Vascular Dynamics

Physiological Perspectives

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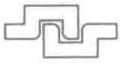

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PREFACE

The function of the vascular system is to transport oxygen and nutrients to the cells and to remove carbon dioxide and metabolites. It also transports hormones and locally produced neurohumoral substances which, in part, regulate its own function. These interrelationships are essential to homeostasis.

The vascular system is not an assembly of simple (elastic) tubes but a dynamic system with many external and intrinsic regulatory mechanisms. The endothelium plays a major role in the intrinsic regulation of the system. The system is also often subject to disease processes of which atherosclerosis is the most important. As a result of atherosclerosis, and other disease processes, replacement of vessels with prosthetic devices may be required to reestablish adequate tissue blood flow. It is therefore imperative to gain insight into the details of vascular function, especially the dynamics, and the endothelium, the processes of atherosclerosis development, the vascular prosthetic possibilities and, last but not least, the interrelationships between these sub-specialties.

The organizing committee of this NATO sponsored Advanced Research Workshop therefore had as its goal to put together a program that would provide; 1) a wide base of representation from all disciplines involved, 2) communication between disciplines that do not usually exchange information in the setting of normal scientific meetings, and 3) ample opportunity for discussion, debate, and free exchange of ideas in an informal atmosphere. The charge to each participant was to present a state-of-the-art overview of their topic and to lead a general discussion relating to that sub-field. The organizing committee represented special expertise in endothelial cell physiology and function (R. Busse), vascular prosthetics (N.H.C. Hwang), atherogenesis (J.F. Cornhill), cardiovascular physiology (D.R. Gross) and modelling (N. Westerhof). These individuals also have a broad understanding in all of these subject areas. The organizing committee met in Freiburg, West Germany in June of 1987. At that meeting we outlined rather specific subject areas and suggested speakers for each topic. Each of the organizing committee members accepted an appointment as a Section Leader and was responsible for recruiting outstanding scientists to cover each topic and to be the host for their section. The Section Leaders also acted as editors of the introductory summaries for each of the sections. The original plan was to cover resistive and conduit vessel dynamics in one section and modelling in another but it soon became apparent that these subjects could not be easily separated and so they were combined. The other sections were most professionally organized and run and we wish to extend our sincere thanks and appreciation for their efforts to: Prof. Dr. N.H.C. Hwang, Cardiovascular Flow Dynamics Laboratory, Department of Civil Engineering, University of Houston; Prof. Dr. R. Busse, Lehrstuhl für Angewandte Physiologie, Albert Ludwigs Universität; and Prof. Dr. J.F. Cornhill, Lab. of Exp. Atherosclerosis, The Ohio State University. Thanks also to all our friends, new and old, who participated in this NATO Advanced Research Workshop and appear as authors in this text. To take a small liberty with Shakespeare (Timon of Athens. Act II, Scene 2); "... we are wealthy in our friends".

N. Westerhof
D.R. Gross

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We are gathered in this garden spot to join in what is arguably the most fulfilling of intellectual activities: a debate with informed peers who together bring breadth of background and experience. The outcome of this debate will be a discovery of new perspectives on old questions, new questions on established positions and new approaches to resolve these questions. The areas of focus of our symposium are of paramount importance to health in the developed world; coronary artery disease in the United states alone kills a million people a year and disables five million more. Peripheral vascular disease is thought to disable roughly one fourth as many. Efforts to assist these patients have led multidisciplinary research and development teams to produce a host of devices and prostheses ranging from patient monitors to prosthetic small arteries seeded with endothelial cells to left ventricular assist devices. The type of physiological and material property data these groups demand continues to provide streams of unresolved problems and unanswered questions.

Efforts to decide on the course of intervention in congestive heart failure based on measurements of the distribution of vascular compliance and peripheral resistance show promise. Determining these quantities requires invasive continuous blood pressure and left ventricular output measurement. Non-invasive alternatives to the same end would greatly enlarge the patient group that could benefit from the procedure.

The effectiveness of left ventricular assist devices depends strongly on a knowledge of the distribution of aortic compliance. Efforts to enhance oxygen delivery to the periphery have introduced new challenges. By far the most important contributor to flow resistance is vessel diameter and it is appropriate that factors which control diameter will be discussed here. In addition resistance vessel pressure gradients are influenced by the local hematocrit which can be lower than the central hematocrit to an inexplicable extent. On the basis of the dependence of *in vitro* blood viscosity on hematocrit we predict maximum oxygen delivery for a given pressure gradient at hematocrit of 27 in the resistance vessels. Research into the mechanism whereby such low hematocrits are achieved in the periphery continues.

