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PERIPHERAL VASCULAR DISEASE

Ray C. Heyn, Guest Editor

CARDIOVASCULAR CLINICS

Albert N. Brest, Editor

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Peripheral Vascular Disease

Ray W. Gifford, Jr., M.D. | Guest Editor

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Albert N. Brest, M.D. | Editor-in-Chief

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Editor's Commentary

In selecting material for the various issues of CARDIOVASCULAR CLINICS, emphasis has been placed on the presentation of subjects which are both practical and topical. No attempt has been made to duplicate the comprehensive coverage one expects to find in a textbook, and this same format has been followed in this issue. Nonetheless, I am confident the reader will find an abundance of clinically useful information in this issue, with attention both to the more common lesions (e.g. aneurysms) and the more esoteric (e.g. arteritides). Similarly, important surgical techniques (e.g. Fogarty) as well as newer medical approaches (e.g. medical treatment of dissecting aortic aneurysm) are described.

It may be more important than ever for the physician to be familiar with both old and new clinical aspects of peripheral vascular disease, recognizing that the ranks of specialists who deal solely with peripheral vascular disorders have been declining in number. Hence I feel especially proud of this issue, and I am enormously grateful to the Guest Editor, Ray Gifford, for his participation in the formulation of this volume.

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The Role of Hypercoagulability in Venous and Arterial Thrombosis*

Stanford Wessler, M.D.

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In the view of some investigators the incidence of the thrombotic process has reached epidemic proportions.[1,2] On the arterial side of the circulation, thromboembolic episodes are frequently associated with initial and recurrent episodes of myocardial infarction, major and minor cerebral vascular accidents, rheumatic and atherosclerotic valvular disease, arrhythmias, and congestive heart failure. Also they are associated with intimal damage to the aorto-iliac area and to the arteries of the lower extremities, obstruction to the carotid arteries, large aneurysms whether of the myocardium or the peripheral vessels, cardiovascular collapse from any cause, certain types of gastrointestinal malfunction, bowel necrosis, gangrene of the extremities, some infections, and several types of blood dyscrasias.

Venous thromboembolism, though perhaps neither as disabling nor as life-threatening as arterial disease, is even more ubiquitous. Aside from aggravating various forms of cardiovascular dysfunction and cancer (in which it may be the ultimate mechanism of death), venous thrombosis may unfavorably alter the course of a normal pregnancy, an otherwise successful surgical procedure, the use of estrogens, the management of bodily trauma, and prolonged immobilization from any cause.

When, for example, the pulmonary arteries of unselected adults are dissected with care at autopsy, more than 60 per cent of the cases reveal antemortem pulmonary emboli.[3] There is strong experimental evidence to support the view that the emboli observed at necropsy reflect only a small portion of the embolic material reaching the lung during life.[4] Since many emboli undergo complete lysis, or eventually become incorporated in the vessel wall, the true incidence of embolic episodes could well be greater than the 60 per cent figure mentioned above. In elderly patients immobilized with fractured hips the most common nonorthopedic cause of death is venous thromboembolism. Similarly, pulmonary embolism is one of the most common nonobstetrical causes of postpartum death.

Between the arteries and the veins is the microvasculature—an area in which classic venous and arterial thrombi do not ordinarily form, probably because of the efficiency of the endogenous thrombolytic activity initiated by tissue activator released from the endothelium of the small vessels. Here, however, is found a third type of thrombotic reaction that is being recognized with increasing frequency. This is the syndrome of diffuse intravascular coagulation, or DIC, in which primarily fibrin deposition occurs in the microcirculation and occasionally frank thrombosis is found in the larger vessels. Synonyms for DIC include the terms "consumptive coagulopathy" and "defibrination syndrome." The inciting cause is unknown, but the phenomenon is being observed in an increasing spectrum of disease states including patients with metastatic carcinoma, leukemia, giant hemangioma, purpura fulminans, drug reactions, hemorrhagic shock, snake bites, transfusion reactions, abruptio placentae, during systemic infections, and during extracorporeal shunts.[5] The clinical picture and laboratory findings are different, however, from the usual patient with venous or arterial thrombosis. Experimentally, DIC may be produced by

infusions of tissue thromboplastin or thrombin and by the generalized Shwartzman reaction.

