MICROCINEMATOGRAPHIC STUDIES OF FLOW PATTERNS IN THE EXCISED RABBIT AORTA AND ITS MAJOR BRANCHES

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ABSTRACT Arterial fluid mechanics may play a role as a localizing factor for early atherosclerosis. Flow patterns in natural rabbit aortas rendered transparent were studied using a microcinematographic visualization technique. The aortic arch exhibited a single cell of clockwise-rotating helical secondary flow along the ventral and inner walls. Flow separation occurred proximal to the two arch branches with flow reversal proximal to the brachiocephalic artery. Sinusoidal flow rendered the helical motion more pronounced in systole, while the reverse flow zone periodically expanded and contracted. Steady flow in the abdominal aorta revealed streamlines which follow slow looping trajectories lateral to ostia before tracing helical paths into the branches. Flow separation was present along the dorsal wall of the aorta opposite the superior mesenteric artery. With the exception of the left renal artery, steady flow wall shear stresses were higher distal to ostia than proximal. Spatial gradients of wall shear stress were larger around branches than elsewhere. Similar to observed flow patterns, sites of enhanced macromolecular permeability, as observed previously in the normal rabbit aorta, follow a clockwise helical pattern in the arch and exhibit a distribution around ostia that correlates to some degree with regions of elevated shear stress gradients. © 1997 Elsevier Science Ltd

Introduction

Localization of early atherosclerotic lesions in regions of arterial branching, curvature, and bifurcation has long implicated localizing factors, particularly arterial hemodynamics, in pathogenesis of the disease (Montenegro and Eggen,

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1968; Schwartz and Mitchell, 1972). Despite numerous investigations over the past three decades, a definitive connection between hemodynamic phenomena and the localization of early atherosclerotic lesions has remained elusive. This is partially due to difficulties in precisely establishing in vivo arterial flow patterns and wall shear stresses due to the complexity of arterial geometry and limitations in both access and resolution. In vivo pulsed Doppler ultrasound and more recently magnetic resonance imaging measurements in the human and in dog aortas have demonstrated extensive secondary flows in the aortic arch, flow recirculation during portions of the cardiac cycle in the abdominal aorta, and large variations in mean and peak wall shear stress (Farthing and Peronneau, 1979; Hutchison et al., 1988; Oshinski et al., 1995). Flow visualization studies in glass models and polymeric casts of large arteries have revealed sharp spatial gradients of wall shear stress in the vicinity of aortic branches (Lutz et al., 1977) as well as large regions of complex time-varying secondary flow motion in the aorta and the carotid artery (Ku et al., 1985; Moore et al., 1991; Pedersen et al., 1992). Two- and three-dimensional numerical simulations have shown complex flow fields including transient flow reversal (Friedman et al., 1975; Zheng and Yang, 1993), helical motion within the daughter branches of aortic bifurcations (Thiriet et al., 1992), and sharp shear stress gradients in the vicinity of aortic branches (Lei et al., 1995).

We have previously described focal sites on the luminal surface of the normal rabbit aorta that are of greatly enhanced permeability to various proteins including radiolabeled low density lipoprotein and horseradish peroxidase (Stemerman et al., 1986; Morrel et al., 1987). About one-third of these sites are associated with abnormally enlarged (bulging) endothelial cells. Topographical mapping of these sites (Barakat et al., 1992) has demonstrated that they are distributed very nonuniformly over the luminal surface; their density is highest in the vicinity of aortic ostia, and they exhibit preferred radial and angular distributions around branches that are generally similar to those of experimentally-induced atherosclerotic lesions in hypercholesterolemic rabbits (Schwenke and Carew, 1988; Cornhill and Roach, 1976; Zeindler et al., 1989). Away from branches, the enhanced permeability sites occur primarily in streaks oriented in the bulk flow direction. These results are consistent with a localizing factor such as hemodynamics.

The objective of the current study is to investigate the detailed flow field in the normal rabbit aorta and to probe possible relationships between it and the distribution of the sites of enhanced permeability. The literature on the flow field in the rabbit aorta is limited to the early studies of Rodkiewicz (1973) in a two-dimensional model of the aortic arch, the qualitative studies of Okano and Yoshida (1992) in the vicinity of the brachiocephalic and left subclavian arteries, and the experimental and computational investigations of Malinauskas et al. (1993) and Lei et al. (1995) in the vicinity of the celiac artery. We used isolated natural aortas rendered transparent to allow flow visualization by the microcinematographic method of Karino and Motomiya (1983). This method, which yields a high level of quantitative fluid mechanical detail, has previously been employed to study details of the flow field in parts of the human and dog arterial systems (Sohara and Karino, 1985; Asakura and Karino, 1990; Karino et al., 1990).

Materials and Methods
Preparation of transparent aorta.
Six transparent rabbit aortas were prepared according to the method of Karino and Motomiya (1983). Normal New Zealand White rabbits (weight 1.6 to
4.9 kg) were anesthetized by intramuscular injection of 50 mg/kg ketamine and 10 mg/kg xylazine. After each rabbit lost consciousness, one ear was shaved, and one of the marginal ear veins was cannulated with a catheter (24 ga. Deseret Pharmaceutical Co., Sandy, VT). The animals were then euthanized by an overdose injection of sodium pentobarbital (about 3 ml at 380 mg/ml, Lemmon Co., Sellersville, PA) into the ear catheter.

The entire aortic tree including the heart, full length of the aorta, and segments of all major aortic branches was isolated from the body shortly after sacrifice and immersed in cold isotonic saline. Excess connective tissue was trimmed, and the intercostal, inferior mesenteric, lumbar, phrenic, and gonadal arteries in each aorta were ligated with 60 nylon suture, paying special attention not to alter the shape of the aortic lumen as a result of the ligations. Smaller microvessels were occluded by ligation and/or coagulation with a fulgurator. The major aortic branches, including the brachiocephalic, left subclavian, celiac, superior mesenteric, right and left renal arteries, and the lower abdominal aorta close to the iliac bifurcation were cannulated with 2.5 cm long square-cut, thin-walled stainless steel catheters (8 to 15 ga) whose outer diameters approximately matched the inner diameters of the branches, and the catheters were tied firmly in place with 3-0 silk suture. In a separate study of aortic and branch flow rates in vivo that we carried out (Barakat et al., 1997), the flow rates through the major branches that we studied here accounted for about 98% of the flow rate in the aorta, on average. Thus, prevention of the normal outflow from the smaller vessels would have minimal effect on our results.

