PROTECTIVE ADAPTATION THEORY FOR THE ORIGIN OF ATHEROSCLEROSIS

Young I. Cho*, Kenneth R. Kensey**

INTRODUCTION

In spite of massive research efforts and numerous hypotheses, the initiating event in atherosclerosis has not yet been identified. Many pieces of the atherosclerosis puzzle seem to be in place, but the absence of this key piece continues to stymie our best efforts to prevent the development of atherosclerosis, predict who will develop it, and gauge the efficacy of its treatment. According to the American Heart Association estimates that 1.1 million Americans in the year 2001 will suffer a myocardial infarction and that more than 40% will not survive the event. The cost to the United States of medical care and lost productivity due to cardiovascular diseases is estimated at $298 billion in 2001 (AHA 2000). Atherosclerotic coronary artery disease is the underlying cause of most ischemic cardiac events and can result in myocardial infarction, congestive heart failure, cardiac arrhythmias, and sudden cardiac death.

To introduce our approach to atherosclerosis and associated cardiovascular disorders let's first consider the progress of cardiovascular research to date. Historically, cardiovascular research has focused on histologic studies of the vascular wall ; the biochemistry of the blood and, to a lesser degree, of the vessel ; analysis of clotting factors ; and investigations of platelets and prostaglandins. This approach to atherogenesis can be summarized as an approach with a biochemical focus.

The results have been a very detailed and accurate histopathology of atherosclerosis, starting with histologic manifestations of fat-filled cells in the intima to the complex series of mechanisms between plasma lipoproteins, which lead to stenotic lesions that may compromise vessel blood flow. Functional impairment of the endothelium may be initiated by endocrine mechanism (e.g., diabetes), hyperlipidemia, toxicity, mechanical factors genetic factors, or a combination of all of these. Subsequently, many theories have arisen from these biochemical studies. However, any theory that embraces only a biochemical, genetic, or environmental perspective leaves many questions unanswered. These questions include the following :

- Why are the arteries leading to the heart and brain so susceptible to atherosclerosis?
- Why do we not observe atherosclerotic plaques developing in the intramyocardial coronary arteries (i.e., those that are "buried" in the heart) (Scher 2000), the arteries of the arms or breasts, or in the veins, for that matter?
- If atherosclerosis is caused by a biochemical process (e.g., hypertension or hyperlipidemia) as purported by current theories, why does it not affect the vascular system uniformly (Kensey and Cho 1992, Kensey and Cho 1994)?
- Why do people with "normal" blood pressure and "normal" cholesterol still have heart attacks?
- Why do men develop cardiovascular diseases at a younger age than do women, especially premenopausal women (Kameneva et al 1998)?
- Why is there a pattern of increased heart attacks in the morning hours (Cohen et al. 1997)?

In the end, there are simply too many questions that cannot be resolved by applying only current biochemical theories. The fundamental shortcoming of current biochemical theories is that they do not

* Drexel University, Philadelphia, PA
** Visco Technologies, Inc. Exton, PA

identify the initiating event that precedes endothelial injury.

In addition, although approximately 300 risk factors for atherosclerosis have been recognized (Hopkins and Williams 1986), how these risk factors correlate with atherosclerosis remains speculative. The absence of a theory to appropriately account for the initiating causal factor or factors in atherosclerosis is unsettling on an individual and a societal level.

In our theory, we have identified the initiating event of atherosclerosis on the basis of two changes in perception about atherosclerosis and the arterial system.

First, we recognize the human vasculature not simply as a passive organic conduit but as a dynamic "organ" that responds to all intrinsic and extrinsic stimuli-not just biochemical ones-with definable and predictable adaptive processes. Second, we believe that the damaged intima, the lesions, and the occlusions in the vascular system are secondary responses to another event-one that causes the end results such as myocardial ischemia and limb amputations, which we confront in the operating room today. By examining the complete life cycle of atherosclerosis from these two perspectives, we have correlated the clinical findings with a logical progression of anatomic changes initiated by one event : mechanical injury that is directly related to the work of the heart.

