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Vascular reactivity in human arteries: from experimental study to clinical application

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Introduction

The main function of vascular smooth muscle (VSM) is the regulation of blood pressure. Blood pressure is dependent upon the driving force of cardiac output and on the myogenic VSM tone through changes in the contraction–relaxation cycle of smooth muscle [1]. Differences in vascular tissues from one region to another, the presence of large conductance vessels, capacitance vessels, and resistant arteries, and differing contributions to the regulation of blood pressure result in the velocity of blood transport varying from one region to another [1].

Understanding of the physiology and pharmacology of vascular tissue has changed dramatically during the past few years. The endothelium is now recognized to elaborate various vasoactive factors and to play a critical part in the regulation of vascular tone. The discovery by Furchgott and Zawadzski [2] of endothelium-derived relaxing factor (EDRF) placed the endothelium at the center of the physiology and pathophysiology of the vascular tree. Prostacyclin is a metabolite of arachidonic acid that is produced (along with other prostaglandins and thromboxanes) by the two isoforms of cyclooxygenase (COX) enzymes: COX-1 and COX-2 [3, 4]. Expression of endothelium-derived hyperpolarizing factor (EDHF) activates K^+ channels in the plasma membrane of VSM and, by hyperpolarizing the plasma membrane, inhibits its depolarization [5, 6].

There has been a large increase in interest in the molecular mechanisms involved in chemomechanical transduction and the regulatory elements determining contraction and relaxation. This article introduces the measurement systems of vascular reactivity and the main results involved in the contraction–relaxation mechanisms in human VSM tissues.

Measurements of vascular activities

Ethical approval of the study protocol

The study protocol was approved by the Ethics Committee of Kagoshima and Miyazaki University Hospital, Miyazaki, Japan.

Samples

Radial arteries (RAs), gastroepiploic arteries (GEAs), and internal mammary arteries (IMAs) were harvested from patients undergoing gastrectomy or coronary artery bypass

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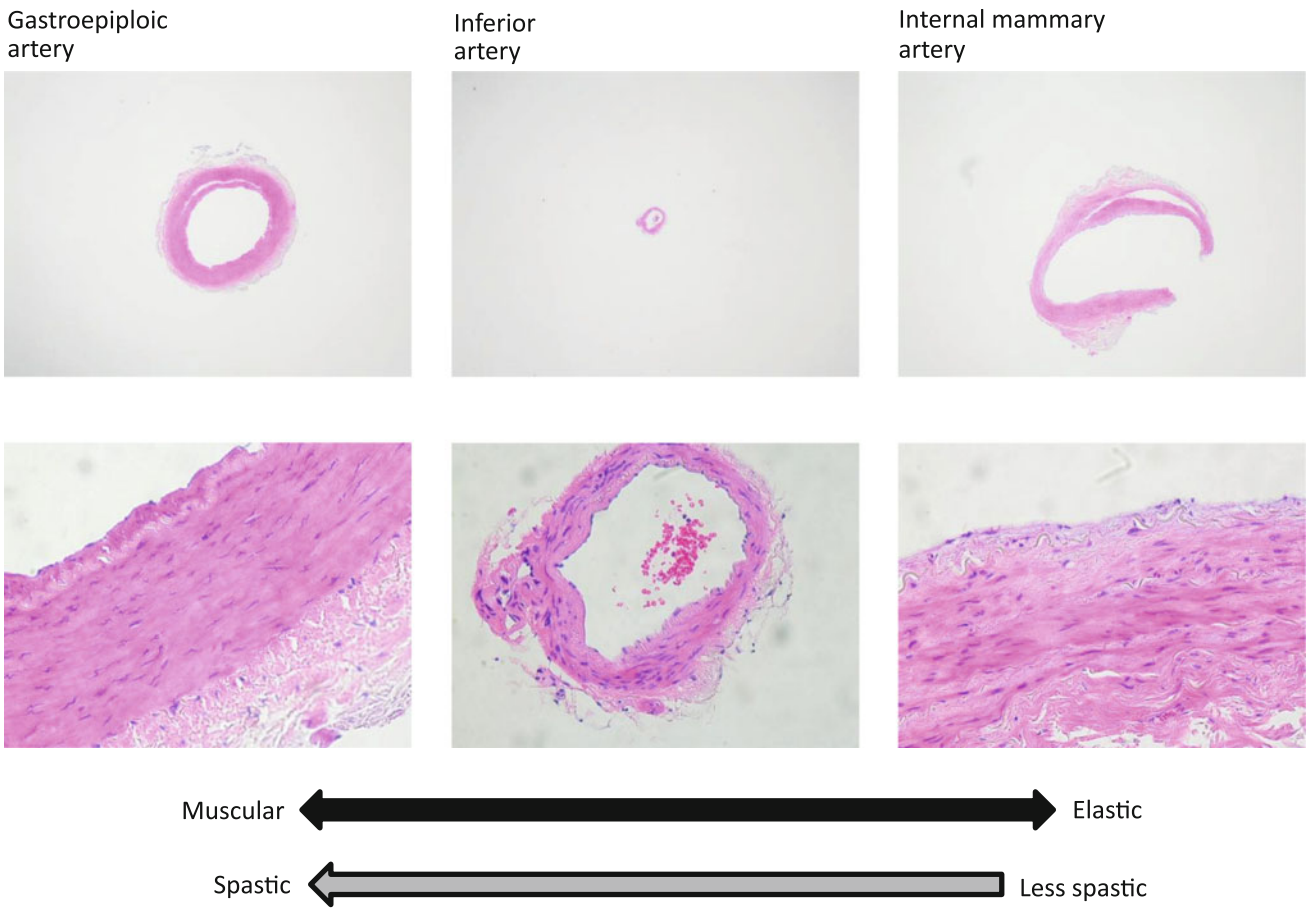

