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Hemodynamic Effects of Long-term Morphological Changes in the Human Carotid Sinus

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Abstract

Previous investigations of morphology for human carotid artery bifurcation from infancy to young adulthood found substantial growth of the internal carotid artery with advancing age, and the development of the carotid sinus at the root of the internal carotid artery during teen age years. Although the reasons for the appearance of the carotid sinus are not clearly understood yet, it has been hypothesized that the dilation of the carotid sinus serves to support pressure sensing, and slows the blood flow to reduce pulsatility to protect the brain. In order to understand this interesting involvement at the carotid bifurcation in the aspects of fluid mechanics, we performed *in vitro* phase-contrast MR flow experiments using compliant silicone replicas of age-dependent carotid artery bifurcations. The silicone models in childhood, adolescence, and adulthood were fabricated using a rapid prototyping technique, and incorporated with a bench-top flow mock circulation loop using a computer-controlled piston pump. The results of the *in vitro* flow study showed highly complex flow characteristics at the bifurcation in all age-dependent models. However, the highest magnitude of kinetic energy was found at the internal carotid artery in the child model. The high kinetic energy in the internal carotid artery during childhood might be one of the local hemodynamic forces that initiate morphological long-term development of the carotid sinus in the human carotid bifurcation.

Keywords

Carotid Sinus; Phase-Contrast MRI; Carotid Morphology; Silicone Model

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Conflict of Interest

None of the authors have any conflict of interest.

Introduction

The morphology and associated local hemodynamics of the adult human carotid artery bifurcation have been studied extensively over the last few decades (Bharadvaj et al., 1982; Ku et al., 1983; Baaijens et al., 1993; Salzar et al., 1995; Affeld et al., 1998; Gijssen et al., 1999; Botnar et al., 2000; Lee et al., 2008). The structure of the adult carotid bifurcation with its sinus is unique. The arterial wall of the carotid sinus is densely innervated and contains baroreceptive neural terminals, and the sinus has been hypothesized to support pressure sensing (Gwilliam et al., 2009). Phenomenological observations have provided another hypothesis that the function of the sinus is to slow the blood flow and reduce the pulsatility in order to protect the brain. Complex flow patterns have been found in the carotid sinus from previous studies. These patterns have been implicated in carotid bulb wall heterogeneity and the subsequent development of atherosclerosis at this site (Kitney et al., 1983; Baaijens et al., 1993; Gijssen et al., 1999; Ku et al., 1983; Botnar et al., 2000; Wakhloo et al., 2004).

Seong and his colleagues reported the morphologic changes of the human carotid bifurcation from infancy to young adulthood (Seong et al., 2005a). Ninety-five digital subtraction angiograms (DSA) from 36 patients ranging in age from newborn infants to 36-year-old adults were analyzed to reveal age-dependent morphology of the carotid bifurcation. The results showed that the calibers of the internal and external carotid arteries are initially similar in infancy and early childhood, and the overall dimension of the bifurcation increases with advancing age, however, the internal carotid artery (ICA) increases more than the external carotid artery (ECA). The carotid sinus seems to be developed during teenage years with a remarkable increase in the ICA. Even though the investigation on carotid artery morphology provided an important insight into its structure with advancing age, the development of the human carotid sinus with associated hemodynamics is not clearly understood yet.

Therefore, this study was initiated to continue the investigation on local hemodynamic forces involved in arterial remodeling of the carotid artery bifurcation using silicone replicas of three age-dependent carotid bifurcations and the phase-contrast magnetic-resonance (MR) imaging technique. Silicone vascular models of the human carotid bifurcations were fabricated using a rapid prototyping technique and dip-spin silicone coating method (Seong et al., 2005b). Geometric information obtained from the previous investigation (Seong et al., 2005a) was applied to create morphologically averaged 3-D human carotid artery bifurcation models for childhood, adolescence, and young adulthood development periods. A Bruker 7T animal MRI system was used to obtain 3-D flow velocity profiles in the carotid bifurcation models. Velocity information were obtained and used to calculate fluid mechanics properties, such as, volume flow rates, pulsatility index (PI), and kinetic energy (KE) in the age-dependent carotid bifurcation models to understand the long-term development of the human carotid sinus with local hemodynamic influence.

