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Recent Research Trends in Biofluid Engineering through Caltech Biofluid Symposium

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Introduction

International Bio-Fluid Symposium and Workshop was held at California Institute of Technology (Pasadena, California) during December 12-14, 2003 under the auspices of the US National Committee on Biomechanics and the Biomedical Engineering Society. The scope of the Symposium included experimental, computational, and visualization issues in the field of biofluid mechanics. Emphasis was given to the cardiovascular system, and the integration of engineering principles and technologies with cellular and molecular biology. The talks spanned the range of challenges encountered, both in research and education, and including visualization of, and understanding, experimental and numerical data sets. The bio-fluid field has evolved from its early years, when engineering principles and technologies were applied, adapted, or devised for biological systems, to modern biofluid mechanics, which currently involves integration of flow and circulatory principles and technologies, with cellular and molecular biology. Many studies have shown that there is a correlation between "disturbed" flow patterns and the development of vascular disease; however, the specific causative link remains unknown. This is in part due to the significant complexity of vascular flow patterns.

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Objectives and Overview

The objectives of the Symposium were to gather scientists, clinicians, and practitioners from around the world to assess the latest frontiers of Bio-Fluid Mechanics, and to set important directions for further research and development, and education. Equally important was to provide bio-researchers, physicians and health care practitioners with fluid mechanics information, such as pressure, flow, shear stress and cellular response. Specific emphasis was given to the interrelationship between numerical and experimental methods. The Symposium explored new experimental and modeling tools to describe complex blood flow patterns, as well as interpretation of imaging modalities in terms of fluid flow, thereby helping to determine the link between biofluid flow patterns and vascular disease. Unsteady, three-dimensional flows that occur in the vasculature were discussed with the aim to link the fast-growing fields of biofluid mechanics, radiology, and bioengineering. A special session was devoted to pedagogical issues in teaching bio-fluid mechanics and to training young students in its foundations and related subjects.

Symposium themes

The Symposium focused on the following themes:

- Blood Flow in Major Blood Vessels-Modeling and Experiments
- Cellular Fluid Mechanics and Mechano-Transduction
- Fluid Mechanics in Nano Scales
- Microcirculatory, Capillary, Microairway, Interstitial and Intra-Bone Flows - Modeling and Experiments
- Air Flow in Large Airways
- Flow Imaging -Ultrasound, MRI, Thermal, Optical
- Flow in Artificial Organs and Vascular Devices
- Correlation of Hemodynamic Events with Clinical and Pathological Observations.
- Cardiac Hemodynamics, Coronary Circulation and Interventional Cardiology
- Delineation of Blood Flow Dynamics, Blood Elements Activation, and Atheroma Progression
- Shear Stress, Blood Pathology, Vascular Growth and Remodeling.
- Intra-Tissue and Intra-Cellular Modeling
- Pedagogical and Educational Issues in Teaching Bio-Fluid Mechanics.

Topical Summary

The Symposium started with two plenary talks: one by Peter Davies from Univ. Penn (Shear stress and the endothelium: Spatial genomics moves in vivo) and Morton Friedman from Duke Univ. (Realizing the potential of biofluid mechanics in the biological century). Both speakers emphasized the importance of involving biology while we study fluid dynamics of blood flows.

There is a web site in which the program and all abstracts are posted (The web site: http://www.gharib.caltech.edu/~biofluid). From this web site, one can take a look at the whole program and download copies of the papers. Thus, in this report, we will summarize several key observations we have made in terms of significance and future research directions.

Glycocalyx

Glycocalyx is a relatively new discovery and one of the hot research topics in the U.S. Previously we knew that the endothelial cells respond to shear stress. When the wall shear stress is equal to or greater than 15 dyne/cm^2, the intima layer releases anti-thrombotic and anti-coagulant agents, whereas it releases pro-thrombotic and pro-coagulant agents when the wall shear stress is less than 4 dyne/cm^2. In particular, when the direction of the blood flow changes from distal to proximal, the pro-thrombotic and pro-coagulant agents are released. Thus, we have been asking how the intima layer knows the magnitude of the shear stress produced by blood flow. Now, it seems clear that the sensor measuring the shear stress is glycocalyx.