Fig. 1 Samples. On the basis of experimental studies on vasoreactivity, together with physiological and embryological considerations, arteries are functionally classified from muscular to elastic

surgery [7–10]. The discarded distal end of each artery was immediately stored in oxygenated Krebs buffer maintained at 4°C. Within 2 h of resection, the distal portion of each artery was isolated from the sample in a dissecting chamber filled with Krebs solution. Fat and connective tissue were carefully removed under a binocular microscope, and one to three vascular rings were prepared from each artery for tension recording. On the basis of experimental studies on vasoreactivity, together with physiological and embryological considerations, arteries are functionally classified from muscular to elastic arteries [11]. In general, muscular arteries are more likely to spasm than elastic arteries because of their higher contractility (Fig. 1).

Organ-chamber experiments

The mechanical activity of each ring was measured using a strain gauge (UL-100GR; Minebea, Tokyo, Japan) in a tissue bath (volume, 1.0 ml) filled with Krebs solution continuously bubbled with 95% O_2 and 5% CO_2 (Fig. 2). The temperature of the solution was maintained at 37°C. The resting tension was set at 20 mN, a value shown by the length–tension relationship to allow a maximal active tension to be induced by norepinephrine (NE, 10^{-6} mol/l). During a 2-h equilibrium period, Krebs solution was continuously infused at 2 ml/min by a Perista pump (SJ-1211; ATTO, Tokyo, Japan) from one end of the bath and simultaneously aspirated from the other. During the experiment, the infusion rate was increased to 10 ml/min

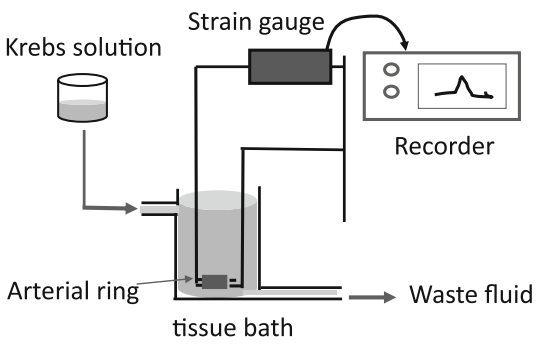

Fig. 2 Organ-chamber experiment

so that the bath solution was exchanged quickly for new solution. In an initial series of experiments, control contractile responses were induced by adding the α-adrenergic agonist NE (10^{-6} mol/l) to the Krebs solution for 7 min every 30 min. Preliminary experiments showed that the responses reached maximal levels within 30 s after application of NE, and that a 23-min interval was sufficient for the tension to return to the control level [12–14].

Perfusion system in the vessel bath

Vascular reactions were measured in blood vessels with a diameter <200 μm using a vessel perfusion system (Fig. 3). Blood vessels were transferred to a water-jacketed vessel bath containing HEPES solution at 37°C and cannulated with glass pipettes (outer diameter of tip, ≈75–100 μm). The vessel bath was then transferred to the stage of an inverted microscope (Diaphot; Nikon, Tokyo, Japan). The intravascular system was closed, and transmural pressure incrementally increased to 40 mmHg with a pressure servo-system. A micrometer attached to one of the cannulae was used to gently elongate the blood vessel to remove redundancy in the vessel walls. The vessel was allowed to equilibrate for 60 min. During this initial period, the blood vessel was checked several times for leaks (i.e., a drop in pressure and diameter when the servo-system was turned off). Blood vessels that developed significant leaks after pressurization were not studied further. We developed a video image analysis system that permitted the internal diameter (ID) and external diameter (OD) of the blood vessel to be continuously monitored and displayed in real time. The ID and OD values obtained for each video line were averaged. These averaged ID and OD values were displayed on a computer video display terminal and recorded on computer hard-disk data files in real time. Data files were analyzed using computer playback programs in which maximum, minimum, and average ID and OD values were extracted from user-defined intervals [15].

