Measurement of hemodynamics in human carotid artery using ultrasound and computational fluid dynamics

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Measurement of hemodynamics in human carotid artery using ultrasound and computational fluid dynamics. J Appl Physiol 92: 957–961, 2002; 10.1152/japplphysiol.00171.2001.—The objective of the study was to investigate the feasibility of using computational fluid dynamic modeling (CFD) with noninvasive ultrasound measurements to determine time-variant three-dimensional (3D) carotid arterial hemodynamics in humans in vivo. The effects of hyperoxia and hypoxic hypercapnia on carotid artery local hemodynamics were examined by use of this approach. Six normotensive volunteers followed a double-blind randomized crossover design. Blood pressure, heart rate, and carotid blood flow were measured while subjects breathed normal air, a mixture of 5% CO2 and 15% O2 (hypoxic hypercapnia), and 100% O2 (hyperoxia). Carotid artery geometry was reconstructed on the basis of B-mode ultrasound images by using purpose-built image processing software. Time-variant 3D carotid hemodynamics were estimated by using finite volume-based CFD. Systemic blood pressure was not significantly affected by hyperoxia or hypoxic hypercapnia, but heart rate decreased significantly with hyperoxia. There was an increase in diastolic flow velocity in the external carotid artery after hypoxic hypercapnia, but otherwise carotid blood flow velocities did not change significantly. Compared with normal air, hyperoxic conditions were associated with a decrease in the width of the region of flow separation in the external carotid artery. During hyperoxia, there was also an increase in the minimum and a decrease in maximum shear stress in the bifurcation and hence a reduction in cyclic variation in shear stress. Hypoxic hypercapnia was associated with a reduced duration of flow separation in the external carotid artery and an increase in the minimum shear stress without affecting the cyclic variation in shear stress. This study demonstrates the feasibility of using noninvasive ultrasound techniques in conjunction with CFD to describe time-variant 3D hemodynamics in the human carotid arterial bifurcation in vivo.

blood flow; hyperoxia; hypoxic hypercapnia; shear stress

Atherosclerosis is a major cause of cardiovascular mortality and morbidity. An important feature of atherosclerosis is the focal nature of lesions and their characteristic location at particular sites in the vasculature, such as regions of marked curvature and branch points (24, 28). It has been proposed that this is a consequence of local hemodynamics in such regions (4) and that shear stress gradients adversely affect endothelial function at such sites (8, 9) and, hence, increase the risk of atheroma formation (11, 23). However, the measurement of flow and shear stress in the regions relevant to atheroma formation (e.g., arterial bifurcations) is difficult because of the complex nature of flows at such sites. Computational fluid dynamic modeling (CFD) is widely used in engineering to calculate flows in complex geometries, and recently this approach has been successfully applied to modeling flow in the cardiovascular system of animals and in idealized models of human arteries (15, 18, 29).

The primary objective of this study was to extend this approach to a nonidealized human arterial bifurcation and show the feasibility of using noninvasive ultrasound techniques to model blood flow by using CFD. The carotid artery was chosen because the superficial location of this vessel means that it can readily be evaluated by ultrasound to obtain geometry and flow data. Data obtained in such studies may therefore be used in conjunction with CFD techniques to derive the hemodynamic parameters of interest. Using this approach, we studied the effects of hyperoxia and hypoxic hypercapnia, cerebral vasodilator stimuli, respectively (7), in six normal volunteers.

SUBJECTS AND METHODS

Study Design

The study was designed as a double-blind, randomized, crossover trial. Three test gases were administered in a balanced, randomly allocated order. Subject and observer were blinded to the order of administration by the gas cylinders being concealed behind a screen. The three test gases consisted of normal air, hyperoxia (100% O2), and hypercapnia (a mixture of 5% CO2 with 15% O2 and balance N2). The gases were inhaled by breathing through a face mask with a flow rate of 10 l/min. These conditions have been previously shown by us to alter alveolar PO2 and P CO2 and to cause retinal arteriolar vasoconstriction and vasodilation, respec-
tively, in normal subjects (5). Before the inhalation of the first gas, a carotid B-mode ultrasound investigation was performed. After 5 min of breathing each gas, carotid blood flow was assessed, followed by a recovery period of 10 min.

