACEI
Flow
OBESITY
Bradykinin,
Ach, NO donors
OBESITY
SOD
eNOS
ROS (H_2O_2)
NO
COX2-
PGs
Endothelium
8Br-cGMP
sGC
cGMP
Ca2+
cAMP
?
PDEs-I
DILATION
Smooth muscle

DUBROVNIK?


DUBROVNIK?
ANYTIME!

Thank you for your attention!

Collaborators: Zs. Bagi, G. Kaley, A., T. Szerafin, G. Tibor Fulop, E. Jebelovszki, N. Erdei, T. Forster, I. Edes,

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