The left ventricle was incised with a 5 cm long 6 ga stainless steel catheter to provide an inlet port into the aorta, and the pulmonary arteries and veins were ligated with 8-0 silk suture. The aorta and all major branches were perfused with isotonic saline until all air in the preparation was removed. The catheters of the major branches and the lower abdominal aorta were capped while the isotonic saline was flowing. The aorta was then subjected to an isotonic saline hydrostatic head at a physiological pressure of 100 mm Hg and consequently took on its natural physiological shape. The pressurized aorta was mounted in this physiological configuration onto a three-dimensional frame consisting of 3 mm diameter stainless steel tubing which was shaped to make contact with all of the catheters thereby providing solid support for the aortic tree. The length was maintained at approximately the same value as measured in situ prior to isolation of the aortic tree (the length from the tip of the aortic arch to the iliac bifurcation ranged from 20 to 24 cm).

The tissue was fixed by pressure perfusion (100 mm Hg) with a solution of 2% glutaraldehyde and 4% formaldehyde in isotonic saline. The preparation was then immersed in the same fixative solution for 24 h. Subsequently, the tissue was dehydrated by simultaneous pressure perfusion with, and immersion in, ethanol-saline mixtures of progressively increasing ethanol concentration and finally suspension in pure ethanol for 2 days. Each cannulated branch was connected to flexible polyethylene tubing (Intramedic, Clay Adams, Parsippany, NJ) whose inner diameter matched the outer diameter of the cannula. The length of each connection tube was adjusted during steady flow so that the flow rate into each branch was consistent with the mean flow divisions previously measured in the rabbit in vivo using transit-time ultrasound flowmetry (Barakat et al., 1997). No change was made in any connection tube length for experiments with pulsatile flow. Finally, the tissue was rendered transparent by pressure perfusion with, and immersion in, methyl salicylate (oil of wintergreen) containing 5% ethanol.
Experimental procedure and data analysis

Each mounted transparent aorta was placed horizontally in a square glass chamber filled with oil of wintergreen containing 5% ethanol and situated on a vertically-moveable horizontal stage. Areas of interest within the aorta were transilluminated with condensed parallel light provided by a Reichert binolux twin-lamp assembly supplying either low intensity light from a tungsten filament lamp or high intensity light from a 200 W dc mercury arc lamp with a filter to eliminate UV illumination. Each area of interest was inspected to determine if it was suitable for flow visualization. Technical problems prevented visualization at some sites. These problems included incomplete clearing of the tissue, vessel damage during isolation or preparation of the tissue, vessel damage during mounting onto the stainless steel frame, and partial blockage of the flow field by the suture used to occlude vessels or by insertion of a catheter too far into a vessel. In addition, it was essential to have the axis of the catheter that was inserted into the left ventricle perfectly in line with the axis of the aortic valve in order to avoid introduction of artefactual secondary flow in the aortic arch. These technical problems led to successful flow field visualization in the entire arch of two rabbits and in 19 of 24 branch sites in the abdominal aorta of all six rabbits.

Each vessel to be visualized was subjected to flow of a dilute suspension containing about 0.3% (v/v) of a mixture of polystyrene microspheres having diameters of 50, 80, 115, and 165 μm (s.g. 1.06, Particle Information Services, Bremerton, WA) in oil of wintergreen containing 5% ethanol (s.g. 1.16, viscosity $2.64 \times 10^{-3}$ kg/(m-s), and refractive index n = 1.53). Steady flow was provided by gravity feed from a head tank; pulsatile flow was produced using the same head tank in combination with an in-line sinusoidal oscillator driving a 3-ml syringe. This generated a sinusoidal flow component with a zero mean flow rate and a frequency of 2.5 Hz (approximately matching the rabbit heart rate) that was superimposed on the steady flow. The resulting Womersley parameter in the experiments based on a nominal aortic diameter of 4 mm was 5.4. This differs from the value of about 4 that would be expected in vivo. The impact of this difference on the flow patterns is not addressed in this study.

Pulsatile flow experiments in the abdominal aorta were not possible because the relatively thin wall collapsed when subjected to a pulsatile pressure wave. This may have been due to loss of wall musculature and/or the lack of tissue tethering. The wall in the aortic arch was sufficiently thick that a sinusoidal flow component with maximum amplitude equal to 93% of the steady flow component (uncertainty ±16% by propagation of error analysis) could be imposed before vessel collapse. That maximum amplitude corresponded to a displaced volume of 0.80 ± 0.05 ml within the oscillating 3-ml syringe during each quarter of a cycle. Sinusoidal flow had the form $(1 + A \sin \omega \tau)$, where A = 0.93 ± 0.16, $\omega = 2\pi / \tau$, and $\tau = 0.38$ s is the period of a single pulsatile cycle. It was intended that $t = 0$ correspond to the beginning of the cycle and that peak systole and diastole occur at $t / \tau = 0.25$ and 0.75, respectively. It was discovered after particle trajectory analysis that $t = 0$ actually corresponds to a time estimated to be about 0.04 s before the beginning of a cycle, and the actual time at which each diagram applies in Fig. 2 corresponds to a time 0.04 s earlier than that listed. Flow field visualization was performed by photographing trajectories of tracer microspheres on 16 mm cine film (Kodak double X-negative) at speeds of 800 to 1400 frames/s using a high-speed camera (Hycam, Red Lake Labs, Santa Clara, CA) with a zoom lens (1 to 5x). Whenever possible, two perpendicular views of the same section were photographed in order to visualize the three-dimensional structure of the flow.
field. This was impossible in some cases due to anatomical complexities or obstruction by the stainless steel frame. The frequency of pulsatile flow was determined by synchronizing the syringe pump sinusoidal oscillator with the film speed counter.