Subjects

Six healthy volunteers (4 men, 2 women) participated in the study. Mean age of the subjects was 21 yr (range 19–23), mean weight was 72 kg (range 62–92), and mean height was 174 cm (range 152–193). They were all normotensive (<120/85 mmHg) and nonsmokers. The study was carried out in accordance with the Declaration of Helsinki of the World Medical Association. All subjects gave written, informed consent, and the local research ethics committee approved the study protocol.

Measurements

All measurements were performed by the same observer after subjects were allowed at least 15 min of supine rest in a quiet room (20–24°C). The subjects abstained from caffeine, alcohol, and vigorous exercise for 24 h before these assessments.

Blood pressure and heart rate. Supine blood pressure and heart rate were measured throughout the whole study at 2-min intervals at the left arm with an automated sphygmomanometer (Omron HEM-705CP, Omron, Tokyo, Japan). The mean of three recordings, measured at the end of the 15-min resting period, and the mean of the final three recordings during the recovery period of the first and second gas were used as baseline values. After subjects breathed the test gas for 5 min, the mean of blood pressure and heart rate recordings during the ultrasound measurements was taken as the test gas value (on average 3–4 recordings).

Ultrasound measurements. Carotid bifurcation geometry and flow were measured using an HDI 3000 ultrasound system with a 7.5-MHz linear array scanhead (ATL, Bothell, WA). Subjects were examined in the supine position with the neck extended and rotated slightly to the contralateral side, and a three-lead electrocardiogram was recorded throughout the study.

Posterolateral and anterolateral longitudinal B-mode images of the right common carotid artery (CC), the bulb, and the internal (IC) and external (EC) carotids were recorded at end diastole (timed on the basis of the peak of the R wave on the electrocardiogram). All images were stored on optical disc for off-line analysis.

Flow velocity was measured by pulsed Doppler in the center of the CC (at least 2 cm proximal to the bulb), IC, and EC (at least 1.5 cm distal from the bulb). Peak systolic (\(V_{sys}\)) and end-diastolic (\(V_{dia}\)) flow velocities were calculated as the ensemble average of six individual measurements, and resistive index (RI) was calculated as \(\frac{V_{sys} - V_{dia}}{V_{sys}}\) (19).

CFD modeling. The two-dimensional longitudinal B-mode images of the right CC, the bulb, and the IC and EC arteries captured at end diastole were segmented manually to extract the geometric dimensions for each subject. These subject-specific dimensional values were then processed by use of a purpose-built three-dimensional (3D) reconstruction and mesh-generation software to create the carotid bifurcation geometry assuming it to be planar with noncompliant walls, and to generate automatically a multiblock-structured computation mesh. Because the accuracy of CFD predictions depends strongly on the grid resolution in the computational mesh, a mesh refinement test was carried out and a final mesh consisting of 17,920 eight-noded cells was chosen. This was based on the fact that further reduction in mesh size by 50% only resulted in an average of 0.7% difference in predicted velocities.

With assumptions that the flow was laminar and that blood behaved like a Newtonian fluid, the Navier-Stokes equations were solved for time-dependent flow in a rigid 3D model of the carotid bifurcation reconstructed for each of the subjects investigated.

A finite volume-based CFD code CFX4 (23) was employed to obtain numerical solutions of the governing equations, subject to the following boundary and initial conditions: at the inlet of the CC artery prescribed axial velocity profile was derived from Womersley’s solution for fully developed pulsatile flow in a straight circular tube (26), together with the CC velocity waveform measured using pulsed Doppler and zero in-plane velocity components. At the outlets of the IC and EC arteries, fully developed flow was assumed with time-varying IC-to-EC division ratio determined from the measured velocity pulse forms in the IC and EC arteries. No-slip conditions were assumed on the walls. Initial conditions assumed zero velocities for all nodes except those at the inlet, where velocities had the values as specified by the boundary conditions.