Do we have any means available for predicting that an arterial or venous thrombus is either about to form or has in fact already occurred? Despite several promising leads this question must be answered in the negative for the present. Particularly in recent years, we have acquired an enormous knowledge of the biochemistry of the coagulation sequence, of the process of platelet aggregation, and of the fibrinolytic mechanism as well as of the effects of the failure of these three interrelated systems. Yet, we have no generally accepted laboratory tools or *markers* for the diagnosis of impending intravascular coagulation comparable to the exquisitely sensitive assays available for the identification of hemolytic anemia.

EFFECT OF CLASSICAL ANTICOAGULANTS ON ARTERIAL AND VENOUS THROMBOSIS

One may gain some insight into the hypercoagulability problem by examining the therapeutic effects of the classical anticoagulant drugs. A number of conditions for which heparin and the coumarin compounds have been recommended as effective antithrombotic agents are listed in Table 1. These include cardiac, cerebral, and peripheral arterial lesions, and venous and pulmonary arterial lesions, as well as several categories of patients that are at special risk from thromboembolism. Those marked with a dagger represent conditions in which the data reflect an unequivocal benefit from anticoagulant therapy, although in some of the situations modifying clauses are necessary, such as *hip fractures*, which applies to individuals over the age of 45 who will remain bedridden for more than a few days. Those marked with an asterisk represent conditions in which the gain from anticoagulants is slight: in the case of an acute or old myocardial infarction, probably due to the decrease in pulmonary or systemic emboli. Moreover, there is reasonable doubt as to the value of anticoagulants beyond 6 to 12 months following recovery from an acute myocardial infarction.

It is apparent from this formulation that heparin and the coumarin drugs are moderately effective on the venous side of the circulation and less so on the

Table 1. Effect of anticoagulation in various clinical conditions

* Acute Myocardial Infarction	† Pulmonary Embolus
* Old Myocardial Infarction	Pulmonary Thrombus
Coronary Failure	Pulmonary Hypertension
Angina Pectoris	† Hip Fracture
Stroke Complete	Postpartum
Stroke in Progress	Pelvic Surgery
* Transient Ischemic Attacks	Atrial Fibrillation
* Cerebral Embolus	reversion
† Acute Peripheral Arterial Occlusion	AF ⟶ RSR
Intermittent Claudication	* Valve Prosthesis
† Phlebitis	† DIC

* = slight benefit from anticoagulation
† = marked benefit from anticoagulation

arterial side particularly in organs, such as the heart and brain, that have physiologically end-arterial circulations. Thus, successful therapy, directed toward arterial thromboemboli, is achieved largely in the extremities where, because of the rich, pre-formed interarterial circulation, extensive intravascular coagulation is necessary to produce arterial insufficiency. Therapy with heparin or coumarin is also effective in the microcirculation in preventing or retarding DIC.

These observations emphasize the inadequacy of any holistic approach to thrombosis. From the results of conventional anticoagulant therapy alone, distinctions between arterial and venous thrombi present themselves, and it is apparent from a therapeutic view that DIC has more in common with venous than with arterial lesions. Whether agents such as aspirin, dipyrimadole, or prostaglandin E_1, which impede platelet aggregation, can prevent arterial thrombosis without interfering with normal hemostasis will only be resolved by careful clinical trials.

