科技资料

Unstable Angina

W. Bleifeld C. W Hamm
E. Braunwald (Eds.)

Unstable Angina

With 75 Figures and 29 Tables

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Front cover: Picture of a sun protuberance, taken at the Sacramento Peak Observatory, Sunspot, New Mexico, USA

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Preface

If you find a man
with cardiac discomfort,
with pain in his arms,
at the side of his heart,
death is near.

The Ébers papyrus 2600 B.C.

This is the first document describing what today are termed "acute ischemic syndromes". These syndromes includes acute myocardial infarction, unstable angina, variant angina (Prinzmetal angina), and some forms of sudden death. Modern understanding of the pathophysiology and therapy of the acute ischemic syndromes developed in four stages: Following the initial description of acute myocardial infarction by Herrick in 1912, up to the early 1960s the therapeutic options available were extremely limited and consisted of pain relief, bed rest, and antithrombotic treatment to protect against pulmonary embolism. The second stage was marked by the introduction of coronary care based on external electrical defibrillation and cardiac pacing. Complications resulting from arrhythmias were effectively treated, resulting in a reduction of the in-hospital mortality of acute myocardial infarction from approximately 30% to between 15% and 20%. The third stage began with the initiation of intracoronary thrombolysis during the early 1980s. Early reperfusion of an acutely occluded coronary artery resulted in preservation of left ventricular function and a further reduction of mortality to between 5% and 10%.

The current, fourth phase in the care of patients with acute ischemic syndromes emphasizes the *prevention* of coronary artery occlusion and thereby of acute myocardial infarction, a condition which is often preceded by unstable angina. Although an acute occluding thrombus is present initially in about 90% of acute transmural myocardial infarctions, and although 10% to 15% of patients with unstable angina develop an acute infarction as a result of an occlusive thrombus, the importance of the link between these two conditions has become appreciated only recently. After documentation of the presence of coronary thrombi in many patients succumbing to sudden coronary death, an occluding thrombus complicating plaque rupture was recognized as the principal etiologic mechanism in the majority of patients with acute transmural myocardial infarction. Nonocclusive intracoronary thrombi have been observed at angioscopy and coronary arteriography in patients with unstable angina. Biochemical evidence of coronary thrombosis has been provided by the finding of platelet release products in the blood and urine of patients with acute ischemic syndromes. Finally, aspirin and heparin have been shown to prevent nonfatal myocardial infarction or cardiac death in several randomized, controlled studies of patients with unstable angina.

Thus, substantial evidence is now available to support the position that an alteration of the vessel wall, the complex interaction between the vascular endothelium and the different components of the blood, especially of platelets and fibrinogen, and the reaction of vascular smooth muscle are responsible in various combinations for the development of acute ischemic syndroms including unstable angina.

In a rapidly expanding field in which there is considerable research the scientific issues are often controversial, but such controversy often stimulates important additional investigations. Accordingly, the editors felt that the time was now opportune to bring together current knowledge, both basic and clinical, concerning acute ischemic syndrome. A symposium on "Unstable Angina" was held in Hamburg, June 3–4th, 1989 and the present volume has emerged from that meeting. Our profound thanks go to the participants in the symposium for their lively ideas, their stimulating presentations and discussions, their high level of scholarship, and their cooperation in the production of this monograph. Both conference and publication were made possible by the support given by Pharma Schwarz, ICI Medtronic, and Bayer to the University of Hamburg. Special thanks go to Mrs. Barbara Kratzenberg for her valued assistance in organizing the symposium. Our work as editors was supported enormously by the efforts of Dr. Wolfram Terres and also Dr. Claudia Osthoff from Springer-Verlag

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Contents

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The Vascular Endothelium: Interactions with Hemostatic Mechanisms (Platelets, Coagulation, Fibrinolysis)

