15:17:40 OCA PAD AMENDMENT - PROJECT HEADER INFORMATION 04/20/92

Active

Project #: E-16-M33 Cost share #: Rev #: 1
Center # : 10/24-6-R7420-0A0 Center shr #: OCA file #:
Work type : RES
Contract#: AGMT DTD 920115 Mod #: LTR DTD 4/8/92 Document : CONT
Prime #: 2 P50 HL15062-21 Contract entity: GTRC

Subprojects ? : N CFDA:
Main project #: PE #: N/A

Project unit: AERO ENGR Unit code: 02.010.110
Project director(s):
GIDDENS D P AERO ENGR (404)894-3781

Sponsor/division names: UNIV OF CHICAGO / CHICAGO, IL
Sponsor/division codes: 400 / 015

Award period: 920101 to 921130 (performance) 930115 (reports)

| Sponsor amount | New this change | Total to date |
|---|---|---|
| Contract value | 0.00 | 133,771.00 |
| Funded | 0.00 | 133,771.00 |
| Cost sharing amount | | 0.00 |

Does subcontracting plan apply ?: N

Title: INFLUENCE OF HEMODYNAMIC WALL SHEAR & PARTICLE RESIDENCE TIME ON ATHEROGENESI

PROJECT ADMINISTRATION DATA

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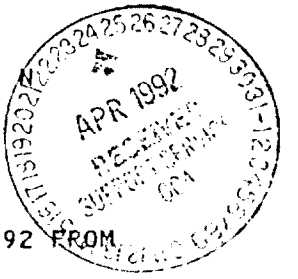
Security class (U,C,S,TS) : U ONR resident rep. is ACO (Y/N): N
Defense priority rating : N/A N/A supplemental sheet
Equipment title vests with: Sponsor X GIT
NONE PROPOSED.
Administrative comments -
PROJECT START DATE REMAINS THE SAME PER CONTRACT, HOWEVER LTR DTD 4/8/92 FROM SPONOSR AUTHORIZES 90 DAY PREAWARD COSTS.



GEORGIA INSTITUTE OF TECHNOLOGY
OFFICE OF CONTRACT ADMINISTRATION

NOTICE OF PROJECT CLOSEOUT

Closeout Notice Date 12/11/92

Project No. E-16-M33 Center No. 10/24-6-R7420-0A0

Project Director GIDDENS D P School/Lab AERO ENGR

Sponsor UNIV OF CHICAGO/CHICAGO, IL

Contract/Grant No. AGMT DTD 920115 Contract Entity GTRC

Prime Contract No. 2 P50 HL15062-21

Title INFLUENCE OF HEMODYNAMIC WALL SHEAR & PARTICLE RESIDENCE TIME ON ATHEROGE

Effective Completion Date 921130 (Performance) 930115 (Reports)

| Closeout Actions Required: | Y/N | Date Submitted |
|---|---|---|
| Final Invoice or Copy of Final Invoice | Y | |
| Final Report of Inventions and/or Subcontracts | Y | |
| Government Property Inventory & Related Certificate | N | |
| Classified Material Certificate | N | |
| Release and Assignment | N | |
| Other | N | |

CommentsEFFECTIVE DATE 1-1-92. CONTRACT VALUE $133,771.

Subproject Under Main Project No.

Continues Project No. E-16-660

Distribution Required:

| | |
|---|---|
| Project Director | Y |
| Administrative Network Representative | Y |
| GTRI Accounting/Grants and Contracts | Y |
| Procurement/Supply Services | Y |
| Research Property Managment | Y |
| Research Security Services | N |
| Reports Coordinator (OCA) | Y |
| GTRC | Y |
| Project File | Y |
| Other HARRY VANN-FMD | Y |
| FRED CAIN-OOD | Y |

NOTE: Final Patent Questionnaire sent to PDPI.

PROJECT 2. INFLUENCE OF HEMODYNAMIC WALL SHEAR AND PARTICLE RESIDENCE TIME IN ATHEROGENESIS

1. Specific Aims

The specific aims funded in Task 2 were as follows:

Specific Aim #1. Design and construct large scale flow models of the coronary arteries based upon anatomic data from humans.

Specific Aim #2. Measure velocity profiles and wall shear at appropriate locations in the models using laser Doppler velocimetry (LDV) under physiologic, pulsatile flow conditions.