Vink et al. from Univ. of Amsterdam presented a paper titled " The Endothelial Cell Glycocalyx: Hydrodynamic Interface Between Blood and Vessel Wall " and gave several key references to the subject. In particular the photograph of the endothelial cell

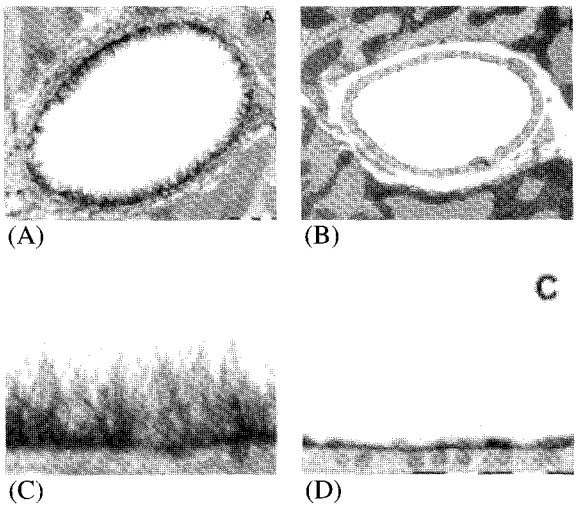

Figure 1 A, Electron microscopic overview of an Alcian blue 8GX-stained rat left ventricular myocardial capillary (bar=1μm). B, After hyaluronidase treatment, before Alcian blue staining (bar=1μm). C, Detailed pictures of glycocalyx on normal (left) and of hyaluronidase-treated (right) capillaries (bar=0.5μm). (From van den Berg, Bernard M.; Vink, Hans; and Spaan, Jos A.E., Circulation Research, Vol. 92(6), 2003, pp 592-594,)

glycocalyx was shown (see Figure 1). Contact between blood and the vascular wall is mediated by the endothelial glycocalyx. A thick endothelial glycocalyx provides the endothelial surface with a nonadherent shield. Oxidized LDL (Ox-LDL) degrades the endothelial glycocalyx. Glycocalyx degradation stimulates leukocyte-endothelial cell adhesion, whereas intravascular supplementation with sulfated polysaccharides reconstitutes the endothelial glycocalyx and attenuates Ox-LDL-induced leukocyte-endothelial cell adhesion.

Weinbaum et al. and Tarbell, both from City College of New York, presented results from in-vitro experimental study and mathematical modeling. Their papers included a number of references for their recent research activities at CCNY. In particular, Weinbaum showed a simplified model of glycocalyx as shown in Figure. 2 and applied a generalized lubrication theory for analytical modeling of a flow over the glycocalyx.

Vulnerable or Volatile Plaques

Tne of the challenging tasks is to determine whether or not a plaque will rupture in the near future. Many ruptured plaques block arteries by only 10-30%, which can be described as mildly-diffused plaques. The plaque which may rupture in the near future can be called vulnerable or volatile plaque. The vulnerable plaque ruptures, and blood begins to clot, blocking the arterial vessel in a matter of minutes (i.e., resulting in heart attack or ischemic stroke). Thus, the question is how we can determine the vulnerability of a plaque. Clearly we need to develop an optical sensor to visually observe plaques in-vivo. We do not understand the exact mechanism of the plaque rupture, i.e., on-set of the rupture. Is a plaque ruptured due to high shear stress produced by blood flow? If this is the case, blood viscosity may play an important role. What is the force that is large enough to initiate the micro-fracture in the beginning of the rupture? In order to answer, we need to move from fluid mechanics to fracture mechanics.

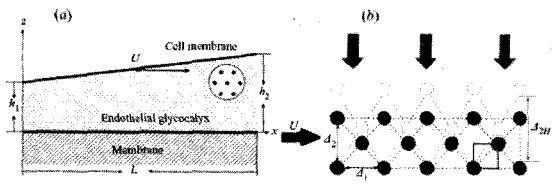

Figure 2 (a) Schematic illustration of the model for sliding motion of a rigid surface over a thin layer of fibre matrix. (b) Blow-up of the inset in (a) shows an idealized model for the fibre matrix which is composed of doubly periodic array of cylindrical fibres of radius a. The undeformed fibre spacings are demoted by Δ_1 and Δ_{2H}. (from Feng and Weinbaum, J Fluid mechanics, Vol. 422, 2000, pp.281-317)

Biofluid-Mems

Several investigators (Noca et al from Caltech, Hove et al. from Caltech; Liepmann from UC Berkeley) showed experimental work carried out in micro and nano scale living biological systems. Biofluid-MEMS is a rapidly growing area enabled by new approaches for fluid control and its potential for biomedical applications. Research on the design and development of microfluidic components such as needles, pumps, valves, and mixers and their integration have been on-going for several years at Berkeley (Liepmann). Many biomedical applications will involve fluid control of complex and two-phase fluids including flows containing bubbles or particles as well as polymers. In the MEMS environment, the characteristic length scales of cells, large molecules, and functionalized beads are similar to the length scales of the micro-flow channels. Hove et al. used embryonic stages of zebrafish to study the physiology and development of the heart linked by Hemodynamics. They demonstrated the utility of the zebrafish model as biofluid-MEMs tool. Westerweel et al from TU Delft, The Netherlands used an embryonic chicken heart to study shear stress responsiveness as shown in Figure 3 and 4. They developed micro-PIV system for in-vivo measurements in blood vessels with a diameter in the order of 100 μm or smaller. They plan to further improve the accuracy and spatial resolution so that they can accurately calculate wall shear stress from the velocity gradients close to the wall.