Methods

1. Human carotid artery bifurcations and silicone vascular replicas

Age-dependent carotid bifurcation models were created to represent human developmental stages of childhood (3–9 years old), adolescence (10–19 years old), and adulthood (20–36 years old). The 3-D structure of the carotid bifurcation was constructed from the average dimensions obtained from 2-D geometric measurements from a previous investigation (Seong et al., 2005a). The intersection point of the centerlines of the three carotid artery branches, common carotid artery (CCA), internal carotid artery (ICA), and external carotid artery (ECA), was selected as the origin of a 3-D coordinate system. The centerlines of the carotid arteries in two orthogonal anterior-posterior (AP) and lateral (LAT) projections were placed in the 3D coordinate system, and then the body of the arterial structure was rebuilt around the 3-D centerline. The perpendicular diameters on the centerlines were measured with 20 pixels intervals, which is a physical dimension of 3 mm (a ratio of 0.15 mm/pixel), from the roots of each branch of carotid bifurcation. The diameters in both AP and LAT projects are not necessarily identical. Therefore, the cross-sectional area of the artery was assumed to be an elliptical shape, but it was closed to be a circular shape in most of locations. Figure 1(A, B) shows a morphological average image and the centerline and edge lines of the carotid arteries with diameter measurements in the LAT projection for the adult model. The three-dimensional reconstruction process was performed using SolidWorks (SolidWorks Corporation, Waltham, MA). Figure 1(C) shows illustrative images of the 3-D reconstruction process, and Figure 2(A) shows 3-D reconstructed models of morphologically averaged carotid bifurcations for childhood, adolescence, and adulthood development periods. The substantial growth of the internal carotid artery (ICA) with the development of a carotid sinus at the ICA root during adolescence is illustrated in Figure 2(A).

Compliant silicone vascular models of the carotid artery bifurcations were fabricated by a rapid prototyping technique with the dip-spin silicone coating method previously reported (Seong et al., 2005b). A fused deposition modeling (FDM) rapid prototyping system (Dimension Elite, Dimension Inc., Eden Prairie, MN) created the ABS core plastic molds for the bifurcation models designed in SolidWorks. The ABS core plastic was then dipped and kept completely submerged in a silicone elastomer (Dimethyl silicone elastomer dispersion in xylene, Applied Silicone Corp, Santa Paula, CA) to ensure complete coverage. The silicone coated core plastic was mounted on a motor-driven spinning shaft to obtain a uniform thickness of the silicone coat. Thereafter, the coated mold was placed in an oven (VWR, West Chester, PA) for curing the silicone at a temperature of 70°C. The core plastic was then removed from the silicone coated replica by immersing it in xylene for about 24 hours. After the ABS plastic core was completely melted out, the silicone vascular model was ready to incorporate with a flow circulation loop. The compliant silicone replicas have good optical clarity for a refractive index value of 1.411 with an average thickness of 0.6 mm as shown in Figure 2(B). The models showed substantial distensibility between systole and diastole during the cardiac cycle.

In order to compare the flow characteristics and fluid mechanics properties among the age-dependent carotid bifurcation models, an identical input flow condition at CCA was applied

for all models. Therefore, two younger models were scaled up to match the diameter of adult CCA. The diameter of CCA was set for 7 mm for all models. The scaling factors of childhood and adolescence models were 1.35 and 1.11 respectively. Figure 2(B) shows the scaled-up silicone carotid bifurcation models for childhood and adolescence periods, and the true scale model for adulthood.