The proposed event of mechanical injury as the initiator of vessel wall injury stems from these two shifts in perspective. First, the arterial system is a dynamic system that naturally responds in various ways to different types of blood flow. In our approach, certain types of blood flow may cause mechanical injury to the vasculature. These types of flow are referred to as injurious pulsatile flow. Second, in response to this mechanical injury, the vasculature develops plaques and other abnormalities in the vessel wall in a predictable pattern. We have presented these various mechanisms in a unified concept called the protective adaptation theory, an examination of how the arterial system responds to mechanical injury.

PROTECTIVE ADAPTATION THEORY

In its most basic form, protective adaptation is a mechanism by which an organism responds to an environmental stimulus. The environmental stimulus may be either stress or injury caused by mechanical forces. The distinctions between stress and injury involve intensity (the strength or degree of the stimulus) and duration (the length of time during which the stimulus is applied). In protective adaptation, injury is defined as a stimulus with a high intensity occurring in a relatively short period of time. Injury usually causes a break in the structural integrity of the organism-macroscopically, microscopically, or both. Stress, on the other hand, is a low-intensity stimulus applied over a longer period of time. As a result of its lower intensity and longer duration, stress deforms the organism, but doesn't compromise its structural integrity. Another important qualitative difference between stress and injury is that injury is irreversible protective adaptation, whereas stress is reversible protective adaptation.

The protective adaptation theory hypothesizes that mechanical stress and injury to the arterial system produced by hemodynamic forces cause the endothelial cells to lose their ability to function (i.e., become dysfunctional) at specific sites in the arterial system. Thus, atherosclerosis can be seen as the arterial system's adaptive response to injurious stimuli-mechanical stress and injury.

"Robbins pathologic basis of disease" book [Cotran et al., 1999] describes endothelial dysfunction as "a potentially reversible change in the functional state of endothelial cells that occurs in response to environmental stimuli," and which inhibits endothelial -cell-derived nitric oxide and increases vascular permeability. Cytokines, bacterial products, lipid products, viruses, hemodynamic forces, and advanced glycosylation end products are examples of en-

dothelial activators. The protective adaptation theory proposes that among these endothelial activators, a hemodynamic force is the key factor that explains the site-specific nature of atherosclerosis. In the arterial system, the protective adaptation theory recognizes that certain types of blood flow produced by the heart can cause mechanical stress and injury to specific sites in the arterial system. These arterial sites respond to the chronic mechanical stress and injury with strengthening adaptive mechanisms that cause the arteries to thicken and stiffen to maintain their structural integrity.

Two Cycles in the Protective Adaptation Theory

The protective adaptation theory organizes and divides the arterial adaptive process into two separate cycles. The first cycle centers on arteriosclerosis and involves the region-specific development of the disease. Since arteriosclerosis is the hardening of the arteries and is associated with disorders that have common symptomatic development of arterial thickening and loss of elasticity, the first cycle follows the pathologic progression of the arterial system due to overstretching and decreased compliance and elasticity in certain regions of the body induced by increased arterial pressure. Study of the second cycle, which focuses on atherosclerosis and examines the site-specific pattern of the disease, involves the pathogenesis of atherosclerosis in regions of arteries that have lost their compliance from blood flow in the first cycle.

Mechanical Stress and Injury

From the perspective of the protective adaptation theory, mechanical stress and injury impact the arterial system in two pathways. Mechanical stress in the form of arterial pressure causes stretching of the arterial wall, where the arterial pressure converts to a circumferential tensile stress. The arterial wall undergoes repeated stretching, which doesn't stop as long as the heart is beating. In fact, the magnitude of the stretching continues to increase beyond a threshold value because the arterial wall tries to protect itself from the fatigue injury of stretching by reinforcing its own strength by thickening. This, in turn, further increases the arterial pressure and circumferential stress inside the thickened wall, thus further increasing the magnitude of the stretching, a process called arterial remodeling. The outcome of the continuous increase in the arterial pressure is arteriosclerosis.