Each transparent vessel, still under physiological pressure, was transilluminated with condensed parallel light from a 200 W ac tungsten filament white lamp through a pair of 16 cm diameter plano-convex lenses in series. Segments of interest were photographed, together with a scale at the same focus, on 35 mm film using a camera (Nikon FE 35 mm) equipped with close-up lenses. These photographs were used to obtain geometric data. The aortic axis and of each branch and the interpolated inner periphery of the aortic wall across each branch entrance were drawn manually, and the points of intersection of each branch axis with the interpolated wall periphery (I) and with the aorta axis (II) were noted. The following parameters were measured in the common median plane: the distance from the entry to the brachiocephalic artery to the carotid flow divider, the center-to-center distance between branches in terms of point I for each branch and measured parallel to the aorta axis (shortest distance for brachiocephalic-left subclavian arteries), the diameter of the aorta at various points, the minimum diameter of each branch, and each branch angle, defined as the angle between the branch and aorta axes measured at point II for each branch (acute in direction of flow, obtuse in the direction opposite the flow).

Developed films were projected on a drafting table and analyzed frame by frame with a stop-motion 16 mm movie analyzer (Vanguard Instrument Corp., Melville, NY) to yield trajectories of individual tracer microspheres as well as quantitative information on fluid velocity and wall shear rate. The wall shear stress was calculated as the product of the wall shear rate and the viscosity of the dilute suspension. An approximate estimate of the wall shear rate at any point on the aortic surface was calculated from the velocity component parallel to the wall divided by the distance to the wall of the center of the tracer microsphere observed closest to the wall. That distance ranged from 45 to 600 μm and averaged 260 μm for all steady state measurements. About two-thirds of all measurements were within 300 μm of the wall, and about 90% of the measurements in the aorta were within a distance of less than 10% of the local vessel diameter. There are two independent sources of error in the quoted wall shear stress values. The first is due to the error in the measurement of both the velocity of the near-wall microsphere and its distance from the wall. The second source of error is due to the assumption of a linear velocity profile near the wall (inherent in basing the shear stress data on the velocity of the microsphere nearest to the wall). We estimate that the error in the measurement of microsphere velocity is about 5%, as is the error in the measurement of the distance of the microsphere from the wall. By standard propagation of error analysis, this gives a relative error in the computed shear rate (and hence shear stress) due to the first source of error of about 7%. Regarding the second source of error, since the flow visualization particles used to derive shear rate data were generally within a distance of less than 10% of the local vessel diameter, the use of a single data point, i.e., the assumption of a linear velocity variation near the wall, is largely valid. For a parabolic (Poiseuille) profile, the error in the shear rate induced by assuming a linear velocity gradient over a distance of 10% of the local vessel diameter is 10%. Thus, the maximum error in shear stress is the combination of the 7% estimated measurement error and the 10% estimated error due to the assumption of a linear velocity profile near the wall.
Results

Anatomic and geometric variability

In the rabbit, the ascending aorta emerges from the left ventricle and curves with a twist towards the dorsal side of the heart to form the aortic arch. The brachiocephalic and left subclavian arteries emerge from the arch with ostia tilted towards the dorsal aspect. The geometric parameters of the aortic arch and its branches are summarized in Table 1 for five of the six rabbits studied (no geometric parameters were obtained for rabbit 1), and flow field visualization was achieved in rabbits 2 and 3 (data underlined). In some rabbits, the right and left carotid arteries insert directly into the aortic arch rather than branching several mm from the brachiocephalic entrance. The flow patterns in the vicinity of and within the brachiocephalic artery reported here would not apply to this anatomical variant.

In the abdominal aorta of all rabbits studied, both the celiac and superior mesenteric arteries emerge from the ventral aspect, and the right and left renal arteries emerge respectively from the right and left sides (in some rabbits they emerge slightly ventrally). The right renal artery is always proximal to the left renal artery. The geometric parameters of the abdominal aorta and its branches are summarized in Table 2. These parameters generally exhibited greater variability than those of the aortic arch. As in Table 1, underlined data indicate vessels for which flow visualization was carried out.

Aortic arch: steady flow

Steady flow in the arch gives rise to different categories of streamlines. These are depicted for rabbit 3 in Fig. 1. In this and subsequent flow pattern figures, all streamlines are combined in the composite drawing at the left side of the figure, while individual categories of streamlines are displayed in the four panels to the right for ease of visualization. Three line patterns are used to give a three-dimensional sense of the flow field. Solid lines denote streamlines in

<p>| Table 1 |
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| <strong>Length (mm)</strong>   | <strong>Diameter (mm)</strong> | <strong>Angle (degrees)</strong> |</p>
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*L_{bf} = distance from center of brachiocephalic entrance to carotid flow divider; L_{bbs} = shortest distance between centers of brachiocephalic and left subclavian entrances; D = diameter of aorta, minimum diameter of each branch; \theta = angle between branch axis and aorta axis (\theta = 0 means in the direction of flow); aa = ascending aorta; ma = middle of arch; da = descending thoracic aorta; b = brachiocephalic artery; Is = left subclavian artery. Underlined numbers indicate vessels for which flow visualization could be carried out.
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*L = distance between vessel axes where they intersect interpolated vessel periphery. D = diameter of aorta, minimum diameter of each branch; θ = angle between branch axis and aorta axis (θ = 0 means in the direction of flow); c = celiac; s = superior mesenteric; r = right renal; l = left renal; 1 = proximal to celiac; 2 = between celiac and superior mesenteric; 3 = between superior mesenteric and right renal; 4 = between right renal and left renal; 5 = distal to left renal. Underlined numbers indicate vessels for which flow visualization could be carried out.
the common median plane, i.e., in the plane of the figure; long dashed lines represent streamlines some distance either above or below the common median plane; and small dashed lines correspond to streamlines that are farthest away from the common median plane and near the walls closest to or farthest from the reader.

Panel A consists of relatively undeflected flow that originates in or near the common median plane and flows into the descending thoracic aorta with streamlines virtually parallel to the walls of the aortic arch. Panel B consists of secondary flow streamlines induced by the curvature of the aortic arch which originate in or slightly above the common median plane and trace a single helical clockwise spiral motion along the inner and ventral walls prior to rejoining the flow in the descending thoracic aorta. Streamlines in C and D originate in or below the common median plane. All of C and D enter the brachiocephalic artery and exhibit varying degrees of helical motion. The streamlines are deflected onto the lateral sides of the branch by the flow divider on the distal lip, proceed slowly in counterclockwise fashion along the periphery, then join the main parallel flow in the branch. Panel D also contains streamlines representing both direct flow (D1, D2) and helical flow deflected off the flow divider (D3) into the left subclavian artery. A small region of reverse flow occurred adjacent to the proximal lip of the brachiocephalic artery in association with streamlines (D4) that slowly looped around the periphery of the entrance to that artery. A region of unstructured chaotic flow recirculation was observed at the entrance of the aorta slightly downstream of the aortic sinus (not shown in Fig. 1). This region was characterized by particles that followed highly erratic trajectories. It is unclear whether this region exists physiologically or if it is an artefact of the preparation caused by an incompletely opened aortic valve.