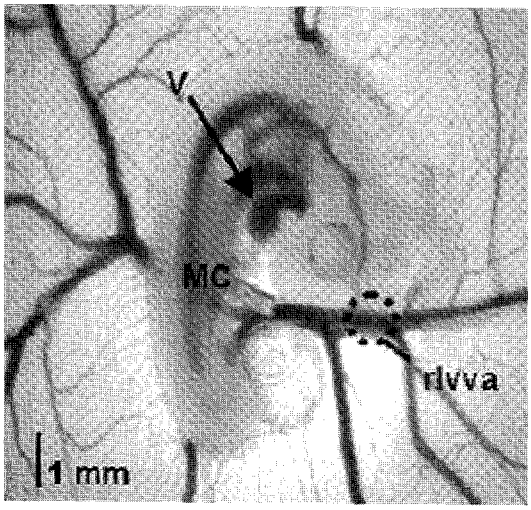

Figure 3 Chicken embryo and artery system. V = ventricle; MC = micro chip; Length of heart = 1 mm; diameter of heart = 0.3 mm. (from Westerweel et al. Caltech Biofluid Symp)

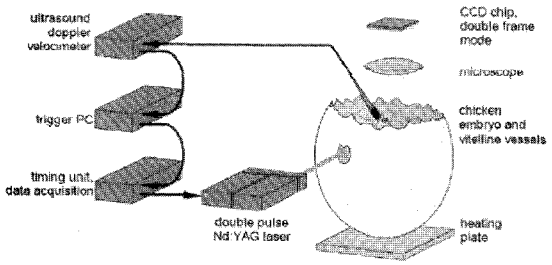

Figure 4 Set-up for synchronized micro-PIV image acquisition to measure the cardiac cycle (from Westerweel et al. Caltech Biofluid Symp)

Patient-Specific CFD

About one third of the papers showed results of numerical modeling of blood flows in major vessels. In 1980s, it was not uncommon to model blood flows using a steady state flow, rigid wall, axi-symmetric plaques, 2-dimensional vessel geometry, etc. The area of CFD of blood flow modeling has progressed significantly for the past decade. One can see that most researchers start with MRI images of complicated blood vessels, produce three-dimensional meshes of vessel geometry almost automatically, solve full Navier-Stokes equation for unsteady state conditions, and make a movie to show their numerical results. The process of automatically generating 3-D meshes from the MRI scanning was demonstrated by

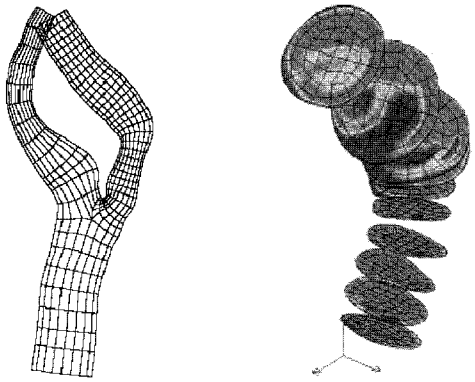

Figure 5 Carotid artery simulation and results.
(a) cross section of 2544 element meshes and
(b)contours of axial velocity at the ICA (internal carotid artery) at peak systole (from Fischer et al. Transitional Flow in Stenosed Carotid Arteries, Caltech Bio-Fluid Symp)

several researchers including Fisher et al at Argonne National Lab (see Figure 5), Jin et al. at Georgia Tech., and Berger at UC Berkeley. "Open software effort" to automatically generate 3-D meshes from MRI images will continue (Fisher et al. Caltech Symp).

The goal of most CFD studies was to show the detail flow structures of disturbed flows in various bifurcation sites such as coronary, carotid, femoral, etc. The ultimate goal of the numerical modeling of blood flows is to have physicians to use such results in diagnosis and treatment of patients. In other words, the CFD effort of engineers must be accepted by physicians. Here, we thought that unless the CFD results are patient-specific, the physicians will not accept them. In this regard, CFD modeling should include the blood rheology of each patient.

Hemorheology

As mentioned in the CFD section above, although the need to have blood viscosity data for individual patient is rather obvious for modeling of blood flows, it has not been done due to the lack of clinically available blood viscometer. In particular, the vascular disease is directly correlated to so-called "disturbed flow" at a bifurcation site.Hence, if the blood viscosity of a patient is significantly elevated at low shear, one can imagine that the patient's disturbed flow can be significantly amplified and the residence time of blood can be substantially increased. This

should render increased attachment of oxidized-LDL at the low shear zone, leading to early inflammation and subsequent biochemical pathogensis to plaque development.