Numerical calculations were performed for three consecutive cycles, and each cycle was subdivided into 100 uniform time increments. The execution time required on a Sun Ultra 10 workstation (Sun Microsystems) with 256-MB RAM and a single 333-MHz processor was about 10 h for each complete cycle.

The computational results contained information regarding spatial and temporal patterns of flow velocity and shear stress in the carotid bifurcation. For the purposes of analysis, time-averaged maximum and minimum wall shear stress and cyclic variation in shear stress (maximum — minimum) were obtained by averaging each spatial point over one cardiac cycle and deriving the maximum and minimum of this value in the whole carotid bifurcation. Negative values for shear stress indicate that shear stress at a particular point acted in the direction of flow. The width and duration of areas of disturbed or low flow velocities (region of flow separation) were calculated. Duration of flow separation was expressed as percentage of cardiac cycle.

Data Analysis

Results are reported as means (lower–upper 95% confidence interval). Statistical comparisons were performed by using ANOVA (repeated measures) followed by Dunnett’s test for comparison with control conditions (normal air) using Instat 3.0 (GraphPad Software).

RESULTS

All six volunteers completed the study. None reported adverse effects while breathing the test gases. Blood pressure did not change significantly during hypoxia or hypoxic hypercapnia (Table 1). Heart rate decreased significantly during hypoxia but was not changed significantly by hypoxic hypercapnia (Table 1). Diastolic blood flow velocity increased significantly only in the external carotid. Consequently, resistive index in the external carotid fell slightly during hypoxic hypercapnia; otherwise, there were no marked changes in carotid blood flow after either gas (Table 2).

Examples showing the regions of flow separation and the distribution of wall shear stress in an individual breathing normal air at the indicated point in the
Effects of air, hyperoxia, and hypoxic hypercapnia on haemodynamics in the carotid bifurcation

Table 1. Effects of air, hyperoxia, and hypoxic hypercapnia on blood pressure and heart rate

<table>
<thead>
<tr>
<th></th>
<th>Air</th>
<th>Hyperoxia</th>
<th>Hypoxic Hypercapnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pressure, mmHg</td>
<td>112(107–117)</td>
<td>113(110–116)</td>
<td>115(109–121)</td>
</tr>
<tr>
<td>Diastolic blood</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pressure, mmHg</td>
<td>65(59–71)</td>
<td>64(60–68)</td>
<td>64(59–69)</td>
</tr>
<tr>
<td>Heart rate,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>beats/min†</td>
<td>70(60–80)</td>
<td>66(58–74)</td>
<td>73(63–83)</td>
</tr>
</tbody>
</table>

Data are means (lower-upper 95% confidence limits). *P < 0.05 by Dunnett’s test compared with control (air); †P < 0.05 by ANOVA for repeated measures.

Cardiac cycle are shown in Fig. 1. Overall, these data consistently showed that two regions of flow separation were seen on the outer walls of the carotid bifurcation in the external and internal carotid arteries. Similarly, the regions of minimum shear stress were located on the outer walls of the bifurcation, whereas regions of high shear stress were evident at the flow divider, at the inner walls of the internal and external carotid arteries, and in the bulb before the bifurcation.

From these data, hyperoxia was found to be associated with a significant decrease in the width of the region of flow separation in the external carotid artery compared with air (Table 2). Also, during hyperoxia, there was a significant increase in minimum and a decrease in maximum shear stress in the bifurcation (Fig. 2), resulting a significant increase in the cyclic variation in shear stress by 1.0 (0.5–1.5) N/m². Hypoxic hypercapnia was associated with a significant reduction by 26 (5–46)% in the duration of flow separation in the external carotid, and there was also a significant increase in minimum shear stress (Fig. 2), but the cyclic variation in shear stress did not differ from air. Other hemodynamic parameters were not significantly affected (Table 2), and there was no obvious change in the pattern of flow separation under the different experimental conditions.