Figure 2A contains the steady flow velocity profiles and resulting wall shear stresses in the common median plane at various locations of the aortic arch and its branches. Flow enters the aorta slightly skewed towards the outer wall. The inequality of shear stress on the inner and outer walls is more pronounced proximal to the brachiocephalic artery, is minimal distal to that branch, increases around the flow divider of the left subclavian artery, and persists into the descending thoracic aorta. Shear stress over the entire arch is less than about 20 dyne/cm² except for higher values near the left subclavian flow divider and the outer wall of the upper descending thoracic aorta. Shear stress distal to both arch branches exceeds that proximal. The ratio of distal to proximal shear stress is 1.5 and 4.1 in the brachiocephalic and left subclavian arteries, respectively.

The shear stress along the outer wall at the entrance of the brachiocephalic artery has a small negative value because of an adjacent flow recirculation zone, within which fluid moves slowly. This zone extends about 0.4 mm from the wall (10% of the branch diameter) in the common median plane. Within the left subclavian artery, the velocity profile is sharply skewed towards the downstream wall; the region near the upstream wall is occupied primarily by slowly-moving helical flow that is deflected off the branch flow divider. Except in the immediate vicinity of branches, the spatial shear stress gradients are larger along the inner wall of the arch than along the outer. For instance, proximal to the brachiocephalic artery, the estimated shear stress gradient is about 4 dyne/cm²/mm along the inner wall and 1 dyne/cm²/mm along the outer wall. Distal to the left subclavian artery, these values are 2.5 and 0.12 dyne/cm²/mm, respectively.

Flow visualization in the aortic arch of another rabbit (rabbit 2) was carried out in the same way as with rabbit 3 except that the flow division into
Fig 1. Steady flow patterns in the aortic arch of rabbit 3. The inner diameter (id) of the aorta is 6.3 mm (root), 6.8 mm (apex), and 5.5 mm (upper descending thoracic). The brachiocephalic artery has an id of 4.6 mm and divides after a length of 4.5 mm into the right and left carotid arteries (id of 2.7 and 2.4 mm, respectively). The left subclavian artery has an id of about 2.0 mm; it emerges from the arch at about 60° from the horizontal. The ventral surface is closest to the reader. Plane A-A' is a cross-sectional view of the aorta near its root illustrating the approximate origin of the various streamline categories. It is anatomically correct when rotated counterclockwise 90° on its horizontal axis (top towards reader).
Fig. 2. Flow velocity profiles in the common median plane at selected locations of the aortic arch and its branches of rabbit 3. Numbers on the aortic wall are wall shear stresses in dynes/cm²; the number associated with each profile is the maximum velocity in mm/s in that profile. Negative values of shear stress denote flow in the direction opposite to that of the time-mean bulk flow. (A) steady flow. (B) through (F) sinusoidal flow at five equally-spaced time points within a single pulsatile cycle. The vessel in Figs. 2B–2F is the same as that shown in Fig. 2A but photographed from a slightly different angle. A different scale is used in Fig. 2A as compared to Figs. 2B–2F for the size of arrows representing velocity.
the brachiocephalic artery was reduced from 0.17 to 0.12. The resulting flow patterns were very similar to those shown in Figs. 1 and 2 except in the entrance to the brachiocephalic artery where the zone of flow reversal was larger (25% of the branch diameter).

Aortic arch: pulsatile flow

Pulsatile flow in the arch of rabbit 3 was studied with a sinusoidal component superimposed on the steady flow. The sinusoid had an oscillatory frequency of 2.6 Hz and a maximum amplitude 93±16% of the mean flow. The mean flow divisions, measured by collecting the effluent from each branch over many cycles, were similar to those of steady flow (Fig. 1).

The major qualitative features observed in steady flow persist in pulsatile flow. At peak systole, the ventral-inner wall helical flow is more pronounced than in steady flow (shown for steady flow in Fig. 1, Panel B), and it disappears during a portion of diastole. The flow separation zone at the entrance of the brachiocephalic artery periodically expands and contracts, attaining its maximum extent at peak systole and disappearing completely during a portion of diastole. Near the end of the diastolic phase, flow along the inner wall and across much of the arch reverses direction and flows towards the heart. Flow along the outer wall continues in the forward direction throughout most of the flow field. Flow within the two arch branches remains in the forward direction throughout the cardiac cycle.

Figures 2B through 2F show velocity profiles and resulting wall shear stresses in the common median plane at five equally-spaced time points within one pulsatile cycle of period t. At t = 0, the velocity profile is unskewed at the inlet but becomes sharply skewed towards the inner wall proximal to the brachiocephalic artery and throughout the remainder of the aortic arch. Wall shear stress is maximal in the descending thoracic aorta, 61 and 105 dyne/cm² on the outer and inner walls, respectively. Elsewhere on the outer wall, including flow dividers, the shear stress is less than 10 dyne/cm². The reverse flow zone at the entrance of the brachiocephalic artery is absent.

At t = 0.2t (panel C), the flow has undergone sharp acceleration, and the wall shear stress is higher everywhere except in the descending aorta. The same trends are observed at t = 0.4t (panel D). The wall shear stress in panel D is higher, almost everywhere, than at t = 0.2t (panel C) except in the descending aorta. Spatial shear stress gradients are larger in the vicinity of the flow dividers of the two branches than elsewhere. At 0.6t, the flow has undergone substantial deceleration. All velocities and wall shear stresses are reduced from the previous time, with only a few sites greater than 10 dyne/cm². The reverse flow zone at the entrance of the brachiocephalic artery is absent. At 0.8t, slightly beyond peak diastole, flow reverses throughout most of the arch. The most negative shear stress, -24 dyne/cm², occurs at the inner wall of the descending aorta. Forward flow exists in a narrow region along the outer wall around the brachiocephalic artery and proximal to the left subclavian artery, and the two arch branches remain in forward flow. The reverse flow zone at the entrance of the brachiocephalic artery appears with a width of about 0.5 mm at t = 0.2t, widens to about 0.6 mm at 0.4t, and disappears for the rest of the cycle. The results in Fig. 2 indicate that at any point on the aortic wall, not only the magnitude but also the sign of the pulsatile flow shear stress may be different from its steady flow counterpart, depending on the location and the portion of the cycle examined. Furthermore, the impact of pulsatility on wall shear stress is spatially heterogeneous: at the same time point within the cycle, some shear stresses are increased while others are decreased relative to steady flow values.
Finally, no generalizations can be made in pulsatile flow regarding relative magnitudes of wall shear stress proximal and distal to aortic branches. For instance, while the shear stress distal to the brachiocephalic artery is substantially higher than that proximal at $t = 0.2\pi$ (15 vs. -3 dyne/cm$^2$, respectively), the situation is completely opposite at $0.8\pi$ (1 vs. 13 dyne/cm$^2$).