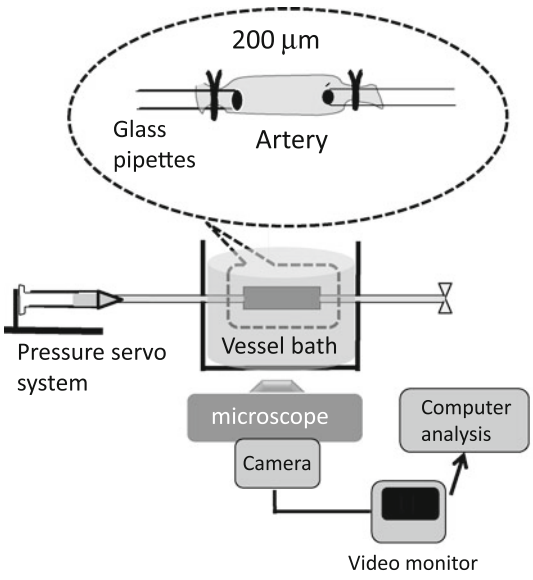

Fig. 3 Perfusion system in the vessel bath

Hormonal control in VSM

Many circulating hormones have an effect on vascular tone that is mediated via multiple receptors. The effects of these hormones on vascular tone vary with species. Our experimental models using human VSM may reflect the physiological and pharmacological vascular reactivity in human bodies more exactly than studies using animal VSM.

NE released from sympathetic nerves and epinephrine secreted by the adrenal medulla act on multiple adrenoceptor subtypes. This hormone is a potent agonist at α-receptors and induces vasoconstriction. Epinephrine is an α- and β-adrenergic agonist; it is one of the most potent vasopressors and a powerful cardiac stimulant. In addition, epinephrine enhances release of NE from sympathetic neurons. Dopamine is the immediate metabolic precursor of NE and epinephrine. It is synthesized from tyrosine by cytoplasmic enzymes at a sympathetic neuroeffector junction. At low concentrations, dopamine activates adenylyl cyclase to raise the intracellular concentration of cyclic adenosine monophosphate (cAMP) through stimulation of D_1 receptors, and thus mediates vasodilation [16]. At higher concentrations, dopamine exerts a positive inotropic effect on the myocardium, causing activation via β_1-adrenergic receptors [16]. At high concentrations, it activates vascular α_1-adrenergic receptors, leading to vasoconstriction [16]. Vasopressin (AVP) is a circulating neurohormone and a potent systemic vasoconstrictor. Most of the vascular actions of AVP are mediated by activation of V_1 receptors, which leads to activation of protein kinase C (PKC) and production of inositol triphosphate (IP_3) and diacyl glycerol (DAG), as well as mobilization of intracellular calcium [17]. In contrast, the intracellular signal for the V_2 receptor (which is responsible for altering reabsorption of water from the collecting duct in the kidney) is via activation of adenylate cyclase [18]. AVP has recently been used to treat hypotensive crises to maintain blood pressure. Hypotension has been reversed, minimized, or prevented by AVP in patients with septic shock, hypovolemic shock, and refractory hypotension after cardiopulmonary bypass [19, 20]. We have reported that pharmacological manipulation of AVP can be beneficial with regard to improved physiological variables and short-term outcomes in these situations [21, 22].

Pharmacological and clinical use of vasodilators

Directly or indirectly, blood vessels are the source of many serious diseases that affect millions of people. Vasodilator agents exert their effects on tissues by acting on one or more processes in the VSM contraction–relaxation cycle.