Another type of the mechanical stress is shear stress caused by blood flow. The shear stress is a tangential force per unit area, acting like a frictional resistance to the blood flow. In a straight, healthy arterial vessel the shear stress is maintained within a physiological range of 10-15 dyne/㎠ [Fung, 1990], which controls the release of various antithrombotic agents such as nitric oxide and prostacyclin from endothelial cells [Cotran et al. 1999].

The shear stress becomes much greater than 15 dyne/㎠ at flow dividers of bifurcations and branches. The high shear stress often tears off endothelial cells, a process known as denudation of the intima. This is a mechanical injury, which is reversible because the denudation can be prevented if the shear stress can be reduced from an excessive to a moderate level.

The intima exposed by this injury allows the adhesion of platelets and forms neointima, involving smooth muscle cell migration to the intima. When the denudation persists, it leads to intimal thickening and eventually atherosclerosis. This is an adaptive response to a mechanical injury caused by blood flow when the excessively high shear stress continues to exist at the specific sites of bifurcations and branches. Although the intimal injury is reversible initially, when the intimal thickening results in a severe occlusion of an artery the injury may not be reversible.

Mechanical injury is also caused by low shear, since blood flow at the low shear area often becomes intensely turbulent. Examples of the low shear areas include the wall opposite to a branch,

the proximal wall of a branch vessel, and the inner wall of a curved vessel. The turbulent flows observed in the recirculating flows are characterized by low shear stress, making endothelial cells rounded in shape with increased vascular permeability. The round-shaped endothelial cells, which are dysfunctional because they do not protect the arterial wall from the blood stream, are one of the most important forms of mechanical injuries created by hemodynamic forces.

Injurious Pulsatile Blood Flow

The next step is to examine the type of blood flow that causes mechanical injury. Pulsatile blood flow that causes mechanical injury to the arterial system is defined as injurious pulsatile blood flow. Pulsatile blood flow that does not cause mechanical injury is called normal pulsatile blood flow. Three key parameters determine whether a particular pulsatile blood flow will be injurious or normal and whether it will subsequently cause mechanical injury :

- Peak systolic blood pressure, more specifically peak pulse pressure
- Contractility of the left ventricle
- Circulating whole blood viscosity.

An increase in any one of these three parameters can cause injurious pulsatile blood flow that will in turn create mechanical injury to the arteries.

CLINICAL SIGNIFICANCE OF BLOOD VISCOSITY

We believe that whole blood viscosity is the most important risk factor for atherosclerosis and its associated clinical disorders. Unlike blood pressure and to a lesser extent left ventricular contractility, which are well-accepted risk parameters, whole blood viscosity is not routinely measured in the clinical setting. Although the science of viscosity has existed for almost two centuries and its basic principles and theories are well established, the medical community at large has not recognized whole blood viscosity as a significant physiologic parameter. Fortunately, in recent years physicians and researchers have shown an increased interest in the role of whole blood viscosity in the pathogenesis of cardiovascular and cerebrovascular diseases. Clinical studies are confirming whole blood viscosity and its determinants as some of the most important parameters in assessing a person's risk for atherosclerosis-related diseases (heart attacks and strokes). The determinants of whole blood viscosity include hematocrit, red blood cell (RBC) deformability, RBC aggregation, and plasma viscosity (influenced to a large degree by fibrinogen).

Clinical and epidemiologic studies provide compelling evidence that whole blood viscosity may be a significant causal determinant of atherosclerosis in the following areas : * Myocardial Infarction

- Peripheral Arterial Diseases
- Stroke
- Diabetes

Conventional Risk Factors for Cardiovascular Diseases

Approximately 300 risk factors have been identified for atherosclerosis (Hopkins and Williams 1986). In spite of this impressive figure, conventional risk factors can predict and account for only about 30% to 50% of incidental cases of cardiac and vascular diseases. Elevated whole blood viscosity may be the parameter or mechanism by which other conventional risk factors influence atherosclerosis development such as

- hypertension
- hyperlipidemia
- smoking
- exercise
- obesity
- age
- gender

In other words, whole blood viscosity can be considered the common denominator. An examination of several studies that have correlated whole blood viscosity and conventional risk factors for car-

diovascular disease can provide a sound basis for evaluating the validity of this statement.

