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Asymmetric radial expansion and contraction of rat carotid artery observed using a high-resolution ultrasound imaging system

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ABSTRACT

The geometry of carotid artery bifurcation is of high clinical interest because it determines the characteristics of blood flow that is closely related to the formation and development of atherosclerotic plaque. However, information on the dynamic changes in the vessel wall of carotid artery bifurcation during a pulsatile cycle is limited. This pilot study investigated the cyclic changes in carotid artery geometry caused by blood flow pulsation in rats. A high-resolution ultrasound imaging system with a broadband scanhead centered at 40 MHz was used to obtain longitudinal images of the rat carotid artery. A high frame rate retrospective B-scan imaging technique based on the use of electrocardiogram to trigger signal acquisition was used to examine precisely the fast arterial wall motion. Two-dimensional geometry data obtained from nine rats showed that the rat carotid artery asymmetrically contracts and dilates during each cardiac cycle. Systolic/diastolic vessel diameters near the upstream and downstream regions from the bifurcation were 0.976 ± 0.011/0.825 ± 0.015 mm and 0.766 ± 0.015/0.650 ± 0.016 mm, respectively. Their posterior/anterior wall displacement ratios in the radial direction were 41.0 ± 14.9% and 2.9 ± 1.6%, respectively. These results indicate that in the vicinity of bifurcation, the carotid artery favorably expands to the anterior side during the systolic phase. This phenomenon was observed to be more prominent in the downstream region near the bifurcation. The cyclic variation pattern in wall movement varies depending on the measurement site, which shows different patterns at far upstream and downstream of the bifurcation. The asymmetric radial expansion and contraction of the rat carotid artery observed in this study may be useful in studying the hemodynamic etiology of cardiovascular diseases because the pulsatile changes in vessel geometry may affect the local hemodynamics that determines the spatial distribution of wall shear stress, one of important cardiovascular risk factors. Further systematic study is needed to clarify the effects of wall elasticity, branch angle and vessel diameter ratio on the asymmetric wall motion of carotid artery bifurcation.

1. Introduction

Stroke is the second most common cause of death and a leading cause of serious long-term disability in the world population [1–3]. Carotid atherosclerosis is a major cause of stroke and transient ischemic attack in the adult population [4,5] because atherosclerotic plaques are a major source of brain embolism [6]. Numerous studies have been conducted to understand the mechanisms of the formation and development of carotid stenosis because of its significant influence on neurological morbidity and mortality [7–10]. Local hemodynamic conditions, such as low and oscillatory wall shear stress (WSS), are now understood to be the primary etiological factors that are responsible for the formation of carotid stenosis [11,12]. Nowadays, many efforts are devoted to clarify the effect of bifurcation geometry on WSS distribution and to predict the likelihood of stenosis and the regions of its occurrence [9,12,13].

The formation of atherosclerotic plaques at the carotid bifurcation is known to begin preferentially at the posterior wall of the internal carotid artery (ICA) that supplies blood to the brain [11,14]. Severe stenosis provides an irregular surface prone to thrombus formation as well as reduces blood supply to the brain. In addition, when the plaque ruptures, atheroma tissue debris is released into the blood stream. If the thrombi and/or plaque debris occlude blood vessels of the brain, an ischemic stroke occurs at the affected area of the brain [15,16]. The development of atherosclerotic stenosis can be explained via biochemical and pathophysiological mechanisms at cellular and subcellular levels, such as the

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formation of foam cell and inflammatory responses, and the prevalence and predilection sites for carotid stenosis have been reported to be closely related with the spatial distribution of WSS in the carotid artery bifurcation [7,11,12,14,17–20].

Based on a generally accepted principle in hemodynamic etiology of carotid stenosis, the laminar flow of blood formed in the common carotid artery (CCA) turns into unstable flow characterized by the formation of a complex flow recirculation zone as the blood flow enters the carotid bulb (posterior wall of the ICA), whereas rapid laminar flow is present along the anterior wall of the ICA [13,14]. Flow recirculation is associated with low blood velocity, low WSS, and higher oscillatory shear index, which are favorable conditions for the formation of atherosclerotic plaques [11,12]. However, plaques do not always occur in the same place because the local hemodynamic properties in the area of arterial bifurcation vary depending on vessel geometry, such as bifurcation angle and the ratios of vessel diameter (daughter to mother and daughter to daughter) [9,12,21]. Thus, the individual differences in carotid geometry affect the location of plaque occurrence as well as the degree of atherosclerosis.