2. Working fluid and hydrodynamic flow experiment set-up

The silicone model was incorporated into a mock circulation loop with a programmable reciprocating piston pump (CompuFlow 1000MR, Shelly Medical Imaging Technology, Ontario, Canada). An aqueous glycerol mixture consisting of 40 parts pure glycerin and 60 parts water by volume was used to obtain a density of 1098 kg/m^3 and a viscosity of 3.6 cP ($0.0036 \text{ kg/m}\cdot\text{s}$) which is similar to the conditions found in blood. The piston pump simulated a pulsatile carotid artery flow waveform. The average pulse duration was set at 840 ms and the peak and mean flow rates were 12 mL/s and 6 mL/s at the CCA of the carotid artery models. The Womersley and Reynolds numbers with average velocity during peak systole were calculated to be 5.3 and 666, respectively. Before the phase-contrast MR imaging scans, the volumetric flow rates in the mock circulation loop were checked by a transit time tubing flowmeter system (T402&TS410, Transonic Systems Inc, Ithaca, NY) with flow tubing sensors (5PXL, 6PXL and 10PXL) at the inlet and two outlets of the silicone vascular models. The flow meter system was connected to a data acquisition system (PowerLab 8/30, ADInstruments, Colorado Springs, CO) coupled through data acquisition software (Chart for Windows 7) to a PC.

Volume flow rates in the carotid arteries from various age groups were reported by Schöning and his colleagues (Schöning et al., 1996; Schöning et al., 1998; Scheel et al., 2000). Their studies showed that ECA volume flow was significantly increased from early childhood to adulthood, however, ICA volume flow was found to be relatively constant. The flow separation ratios between ICA and ECA for childhood, adolescence, and young adulthood were reported to be 84/16(ICA/ECA), 74/26, and 66/34, respectively. In this study, the flow separation ratios between ICA and ECA were adapted rather than using the actual volume flow rates from the previous publications because an identical input flow condition at CCA was applied for all age-representative models. The volumetric flow waveforms at the inlet of the proximal CCA and two outlets for distal ECA and ICA in three age-dependent models are shown in Figure 3. The figure shows distinct flow separation ratios among the models.

3. Phase-contrast magnetic resonance (MR) imaging

Phase-contrast MR imaging was performed using a small animal MRI system, a Bruker Biospec 7T 30 cm (Bruker Biospin, Ettlingen, Germany) with a 72 mm volume coil. The MRI scans were obtained using ParaVision software from three single slice gradient echo phase-contrast quantitative flow sequences. The imaging protocol utilized a TR of 15 ms, a TE of 5 ms, a slice thickness of 1 mm, a field of view (FOV) of $20 \times 20 \text{ mm}^2$, an image matrix of 81×81 pixels, and a physical in-plane resolution of 0.247 mm/pixel . Velocity encoding was adapted for the expected velocity range, and maximum magnitudes of 520 mm/s for through plane and 240 mm/s for in-plane velocities were used. The full cardiac

cycle of 840 ms was scanned by gating with 12 different cycles of delays to sample the entire waveform. The interval of each subsequent cycle was set to 70 ms. The cardiac cycle indicator (ECG) port of the pulsatile pump was connected to a spectrometer gating system (Small Animal Monitoring and Gating System, SA Instruments, Inc., Stony Brook, NY) through an auxiliary coaxial cable for gating. Figure 4 shows the schematic diagram of the phase-contrast MR imaging unit with the mock circulatory system.

Phase-contrast MR imaging scans were performed at 20 mm proximal to the apex of the bifurcation: FOV1 (CCA), 1 mm distal to the apex of the bifurcation: FOV2 (ICA root and ECA root), and 11 mm distal to the apex of the bifurcation: FOV3 (ICA and ECA). Five regions of interest (ROI1: CCA, ROI2: ECA root, ROI3: ICA root, ROI4: ECA, and ROI5: ICA) from the three FOV planes were analyzed to obtain the 3-D velocity profiles. The locations of ROI and FOV of the phase-contrast MR imaging experiments are shown in Figure 5.