Nitroglycerin and isosorbide dinitrate act on the VSM of venous capacitance vessels to produce pooling of peripheral blood, resulting in a reduction in venous return and a decrease in cardiac wall tension. As a consequence, organic nitrates reduce myocardial oxygen demand and thus relieve angina pectoris. At higher doses, organic nitrites also relax arterial smooth muscle. This effect is a useful way to increase oxygen delivery and relieve spasm in coronary arteries. We have reported on the sensitivities to isosorbide dinitrate and to diltiazem in ITA and GEA grafts for coronary artery bypass grafting surgery. We suggested that vasodilators such as nitrates may increase the safety of arterial revascularization by reducing the risk of graft-hypoperfusion syndrome [9].

cAMP produced by the activation of adenylate cyclase activates PKA, which has multiple actions, including phosphorylation of myosin light-chain kinase, leading to reduced efficacy of contraction [23]. Inhibitors of phosphodiesterase (PDE) also inhibit cAMP phosphodiesterase and increase cAMP concentrations in smooth muscle. In our study, milrinone, olprinone, and amrinone exerted concentration-dependent relaxations in NE-constricted human arterial rings [24]. However, we found that relaxation responses to these phosphodiesterase-3 (PDE3) inhibitors differed considerably among human arteries located in different parts of the body [24].

Dexmedetomidine (DEX) is a highly selective α_2-adrenergic agonist. DEX is used for its sedative and analgesic actions. DEX use is associated with a reduction in the dose requirement for anesthetic and analgesic drugs in the perioperative period, and minimal cardiovascular side effects have been reported [25]. DEX use has been said to be associated with modest decreases in blood pressure and heart rate in some studies, whereas other reports have suggested that intravenous administration of high doses of DEX can result in acute increases in arterial pressure and peripheral vascular resistance [25]. The range of cardiovascular effects reported to be exerted by DEX may reflect the physiological consequences of activation of peripheral or central α_2-adrenergic receptors. We have demonstrated that DEX has little direct effect on the smooth muscle in human resistance arteries at the steady-state plasma concentrations normally achieved in clinical practice (i.e., $<10^{-7}$ M), but that higher concentrations of DEX have dual α_2-agonist and α_1-adrenergic antagonist actions [26].

Volatile anesthetics are also potent vasodilators. Halothane, isoflurane, and sevoflurane attenuate the increased intracellular concentration of calcium ($[Ca^{2+}]_i$) and contraction induced by high concentrations of K^+ and NE in the rat aorta [27]. There are five main mechanisms of vascular relaxant effects mediated by volatile anesthetics. First, there is inhibition of Ca^{2+} influx by suppression of voltage-dependent Ca^{2+} channels. Second, increases in cAMP or cyclic guanosine monophosphate (cGMP) are noted. Third, there is inhibition of receptor-mediated signal transduction, resulting in the inhibition of all the effects of agonists, the release, influx, and sensitization of Ca^{2+}. Fourth is the decrease in Ca^{2+} stores in the sarcoplasmic reticulum. The final mechanism is induction hyperpolarization in VSM. We have reported that halothane induced Ca^{2+}-desensitizing effects without affecting myosin light-chain (MLC) phosphatase activity in high K^+-contracted small mesenteric arteries in rats [15].

Summary

The principal function of VSM cells in mature animals is contraction. The endothelium is now recognized to elaborate various vasoactive factors and to play a critical part in regulation of vascular tone. Many circulating mediators and hormones have effects on vascular tone that are mediated via multiple receptors. Vasoactive agents also exert their effects on tissues by acting on one or more processes in the contraction–relaxation cycle in VSM. In humans, systemic, pulmonary, and various organ circulation(s) are maintained by an intricate and complex cardiovascular system. We expect future studies to clarify the sophisticated but complex mechanisms of VSM in humans.

References

1. Kuriyama H, Kitamura K, Nabata H. Pharmacological and physiological significance of ion channels and factors that modulate them in vascular tissues. Pharmacol Rev. 1995;47:387–573.
2. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature (Lond). 1980;288:373–6.
3. Mitchell JA, Larkin S, Williams TJ. Cyclooxygenase-2: regulation and relevance in inflammation. Biochem Pharmacol. 1995;50:1535–42.
4. Wu KK. Inducible cyclooxygenase and nitric oxide synthase. Adv Pharmacol. 1995;33:179–207.
5. Feletou M, Vanhoutte PM. Endothelium-dependent hyperpolarization of canine coronary smooth muscle. Br J Pharmacol. 1988;93:515–24.
6. Chen GF, Suzuki H. Calcium dependency of the endothelium-dependent hyperpolarization in smooth muscle cells of the rabbit carotid artery. J Physiol. 1990;421:521–34.
7. Tsuneyoshi I, Kanmura Y, Yoshimura N. Lipoteichoic acid from *Staphylococcus aureus* depresses contractile function of human arteries in vitro due to the induction of nitric oxide synthase. Anesth Analg. 1996;82:948–53.