Cho et al. presented that hemorheological disorders play an important role in the genesis and progression of vascular disease. Hemorheology is the science of flow properties of blood and their relationship to normal and abnormal physiology. The rapidly expanding science of hemorheology concerns blood, its components and the blood vessels with which blood interacts. It includes the rheology of fluid and structures in the perivascular and interstitial spaces as well as the lymphatic system. The clinical aspects include pathogensis, symptomatology and diagnostic methods, and the fields of prophylaxis and therapy in all branches of medicine and surgery, pharmacology and drug research.

Impeded blood flow is a central pathophysiologic feature in a variety of vascular diseases, among them ischemic heart disease, stroke, and peripheral arterial disease. Elevated blood and plasma viscosity may contribute to atherothrombosis through impaired microcirculatory flow, shear stress damage at the blood-endothelial interface, facilitation of plasma protein interaction with the endothelium in post-stenotic recirculation zones, and increased propensity for thrombosis. Elevated blood and plasma viscosities are independent predictors of subclinical atherosclerosis, initial and recurrent myocardial infarction, coronary heart disease death, stroke and all-cause mortality.

Cho et al. introduced a new technology, the Scanning Capillary Viscometer (SCV) (see Figure 6) for measuring and reporting blood viscosity. They utilized a variation of the Casson constitutive model for the mathematical data reduction procedure. Normal and pathological whole blood viscosity profiles, and alternate rheological measures derived from the profiles were presented as evidence of the clinical utility of such data. Such a clinical blood viscometer can be useful in providing patient-specific rheological data for CFD modeling and the diagnosis

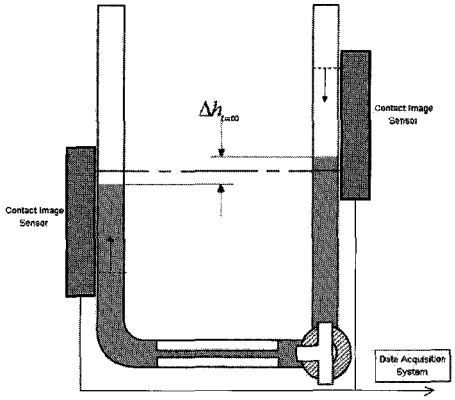

Figure 6 Scanning Capillary Viscometer measures whole blood viscosity over a range of shear. The capillary tube is disposable so that there is no need to clean blood-contaminated tube.

of vascular diseases.

Teaching Bio-fluid mechanics course

The field of biomedical engineering has seen a rapid growth in the last decade and numerous new undergraduate and graduate programs have been established in many universities (Chandran et al., Caltech Symp.). Subsequently, biofluid mechanics attracts students from varied backgrounds, making it challenging to teach. Several papers were presented to deal with the various issues involved in teaching students the subject of biofluid mechanics. The lack of proper textbook was one of the key issues. Currently, there are several biofluid books available as listed below. However, these may not be suitable for classroom teaching as they do not have good example and homework problems. An introductory textbook in biofluid mechanics will be published by Chandran et al. in the near future, which appears to be the first biofluid mechanics textbook designed for classroom teaching. The contents of Chandran's book are briefly described by Chandran et al. (Caltech Symp). Bluestein from Stony Brook (NY) gave his expeience of teaching biofluid course. He said, one of the challenges was how to reconcile the rigor required to master biofluids fundamentals with the extensive subjects that need to be covered. At Stony Brook, they offer four courses (Bioelectricity, Biomaterials, Biomechanics, and Biofluids) in the context of

biomedical engineering instead of offering courses in the traditional engineering departments. Students select three out of four bio courses. At Georgia tech, Biotransport course is required to take for all juniors and Biofluid course is offered as one of the electives. At MIT, ME students are recommended to take both biology and physiology courses. In addition, it would be nice for students to learn commonly used devices related to vascular diseases in clinical world such as heart-lung machine, dialysis machine, Swan-Ganz catheter for cardiac output measurements, etc.

List of biofluid books

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Concluding Remarks

The Bio-Fluid Symposium had an important mission: To explore and discuss the foundations of fluid dynamics as applied to biological systems. This mission and the above objectives were achieved by bringing together top researchers from Academia, Research and Medical Institutions, and Industry, to explore the state of the art of Experimental, Computational and Clinical Bio-Fluid dynamics, and to nurture the next phase of advances and activities. The authors wish that this short report can help researchers to see the trends of biofluid research in the area of vascular diseases in the future.