Specific Aim #3. Measure the particle residence time (PRT) of small, neutrally buoyant particles under pulsatile, physiologic flow conditions in the coronary artery models.

Specific Aim #4. Measure intimal thickness and atherosclerotic plaque thickness in human coronary arteries harvested at autopsy. The arteries will be selected to be close to the geometry of the flow models.

Specific Aim #5. Correlate the hemodynamic data with the morphometric data using appropriate statistical methods to determine those hemodynamic variables that are associated with intimal thickness/plaque localization to a significant degree.

Specific Aim #6. Pool all data from the human coronary and (previously studied) human carotid arteries to determine those hemodynamic variables which are significantly associated with intimal thickening/plaque localization in both vessels.

Specific Aim #7. Repeat Specific Aims #2 and #3 for flow conditions which simulate various heart rates and degrees of exercise and correlate the results with studies of coronary atherosclerosis performed in cynomolgus monkeys at The University of Chicago under the previous SCOR.

These specific aims were designed, in combination with Tasks 1 and 3 of the SCOR, to provide the hemodynamic information necessary to develop and test hypotheses relating to mechanisms linking hemodynamic factors with atherogenesis.

2. Studies and Results

Specific Aim #1 has been completed. Two large scale models that simulate the geometry of human coronary arteries were constructed. The models were of the same dimensions except for the angle of bifurcation of the left main (LM) coronary artery into the left anterior descending (LAD) and left circumflex (LCX) vessels, which were chosen in this manner so that the effects of bifurcation angle on flow patterns could be studied. Model 1 has the characteristic of being more nearly a Y-bifurcation, while Model 2 is such that the LAD is more nearly a continuation of the LM with the LCX being a side branch. Both such configurations are common among human subjects.

Specific Aim #2 has been completed for Model 2. Extensive LDV measurements of velocity profiles and wall shear have been performed under physiologic flow conditions with flow waveforms simulating those found in the human LM coronary artery. A manuscript is in preparation describing these results. Regions of low wall shear occur along the outer walls of the bifurcation, i.e., at the lateral walls of the LCX and LAD vessels. Relatively high wall shear was present along the flow divider surfaces. A brief summary of the wall shear results is presented in Table 1.

Specific Aim #3 has been partially accomplished. Prior to being able to measure particle residence time (PRT) in the coronary models, it was necessary to perfect the experimental tool of particle tracking, a technique that began its development under previous SCOR funding. The particle tracking scheme permits a computer to identify the position coordinates of small, neutrally buoyant particles in three spatial dimensions, from which particle trajectories and velocities can be reconstructed. This *automated* image processing method has been verified in separated flow conditions under steady flow using a 50% axisymmetric stenosis model. Two manuscripts (MS #1 and #2) have been written describing the method and the stenosis results, and these will be submitted before the end of the first year of current SCOR funding. The software to determine PRT is under development and has been tested for the stenosis model

with success. A manuscript describing these initial PRT results has been written and submitted for presentation and publication (MS #3). Figure 1 presents an example result from the particle residence time measurements.

Specific Aim #4 has been partially accomplished. Two life size templates which capture the two model geometries (i.e., mimic the coronary artery vessel diameters and the two bifurcation angles) have been prepared. These templates are overlaid upon the human hearts harvested at The University of Chicago by Dr. Glagov in order to select those coronary arteries which closely follow the two flow model geometries. This gives two sets of human coronary arteries, one set for each bifurcation angle. The vessels are then studied by measuring intimal thickness as a function of spatial location at those sites where velocity and wall shear were determined in the flow model studies. To date, approximately 20 such coronary arteries have been studied.

No work has been performed on Specific Aims #5-#7. However, qualitative observation of the regions of increased intimal thickening and low wall shear appears to confirm the hypothesis that the coronary arteries develop plaques preferentially at sites of low wall shear.