The successful arterial substitute 3 mm diameter or smaller continues to be elusive. The hope for endothelial cell seeded prostheses now is being cooled by evidence that stressed endothelial cells secrete potent mitogens which lead to unwanted cell invasions or proliferations.

In both coronary artery disease and peripheral vascular disease the atherosclerotic plaque is thought to be the major source of the pathological outcome. The siting of plaques, particularly in the peripheral arteries, suggests to many a fluid mechanical association. This has prompted the emergence of interdisciplinary groups that have pooled

resources to plan and execute research and interpret the results. These groups have been drawn together in symposia such as this and as a result the present consensus and current research have been strongly influenced by efforts to resolve the questions raised in past debates. There are a number of aspects of the debate on the role of fluid mechanics in determining the site of atherosclerotic plaques that bear on what we attempt here. There have been debates and nearly always there is a dominant view of the important mechanisms. These views are frequently put forward as a result of a combination of solid experimental evidence and some bold, imaginative hypothesis building. Many of the research efforts that resulted from these past debates have been based on the then current dominant views. It is reassuring to us here that even when these dominant views are subsequently undermined the results of the research they engendered are instructive and useful. I would argue that when the data and the investigator's imagination supports a particular hypothesis the hypothesis should be aired and used as a basis for further research.

An illustration of the utility of such conduct of research can be seen in the aftermath of the Ross and Glomset (1976) model of atherogenesis: "...an injury causes local endothelial cell desquamation; in the process of repair platelets release a growth factor that causes intimal proliferation of smooth muscle cells which become lipid filled and calcified when the serum cholesterol is elevated". As a result of the wide acceptance of this view a great deal of work went into the isolation of the platelet derived growth factor and a search for fluid mechanic mechanisms which could lead to desquamation. Mechanisms proposed for generating the initial trauma included high shear stress, local pressure minima and even transmural water flux resulting from postural change. The desquamation model was an excellent hypothesis on which experiments could be based.

Our group at the U of Minnesota explored the influence of transient transmural water flux resulting from a sudden change in transmural pressure difference. We found that when an artery without an endothelial layer was exposed to a sudden drop in inflation pressure, water movement from the media to the lumen would be sufficient to cause desquamation under some conditions. For an air inflated artery (simulating a water-tight endothelial layer) no such water flux is observed. Experiments were then performed in which sections of rabbit aortas were suddenly deflated *in situ*. Blisters were observed on the endothelial surfaces near sites of trauma on the section of the aorta tested but not in the control. On the basis of these observations and a one dimensional consolidation model we predicted that the risk of desquamation would be high if the local endothelial layer's hydraulic conductivity were elevated and the product of unvascularized media thickness with the magnitude of the pressure change exceeded a threshold value. Assuming that the pressure change was that encountered when suddenly lying down we constructed a risk distribution and compared it with the frequency of occurrence of atherosclerosis in individuals who died of other than cardiovascular disease; the agreement was promising.

Since then the dominant view of the importance of desquamation has changed. The history of this change also has a lesson for us here. Even when the Ross and Glomset hypothesis was most widely accepted there were investigators who produced atherosclerosis in rabbits who never saw desquamation (notably Seymor Glagov) and who refused to accept the dominant view. There was a time in this debate when it was observed that Seattle rabbits showed missing endothelial cells because they were older and Chicago rabbits did not because they were younger. A key experiment was performed by Reidy and Walker (1987). They found that when care was taken to gently remove the endothelial layer and leave the basement membrane undisturbed the endothelial layer adjacent to the injury would quickly cover the site without provoking platelet excitation and the consequent release of platelet derived growth factor from platelets.

Now the dominant view holds that when vessel injury causes desquamation the period of denudation is brief and the injury site is either quickly covered by endothelial cells migrating from the periphery, producing an altered, more permeable, more stressed endothelial layer, or a passivated cell-free layer, which nevertheless covers the basement membrane and prevents platelet excitation. Experiments by DiCorleto and Fox (1987), show that such endothelial cells in culture produce a factor identical to the platelet derived growth factor but another mitogen as well in amounts 10 to 100 times the amount produced by endothelial cells in repose. They argue that such endothelial cells will stimulate the proliferation of a smooth muscle cell colony in the intima. Monocytes, intimal smooth muscle cells, and platelets are also potent sources.