HEMATOLOGIC DISORDERS AND HYPERVISCOSITY

Although the focus of this paper is on the implications of whole blood viscosity and atherosclerosis, it is nevertheless worthwhile to discuss certain hematologic disorders associated with elevated whole blood viscosity. Many of these disorders entail abnormalities of one or more of the basic determinants of blood viscosity : plasma viscosity, hematocrit, RBC aggregation, and RBC deformability. Of these, we have considered three specific disorders-increased RBC concentration, excessive plasma proteins causing increased RBC aggregation, and loss of RBC deformability-and examined the underlying mechanism by which each disorder causes hyperviscosity.

SCIENCE OF HEMORHEOLOGY

The science of hemorheology is the study of the deformation and flow of blood and its effects on the vessel wall. Blood is a non-Newtonian fluid because its viscosity varies with shear rate. The non-Newtonian characteristics of blood come from the presence of various cells in the blood (~45% by volume), which make blood a suspension of particles. When the blood begins to move, these particles (or cells) interact with plasma and among themselves. Furthermore, they tend to migrate into the center of the vessel as the blood moves, leaving more plasma near the vessel wall. The overall blood flow is critically affected by the magnitude of flow velocity, the percentage of cells, and the size and wall conditions of the vessels. Hence, the science of hemorheology involves not only the rheology of blood but also the fluid dynamics of blood flow.

Hemorheologic parameters of blood include whole blood viscosity, plasma viscosity, red blood cell (RBC) aggregation, RBC filterability, and RBC deformability (or rigidity). These parameters are influenced by certain biochemical variables in the blood, such as hematocrit, total cholesterol, triglyceride, plasma proteins (fibrinogen and various classes of immunoglobulins), albumin, and oxygenation level (which depends on blood pressure).

Properties of Red Blood Cells

The study of the biomembranes and properties of red blood cells is an important aspect of blood rheology, because the biomembranes strongly influence whole blood viscosity. These membranes exhibit fascinating properties of viscous and elastic behavior. In the low shear region, the aggregation of red cells forms polymerized cell networks, whereas in the high shear region red cells are continuously deformed and dispersed by the shear field.

Since a red blood cell does not have a nucleus, it behaves like a fluid drop (Dinnar 1981). Hence, when a number of red blood cells cluster together, as in the flow of a low shear rate, they aggregate together. These aggregates, which look like stacks of coins, are known as rouleaux (rolls). Rouleaux formation is highly dependent on the concentration of fibrinogen and globulin in plasma, and rouleaux cannot form at all in the absence of fibrinogen and globulin.

Rouleaux formation of healthy red blood cells increases at decreasing shear rates. As red cells form rouleaux, they will tumble while flowing in large vessels. The tumbling disturbs the flow and requires consumption of energy, thus increasing blood viscosity at low shear (Fung 1981). As shear rate increases, blood aggregates tend to be broken up, resulting in a drop in blood viscosity.

Scanning Capillary Tube Viscometer

We have developed a scanning capillary tube viscometer (SCTV). Note that both flow rate and pressure drop must be measured to calculate the viscosity of a liquid in a conventional capillary tube

viscometer. This old paradigm has been broken by the SCTV, in which a U-shaped tube is used so that both flow rate and pressure drop measurements are replaced by a single measurement of height variation, h(t), in the tube. Furthermore, by having blood rise and fall by gravity in the U-shaped tube, shear rate is gradually and continuously varied from high (400 s^{-1}) to extremely low values (0.1 s^{-1}), thus allowing whole blood viscosity measurement over a wide range of shear rates in a matter of 2 minutes. Since the SCTV uses only gravity as the source of power, it is an absolute measurement device.

