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Effects of hypothermia on the mechanical behavior of rabbit femoral arteries

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ABSTRACT

The need to better understand the effects of non-physiological temperatures on arterial wall behavior is becoming more important because of the increased clinical use of hypothermal and hyperthermal treatments. The present study was performed to examine the effects of temperature on the mechanical behavior of femoral arteries excised from rabbits. Among 17, 27, 37, and 42 °C, there were no significant differences in their diameter, stiffness, and P-D relations under the physiologically normal, control condition, although the arterial diameter was slightly smaller at 42 °C than at the other three temperatures. Under the SMC-activated condition, on the other hand, we observed significant effects of temperature. For example, arterial diameter at 100 mmHg was significantly larger at 17 and 27 °C and smaller at 42 °C compared with 37 °C. Arterial stiffness at 40 mmHg were significantly smaller at 17 and larger at 42 °C than at 37 °C, while the stiffness at 160 mmHg were significantly larger at 17 °C than at 37 °C; however, there were no significant differences in the stiffness at 100 mmHg among the four temperatures. Arterial contraction induced by SMC-activation was significantly different between 37 °C and the other three temperatures; both of the maximum diameter response and diameter response at 100 mmHg were significantly smaller at 17 and 27 °C and larger at 42 °C compared with 37 °C. These results indicate that in the hypothermic range under the control condition, arteries are dilated when cooled, while they are constricted when heated. On the other hand, arterial response to SMC activation is significantly affected by the alterations of temperature.

These results indicate that in the hypothermic range under the control condition, arteries are dilated when cooled, while they are constricted when heated. On the other hand, arterial response to the activation of vascular smooth muscle cells is significantly affected by the alteration of temperature. As the mechanical behavior of arterial wall is significantly influenced by temperature, this should be considered in the development of therapeutic methods and techniques for cardiovascular diseases.

1. Introduction

The need to better understand the effects of non-physiological temperatures on arterial wall behavior is becoming more important because of the increased clinical use of hypothermal and hyperthermal treatments, including localized heating and cooling, and cryotherapies. For example, hot balloon-based and cryoballoon-based ablation catheters are rather widely used for the treatment of atrial fibrillation (Roten et al., 2012; Metzner et al., 2015). Many cardiac surgical procedures and organ preservation are commonly performed under conditions of hypothermia (Guinea et al., 2005; Herrera et al., 2000). Mild hypothermia decreases inflammatory responses in both brain inflammation and stroke (Deng et al., 2003), which is recognized as a useful therapeutic approach to reducing cerebral infarction (Barone et al., 1997). On the other hand, moderate hyperthermia is reported to be effective in suppressing the proliferation of vascular smooth muscle cells (SMCs) that causes one of the most critical problems, i.e. restenosis, after percutaneous transmural coronary angioplasty (PTCA) (Orihara et al., 2002). Similarly, Mueed et al. (2011) observed a significant attenuation of arterial contractile response, most probably due to the loss of vascular SMCs, after moderate heat treatment, and suggested that a moderate heat therapy is useful for the reduction of vasospasm after the anastomotic treatment of coronary arterial stenosis.

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Regarding basic studies, Kang et al. (1995) performed in vitro biomechanical experiments on passive bovine coronary arteries at different temperatures having thermal balloon angioplasty into mind, and observed that the mechanical behavior did not change much between 21 and 60 °C, although vascular stiffening and shrinkage seemed to occur at 70 and 80 °C. On the other hand, significant attenuations of contractile response to KCL were observed in vitro in human radial arteries heated at 55 and 60 °C (Mueed et al., 2011). With respect to the effects of hypothermia, Guinea et al. (2005, 2008) studied passive pressure (P)-diameter (D) relations of the human carotid artery and the rabbit thoracic aorta between 17 and 42 °C. They observed no significant effects of temperature changes on the relations in the physiological pressure range, but found shrinkage (diameter reduction) below 10–20 mmHg when heated. Similarly, Dobrin and Canfield (1977) reported that there were no significant differences in passive P-D relations in the physiological pressure range between 33 and 39 °C in the canine carotid artery, although contractile responses to norepinephrine declined with decreased temperature. On the other hand, Herrera et al. (2000, 2002) obtained the results showing paradoxical effects of temperature on arterial diameter; in the range of 8 to 37 °C, the decrease of temperature induced relaxation in rat aortas while contraction in pig renal arteries.

A detailed understanding of the fundamental thermomechanics of arterial tissues should offer clues to the development of thermal therapeutic techniques and also provide further insight into the basic biophysics and biomechanics of biological tissues. Humphrey (2003) reviewed the continuum thermomechanics of biological tissues and cells, and pointed out that there are not many fundamental studies on the effects of heating and cooling on the mechanical behavior of arterial wall. As a whole, there seems to be little temperature-related alteration in the passive mechanical properties of arterial wall below and near body temperature, although shrinkage (contraction) occurs with increase in temperatures below 40 °C. Contractile response induced by SMC-activation is maximal around body temperature and decreases with decrease in temperature. As far as the authors know, however, there is a paucity of precise and detailed studies on the effects of temperature on the P-D relations and stress-strain data of vascular wall; the results obtained so far are not conclusive. In the present study, therefore, we performed precise biomechanical studies on the effects of hypothermia on the arterial diameter, P-D relation, wall stiffness, and contractile response to SMC activation, using the rabbit femoral artery.