The new dominant view has been summarized by Nerem (1987), Goldstick and Dobrin (1987) and others, and is briefly: Vascular geometry [which Friedman (1981) shows has significant variability between individuals] promotes the occurrence of focal fluid mechanic shear stress and transport process variations which lead to locally physiologically stressed endothelial layers. These physiologically stressed regions occur at regions of depressed fluid shear stress and presumably depressed oxygen transport in arteries with thick avascular media. These locally altered cells allow elevated ingress of lipids and exacerbate the anoxic injury resulting ultimately in placque formation. The endothelial cell remains a notable participant in this new picture, not because of its absence, but because of its presence in an altered metabolic state.

Work by Vargas (1988) and others have shown that the hydraulic conductivities of cultured endothelial layers are at least ten times greater than of an undisturbed endothelium. These disturbed layers of the vasculature are also known to show evidence of enhanced permeability to various dyes. So even though the nature of the injury to the artery wall is different in this current view than the one put forth by Ross and Glomset virtually all of the research the latter influenced contributes to an appreciation of the consequences of the present dominant view.

I feel this history supports the argument that it is helpful to plan future research on the basis of the current dominant view, either to demolish it or extend it without feeling the paralysis that uncertainty raises; the past argues that there will be a useful outcome whether the dominant view topples or not.

In reflecting on this history , in addition to role played by the bold imaginative Model Builder and the Model Challengers, there has been another important contributor, the Book Keeper, who attempts to fit the pieces into the emerging new view. I have the feeling that the organizers wish the session chairmen and me to help in this regard. It would be most helpful to hear ideas or models that might tie disparate elements together. As we've seen above, even a subsequently replaced dominant view is extremely useful in focusing attention on needed research; so there is really no need to be reticent.

The four subject areas discussed at this meeting are closely enough related to be mutually supportive. And still the backgrounds of the participants are sufficiently diverse to enrich the debate and make it a learning experience for all. Clearly the group gathered here represents a breadth and depth of background and inventiveness that one individual research team could not hope to achieve. Our task is to see it become an effective instrument of progress.

My encyclopedia tells that north of here, in Naples, Virgil was schooled and there composed the poems, The Georgics. Virgil's fourth Georgic concerned the bee; the poem dwelt at length on the great wealth which cooperating individuals brought to the common good. In addition he writes "Some say that unto bees a share is given of the Divine Intelligence...the fine essential flame". We may hope that from the collected experience we bring here will emerge a glimpse of the fine essential flame.

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SECTION I: CONDUIT AND RESISTIVE VESSEL DYNAMICS

Compliance, Modelling and Physiopathology

N. Westerhof and D.R. Gross (with input from section participants)

This section contains chapters dealing with the arterial delivery system, from the aortic valve to the small resistance vessels. The emphasis is upon the contribution of vascular compliance and upon physiological characterization of this system using a variety of techniques. Modelling is necessary to enable us to describe the function of a physiological system in precise terms. Based on this description it is then possible to generalize and predict. A particular model, as a stage in the description process, codifies current knowledge about a system of interest and exposes contradictions in the hypothesis. Models found in this section include mathematical models, hydraulic models, electrical models, animal models and lumped transmission line models. The basic philosophy expressed in these chapters is that in our striving for understanding we all create models, in our minds if not on paper. The model is a simplified version of reality, one which we can comprehend ourselves and communicate to others. To be communicable a model should be implemented in forms that are easy to understand. This goal is accomplished when models are simple. However, simple models may not provide a satisfactory explanation for the behavior of the system of interest because physiological systems are complex. A desirable model is the one which constitutes the best compromise between simplicity and the ability to account for the system's essential properties and phenomena.

Four characteristics of good modelling were identified by the participants in this Workshop: 1) A good model is not only a simplified version of reality but one which relates to a specific goal; 2) A good model uses measurable parameters to describe (overall) system function; 3) A good model helps to identify and define specific future experiments which are required to more realistically describe system function; 4) A good model allows us to use accessible measurements to predict parameters that are presently impossible or impractical to measure directly.