**Celiac artery**

The celiac artery is typically several aortic diameters away from its nearest major neighbor, the superior mesenteric artery, so that there is little chance of fluid mechanical interaction between the two vessels. The wall curvature at the celiac junction is sharp at the distal lip and gently rounded at the proximal lip. Steady flow patterns (rabbit 4) are illustrated in Fig. 3. The aortic flow field in the vicinity of the celiac artery is generally symmetric about the common median plane. Panel A represents relatively undisturbed flow in or near the common median plane which proceeds into or past the celiac branch with streamlines more or less parallel to the aortic walls. Panel B represents an annulus of flow slightly above and below the common median plane which curves towards the branch but is deflected downstream by the celiac flow divider. Panel C corresponds to an annulus of flow originating at regions farther from the common median plane than Panel B which encircles the core flow of Panels A and B before entering the branch, usually tracing helical trajectories. Finally, Panel D represents flow originating at both lateral walls which is deflected by the flow divider and loops very slowly along the lateral walls before moving in a helical fashion into the celiac artery. This last flow category leads to the formation of a pair of thin-layered spiral secondary flow cells along the lateral walls of the aorta adjacent to the celiac artery. The largest loop observed in rabbit 4 and shown in panel D extended about 65% of the distance from the ventral to the dorsal wall. Fluid streamlines separate from the upstream wall at the proximal lip of the celiac artery (Panel A), and the separation region is occupied by helical streamlines that enter the celiac branch (Panels C and D).

In a separate experiment with rabbit 4, the local celiac flow division $Q_2/Q_3$ was reduced from 0.30 (Fig. 3) to 0.21 as might occur in vivo during exercise. The flow patterns were generally similar except for the slowly-moving spiral secondary flow cells along the lateral walls of the aorta (panel D) which extended to only 12% of the distance towards the dorsal wall.

Velocity profiles and wall shear stresses in the common median plane in the vicinity of and within the celiac artery are illustrated in Fig. 4. Flow approaches the branch with a profile skewed towards the dorsal wall. The wall shear stresses are 30 and 13 dyne/cm$^2$ at the dorsal and ventral walls, respectively. However, immediately proximal to the celiac, the skewness shifts to the ventral wall. The asymmetry is even more pronounced immediately distal to the branch where the ventral and dorsal wall shear stresses are 51 and 6 dyne/cm$^2$, respectively. The higher shear stress along the ventral surface persists for the entire length studied. Despite the very low velocities along the dorsal wall, boundary layer separation was not observed. Within the celiac artery, flow is heavily skewed towards the distal wall. Along the ventral wall of the aorta, the spatial shear stress gradient is larger downstream of the celiac artery than upstream (13.4 and 8.6 dyne/cm$^2$/mm, respectively).
Fig. 3. Steady flow patterns in the vicinity of the celiac artery of rabbit 4. Diameter proximal to the branch is 4.2 mm and distal is 3.8 mm. Plane A-A' is anatomically correct when rotated clockwise 90° on its horizontal axis (bottom towards reader). The celiac flow rate to cardiac output ratio is 0.23.

The flow patterns in rabbits 1, 2, 5, and 6 were very similar to those of rabbit 4 except for the size of the looping spiral streamlines along the lateral walls. The domain of these streamlines in rabbits 1, 2, 4, 5, and 6 extended 70, 100, 65, 20, and 90% of the diameter towards the dorsal wall, respectively. In rabbit 5 there was also a long and thin (about 14% of the aortic diameter) region of reverse flow along the dorsal wall immediately downstream of the celiac artery. Differences among rabbits could not be attributed to variations in flow divisions since these were maintained constant (29, 33, 30, 29, and 28% for rabbits 1, 2, 4, 5, and 6, respectively). Although there were variations in local geometry (Table 2), including the aortic diameters proximal and distal to the branch (sometimes increasing, other times decreasing), branch diameter, and branch angle, there was no systematic correlation with any one variable.

Superior mesenteric artery
In the rabbit, the superior mesenteric artery is the largest abdominal branch. Like the celiac artery, the curvature of the junction is sharp at the distal lip and
gently rounded at the proximal lip. In some rabbits, the superior mesenteric and right renal arteries are sufficiently far apart that fluid mechanical interactions do not occur, and the flow field near the superior mesenteric artery resembles that observed near the celiac artery. In others, however, the superior mesenteric and right renal arteries are anatomically very close, leading to a more complex and highly asymmetric flow field such as that from rabbit 3 in Fig. 5.

Panel A contains flow originating in or near the common median plane and along the right lateral wall (toward the reader) which proceeds down the aorta past both the superior mesenteric and right renal arteries (streamlines A₁ and A₂), enters the superior mesenteric artery directly (A₅–A₇), or traces helical patterns into the superior mesenteric artery (A₃, A₄). Panel B contains streamlines originating slightly to the anatomical left of the common median plane (B₁, B₂) that curve towards the ventral wall due to the presence of the
Fig. 5. Steady flow patterns in the vicinity of the superior mesenteric artery of rabbit 3. Aortic diameter proximal to the branch is 4.0 mm, that distal is 3.1 mm. The superior mesenteric and right renal arteries emerge from the aorta almost at a right angle to one another; the portion of the right renal artery shown is the projection in the plane of the superior mesenteric artery. The superior mesenteric and right renal flow rates to cardiac output ratios are 0.33 and 0.06, respectively. Plane A-A' is anatomically correct when rotated clockwise 90° on its horizontal axis (bottom towards reader).
branches but continue downstream past both branches; streamlines originating at the dorsal wall (B3–B5) encircle the core flow before entering the superior mesenteric artery. Panel C also combines two groups of streamlines. C1 and C2 originate near the common median plane and pass the superior mesenteric artery before entering the right renal artery. C3 to C6 originate at the left lateral wall and curl counterclockwise onto the dorsal wall and then the right lateral wall where they proceed upstream and enter the superior mesenteric artery along the right lateral wall. This last streamline group leads to flow reversal along the right lateral wall. Panel D contains flow originating near the left lateral wall which curls in clockwise helical motion onto the ventral and then the right lateral wall (where it attains its maximum distal penetration) until it reaches the left lateral wall (while at the same time moving upstream); it enters the superior mesenteric artery from the left lateral side where it spirals into the branch.

