Microvascular Research 98 (2015) 139–144

Contents lists available at ScienceDirect

Microvascular Research

journal homepage: www.elsevier.com/locate/ymvre

Baroreceptor stimulation enhanced nitric oxide vasodilator responsiveness, a new aspect of baroreflex physiology

Juraj Gmitrov *

National Institute of Public Health, Department of Environmental Health, Tokyo 108, Japan [1]
Pro Vitae Hospital, Diabetology Clinic, Nemocnicna 33, Gelnica 05601, Slovak Republic [2]
Krompachy Hospital, Agel SK Inc., Diabetology Clinic, Banicka stvrt 1, Krompachy, 05642, Slovak Republic [3]

ARTICLE INFO

Article history:
Accepted 17 November 2014
Available online 24 November 2014

Keywords:
Static magnetic field
Baroreflex sensitivity
Microcirculation
Nitric oxide
Vascular smooth muscle sensitivity to nitric oxide

ABSTRACT

Objective: Increasing evidence suggests that endothelial nitric oxide (NO) deficit and baroreflex dysfunction are associated with a variety of cardiovascular conditions, ranging from arterial hypertension to stroke and coronary heart disease, importantly appearing even in preclinical stages of the disease. To test the hypothesis that the arterial baroreflex has a modulatory effect on NO-dependent vasodilation, sodium nitroprusside (SNP), a spontaneous NO-donor, vasodilatory effect was studied in conjunction with sinocarotid baroreceptor magnetic stimulation and potential implementation in NO deficiency states.

Methods: Mean femoral artery blood pressure (MAP), heart rate (HR) and ear lobe skin microcirculatory blood flow, measured by a microphotoelectric plethysmogram (MPPG), were simultaneously recorded in conscious rabbits before and after 40-min sinocarotid baroreceptor exposure to 350 mT static magnetic field (SMF), generated by Nd_2–Fe_4–B alloy ($n = 8$) or sham magnets ($n = 8$, controls). Arterial baroreflex sensitivity (BRS) was measured by changes in HR and MAP ($\Delta HR / \Delta MAP$) after intravenous bolus injections of SNP and phenylephrine.

Results: The vasodilatory effect of SNP significantly increased after SMF sinocarotid baroreceptor exposure ($MPPG_{beforeSMF}$: 2.57 ± 0.81 V vs. $MPPG_{afterSMF}$: 7.82 ± 1.61 V, $p < 0.0001$) and positively correlated with significant increase in BRS ($r = 0.51$, $p = 0.01$).

Conclusions: Baroreflex-mediated increment in vessel sensitivity to NO is suggested to be a new mechanism in baroreflex physiology with potential implementation in cardiovascular conditions where NO deficit and autonomic dysfunction increase the risk of morbidity and mortality substantially.

Introduction

Arterial baroreceptors play a key role in the operation of cardiovascular functions and in the reflex regulation of blood pressure, located in the carotid sinuses and aortic arch, normally respond to stretch by initiating reflexes that promote parasympathetic and restrain sympathetic activities, significantly modifying heart rate, peripheral vasoconstriction and cardiac output. These powerful negative feedback responses result in hemodynamic stability protecting vessels and the heart from extensive blood pressure fluctuations and arrhythmias, adjusting peripheral tissue perfusion to meet the optimal metabolic demands (Chapleau and Abboud, 2004).

However, arterial baroreflex direct regulatory effect on microcirculatory blood flow is less explored. The microcirculatory network of the skin, like other body tissues, continuously exhibits vasomotion, rhythmic changes in diameter and flow reflecting central baroreflex-mediated neurogenic adjustments (Bernardi et al., 1997; Szili-Torok et al., 2002) and local intrinsic myogenic activity modulated in addition by a variety of endothelial vasoactive compounds including nitric oxide (NO) (Harrison and Cai, 2003; Napoli et al., 2006). NO is a highly reactive signaling molecule that has pivotal role in a spectrum of fundamental intracellular events that lead to vasorelaxation, inhibition of platelet aggregation, endothelial regeneration, suppression of abnormal proliferation of vascular smooth muscle cells and cardiovascular remodeling (Harrison and Cai, 2003). The clinical importance of the NO is so large that this gas is suggested to be the most important affecting almost every aspect of cardiovascular physiology extended to metabolic disorders, insulin resistance and atherosclerosis (Harrison and Cai, 2003; Kim et al., 2006; Napoli et al., 2006). A mounting evidence indicates that NO has an outstanding modulatory effect on sympathetic and parasympathetic control of