2. Materials and methods

2.1. Materials

We used seven female Japanese white rabbits having the body weight of approximately 3 kg and the age of 11 to 14 weeks. Each animal was anesthetized by the injection of pentobarbital sodium (30 to 50 mg/kg body weight) via the auricular vein, and the left and right femoral arteries were exposed. After the surface of each artery was marked with India ink at 5 mm intervals to identify the *in situ* length, a 30 mm long arterial segment was excised and stored in a Krebs–Ringer bicarbonate buffered solution at 4 °C until P-D testing. Finally, all the animals were euthanized with an overdose injection of sodium pentobarbital. We selected the femoral artery as a model for the present study, because it is more abundant in SMCs compared with more proximal conduit aortas and arteries, and therefore it is useful also for the study of vascular contractile responses.

2.2. Biomechanical studies

Biomechanical experiments were performed in a fashion similar to those reported previously (Naiki et al., 2012). Briefly, each arterial tubular specimen was mounted onto the experimental apparatus designed for the measurement of intraluminal pressure (P) - external diameter (D) data, and stretched to its in situ length referring to the interval between the above-mentioned marks attached on the specimen surface. The specimen was immersed in a test bath containing Krebs-Ringer solution kept at 37 °C, and aerated with a wet mixture gas of 95% O_2 and 5% CO_2. The specimen lumen was also filled with the same solution of 37 °C. The intraluminal pressure was measured with a pressure transducer (Statham P23XL, Viggo-Spectramed, FL, USA), while the outer diameter of the specimen was done with a video dimension analyzer (Percept Scope C8840, Hamamatsu Photonics, Hamamatsu, Japan) combined with a CCD camera (C5405-50, Hamamatsu Photonics, Hamamatsu, Japan). These data were digitized and recorded on a thermal array coder (WR300, Graphtec, Yokohama, Japan) at the sampling rate of 5 Hz. The accuracies of the measurements of pressure and diameter were ± 1.6 mmHg and ± 9.3 μm, respectively.

Each artery was first inflated and deflated several times between the internal pressures of 0 and 200 mmHg at the rate of 3 mmHg/s, for preconditioning until a reproducible P-D curve was obtained. The average of the inflation and deflation data obtained from the last stable loop was used as the data for “Control condition”. The internal pressure was then elevated up to 100 mmHg and maintained at the level. Subsequently, norepinephrine was added to the Krebs-Ringer solution inside the test bath to the concentration of 10^{-5} M; our preliminary experiments indicated that the maximal and stable contraction is induced with this dosage. After confirming the stable contraction, the internal pressure was reduced to 0 mmHg, and then elevated to 200 mmHg. The data obtained during this inflation process was used as the P-D data for “Activated condition”. Then, the specimen, perfusion lines, and test bath were rinsed with Krebs-Ringer solution three times. After changing the solution temperature to 17 °C, the above-stated P-D testing was repeated for the same specimen. These procedures were repeated after sequentially changing the solution temperature to 27 and 42 °C.

The temperature of 42 °C was selected, because it is just below the temperature at which biological tissues and cells start receiving heat damage (Emami et al., 1981; Birch et al., 1997). Because heart surgeries are ordinarily performed in the condition of hypothermia, for example at 26 to 31 °C (Guinea et al., 2005), we selected 27 °C as one of the test temperatures. The temperature of 17 °C was selected from a scientific interest. In our preliminary experiments, moreover, we confirmed that the order of temperature changes among 17, 27, 37, and 42 °C induces no significant effects on the results, and also that the results obtained at 37 °C after changing temperature from 42 °C were similar to the initial results obtained at 37 °C prior to changing temperature.

These series of P-D experiments at the four different temperatures were completed within 12 hours after the start of testing on each specimen and within 24 hours after its excision from the animal body.

2.3. Data analysis

Under the physiologically normal condition (control condition in the present study), the P-D relationship is J-shaped, and the relation in the physiological blood pressure range, say between 60 and 160 mmHg, is mathematically described by (Hayashi et al., 1980 and 2015):

$$\ln(P/Ps) = b(D/Ds-1), \quad (1)$$

where Ps is a standard pressure, for example 100 mmHg, and Ds is the external diameter at Ps. The coefficient, β, called stiffness parameter, represents the structural stiffness of vascular wall. As this parameter does not depend on pressure, it has been widely used for the quantitative evaluation of arterial stiffness not only in basic studies, but also in clinical medicine (Hayashi and Naiki, 2009; Hayashi et al., 2015). Although this logarithmic equation is applicable to P-D relations