ARTERIAL THROMBOSIS—THE BASIC LESION

In the artery thrombosis can be readily visualized as an extension or exaggeration of the hemostatic plug that forms in response to injury, such as may be seen on atheromatous plaques. In the hemostatic plug, exposed collagen causes the adherence of platelets, resulting in the release of platelet ADP which in turn induces reversible platelet aggregation. Collagen also is believed to have the capacity to activate Hageman factor (factor XII), thus starting the sequential biochemical reactions leading to thrombin formation. Thrombin itself is responsible for converting the loose and reversible ADP-induced platelet plug into a consolidated or irreversible phase with the entire aggregate contracting. It is important to appreciate that the concentration of thrombin necessary to make platelet aggregation irreversible is believed to be distinctly less than that required for fibrin formation. The second effect of thrombin as it accumulates, of course, is on its principal substrate, fibrinogen, which is converted to fibrin, microscopic strands of which appear at the periphery of the platelet plug and further reinforce it. This overall series of reactions yields what is known classically as a white thrombus. And it is this type of lesion—an exaggeration of the hemostatic plug forming in response to injury—that represents the morphology of the typical arterial thrombus. Thus, it is believed that the mechanism involved in these two processes is the same.

Mustard has suggested that blood responds to intravascular stimuli as it does to vessel wall injury. Here, too, platelet aggregation is the pivotal thrombotic reaction to such intravascular stimuli as antigen-antibody complexes, viruses, bacteria, endotoxin, epinephrine, serotonin, thrombin, and trypsin.[6] This view has been supported and extended by the recent observations of Gaynor and associates who, by electron microscopy, found vascular injury in rabbits after a single dose of Escherichia coli endotoxin.[7]

It has also been reported that arterial thrombi, viewed as extensions of the hemostatic plug, can be initiated by states of systemic hypercoagulability that favor platelet aggregation.[6] However, the observed arterial lesions do not

require the assumption of a systemic hypercoagulable state to explain their genesis or evolution in all instances. There are, moreover, two further difficulties with the platelet plug as the single prototype for all thromboses. First, it has not been possible in experimental animals to induce the platelet thrombus to extend beyond the zones of endothelial injury. Second, while explaining how the white thrombus causes ischemia primarily in physiologically end-arterial circuits, such as the heart, brain, and kidney, where even complete vessel occlusion is not required, this model fails to account for the extensive growth of red cell-fibrin coagula in the major veins and peripheral arteries.

VENOUS THROMBOSIS—THE BASIC LESION

Venous thrombi, although perhaps requiring a platelet nidus for their origin, present essentially as red thrombi consisting principally of fibrin and erythrocytes with white blood cells and platelets randomly distributed. The morphology cannot be explained by an analogy to the hemostatic plug. Under light microscopy one finds red blood cells enmeshed by fibrin, and when the red blood cells are laked by a hypotonic fixative the fibrin strands are readily discernible. With the scanning electron microscope this thrombus is readily seen to consist of biconcave erythrocytes and fibrin strands wherein one hardly sees a platelet or platelet debris.

Moreover, in the veins and in the peripheral arteries, in contrast to most of the visceral arterial circuits, the issue is not only whether venous thrombosis starts as a platelet or a fibrin coagulation, but also what is it that facilitates the marked growth of the red thrombus? For in the venous system and in the peripheral arteries the collateral circulations are so rich that extensive thrombus formation is necessary to produce evidence of peripheral venous and arterial insufficiency. Extensive thromboemboli are also required to embarrass the pulmonary circuit.

STASIS—FACILITATOR OF THROMBOSIS

Retarded blood flow has long been associated with thrombogenesis. Although this cumulative association of stasis and thrombosis appears valid, data both in animals and in man indicate that retarded blood flow alone does not initiate intravascular coagulation.[8] If this be true, some alteration of the circulating constituents of the blood must be present to trigger intravascular coagulation in areas of retarded blood flow.

If clotting factors in their activated form do have a role in either the initiation or propagation of thrombi, stasis facilitates the progress of intravascular coagulation by protecting such thrombogenic species from dispersion, from neutralization by circulating inhibitors, and from clearance by the liver.[8] In addition to these three mechanisms, retarded blood flow favors intravascular coagulation by profoundly altering the physical and chemical properties of a column of blood so as to predispose to fibrin formation.[9]

HYPERCOAGULABILITY—THE EVIDENCE

Since neither trauma to the intima alone nor retarded blood flow per se can account for the dramatic growth of red thrombi, it is not unreasonable for in-