Mechanism of Operation

The SCTV consists of two parts : a height detection system and a disposable U-shaped tube. Figure 1 is a drawing of the U-shaped tube showing that blood is introduced into the right column from a venipuncture. Once the right column is filled with blood, blood is introduced into the left column through the manipulation of a four-way stopcock. At t = 0, the valve operation allows the blood in the right side to fall and the blood in the left side to rise. Ideally, the right and left fluid levels come to an equilibrium or asymptotic point as indicated by a dashed line.

As two fluid levels approach each other, the blood in the U-shaped tube slows down because the flow velocity depends on the pressure differential between the two fluid levels.

$$\text{Pressure drop} = \rho g[h_1(t) - h_2(t)] \tag{1}$$

where ρ is the density of fluid, g is gravitational constant, and $h_1(t)$ and $h_2(t)$ are the fluid levels in the right and left sides, respectively. Flow rate through the capillary tube can be calculated from $h_1(t)$ and $h_2(t)$ measurements since the flow velocity in the two vertical riser columns, $v_r(t)$, can be expressed as

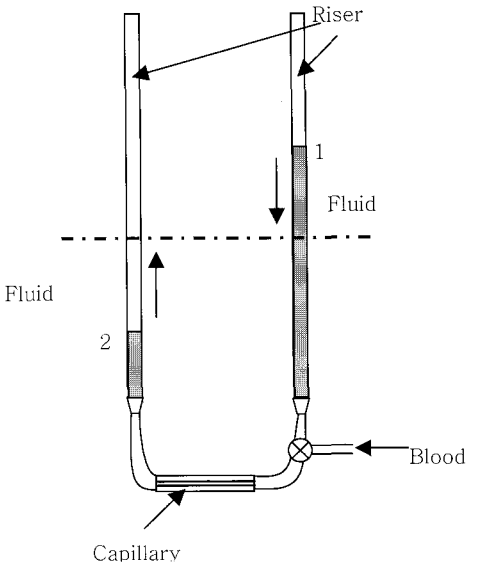

Fig. 1 Drawing of the operational principle of the Scanning Capillary Tube Viscometer (SCTV).

$$v_r(t) = \frac{dh(t)}{dt} \tag{2}$$

Note that the mathematics developed for a steady-state Poiseuille flow was used for a quasi-steady laminar flow within the capillary tube, a procedure that was validated through experiments (Cho et al. 1999, Kim et al. 2000a, Kim et al. 2000b). For non-Newtonian fluids, a standard power-law model was used to consider the variation of the viscosity with shear rate. When applying the power-law model to whole blood, the pressure drop at the capillary tube can be described as follows (Kim et al. 2000a) :

$$\Delta P_c = \frac{4\eta L_c \dot{\gamma}}{d_c} = \frac{4kL_c \dot{\gamma}^n}{d_c} = \frac{4kL_c}{d_c}\left\{\left(\frac{3n+1}{n}\right)\frac{8Q}{\pi d_c^3}\right\}^n$$
$$= \frac{4kL_c}{d_c}\left\{2\left(\frac{3n+1}{n}\right)\cdot\left(\frac{d_r^2}{d_c^3}\right)\cdot\left|\frac{dh}{dt}\right|\right\}^n \tag{3}$$

where $\eta = k\dot{\gamma}^{n-1}$ (4)

and $\dot{\gamma} = \left(\frac{3n+1}{n}\right)\frac{8Q}{\pi d_c^3}$ (5)

Applying Equations (1~3), we can rewrite the energy conservation equation as follows :

$$\rho g\{h_1(t)-h_2(t)-\Delta h_{t=\infty}\}=\frac{32\mu L_c d_r^2}{d_c^4}\left|\frac{dh}{dt}\right|$$

for Newtonian fluids (6)

$$\rho g\{h_1(t)-h_2(t)-\Delta h_{t=\infty}\}=\frac{4kL_c}{d_c}\left\{2\left(\frac{3n+1}{n}\right)\cdot\left(\frac{d_r^2}{d_c^3}\right)\cdot\left|\frac{dh}{dt}\right|\right\}^n$$

for power-law fluids (7)