E. GERLACH and B. F. BECKER [1]

Introduction

The vascular endothelium, which lines all blood vessels like a continuous sheet, must nowadays be regarded as a rather large tissue compartment of particular functional importance. With respect to its size, one should realize that in a person with 70 kg body weight the endothelial mass amounts to about 1000–1500 g, comparable to the mass of the liver [10]. Even more impressive is the size of the endothelial surface, estimated to be about 800–1000 m^2 [47]. This huge surface is in continuous contact with the 5–6 l of circulating blood, or, in other words, 5–6 ml of blood are on the average exposed to an endothelial area of 0.8–1 m^2. As an interesting consequence, one can calculate that the mean thickness of the blood film covering the endothelial surface amounts to about 5 μm, a value corresponding to the thickness of two red blood cells. These figures are merely intended to illustrate that intimate interactions of the streaming blood and its constituents with the endothelium are readily possible.

Detailed studies on interactions between endothelium and blood have become possible only within the past decade. In this period newly elaborated, sensitive analytical methods, culture techniques as well as suitable in vitro and in vivo vessel preparations have become available. These innovations have enabled an extensive characterization of endothelial cells, particularly with respect to their biochemical, immunological, and physiological properties [13, 18]. The results obtained leave no doubt that the vascular endothelium plays a decisive and active role in the interactions of blood with the vessel wall and the adjacent tissues.

Various Functional Features of the Vascular Endothelium

Some important functional features of the vascular endothelium are summarized in Table 1. First of all, the endothelium controls exchange processes between the intra- and extravascular spaces. The physical barrier function preventing simple passive transfer of blood cells or larger molecules has long

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Table 1. Functional features of the vascular endothelium

Control of exchange processes
– Physical barrier
– Metabolic barrier
Modulation of vascular tone
– Dilatation: PGI_2, EDRF (NO), adenosine
– Constriction: Angiotensin II ↑, bradykinin ↓, endothelin, EDCF
Influence on hemostasis
– Antithrombogenic surface (physiological state)
– Thrombogenic surface (perturbed state)
Participation in inflammatory and immune reactions
– Leukocyte adhesion, activation, and emigration
– Antigen presentation, T-lymphocyte activation, binding of complement factors

been known. The metabolic barrier function, however, was only recently recognized. It applies, for instance, to substances such as ATP and ADP [26, 33] or lipoproteins [12], which become degraded by ectoenzymes at the luminal surface and therefore, as such, cannot cross the endothelial layer. Another example is the nucleoside adenosine. When presented in low but vasoactive concentrations to the luminal surface, for example, of the coronary endothelium, adenosine is rapidly taken up by the endothelial cells, where it becomes fully metabolized [19, 28]. Nevertheless, though it does not reach the smooth muscle cells, adenosine in low concentrations induces coronary dilatation. From these findings it has been concluded that this dilatation must be mediated by the endothelium [27, 29, 30].

A second aspect, receiving widespread attention today, is the role of endothelial cells in modulating vascular tone. Three vasodilating substances are formed and released by the endothelium: prostacyclin (PGI_2), endothelium-derived relaxing factor (EDRF), and adenosine [18]. EDRF has recently been identified as nitric oxide (NO) [31]. Since these substances also affect platelet aggregation, they are discussed in greater detail below. Under certain circumstances endothelial cells can promote vasoconstriction. For instance, angiotensin-converting enzyme, located at the endothelial surface, forms the constrictory angiotensin II; at the same time it degrades dilatory bradykinin to vasoinactive products, thereby potentiating the vasoconstriction (for review, see [18]). Furthermore, endothelial cells are the source of the newly detected polypeptide endothelin, a very potent vasoconstrictor [48]. Finally, endothelial cells of lung and brain vessels appear to be capable of producing another, still unidentified constrictory factor, called EDCF [45]. At present, it is a matter of debate to what extent endothelium-dependent dilatory and constrictory mechanisms contribute to the modulation of general vascular tone, or whether they are only of local importance.