Results

1. Velocity profiles in the carotid artery bifurcation models

The velocity fields at each ROI in the carotid bifurcation models were measured by medical image post-processing techniques using MATLAB (MathWorks, Natick, MA). Flow in the parent artery, CCA, is highly pulsatile during a cardiac cycle and has similar pulsatile flow behaviors in a straight circular pipe. At the apex of the bifurcation, CCA flow divides into two daughter branches. Figure 6 shows the 3-D velocity profiles at ROI2 and ROI3 during a cardiac cycle in childhood, adolescence and adulthood models. At peak systole, flow shows the highest magnitude during the entire cycle. Figure 6(A1) shows unbalanced velocity magnitudes in ROI2 and ROI3 due to the highest volume flow rate for the child ICA, however, the adulthood model shows balanced velocity magnitudes for both the ECA and ICA (Figure 6(C1)). The flow separation ratios between ICA and ECA for childhood, adolescence, and young adulthood were set at 84/16(ICA/ECA), 74/26, and 66/34, respectively, in order to match the clinical data by Schöning and his colleagues. Figure 7 shows flow patterns in the plane for ROI2 and ROI3 during a cardiac cycle in all models. During the deceleration phase of systole, double vortex flow patterns appear in both the ECA and ICA bifurcation areas in all models (Figure 7 (A2, B2, C2)). The childhood model clearly shows a pair of clockwise and counter clockwise vortex flow patterns in both daughter branches, and the circulation pattern diminishes gradually during diastole but remains slightly until late diastole. In adolescence and adulthood models, the similar pattern of double vortex flow appears during mid systole, but the pattern disappears during diastole period.

Flow waveforms at each ROI location were also obtained from the 3-D velocity profiles as shown in Figure 8. The child ECA (ROI2) shows a momentarily reverse flow pattern between late systole and early diastole.

2. Pulsatility index

The pulsatility index (PI) is a measure of the difference between the peak systolic and minimum diastolic velocities divided by the mean velocity during the cardiac cycle.

$$Pulsatility\ Index(PI) = \frac{V_{Max\ Systole} - V_{Min\ Diastole}}{V_{Ave\ during\ cardiac\ cycle}}$$

The measures of PI in the three age-representative models are reported in Table 1. The values of PI at CCA and ICA show that the flow pulsatility is slowly reduced in the stream from CCA to ICA. However, the stream from CCA to ECA shows a significant increase of PI at the ECA bifurcation (ROI2), and rapid reduction of pulsatility at ROI4. The adulthood model shows the reduction of pulsatility in both daughter branches at ROI4 and ROI5 with an identical PI value of 1.2. Younger age models also show similar magnitudes of PI at the ICA (ROI3 and ROI5) compared with that of the adulthood model, however, they have unbalanced pulsatility indices in the daughter branches. The PI values at ECA (ROI2 and ROI4) in childhood and adolescence models show significantly higher PI values than those at other ROI locations in the bifurcation models.

3. Kinetic Energy (KE)

An additional quantifiable index to understand hemodynamic influence of the morphological change in the carotid artery bifurcation would be kinetic energy. Kinetic energy is insensitive to flow direction, and it can be interpreted as a dynamic pressure in the fluid stream. Dynamic pressure changes in the bifurcation models might provide one of the possible reasons for arterial remodeling in the carotid bifurcation associated with aging. The measure of kinetic energy in the carotid artery models was obtained by squares of the average magnitude of the instantaneously measured velocity vectors at each ROI.