Any model requires, in addition to the contributing equations, a number of parameters which may not be known or whose determination is difficult. In the latter case parameter estimation procedures are necessary, but these will not always solve the problem. Assume the model structure for the arterial system as shown in figure 1a. The constituting equation is Pm=Fm x R, Pm and Fm are mean pressure and mean flow, and R is resistance. From the measurements of mean pressure and mean flow, R can be obtained. When separate organ systems are considered, many resistances must be employed. If we assume that the systemic tree consists of a cranial part and a caudal part the model of Fig. 1b is obtained. From the measurement of mean aortic pressure and flow alone the values R_1 and R_2 cannot be obtained. Rather, many values of R_1 and R_2 can be combined to obtain the correct ratio of mean pressure and flow. Even parameter estimation will not solve the problem. To obtain the solution more measurements, for example flow through one of the resistors, is necessary.

When trying to describe pressure and flow waveforms the model of Fig. 1a is too simple. Figure 2 (left two panels) shows the two possibilities that exist if model 1a were to represent the systemic arterial tree, i.e. pressure and flow would have exactly the same shape. To obtain a realistic flow waveform it is at least necessary to introduce vascular

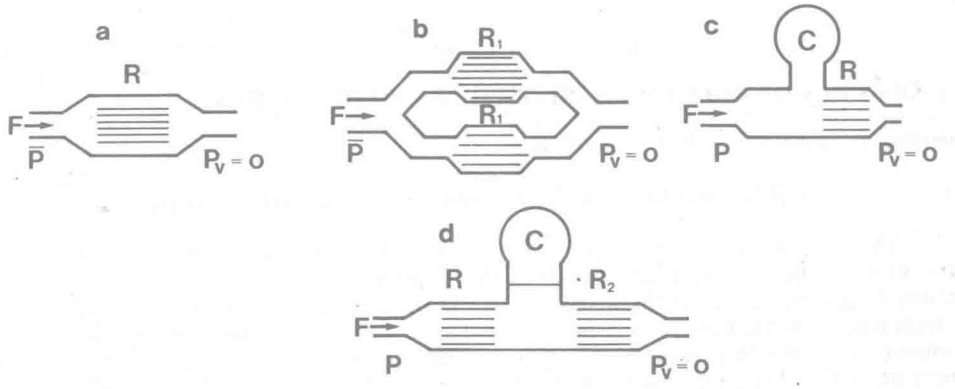

Figure 1

a) *If the arterial tree could be modelled by means of a resistor (R) only the measurement of mean pressure (Pm) and flow (Fm) would be sufficient to characterize the system, i.e. to determine R.*

b) *When pressure and flow are known but the system consists of two or more resistances (organ beds) the full characterization would be impossible. More measurements are necessary (i.e. flow through one of the resistors).*

c) *To include in the description the arterial pressure and flow waveforms, and not only mean values, vascular compliance needs to be taken into account. Resistance alone is therefore an incomplete model.*

d) *The introduction of characteristic impedance (R_c, which takes into account compliant properties of the proximal aorta and blood mass), adds a third element in the model and results in a system description which can fairly accurately describe pressure and flow waveforms.*

compliance. As shown in Burattini's chapter the introduction of compliance, leading to Frank's windkessel, gives better, but not yet fully acceptable, pressure and flow waves. The introduction of a third element, leading to the three-element windkessel model, (Fig. 1d) gives acceptable pressure and flow waves. Any realistic representation of vascular system must include compliance and inertial (inductive) components. One of the strengths of the determination of input impedance as a description of the vascular tree is the compliance and inductance effects became clear.

The concept of compliance is a functionally important one. Ventricular loading and unloading have been repeatedly shown to be dependent upon arterial compliance. The compliance component of afterload, often represented as a Windkessel, has a "cushioning" effect on the pressure waveform. It also tends to damp step increases or decreases in pressure, such as those that might be induced by the sudden onset of exercise, stress, shock, hemorrhage, etc. This windkessel, which, if the evidence presented in this section is true, resides primarily in the ascending portion of the thoracic aorta, has an extremely important influence on coronary flow, since in systole coronary