**DISCUSSION**

This study reports the novel application of CFD techniques to ultrasound data derived from the human carotid artery. The use of ultrasound techniques to derive these data represents a rapid, cheap, and widely

Table 2. Effects of air, hyperoxia, and hypoxic hypercapnia on haemodynamics in the carotid bifurcation

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Air</th>
<th>Hyperoxia</th>
<th>Hypoxic Hypercapnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common carotid artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic flow velocity, cm/s</td>
<td>104(90–119)</td>
<td>105(84–125)</td>
<td>101(74–125)</td>
</tr>
<tr>
<td>Diastolic flow velocity, cm/s</td>
<td>17(15–19)</td>
<td>17(14–19)</td>
<td>16(12–21)</td>
</tr>
<tr>
<td>Resistive index</td>
<td>0.84(0.81–0.86)</td>
<td>0.83(0.81–0.86)</td>
<td>0.83(0.79–0.87)</td>
</tr>
<tr>
<td>Internal carotid artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic flow velocity, cm/s</td>
<td>89(70–109)</td>
<td>88(70–106)</td>
<td>78(57–100)</td>
</tr>
<tr>
<td>Diastolic flow velocity, cm/s</td>
<td>19(14–24)</td>
<td>16(9–22)</td>
<td>15(13–18)</td>
</tr>
<tr>
<td>Resistive index</td>
<td>0.78(0.71–0.84)</td>
<td>0.81(0.72–0.90)</td>
<td>0.78(0.7–0.86)</td>
</tr>
<tr>
<td>Flow separation duration, %</td>
<td>21(1–41)</td>
<td>22(5–29)</td>
<td>33(6–59)</td>
</tr>
<tr>
<td>Width of flow separation, mm</td>
<td>1.2(0.0–2.4)</td>
<td>1.4(0.4–2.5)</td>
<td>1.5(0.7–2.3)</td>
</tr>
<tr>
<td>External carotid artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic flow velocity, cm/s</td>
<td>90(68–112)</td>
<td>89(76–102)</td>
<td>96(78–114)</td>
</tr>
<tr>
<td>Diastolic flow velocity, cm/s†</td>
<td>7(4–10)</td>
<td>7(5–9)</td>
<td>10(7–12)‡</td>
</tr>
<tr>
<td>Resistive index</td>
<td>0.92(0.89–0.95)</td>
<td>0.92(0.89–0.94)</td>
<td>0.89(0.87–0.92)</td>
</tr>
<tr>
<td>Flow separation, %‡</td>
<td>46(24–67)</td>
<td>33(12–53)</td>
<td>20(14–26)‡</td>
</tr>
<tr>
<td>Width of flow separation, mm†</td>
<td>1.7(1.1–2.2)</td>
<td>1.2(0.7–1.6)‡</td>
<td>1.2(0.6–1.9)</td>
</tr>
</tbody>
</table>

Data are means (lower-upper 95% confidence limits). *P < 0.05 by Dunnett’s test compared with control (air); †P < 0.05 by ANOVA for repeated measures. ‡P = 0.05 by ANOVA for repeated measures.
applicable method that can acquire data suitable for CFD modeling in superficial arteries. Even with modern imaging techniques such as magnetic resonance imaging (MRI) and Doppler ultrasound, it is difficult to obtain accurate measures of velocity with sufficient temporal and spatial resolution to determine parameters of biological interest, such as wall shear stress in the region of arterial bifurcations, and CFD simulation may offer superior accuracy (16, 30), although validation studies are difficult in the absence of a “gold standard.” The accuracy of the CFD numerical solution procedures used for this study has been tested, and it has been found that, for a Reynolds number of 300 and the grid density used in this study, the errors can be estimated to be within 0.4% of the axial velocity and 2% of wall shear stress for fully developed flow in a straight circular tube. Other studies have used a comparable approach with either idealized geometries or data from animal models (15, 18, 29). However, because local geometry of an individual artery is very important for local shear stress, it is difficult to extrapolate previous findings to the in vivo human situation. Krams et al. (13a) used a CFD technique for determination of hemodynamics in individual human coronary arteries, but invasive techniques were necessary to visualize the vessel of interest.