$$Kinetic\ Energy(KE) = \frac{1}{2} m V^2$$

Figure 9 shows a time dependent measure of the kinetic energy throughout the pulse in the three models. Kinetic energy at ICA and ECA branches in the childhood model shows a significant difference during the cardiac cycle in the figure. Kinetic energy during peak systole at the child ICA (ROI5) shows the highest magnitude of KE in all ages, and it is even higher than the kinetic energy at the child CCA. When the maximum values of KE at peak systole in two downstream positions were compared, the ICA root (ROI3) has seven times greater kinetic energy than the ECA side (ROI2), and the ICA (ROI5) has nine times a higher energy level than the ECA (ROI4) in the childhood model. It seems that most of the kinetic energy at the CCA transfers to the ICA branch during childhood. The adolescence model also has unbalanced KE in between ECA and ICA, but the energy difference in the daughter branches is significantly reduced compared to that of the childhood. Interestingly, adulthood shows much closed magnitudes of KE in both daughter branches and bifurcation area.

Discussion

The carotid bulb has been reported to be an important site for baroreceptors in the human vascular system. The role of baroreceptor is to regulate heart rate and vasodilation, and both these factors cannot be decoupled from pulsatility, flow patterns and volume flow waveforms. Therefore, it has been hypothesized that the focal dilation of the carotid sinus slows blood flow and reduces the pulsatility in order to protect the brain (Gwilliam et al. 2009). Even though the importance and function of the carotid sinus have been reported, the development of the sinus is not yet well understood. A previous investigation on age-dependent morphology of the human carotid bifurcation unveiled that the carotid bulb does not exist at childhood and develops during teen age years (Seong et al., 2005a).

In this study, 3-D velocity measurements in anatomically averaged silicone carotid bifurcation models were performed using the phase-contrast MR imaging technique to understand the reason of focal dilation within the carotid sinus. The in-plane image resolution was $250 \times 250 \mu\text{m}^2$, which is equivalent to a group of ~ 100 red blood cells. *In vitro* phase-contrast MR results in three human developmental stages of childhood, adolescence, and young adulthood showed highly complex flow characteristics at the carotid bifurcation. The double vortex flow pattern in both ECA and ICA can be found during late systole in all ages. In the childhood model, the flow pattern remains until late diastole, but the double vortex flow disappears during diastole in adolescence and adulthood models. It is assumed that relatively larger cross-sectional areas for the ICA bifurcation in adolescence and adulthood models possibly decreases the flow velocity and minimizes the vortex pattern in that region. Therefore, one of the hypotheses can be confirmed that the dilation of the carotid sinus causes slower flow and less flow activity at the bifurcation.

Another hypothesis on the morphology of the carotid sinus was the reduction of blood flow pulsatility to protect the brain. According to the experimental results for PI in Table 1, the pulsatility in the flow stream from CCA to ICA does not change much for all ages. The flow pulsatility in the ICA direction stream is slightly reduced after the flow separation at the bifurcation even without the existence of the carotid bulb. Clinical measurements of PI in human carotid arteries from 117 patients confirm that the trend of pulsatility changes in the ICA stream from this study is relevant to the physiological data with a minor discrepancy as shown in Table 1. Therefore, we assume that the hypothesis of pulsatility reduction at the sinus might not be realistic. However, an interesting point might lie on the ECA side because the pulsatility in the ECA territory shows a significant increase at the bifurcation area then appears to gradually decrease at the distal part of the ECA. This phenomenon could be related to a very low volume flow rate with flow fluctuation in the ECA during childhood as shown in Figure 8. The clinical data of PI at the ECA in Table 1 show less variation in all age groups compared to the results of this study, but the trend of pulsatility reduction and higher values of PI in the ECA can also be found. A continuously increasing proportion of the CCA volume flow from infancy to young adulthood feeds mostly the ECA branch. However, the ICA volume flow rate is relatively constant from early childhood to young adulthood (Schöning et al., 1996). The physiological mechanism of the significant volume flow rate increase in the ECA with advancing age is not well understood. It would

be an interesting point to understand the underlying physiology in extracranial flow with the maturation of the human cerebral circulation system.