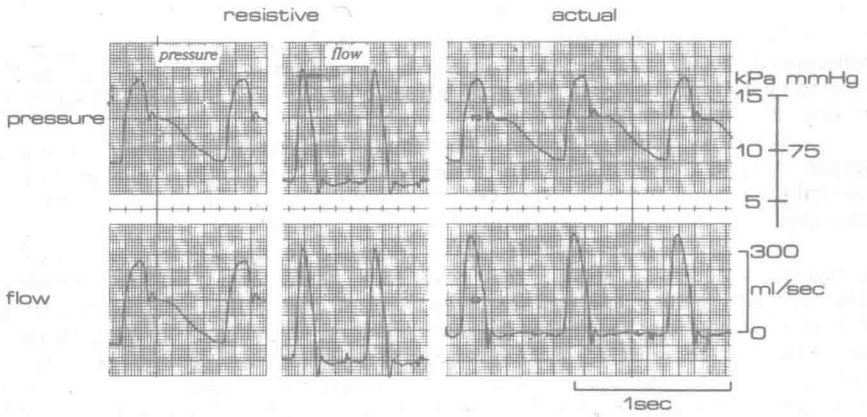

Figure 2 *If the arterial system is modelled with a resistor only, aortic pressure and flow wave forms would be identical while the actual wave shapes are different.*
Left : *When aortic pressure would be taken as the actual waveform then flow has an unrealistic wave shape.*
Middle: *When flow wave shape is acceptable the pressure pattern is not.*
Right : *Actual pressure and flow waves.*

flow is impeded by cardiac contraction and compliance ensures that diastolic pressure is maintained as a high level for coronary perfussion to take place. Furthermore it provides also diastolic forward flow throughout the arterial tree.

The importance of total systemic compliance, as a concept, is emphasized throughout this section of the text, as it was during the Workshop. However, the relationship $C = \Delta V/\Delta P$ where C = compliance, ΔV = volume change, and ΔP = pressure change has not been possible to measure directly. Compliance is not a constant but is defined as the slope of the pressure-volume curve. As both Yin and Westerhof discuss in this section this function is nonlinear, and can and does shift as a function of neuro-humoral tone (see Pagani) and a wide variety of physiological, pharmacological and pathological perturbations (see Gross). Therefore compliance, in any arterial system, must be expressed as a function of mean pressure. There is no technique now available to measure total arterial compliance directly. This unfortunately, means that we do not have an objective value of compliance against which any model derived compliance can be tested and compared for model validation. As both Yin and Latham show in their chapters compliance may be derived indirectly from diastolic pressure or pressure and flow measurements, but again a standard is not available. This poses problems in the interpretation of the importance of compliance. The arterial tree is composed of an extremely complex geometry of curving, tapering, branching, tubes, each with it's own elastic properties. These elastic properties can, and do, vary with location, function, physiological state of the organism, other environmental conditions and, as Gross discusses, species. To represent this system as a lumped compliance should be considered as only a first order approximation. Westerhof and Patel, in his chapter, point out that compliance is also of importance in the understanding of peripheral pressure-flow relations. Changes in small vessel vascular diameter, and thus resistance, with pressure may explain the zero flow pressure intercept.

The elastic properties of the blood vessels also relate to wave travel and consequently to wave reflection. To describe these phenomena distributed rather than lumped models are required. These models are also discussed in several chapters in this section (Burrattini and Latham).

The participants, united in their common interest in cardiovascular dynamics, agreed that all living systems are characterized by variability. the models must, inevitably, account for this. However, it is essential to be able to comprehend steady state models before adding variability.

One more aspect of modelling is addressed in this section. Localized flow disturbances and wall shear stress have long been considered major factors in atherogenesis, vascular lesion development, and proper healing after vascular surgery. Researchers agree that the simple Poiseuille model is not adequate to describe the fluid mechanical factors involved in these phenomena. For nearly a century, hemodynamists and fluid mechanicians have tested various theoretical and experimental techniques, striving for a method to accurately assess these values, with only limited success. Hwang introduces a new concept of combining the exact solution from a mathematical model and experimental data from an *in vitro* flow model. The method, though preliminary at present, provides a promising approach to this problem.

The major charge of this Workshop was to define future trends and to identify specific areas where research efforts should be directed. As is usual in a gathering of scientists with diverse backgrounds and common interest the discussion of future research divided into basic and clinical aims. The common unification of these aims was the caveat that good research has a well defined hypothesis that can be and is tested by the experimental design. In general it was determined that we must develop good criteria to enable us to decide if a proposed model is a good representation of reality. It was clear, from the discussion, that both basic and clinical scientists must strive to understand the effects of a wide variety of environmental perturbations of the function of the arterial system. Theses should include the effects of neuro-humoral control, body position, exercise (both acute and longterm effects), and the influence of such physiopathological states as age, atherosclerosis and hypertension. There is a great need for basic scientists to reach some agreement on the usefulness of the various expressions of compliance and to validate the basic concepts involved in the systemic representation of arterial function. Clinical scientists should direct their efforts to the validation of noninvasive techniques, and the effects of various manipulations of the cardiac load including pharmacological interventions intended as afterload reduction.