The model used in this study is simplified in that it assumes fully developed flow at the inlet and outlet boundaries, a planar bifurcation, and noncompliant walls. These assumptions will influence the estimates of hemodynamic parameters presented here: the velocity profile in the common carotid artery may not conform precisely to that predicted by the Womersley solution, although previous studies suggest this is a reasonably realistic assumption (20, 25). Nonplanar features of bifurcations have been reported to influence secondary flow patterns (3, 16, 27, 29, 30). Previous modeling studies suggest that the assumption of noncompliant walls has only modest effects on flow patterns (18, 30) but may reduce average shear stress by ~20–30% (1) and instantaneous maximum and minimum shear stress to a greater degree (1, 30). Despite these possible limitations, the general spatial pattern of wall shear stress distribution is similar to that seen when using other approaches (14, 30) and quantitatively in keeping with those reported previously in the in vivo carotid artery of young subjects by using either ultrasound (20), MRI (17), CFD based on MRI data (30), or laser Doppler anemometry in an in vitro model of a human carotid artery (14). In the future, the modeling approach presented here could be modified to incorporate more realistic individual flow velocity data, geometry, and wall properties based on 3D ultrasound, as already performed by us using a combination of MRI- and ultrasound-derived data (16, 30). However, the cost and efforts required to collect and process the 3D geometry and velocity data would be considerably greater.

In the present study, hyperoxia and hypoxic hypercapnia were used as interventions that were anticipated to selectively affect cerebral blood flow. Systemic blood pressure was not affected significantly by either gas mixture, whereas heart rate decreased slightly after exposure to hyperoxia, which could suggest some degree of systemic vasoconstriction, although it has also been suggested that hyperoxia lowers efferent sympathetic nerve activity to skeletal muscle (21). These modest systemic effects are in keeping with previous studies in humans (2, 7, 13).

Hypercapnia and hypoxia are considered to cause decreased cerebrovascular resistance because of their effect on cerebral arteriolar tone (6, 10, 22). The effect of hyperoxia and hypercapnia on carotid artery blood flow has been reported to be variable (2), and our findings are similar to a previous report (12) that found no significant effect of hypercapnia on carotid artery flow, although middle cerebral artery flow was increased.

Despite the small changes in carotid artery flow velocities, it was possible to observe significant changes in local hemodynamics and shear stress by using CFD. In particular, hyperoxia decreased the cyclic variation in shear stress as a result of increasing minimum and decreasing maximum shear stress. In contrast, after hypoxic hypercapnia there was a marked reduction in duration of flow separation in the external carotid artery. In addition, minimum shear stress was reduced by hypoxic hypercapnia, but there was no significant effect on cyclic variation in shear stress. It is possible that these changes reflect regional alterations in cerebrovascular impedance, particularly affecting the territory supplied by the internal carotid artery, causing changes in local hemodynamics in the carotid bifurcation.

In summary, this study has demonstrated the feasibility of applying CFD to individual arterial geometries derived from ultrasound data to reconstruct time-variant 3D local hemodynamics and shear stress distribution in the carotid bifurcation in vivo. Both hyperoxia and hypercapnia were found to induce distinct changes...
in local hemodynamics in the carotid bifurcation, despite no major changes in overall carotid blood flow. Given the importance attributed to local hemodynamic factors, such as shear stress, in the development of atherosclerosis, this type of noninvasive approach offers promise for future investigations of the possible relationship of local hemodynamic factors and the development of early atherosclerosis in a susceptible individual’s arteries in vivo.

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REFERENCES