Because of our interest in using the correlative studies of Task 2 to hypothesize mechanisms for atherogenesis, we also undertook a set of preliminary studies on the effects of flow patterns on monocyte adhesion in model studies. Monocytes appear to be early participants in atherogenesis, and it is our hypothesis that the distribution of monocyte adhesion is affected strongly by hemodynamic factors. We constructed tubular flow models of a novel design that produced various levels of wall shear in the same model. The geometry was such that the first segment of the tube was of constant cross sectional area, providing a region of constant wall shear. This was followed by a tapered section which causes an increasing wall shear. The tapered section terminates in an abrupt expansion into a larger cross sectional area, resulting in flow separation and low shear. The model construction allowed the introduction of chemoattractants at selected sites without disturbing the flow field. We performed measurements of U937 cell adhesion under steady flow conditions in the models using video phase microscopy and measured cell rolling velocity along the tube walls. This cell line is readily available in adequate quantities and has characteristics sufficiently close to isolated human monocytes that it is appropriate for surface adhesion investigations. Using computational fluid dynamics, i.e., the numerical solution of the Navier-Stokes equations for the flow conditions studied, we determined the velocity field and the wall shear. Data show that (i) the rolling velocity follows the wall shear very precisely, and (ii) cell adhesion was increased in regions of low shear and eliminated in regions of high shear. Additionally, the asymmetrical introduction of a chemoattractant agent in the flow separation region affected the symmetry of cell adhesion there. The results have been presented at a recent FASEB meeting and have been accepted for presentation and publication at the coming ASME Meeting, Bioengineering Division (MS #4). Figure 2 presents the measured results for U937 cell rolling velocity along the model surfaces and compares these with the normalized values of wall shear stress as calculated from the Navier-Stokes equations (solid line). The direct relationship between theory and experiment is indicative of the strong effects exerted by near wall hemodynamic behavior upon cell motion.

3. Significance

Studies in the first year of SCOR have provided the following significant results:

(i) The development of our computerized particle tracking method and the PRT software has been completed for steady flow applications, thus providing a major tool for biofluid dynamic research. This new experimental method will permit much more comprehensive fluid dynamic studies to be performed than are currently possible with the LDV method, and it is particularly important in the investigation of cell and particle motion near surfaces. (ii) Indications to date are that the same hemodynamic factors associated with plaque localization in human carotid arteries will be found to hold for human coronary arteries. If this early indication holds up under further scrutiny, it will demonstrate that the relationship between low wall shear and localization of atherosclerosis is not specific to the carotid bifurcation only. (iii) The monocyte adhesion experiments show the strong effect of wall shear on monocyte rolling velocity and

adhesion in models, thus providing a direct link with near wall fluid dynamics and cell behavior near surfaces. These results suggest the possibility that monocyte adhesion is more likely in regions of low wall shear, a factor which may partially explain the predilection of atherogenesis for low shear sites. Clearly, additional studies with biologic surfaces are needed.

4. Plans

During the remainder of year one and for year two of the SCOR we will complete Specific Aim #2 for Model 1 of the coronary arteries and will correlate the morphometric data on intimal thickness from the human vessels harvested and studied at Chicago. The particle tracking and PRT measurements will be extended to steady flow in the coronary artery models, i.e., Specific Aim #3, so that these data will be available for correlation (Specific Aim #5) with intimal thickness measurements (Specific Aim #4) as well as the LDV data. Thus, we are making good progress in achieving the specific aims of Task 2. However, the results obtained in the monocyte adhesion studies have proven extremely interesting and relevant to the scientific nature of the project, and we plan to continue the analysis of these data in order to determine whether this line of investigation will elucidate the mechanisms through which low wall shear and long particle residence time are associated with atherogenesis.

Finally, we collaborate frequently with investigators in Tasks 1 and 3 of the SCOR to help bring to bear engineering principles upon the interpretation of biologic data. The presentations and publications co-authored with investigators in these tasks are illustrative of this close collaboration.