For convenience, we may define a new function, $\theta(t)=h_1(t)-h_2(t)-\Delta h_{t=\infty}$ so that we have : where

$$\frac{d\theta}{\theta}=-\alpha\,dt \quad \text{where} \quad \alpha=\frac{\rho g d_c^4}{16\mu L_c d_r^2}$$

for Newtonian fluids ; (8)

$$\frac{d\theta}{\theta^{\frac{1}{n}}}=-\beta\,dt \quad \text{where} \quad \beta=\frac{\left(\frac{\rho g d_c}{4kL_c}\right)^{\frac{1}{n}}}{\left(\frac{3n+1}{n}\right)\cdot\left(\frac{d_r^2}{d_c^3}\right)}$$

for power-law fluids. (9)

Since α and β are constants, these equations can be integrated as follows :

$$\theta(t)=\theta\ (0)\ e^{-\alpha t} \quad \text{for Newtonian fluids} \quad (10)$$

$$\theta(t)=\left\{\theta\ (0)^{\frac{n-1}{n}}-\left(\frac{n-1}{n}\right)\beta t\right\}^{\frac{n}{n-1}}$$

for power-law fluids (11)

Using curve fitting of the experimental data, both $h_1(t)$ and $h_2(t)$, one can determine the power-law index, n, and the consistency index, k. As n and k values are determined, the shear rate and subsequently viscosity can be determined as follows :

$$\dot{\gamma}=\frac{\rho g d_c}{4\mu L_c}\theta(t) \quad \text{for Newtonian fluids} \quad (12)$$

$$\dot{\gamma}=\left\{\frac{\rho g d_c}{4kL_c}\theta(t)\right\}^{\frac{1}{n}} \quad \text{for power-law fluids} \quad (13)$$

when n becomes 1, μ is equal to k, whereas when $0< n<1$, the viscosity is calculated using Eq. (4).

CLINICAL APPLICATIONS AND IMPLICATIONS OF THE PROTECTIVE ADAPTATION THEORY

This section examines how protective adaptation can serve in this clinical role as both a therapeutic method and a prognostic tool. Logically, the best way to prevent or reduce any pathologic condition is to make appropriate changes to its initial cause. In atherosclerosis, affecting the initial cause requires altering the three principal determinants of injurious pulsatile flow. The degenerative nature of atherosclerosis requires prevention of injurious pulsatile flow to begin at an early, though yet unspecified, age. Since atherosclerosis has been observed clinically in patients as young as 10 years old, the appropriate age for preventive measures may be even earlier than previously supposed.

In early- and middle-stage atherosclerosis, the therapeutic objective is to reverse or transform injurious pulsatile blood flow into normal pulsatile flow by reducing the three determinants. According to the American Heart Association (2000), the death rate in U.S.A. from coronary heart disease (a category that includes myocardial infarction, ischemic heart disease, and angina pectoris) decreased 26.3% in the 10 years from 1988 to 1998. One of the reasons cited for this welcome decrease is the emphasis that has been placed on reducing cardiovascular risk factors. According to the protective adaptation theory, by following recommendations for healthy living and taking medication to lower blood pressure and reduce cholesterol, people in the United States actually have been favorably affecting injurious pulsatile blood flow and helping to avoid mechanical injury to their arteries-thus reducing the risk of atherosclerosis. However, without a clinically practical way of measuring all of the determinants of injurious pulsatile blood flow, physicians are handicapped in their ability to fine-tune therapy and

predict treatment outcomes.

If atherosclerosis progresses to the end stages, it is usually life-threatening, since an acute occlusion prevents all blood flow beyond the occlusion point. In this situation the requirements are immediate medical intervention and a follow-up regimen to decrease blood pressure, left ventricular contractility, and blood viscosity-the three determinants of injurious pulsatile flow. A physician must have the therapeutic means to alter the three determinants of injurious pulsatile flow.