Kinetic energy as an index of hemodynamic influence for arterial remodeling of the carotid sinus is attractive because it could be interpreted as a dynamic pressure in fluid flow. A significant difference of kinetic energy in childhood ICA is shown in Figure 9. The blood flow in childhood ICA carries about seven times higher kinetic energy in the flow stream compared to that of the ECA stream. On the contrary, the adult carotid bifurcation has similar KE magnitudes in two daughter branches. The interesting point is that the child carotid bifurcation has similar diameter sizes in two daughter branches as shown in Figure 2(A). Therefore, the dynamic pressure induced by high kinetic energy in childhood ICA might initiate the dilation of ICA root in childhood carotid bifurcation, and it might be one of the important hemodynamic forces for developing morphological changes in the human carotid bifurcation.

One limitation of the current study was that an identical input flow condition for all age-representative models was used. Due to the lack of physiological information for carotid artery flow in young ages, an adult common carotid artery flow was used as an input flow condition for the scaled-up childhood and adolescence models. For a more clinically relevant analysis, actual flow waveforms in childhood and adolescence models should be obtained and applied for *in vitro* flow experiments.

This *in vitro* experimental study allowed us to analyze the characteristics of local flow phenomena such as volume flow waveform, pulsatility index, kinetic energy, and changes in these parameters as a result of long-term morphological changes in the human carotid bifurcation. However, clinical studies will help more fully understand the cause of arterial remodeling in the carotid bifurcation with the maturation of the human brain.

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Figure 1.

Morphological average image (A) and the centerline and outline of the carotid arteries with diameter measurements (B) in the LAT projection of adulthood (unit: pixel), and (C) three-dimensional reconstruction processes of the carotid artery bifurcation model using geometric dimensions from AP and LAT projections

Figure 2.
Three-dimensional morphology (A) and silicone replicas (B) of human carotid artery bifurcation in childhood, adolescence, and adulthood development periods

Figure 3.

The inlet and outlet flow waveforms produced by the heart mimicking pulsatile pump in this study

Figure 4.
Schematic diagram of the phase-contrast MR imaging experiment set-up with a mock circulatory system

Figure 5.
Locations of the FOV planes and ROIs for the phase-contrast MR imaging in the carotid bifurcation model

Figure 6. PC-MR results of 3-D flow patterns in ROI2 and ROI3 of the carotid bifurcation models during a cardiac cycle in childhood, adolescence, and adulthood development periods. (1: Peak systole, 2: Mid systole, 3: Late systole, 4: Early diastole, and 5: Late diastole)

Figure 7. Secondary flow patterns in the planes for ROI2 and ROI3 of the carotid bifurcation models during a cardiac cycle in childhood, adolescence, and adulthood development periods. (1: Peak systole, 2: Mid systole, 3: Late systole, 4: Early diastole, and 5: Late diastole)

Figure 8.
Phase-contrast MR results of volumetric flow waveforms at the ROI locations in the carotid artery bifurcation models

Figure 9.
Kinetic energy (KE) at the ROI locations in the carotid artery bifurcation models

Pulsatility index (PI) from the *in vitro* phase-contrast MR experiments and clinical data of PI from previous publications (Schöning et al. 1998 and Scheel et al. 2000, n=number of cases)

Table 1

Pulsatility Index (PI)		CCA (ROI1)	ECA Root (ROI2)	ICA Root (ROI3)	ECA (ROI4)	ICA (ROI5)
<i>In vitro</i> pc-MR experiment results	Childhood	1.37	5.14	1.08	2.55	0.98
	Adolescence	1.37	2.72	1.28	1.45	1.07
	Adulthood	1.49	1.96	1.49	1.17	1.18

Clinical data from previous publications	CCA		ECA	ICA
	Childhood (n=44)	1.73±0.31	2.72±0.63	1.16±0.25
	Adolescence (n=49)	1.97±0.42	2.53±0.56	1.18±0.30
	Adulthood (n=24)	1.89±0.39	2.32±0.46	1.16±0.30