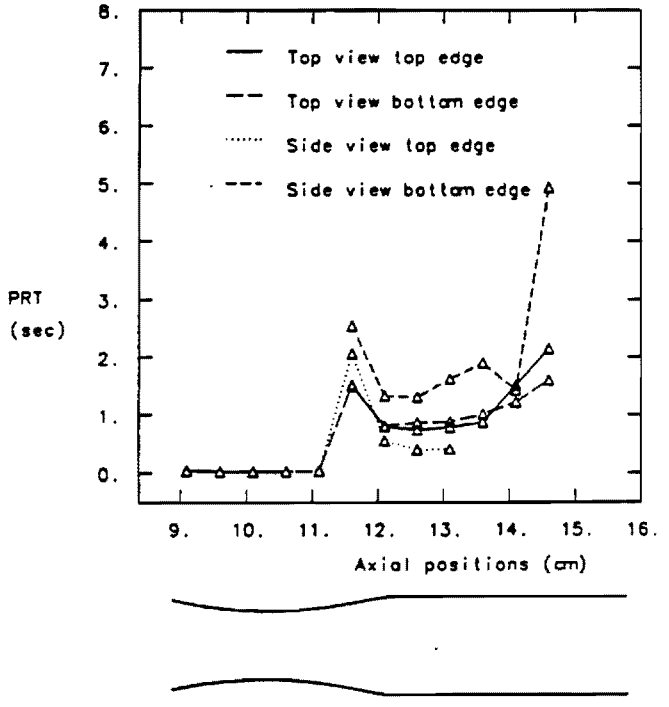



Figure 1. Particle residence time data from a stenosis model with 50% area reduction and a Reynolds number of 450. The lower portion of figure shows the model geometry with flow from left to right. Flow separates from the model surface immediately downstream of the throat and reattaches approximately 4.5 cm down-stream. The increased particle residence time in the separation region is indicative of the lower wall shear in this zone.

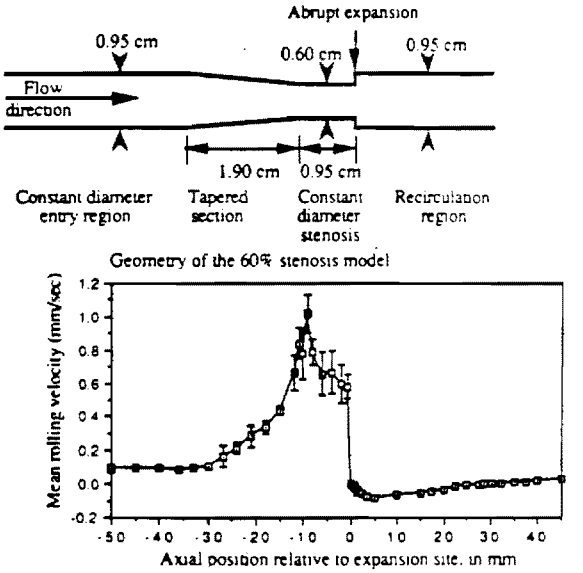



Figure 2. Comparison of measured cell rolling velocity with calculated normalized wall shear in the monocyte adhesion model. Bottom view shows the model geometry. The rolling velocity is graphed as a function of axial location and illustrates the increased velocity in the tapered region, followed by velocities of low magnitude and retrograde direction in the separation region.

**MEAN WALL SHEAR STRESS**
**AXIAL COMPONENT - DYNES/CM²**

| SITE | EPICAR | MYOCAR | OUTER | INNER |
|---|---|---|---|---|
| LM1 | 21.8 | 10.4 | 23.5 | 25.0 |
| LAD1 | 17.6 | 8.9 | 10.2 | 27.5 |
| LCX1 | 25.3 | 10.5 | 5.4 | 29.2 |

Table 1. Measured values of mean (time-averaged) wall shear stress at selected sites in coronary artery model #2. The three sites shown are each in the immediate neighborhood of the bifurcation, and the columns refer to epicardial, myocardial, outer (opposite flow divider) and inner (flow divider) surfaces. Average wall shear stresses in straight arteries are typically approximately 15 dynes/cm². It is seen that the myocardial and outer walls of the coronary arteries in the vicinity of the bifurcation tend to have significantly lower shear stress than the epicardial and flow divider surfaces.

Papers Presented

1. A.S. Anayiotos, D.P. Giddens, S. Glagov, and C.K. Zarins; December 1-6, 1991, "Effects of Arterial Wall Distensibility on the Near Wall Flow Field in a Model of a Human Carotid Bifurcation," ASME Winter Annual Meeting, Atlanta, Ga.

2. D. O'Leary, S. Glagov, C. Zarins and D. Giddens, December 1-6, 1991, "Carotid Artery: Disease," Syllabus: Special Course "Ultrasound 1991," 77th Scientific Assembly and Annual Meeting of the Radiological Society of North America, pp. 189-200.