When the arterial wall is assumed to be rigid, the blood flow structure in arteries is determined by their fixed geometry that remains constant during a cardiac cycle. The arterial vessel, however, is an elastic tissue that reversibly transforms in response to external or internal pressure. Thus, pulsation of blood flow causes cyclic changes in the cross-sectional area of the artery. Arterial wall dynamics is of particular interest because it is related to wall elasticity and WSS that are associated with pathologic mechanisms for cardiovascular diseases. In computational predictions of WSS of arteries, accurately simulating wall thickness, vessel geometry, and wall distensibility is necessary. However, because wall elasticity and thickness are not homogeneous, and the solidity of the surrounding tissues varies depending on the location of the vessel wall [22,23], the vessel cross-section may show asymmetric variations during a cardiac cycle, which are considered to be more complicated in the region of arterial bifurcation, stenosis and aneurysm than those in the normal straight artery. Until now, most of computational simulation studies have been conducted on the basis of simplified models that neglect vessel wall motion [24–26], except for some studies carried out considering the wall motion and its asymmetric features in limited conditions [23,27]. One of the main reasons that made the research in this field difficult was the lack of *in vivo* information on arterial wall dynamics. Although, many experimental studies on the cyclic variations of the vessel wall movement of the carotid artery were performed using ultrasound and magnetic resonance imaging techniques, most studies mainly focused on measuring the changes in lumen diameter [28], area [29], and longitudinal wall motion [30–34] in the CCA, but the directivity and asymmetry of radial wall motion, especially near the carotid artery bifurcation, have not been investigated in detail. This may be because the pathophysiological significance of the information on the directivity of radial movement of the carotid artery wall has been overlooked, while the diameter change has been used as an index of arterial stiffness [35] and longitudinal displacement was also suggested as an important marker of cardiovascular risk [30].

To investigate the characteristics of arterial wall motion and geometry, high-frequency ultrasound (HFUS) (>20 MHz) imaging using small animal models, such as rats and mice, has been applied [36–40]. The small animal models for cardiovascular imaging are increasingly popular because HFUS systems have recently become commercially available and their spatial and temporal resolutions are high enough to image submillimeter-sized blood vessels. However, most of the studies were performed in non-bifurcated regions of arteries, such as common carotid artery and aorta, thus the wall motion and geometry change of carotid artery bifurcation have not been investigated in detail.

In the present study, the pulsatile variations of arterial movement in the vicinity of rat carotid artery bifurcation were investigated using a high-resolution ultrasound imaging system. Analysis of the experimental data was performed mainly focusing on investigating the arterial wall displacement in the radial direction. The changes in the bifurcation geometry, vessel diameter, and regional variations in wall expansion parameters at systole and diastole were investigated using semi-automatic image analysis methods.

2. Materials and methods

2.1. Animal experiments

Nine male Sprague–Dawley rats weighing 297.3 ± 44.9 g (7–10 weeks old) were anesthetized with isoflurane via a vaporizer and placed in a supine position on a heated stage. A physiological monitoring unit (THM 100, Indus Instruments, Houston, TX, USA) was connected to the imaging stage for monitoring rectal temperature, heart rate, and electrocardiogram (ECG). The fur on the left side of the neck was removed using thioglycolate depilatory cream (Veet, Reckith Benckiser Inc., Toronto, ON, Canada) to prevent air from being trapped between the fur and ultrasound coupling gel. All procedures performed on animals were approved by the Animal Care and Use Committee of Jeju National University (Jeju, South Korea) to ensure that they were appropriate and humane.

2.2. Image acquisition

A Vevo 770 high-resolution ultrasound imaging system (VisualSonics, Toronto, ON, Canada) with a 40 MHz center frequency mechanical sector-scan probe (RMV 704) was used to obtain the longitudinal cross-section image of the wall motion of rat left carotid artery. The axial and lateral resolutions of the RMV 704 probe were 40 and 80 μm, respectively. The probe had a focal length of 6 mm and a depth of field (DOF) of 1.5 mm. DOF refers to the range of distance that appears to be in focus. A 7 × 7 mm field of view was used to obtain the longitudinal carotid artery images. Blood velocity was measured at the center of the CCA by using pulse-wave Doppler (sample volume 0.1 mm). Using an integrated rail system with an animal imaging stage, an XYZ positioner, and a scanhead mounting module that allowed precise image acquisition from a variety of positions and angles, the RMV 704 probe was properly positioned and aligned to observe longitudinal cross-section image of the carotid artery bifurcation. When the region of interest was displayed on the B-mode window, the imaging mode was switched to EKV (ECG-based kilohertz visualization) mode to acquire high-temporal resolution images. Several minutes were required to obtain a single cycle of EKV cine loop depending on the image sector size. The obtained EKV cine images were stored for further analysis. The EKV reconstruction technique [36,40–42] provided a representative cine loop of one cardiac cycle at a high-temporal resolution of 1000 frames per second, which were a B-mode-like cine display obtained by the line-by-line operation of a single-element scan head during a series of cardiac cycles. The system used rat ECG signals obtained by the physiological monitoring unit to synchronize the ultrasound signals and heart cycles. Precise examination of the pulsatile changes of the rat arterial movement was possible in spite of its rapid heart rate because of the high temporal resolution of the EKV mode: the heart rate of the nine rats tested in this study was 360.8 ± 33.3 bpm.