Abbreviations: BRS, arterial baroreflex sensitivity; BRS_{Ni}, arterial baroreflex sensitivity tested by nitroprusside; BRS_{Ph}, arterial baroreflex sensitivity tested by phenylephrine; HR, heart rate; MAP, mean femoral artery blood pressure; MPPG, microphotoelectric plethysmography; NO, nitric oxide; REC, rabbit ear chamber; SMF, static magnetic field.

* Corresponding author at: Visnova 6, Presov 08001, Slovak Republic.
E-mail address: gmitrovj@yahoo.com.

[1] Institution where the experimental part of the study was made.
[2] Current affiliation.
[3] Current affiliation.

http://dx.doi.org/10.1016/j.mvr.2014.11.004
0026-2862/

cardiovascular function at all levels of the autonomic regulation including central arterial baroreflex pathways (Schultz, 2009). However, no studies demonstrated arterial baroreflex feedback coupling with NO-mediated vasodilation which may have a particular clinical importance.

Previously we found in rabbits that a 350 mT static magnetic field (SMF) when locally applied to sinocarotid triangles enhanced microvascular dilation and blood flow in the visualized cutaneous vasculature of the ear and that this effect is significantly correlated with an increase in baroreflex sensitivity (Gmitrov, 2007). To test the hypothesis that the underlying mechanism lies in baroreflex modulatory effect on NO-dependent vasodilation the magnitude of the cutaneous vasodilator response to sodium nitroprusside, a spontaneous NO donor (Schröder, 2006), was determined in relation to an increase in baroreflex sensitivity generated by carotid baroreceptor magnetic activation.

Methods

Animals

Sixteen experiments were performed in 11 adult males of Japanese domestic white rabbits (*Oryctolagus cuniculus domesticus*), weighing 3.5–4.2 kg (Nihon Ikagaku Shizai, Tokyo, Japan). Eight runs with the sinocarotid baroreceptors exposed to a SMF and 8 controls with sham magnet exposure. The time when these experiments were performed was chosen randomly from 10 a.m. to noon (local time). The rabbits were given free access to laboratory chow (RM4; Funabashi Nohjoh, Chiba, Japan) and tap water. They were housed in a room with a light/dark cycle of 12 h, with a temperature of 22.5 ± 0.5 °C and a relative humidity of 50 ± 5%. All the procedures conform with the “Guide for the Care and Use of Laboratory Animals” published by the US National Institute of Health (NIH publication no. 85-23, revised 1996), and with the guidelines of the Japanese national ethics committee. A polyvinyl catheter was introduced into the femoral artery to make hemodynamic recordings of mean femoral artery blood pressure (MAP) and heart rate (HR) resulting from blood pressure fluctuations. Rabbits were anesthetized for the operation with sodium pentobarbital (Nembutal Sodium Solution; Abbott Laboratories, Co., Ltd., Chicago, IL, USA), 30 mg/kg, intravenous (iv), supplemented later as needed to maintain deep anesthesia. The catheter was fed subcutaneously into the back of the animals, filled with 0.9% NaCl solution containing heparin 2000 U ml/l and plugged with a polyvinyl plug. Catheters were flushed daily. An average of 1–2 experiments was performed on each rabbit. One experiment was performed per day per animal, the first commencing 24 h after catheterization alternating sham and SMF experimental runs. The rabbits were not sacrificed at the end of the experiments.