3. Francis Loth, M.S. Hisham, S. Bassiouny, S.A. Jones, D.P. Giddens, S. Glagov, and C.K. Zarins, December 4-15, 1991, "Velocity and Wall Shear Measurements in an end-to-side Vascular Anastomosis Model," NATO Advanced Study Institute on "Frontiers in Cardiovascular Engineering" at Malaga, Spain.

4. S. Glagov, R. Vito, D.P. Giddens and C.K. Zarins, "March 6-7, 1992, "Microarchecture and Composition of Artery Walls: Relation to Location, Diameter and the Distribution of Mechanical Stresses," A. Workshop of the International Society of Hypertension on Arterial Compliance, Paris, France.

5. W.F. Pritchard, P.F. Davies, D.C. Polacek, R.O. Dull, S.A. Jones and D.P. Giddens, April 4-8, 1992, "The Pattern of Adhesion of &937 Cells in a Flow Model is Determined by Local Hemodynamic Factors and is Modulated by Chemoattractant Gradients," Poster Session, FASEB, Anaheim, CA.

6. S. Glagov, R. Vito, D.P. Giddens and C.K. Zarins, "April 9, 10, 14, 1992, "Ultrastructure and Organization of the Extracellular Matrix of Arteries," Meeting of British Connective Tissue Society on "The Role of Connective Tissue in Vascular Physiology and Pathology" and on "In Vitro Systems for Cyclic Mechanical Stresses on Cell," Imperial College, London.

7. S. Glagov, H,. Bassiouny, D.P. Giddens and C.. Zarins, September 13-18, 1992, "Induction and Composition of Intimal Thickening and Atherosclerosis," 16th World Congress of the International Union of Angiology, Paris, France.

8. R. Tsao, S.A. Jones, D.P. Giddens, C.K. Zarins, and S. Glagov, September 21-25, 1992, "Measurements of Particle Residence Time and Particle Acceleration in an Arterial Model by an Automatic Particle Tracking System," 20th International Congress on High Speed Photography and Photonics, Victoria, B.C. Canada.

9. W.F. Pritchard, P.F. Davies, D.C. Polacek, Z. Derafshi, R.O. Dull, S.A. Jones and D.P. Giddens, November 9-12, 1992, "Influence of Hemodynamic Factors on the Adhesion Pattern of U937 Cells in a Flow Model: Implications in Atherosclerosis," ASME Winter Annual Meeting, Anaheim CA.

10. S. Glagov, D.P. Giddens, R. Vito, H. Bassiouny and C.K. Zarins, November 9-12, 1992, "Tissue Reactions to Mechanical Stresses in Relation to Artery Stability," ASME Winter Annual Meeting, Anaheim, CA.

Manuscripts Submitted

1. R. Tsao, S.A. Jones, D.P. Giddens, C.K. Zarins and S. Glagov, "Development of an automatic three-dimensional particle tracking technique for the measurement of steady flow in modeled flow fields: I. Theory and Methodology," to be submitted to Experiments in Fluids.

2. R. Tsao, S.A. Jones, D.P. Giddens, C.K. Zarins, S. Glagov, "Development of an automatic three-dimensional particle tracking technique for the measurement of steady flow in modeled flow fields: II. Comparison to laser Doppler anemometry," to be submitted to Experiments in Fluids.

3. R. Tsao, S.A. Jones, D.P. Giddens, C.K. Zarins, and S. Glagov, "Measurement of particle residence time and particle acceleration in an arterial model by an automatic particle tracking system, to be published in the Proceedings, 20th International Congress on High Speed Photography and Photonics, Vancouver, B.C., September 21-25, 1992.

4. W.F. Prtichard, P.F. Davies, D.C. Polacke, Z. Derafshi, R.O. Dull, S.A. Jones and D.P. Giddens, "Influence of hemodynamic factors on the adhesion pattern of U937 cells in a flow model: Implications in atherosclerosis," to be published in the Proceedings, Bioengineering Division, ASME Winter Annual Meeting, Anaheim, November 9-12, 1992.

5. S. Glagov, D.P. Giddens, R.P. Vito, H. Bassiouny and C.K. Zarins, "Tissue reactions to mechanical stresses in relation to artery stability," to be published in the Proceedings, Bioengineering Division, ASME Winter Annual Meeting, Anaheim, November 9-12, 1992.