8. Hidaka T, Tsuneyoshi I, Boyle WA, Onomoto M, Yonetani S, Hamasaki J, Katai R, Kanmura Y. Marked synergism between vasopressin and angiotensin II in a human isolated artery. Crit Care Med. 2005;33:2613–20.
9. Matsumoto K, Tsuneyoshi I, Iguro Y, Kinjo T, Yotsumoto G, Ueno M, Kanmura Y, Sakata R. Effects of ultrasonic skeletonization on internal thoracic and gastroepiploic arteries for coronary artery bypass grafting. Eur J Cardiothorac Surg. 2006;30: 592–6.
10. Moriyama T, Tsuneyoshi I, Kanmura Y. Effects of a novel benzodiazepine derivative, JM-1232(–), on human gastroepiploic artery in vitro. J Cardiothorac Vasc Anesth. 2010;25:72–7.
11. He GW. Arterial grafts for coronary artery bypass grafting: biological characteristics, functional classification, and clinical choice. Ann Thorac Surg. 1999;67:277–84.
12. Tsuneyoshi I, Kanmura Y, Yoshimura N. Methylprednisolone inhibits endotoxin-induced depression of contractile function in human arteries in vitro. Br J Anaesth. 1996;76:251–7.
13. Tsuneyoshi H, Minami K, Nakayama S, Sakaguchi G. A case report of gastric perforation after coronary artery bypass grafting with right gastroepiploic artery. Jpn J Thorac Cardiovasc Surg. 1998;46:719–23.
14. Hamu Y, Kanmura Y, Tsuneyoshi I, Yoshimura N. The effects of vasopressin on endotoxin-induced attenuation of contractile responses in human gastroepiploic arteries in vitro. Anesth Analg. 1999;88:542–8.
15. Tsuneyoshi I, Zhang D, Boyle WA. Ca^{2+}- and myosin phosphorylation-independent relaxation by halothane in K^{+}-depolarized rat mesenteric arteries. Anesthesiology. 2003;99:656–65.
16. Katai R, Tsuneyoshi I, Hamasaki J, Onomoto M, Suehiro S, Sakata R, Kanmura Y. The variable effects of dopamine among human isolated arteries commonly used for coronary bypass grafts. Anesth Analg. 2004;98:915–20.
17. Nemenoff RA. Vasopressin signaling pathways in vascular smooth muscle. Front Biosci. 1998;3:94–207.
18. Vallotton MB. The multiple faces of the vasopressin receptors. Mol Cell Endocrinol. 1991;378:C73–6.
19. Landry DW, Levin HR, Gallant EM, Ashton RC Jr, Seo S, D'Alessandro D, Oz MC, Oliver JA. Vasopressin deficiency contributes to the vasodilation of septic shock. Circulation. 1997; 95:1122–5.
20. Dyke PC 2nd, Tobias JD. Vasopressin: applications in clinical practice. J Intensive Care Med. 2004;19:220–8.
21. Tsuneyoshi I, Yamada H, Kakihana Y, Nakamura M, Nakano Y, Boyle WA. Hemodynamic and metabolic effects of low-dose vasopressin infusions in vasodilatory septic shock. Crit Care Med. 2001;29:487–93.
22. Tsuneyoshi I, Onomoto M, Yonetani A, Kanmura Y. Low-dose vasopressin infusion in patients with severe vasodilatory hypotension after prolonged hemorrhage during general anesthesia. J Anesth. 2005;19:170–3.
23. Kamm KE, Stull JT. Regulation of smooth muscle contractile elements by second messengers. Annu Rev Physiol. 1989;51:299–313.
24. Onomoto M, Tsuneyoshi I, Yonetani A, Suehiro S, Matsumoto K, Sakata R, Kanmura Y. Differential pharmacologic sensitivities of phosphodiesterase-3 inhibitors among human isolated gastroepiploic, internal mammary, and radial arteries. Anesth Analg. 2005; 101:950–6.
25. Venn RM, Bryant A, Hall GM, Grounds RM. Effects of dexmedetomidine on adrenocortical function, and the cardiovascular, endocrine and inflammatory responses in post-operative patients needing sedation in the intensive care unit. Br J Anaesth. 2001; 86:650–6.
26. Hamasaki J, Tsuneyoshi I, Katai R, Hidaka T, Boyle WA, Kanmura Y. Dual alpha(2)-adrenergic agonist and alpha(1)-adrenergic antagonist actions of dexmedetomidine on human isolated endothelium-denuded gastroepiploic arteries. Anesth Analg. 2002;94:1434–40.
27. Tsuchida H, Namba H, Yamakage M, Fujita S, Notsuki E, Namiki A. Effects of halothane and isoflurane on cytosolic calcium ion concentrations and contraction in the vascular smooth muscle of the rat aorta. Anesthesiology. 1993;78:531–40.