Measurement of skin microcirculatory blood flow

Intravital microscopy using a rabbit ear chamber (REC) and microphotoelectric plethysmography (MPPG) was used to measure microcirculatory blood flow in the skin. A REC is a transparent disk (diameter: 6.4 mm) of acrylic resin housing fully ingrown subcutaneous tissue with a microvascular net after around 6–8 weeks following the installation, which is the subject of research (Fig. 1). MPPG is a simple, noninvasive technique used to analyze relative changes in peripheral circulation and is a modification of photo (electric) plethysmography. MPPG was developed to monitor temporal changes in microvascular blood flow in various cutaneous tissues. Microscopic images of the intravital microcirculation are displayed on a video monitor, and light absorbed by hemoglobin in the transparent microvascular net within the REC is

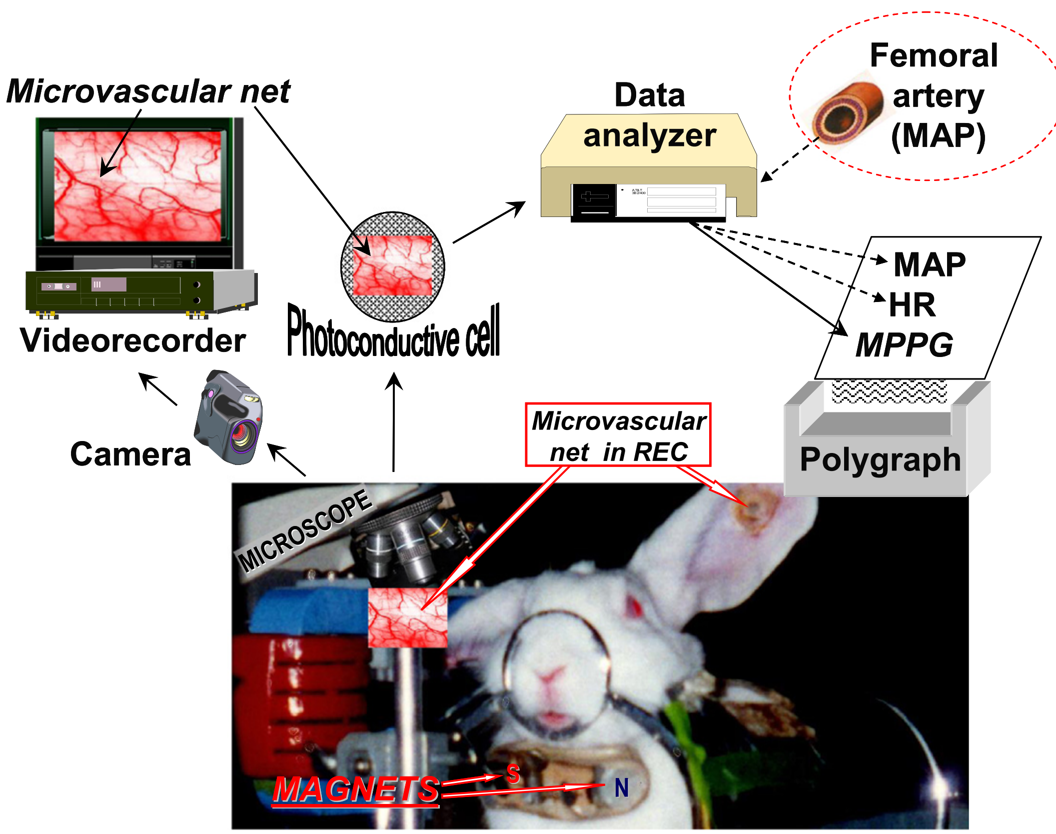

Fig. 1. Experimental set-up to explore static magnetic field effect on baroreflex-mediated macro- and microcirculatory response. The right ear including a rabbit's ear chamber (REC) with ingrown skin microvascular networks was positioned under the objective of the microscope for simultaneous intravital observation of the microcirculation and measurement of the microcirculatory blood flow using microphotoelectric plethysmography (MPPG). Another REC is visible on the left free ear. Simultaneously with microcirculatory blood flow femoral artery mean arterial blood pressure (MAP) and heart rate (HR) were measured.