The relatively large flow rate through the superior mesenteric artery causes fluid streamlines to separate from the wall at the level of and distal to the superior mesenteric artery along the dorsal and left lateral walls (Panel D). As in the case of the celiac artery, fluid streamlines separate from the ventral wall at the proximal lip of the superior mesenteric artery, but flow recirculation is not observed, and the region is occupied by helical flow from the aorta (e.g., streamlines D1 and D2).

When the superior mesenteric flow division Qs/Qa is reduced from 0.63 to 0.34, as may happen during exercise, the looping streamlines on the lateral walls (panel D) are reduced in size. The largest loop no longer reaches the dorsal wall and is comparable to streamline D2, which extends about 50% of the distance towards the dorsal wall and proceeds axially as far as the proximal wall of the right renal artery.

Figure 6 illustrates velocity profiles in the common median plane in the vicinity of and within the superior mesenteric artery. Flow approaches the branch with a nearly parabolic profile and becomes skewed towards the ventral wall immediately proximal and distal to the superior mesenteric artery. The shear stress is relatively high (26 dyne/cm²) along the ventral wall distal to the ostium, while the dorsal wall experiences flow separation and negative values of shear stress (−7 dyne/cm²). Distal to the right renal artery, the ventral wall experiences a relatively high shear stress (33 dyne/cm²), while the dorsal wall remains exposed to reverse recirculating flow (−4 dyne/cm²). Within the superior mesenteric artery itself, the shear stress is considerably higher along the distal wall (55 dyne/cm²) than along the proximal wall (33 dyne/cm²) as the flow negotiates the curvature of the branch.

Two aspects of the flow patterns around the superior mesenteric artery varied from animal to animal. (1) Rabbit 5 gave results very similar to that of rabbit 3 (Figs. 5 and 6) in all aspects. In both rabbits the distance between the superior mesenteric and right renal arteries was within 1 to 2 aortic diameters (from Table 2, Ls/D3 = 1.2 and 1.5, respectively), and interaction of the flow to the two branches occurred, leading to very large looping streamlines that proceeded downstream as far as the right renal flow divider. In rabbits 1, 2, and 6, the branches were further apart (Ls/D3 = 2.1, 3.6, and 2.0, respectively). No interaction occurred, and the flow patterns around the superior mesenteric artery resembled those around the celiac artery (Fig. 3). (2) The size of the lateral helical flow regions, similar to those shown for the celiac artery in Fig. 3D, spanned about 10, 50, and 10% of the aortic diameter in rabbits 1, 2, and 6, respectively, for which the branch flow divisions were 34, 30, and 34%, respectively. As in the case of the celiac artery, there was no systematic correlation with any single geometric parameter in Table 2.
Fig. 6. Steady flow velocity profiles in the common median plane at selected locations in the vicinity of the superior mesenteric artery of rabbit 3.

Right and left renal arteries

A representative steady flow field from rabbit 4 in which there is only slight fluid mechanical interaction between the superior mesenteric and right renal arteries is shown in Fig. 7. Like the celiac and superior mesenteric arteries, the curvature of the renal junctions is sharper at the distal lips than at the proximal lips. Panel A consists of a group of streamlines (A₁–A₃) in the common median plane which flow past both arteries and continue downstream, and a second group (A₄–A₆), originating near the left lateral wall, which flows directly into the left renal artery. Panel B also contains two groups. The first (B₁, B₂) originates near the right lateral wall and is deflected at the right renal flow divider before entering the right renal branch. Streamline B₃, which originates between the common median plane and the ventral wall, follows a small secondary flow loop which is similar to the larger lateral helical zones observed near the celiac and superior mesenteric arteries. The second group (B₄, B₅) originates either in the common median plane or near the dorsal wall (away from the reader), curves toward the right lateral wall due to the presence
Fig. 7. Steady flow patterns in the vicinity of the right and left renal arteries of rabbit 1. The diameter proximal and distal to the renal artery is 3.8 mm. The diameter distal to the left renal artery is 3.4 mm. The right renal and left renal flow rate to cardiac output ratios are 0.05 and 0.04, respectively. Plane A-A is anatomically correct when rotated clockwise 90° on its horizontal axis (bottom towards reader).
of the right renal artery, is deflected off the flow divider and then traverses the dorsal half of the aorta before entering the left renal artery. Panel C contains three groups, C₁ and C₂ originate near the right lateral wall and flow virtually undeflected into the right renal artery. C₃ originates on the ventral wall and enters the right renal artery where it traces a helical trajectory. C₄ and C₅ originate between the common median plane and the dorsal wall and flow into the left renal artery. In panel D, streamlines D₁–D₃ originate slightly above and below the common median plane, are deflected first towards the right lateral wall, then towards the left lateral wall, and finally continue into the lower abdominal aorta. Streamlines in panels B, C, and D demonstrate a mild degree of fluid mechanical interaction between right and left renal arteries in rabbit 4 for which Lₑ₁/D₄ = 1.5. The interaction was correspondingly smaller in rabbits 1, 2, 3, and 6 for which Lₑ₁/D₄ = 1.8, 1.9, 2.5, and 3.7, respectively.