Although the concept of protective adaptation may be novel, at least in the clinical setting, treatments already exist for reducing blood pressure, left ventricular contractility, and blood viscosity. These treatments, which offer promising starting points for future research, are medications (antihypertensives, diuretics, cholesterol-lowering drugs, and anticoagulants), diet (including fish oil and fiber), exercise, and hemorheologic therapies including therapeutic phlebotomy, hemodilution, plasma exchange, apheresis, plasmapheresis, and defibrinogenation.

HEMORHEOLGICAL THERAPIES

Therapeutic Phlebotomy

One of the most promising yet simplest hemorheologic therapies, therapeutic phlebotomy, is one of mankind's oldest remedies and has been used by almost every culture in the world at one time or another. In patients with cerebral stroke, the intentional removal of a small volume of blood from the veins has been practiced widely, even in the twentieth century. The goal of therapeutic phlebotomy is to improve blood circulation.

Since substantial blood loss occurs during an operation, a number of researchers investigated the effect of surgery on blood viscosity. Stormer et al. (1978) measured blood, plasma, and serum viscosities in patients with peripheral vascular disease before, during, and after surgery. Besides plasma and serum viscosity, blood viscosity decreased most significantly during anesthesia and surgery. The decrease in blood viscosity was caused mainly by the falling hematocrit. Moreover, red blood cell aggregation occurring under low-flow conditions was decreased. Corresponding hemodynamic measurements in the study revealed that decreasing viscosity improves cardiac index and total pressure resistance when normovolemia exists, but in general is masked by anesthesia and operation.

Hemodilution

Hemodilution is a broad description of hemorheologic therapies. The goal of these therapies is to improve hemorheologic parameters such as whole blood viscosity over a range of shear rates, plasma viscosity, red blood cell deformability and aggregation, platelet adhesion, levels of plasma proteins (fibrinogen, lipoproteins, and globulins) so that ischemia can be improved or prevented. Obviously, blood letting alone cannot improve all of these hemorheologic parameters.

There are three principal forms of hemodilution used in the clinical setting today : hypovolemic hemodilution, isovolumic hemodilution, and hypervolemic hemodilution. Their respective use in the clinical setting is contingent on the patient's volume balance. Other hemorheological therapies include the followings :

- Hemodilution and Oxygen Transport Capacity, (Borst et al. 1999)
- Hemodilution and Leg Ischemia (Dormandy 1987) (Forconi 1979) (Stuart 1979)
- Hemodilution and Cerebral Ischemia (Dormandy 1987).
- Apheresis : heparin-induced extracorporeal LDL precipitation (H.E.L.P.) (Ernst 1987) (Lechner et al. 1992)
- Defibrinogenation (Ehrly 1973).

Fujioka (1989) conducted a study measuring whole blood in 10 patients with polycythemia vera and 129 normal controls and found that phlebotomy and fluid infusion therapy were valuable in most patients because the viscosity was decreased at once

to the normal level.

Kameneva et al. (1997) point out that hemodilution with plasma expanders is a widely applied practice during extracorporeal circulation and hemodialysis. Despite the immediate beneficial effects of hemodilution, such as reduction of blood viscosity and red blood cell aggregation, elevation of blood flow in the microcirculation, etc., the dilution of plasma, more specifically, a decrease in the concentration of plasma proteins due to hemodilution, may cause some unfavorable effects on red blood cells, amplifying the mechanical damage caused by circulatory assist devices.

FINAL REMARKS

By viewing atherosclerosis from the perspective of protective adaptation, we hope that we have enhanced the effectiveness of the physician's treatments for his or her patients. Once the physician has identified the patient's risk, various therapeutic options are available to reduce that individual's risk. The options discussed here are drugs, exercise, diet, therapeutic phlebotomy, hemodilution, apheresis, and defibrinogenation. All can be used to alter the determinants of injurious pulsatile flow to reduce the incidence of atherosclerotic diseases. We also hope that we have challenged researchers to explore new areas that may result in significant advances and improvements in the management of patients with cardiovascular diseases. In the near future, the therapeutic implications of the changes described in patients at risk for cardiovascular diseases or patients with overt myocardial ischemia are likely to be in the areas of primary and secondary prevention.

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