Velocity profiles and wall shear stresses in the common median plane in the vicinity of and within the two renal arteries are shown in Fig. 8. The inlet profile is sharply skewed towards the right lateral wall due to the presence of the right renal branch. Immediately proximal to the right renal artery, the wall shear stress is 27 and 3 dyne/cm² at the right and left lateral walls, respectively. The profile is even more skewed distal to the right renal branch where the shear stress is 44 dyne/cm² along the right lateral wall and 3 dyne/cm² along the left. As the flow is about to enter the left renal artery, the profile is less skewed towards the right lateral wall. Beyond the left renal branch, the flow remains skewed towards the right (17 dyne/cm² along the right lateral wall and 4 dyne/cm² along the left lateral wall), and this trend decreases but persists further down the abdominal aorta.

The flow field in Figs. 7 and 8 applies when the inferior mesenteric and right renal arteries are relatively far apart. When these two vessels are in close proximity (such as in Figs. 5 and 6), the flow field follows the same general trends as in Figs. 7 and 8, except for the presence of a zone of flow recirculation and reverse flow distal to the right renal artery along the aortic left lateral wall. Under these conditions, the wall shear stress immediately distal to the right renal artery along the left lateral wall is negative.

Discussion

The present study reports the most extensive investigation to date of the flow patterns in the normal rabbit aorta and its major branches. The overall goal of the study was to characterize flow patterns and to investigate their possible connections to the localized distribution of enhanced permeability sites. These sites, which were first discovered in the rabbit, have also been observed in the squirrel monkey (Tomkins et al., 1988) and may play an important role in the development of atherosclerosis. The topography of early atherosclerotic lesions in the rabbit differs from that in man; however, similar processes may occur in the genesis of lesions in both species. The rabbit represents a particularly attractive animal model due to the ease of experimental induction of atherosclerotic lesions as well as the high reproducibility in the topography of early lesions (Schwenke and Carew, 1988).

Flow patterns in this study were investigated using a microcinematographic flow visualization technique in natural isolated aortas that had been rendered transparent. Advantages of this technique include capturing geometric details (natural aorta), minimal optical distortion, and a high level of fluid mechanical detail. Limitations of the method include the inability to perform pulsatile flow experiments in the abdominal aorta due to vessel collapse. The
following assumptions are inherent in the analysis of tracer microsphere trajectories. (1) The microspheres follow the fluid streamlines exactly. This assumption is generally valid when the particle’s Reynolds number based on the slip velocity and microsphere diameter is very small. We estimated the slip velocity for a 100 μm diameter particle flowing at 50 mm/s around a 100 μm radius of curvature by equating the difference in centrifugal force between the particle and fluid to the drag force on the sphere. The resulting Reynolds number is of the order of magnitude of 10^{-2}; thus, particle inertial effects are minimal. In addition, estimates of the lift velocity (Zydney and Colton, 1986) of the smaller particles (in the radial direction across the aorta) arising from the lateral migration phenomenon are roughly three orders of magnitude or more smaller than axial velocities indicating that the effect is minimal. (2) The maximum particle velocity occurs in the common median plane. Microsphere trajectories observed from two orthogonal directions whenever possible demonstrate that this second assumption does not introduce significant error.

Visualization of steady flow reveals the presence of complex flow within the aorta including extensive secondary flow. Separation of streamlines from the
wall is observed at the inner wall of the arch and proximal to both arch branches. A single cell of clockwise-rotating helical flow is present along the inner and ventral walls of the arch. Flow within the two branches contains helical components originating from streamlines deflected off the branch flow dividers, and a region of reverse flow occurs at the entrance of the brachiocephalic artery. The velocity profiles in the entire arch in the common median plane are skewed towards the outer wall. In the abdominal aorta, there are streamlines that deflect off the flow dividers of all branch ostia and follow slow looping trajectories along the lateral walls before tracing helical paths into the branches. Flow separation occurs along the dorsal wall opposite the superior mesenteric artery, and this separated flow region is occupied by recirculating streamlines. The superior mesenteric and right renal arteries are often in close anatomic proximity, resulting in more complex flow in that region.

Wall shear stresses are generally higher distal to aortic branches than proximal with the exception of the left renal artery, upstream of which the velocity profile is sharply skewed towards the anatomical right wall. Thus, care must be exercised in making a priori generalizations about relative magnitudes of proximal and distal shear stresses, particularly in the case of vessels in close anatomic proximity with fluid mechanical interaction. Spatial gradients of wall shear stress are significantly higher in the vicinity of aortic branches than elsewhere, in agreement with the results of Lutz et al. (1977) in a model of the dog abdominal aorta.

Pulsatile flow was studied in the rabbit aortic arch by superimposing a sinusoidal flow component onto steady flow. The sinusoidal waveform we employed differed significantly from the rabbit cardiac waveform (Barakat, 1994). Specifically, at the aortic root (ascending thoracic aorta), the physiological waveform was in forward flow about 40% of the cardiac cycle and in reverse flow about 60%. In contrast, our sinusoidal waveform at its most extreme was in reverse flow during only about 13% of the cycle (from 1.37π to 1.63π out of a complete cycle, 2π). The physiological waveform is also more sharply peaked in forward flow, with a peak forward to mean flow rate ratio of about 2.8 as compared to 1.93 (range about 1.8 to 2.1) for our sinusoid. The ratio of peak reverse to mean flow rate is 15% and 9% for the physiological and sinusoidal waveforms, respectively. Thus, we speculate that the magnitude of the phenomena we observed with pulsatile flow would be even larger with a physiological waveform because of its more sharply peaked forward flow and its larger magnitude and longer period of reverse flow.

In sinusoidal pulsatile flow, the helical motion along the ventral and inner walls of the arch becomes very pronounced at peak systole. That large region, the small region of secondary flow proximal to the left subclavian artery, and the zone of reverse flow at the proximal entrance of the brachiocephalic artery periodically expands and contracts and disappears altogether during portions of diastole. Reverse flow is observed along the entire inner but not the outer wall (except in the descending aorta) during a portion of the diastolic phase. Changes in shear stress and shear stress gradients with pulsatile flow are especially large around the distal flow divider of the left subclavian artery, the inner and outer walls of the descending aorta, and the flow separation zone of the brachiocephalic artery.

The topographical distribution of sites of enhanced permeability to horseradish peroxidase and low density lipoprotein in the normal rabbit aorta is generally similar to that of early atherosclerotic lesions in the hypercholesterolemic rabbit (Barakat et al., 1992). The enhanced permeability sites follow a helical pattern in the arch, beginning along the dorsal wall in the
ascending aorta, ceasing in the clockwise direction onto the outer wall immediately distal to the left subclavian artery, and then continuing onto the ventral wall in the upper descending thoracic aorta. The density around each ostium is diffuse; the highest densities occur distal to the left subclavian artery and proximal to the brachioccephalic artery, on both the outer and dorsal walls. Outside the arch, enhanced permeability sites often occur in streaks oriented in the bulk flow direction. In the abdominal aorta, streaks of enhanced permeability foci are present along the dorsal and lateral walls proximal to the celiac artery and along the ventral wall between the celiac and superior mesenteric arteries. The density of sites is usually highest in the immediate vicinity (within 1-2 mm) of arterial branches with the most elevated density being distal to branches in most cases.

Steady flow in the aortic arch, like the distribution of enhanced permeability sites, exhibits a clockwise helical pattern. However, the helical motion is confined to the inner and ventral wall of the vessel and does not reach the dorsal wall. In pulsatile flow, the flow field displays significant temporal variations, and we speculate that the helical motion may well extend to the dorsal wall of the arch under physiological conditions. The highest density of enhanced permeability sites around ostia in the arch corresponds to the oscillating flow recirculation zone proximal to the brachioccephalic and to the region distal to the left subclavian artery, both of which exhibit large changes in wall shear stress and shear stress gradient in pulsatile flow. These findings are consistent with observations of higher division rates in cultured endothelial cells exposed to large shear stress gradients than those exposed to uniform flow, and are also consistent with the speculation that large shear stress gradients may induce important morphological and functional changes in endothelium (DePaola et al., 1992). In a study of endothelial cell shape distal to the brachioccephalic and left subclavian arteries in the rabbit (Okano and Yoshida, 1992), regions within 150-200 μm of the flow divider exhibited rounded endothelial cells representative of exposure to relatively low shear stress. Steady flow visualization revealed that fluid streamlines which deflected off flow dividers separated from the wall over the 150-200 μm region, and this zone was occupied by secondary flow streamlines. Our pulsatile flow results indicate that the same microscopic separation zones would periodically appear and disappear with pulsatility, thereby exposing underlying endothelial cells to large changes in shear stress and shear stress gradients.

Early lesions around abdominal branches localize lateral and distal to ostia (Zeindler et al., 1989), while the density of enhanced permeability sites is highest distal to ostia. The steady flow results of this study suggest that lateral and distal regions are exposed to significantly different levels of shear stress. Regions lateral to ostia correspond to zones of very slowly moving lateral secondary flow loops and hence to locations of very low shear stress. Conversely, wall shear stress distal to branches is generally high with the exception of the left renal artery where it is low (4 dyne/cm²). Both regions, however, are characterized by large spatial shear stress gradients. Furthermore, in the case of pulsatile flow, the lateral loops may periodically expand and contract in a fashion similar to the recirculation zones in the aortic arch and as has been observed in a model of flow around the rabbit celiac artery (Malinauskas et al., 1993).

The impact of the loss of vessel wall compliance on the flow field is not known because the results of previous studies on the effect of wall motion are not consistent. For example, Reneman et al., (1985) investigated flow velocity patterns of the carotid artery in younger and older normal subjects and reported significantly lower diastolic flow in the older group as well as associated
diminished flow separation and recirculation in the carotid bulb. Conversely, 
Liesch and Moravec (1984) measured the sinusoidal pulsatile velocity profiles 
in rigid and compliant casts of the femoral artery bifurcation and reported that 
wall compliance eliminated flow reversal along the lateral walls of the 
preparation. Duncan et al., (1990) investigated the effect of compliance on wall 
shear stress in casts of a human aortic bifurcation. They reported that 
compliance usually reduced shear rates on the outer walls as compared to that 
in a rigid model but that compliance increased shear rate on the inner walls.

Our results in the arch are in general agreement with qualitative 
observations in scaled-up two-dimensional plastic models of the rabbit aortic 
arch (Rodkiewicz, 1975). In that study, all areas exhibiting secondary flow were 
occupied by recirculating streamlines within closed separated flow regions, the 
boundaries of which oscillated with pulsatile flow. In this study with a three-
dimensional vessel geometry, most regions of secondary flow are occupied by 
helical motion and these regions may disappear completely during a portion of 
the diastolic phase. These findings are also qualitatively similar to observations 
reported for flow in the dog aortic arch, including steady flow measurements 
using microcinematography in transparent vessels (Schara and Karino, 1985) 
and physiological pulsatile flow measurements using in vivo pulsed Doppler 
ultrasound (Farthing and Peronneau, 1979). The latter study revealed reverse 
flow primarily along the inner wall of the arch during the diastolic phase, while 
the flow within the arch branches remained in the forward direction 
throughout the cardiac cycle. Our observation that the velocity profile in the 
aortic arch of the rabbit is skewed towards the outer wall is also consistent with 
previous observations in other species (Caro et al., 1978; Pedley, 1980). The 
occasional occurrence of flow reversal and negative shear stress opposite flow 
dividers has also been reported in several previous studies (Ku et al., 1985; Van 
de Vosse et al., 1990; Moore et al., 1991; Pedersen et al., 1992).

In the abdominal aorta, the steady flow results are qualitatively very similar 
to observations obtained with microcinematography in glass models (Karino et 
al., 1979; Karino and Goldsmith, 1983) and in the dog abdominal aorta 
(Karino et al., 1990). In vivo pulsed Doppler ultrasound measurements on the 
dog abdominal aorta (Hutchison et al., 1988) in the vicinity of the superior 
mesenteric and renal arteries also produced observations of small regions of 
local recirculation during systole as well as large regions of flow reversal 
opposite to aortic ostia during diastole.

This study has demonstrated that, even in steady flow, the flow field within 
the rabbit aorta and its major branches is very complex including extensive 
secondary flow motion and regions of flow separation and recirculation. A 
wide range of wall shear stresses is observed. Flow pulsatility results in periodic 
appearance and disappearance of secondary flows, leads to flow reversal in 
certain locations but not others, and introduces substantial temporal variations 
in wall shear stress and its spatial gradients. Animal-to-animal variations in flow 
patterns consisted of differences in the precise character of the secondary flow 
patterns and the extent of fluid mechanical interaction between vessels in close 
anatomic proximity. The latter depends upon the relative distance between 
ostia; the former may depend in a complex way on geometric parameters and 
flow divisions.

References

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Flow patterns in the rabbit aorta


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