The third functional feature concerns the role of the vascular endothelium in hemostasis. On the one hand, it is well known that under normal physiolog-

ical conditions the luminal surface of the entire vascular system exhibits antithrombogenic properties [18, 34]. These comprise mechanisms directed against platelet aggregation and blood coagulation as well as mechanisms promoting fibrinolysis. On the other hand, in the past few years evidence has been obtained that the endothelial surface can become thrombogenic. However, this appears to be a phenomenon restricted mainly to areas with a perturbed endothelium, as encountered under various pathological conditions, such as inflammatory and immune reactions as well as during development of arteriosclerotic lesions [9, 11, 35, 41].

Finally, in the course of inflammatory and immune reactions the vascular endothelium may not only develop a thrombogenic surface. As indicated in Table 1, the endothelial cells actively participate in the processes of adhesion, activation, and emigration of leukocytes, in particular of polymorphonuclear neutrophils and monocytes [9, 11]. Under certain conditions the endothelium can take part in antigen presentation and activation of T-lymphocytes [3]. Furthermore, binding sites for factors of the complement system can be expressed [36]. Most of these activities involve an endothelial synthesis of new proteins which subsequently are incorporated into the cell membranes. It should be emphasized, however, that many details of these interesting pathophysiologic responses still need to be clarified.

Antithrombogenic Features of the Endothelium

In the physiological state, a truely impressive number of properties of the endothelial surface antagonize platelet aggregation, inhibit blood coagulation, and promote fibrinolysis.

Antiplatelet Actions

Three factors exhibit antiplatelet actions: PGI_2, EDRF, and adenosine. The endothelial formation of PGI_2 from arachidonic acid and its release at the luminal surface is a well-established phenomenon. This ability seems to be almost unimpaired in patients receiving low-dose aspirin treatment [24].

The antiplatelet effect of the EDRF nitric oxide was discovered only about 2 years ago [7, 25]. In Fig. 1 the production and the different actions of EDRF are schematically indicated. A great number of vasoactive substances, including acetylcholine, bradykinin, histamine, thrombin, ATP, and ADP, are known to bind to receptors at the luminal surface, initiating a Ca^{2+}-dependent formation of EDRF (NO) from the precursor substance L-arginine [32, 39]. The precise mechanisms involved in the generation of NO, however, are not yet fully understood. Interestingly, NO is released from the endothelial cells at the basal and also at the luminal side [2]. Through stimulation of the soluble guanylate cyclase and the resulting increase in cGMP levels relaxation of the

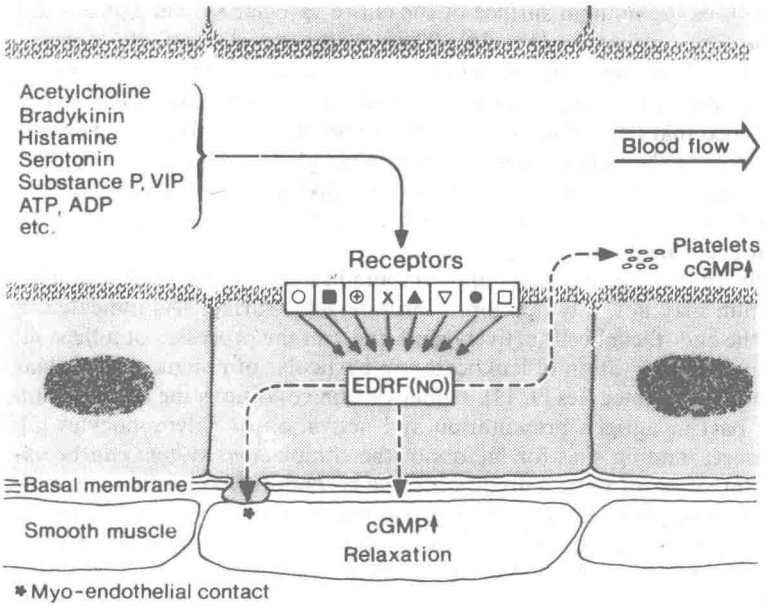

Fig. 1. Schematic illustration of steps involved in the production and action of the endothelium-derived relaxing factor (EDRF) nitric oxide (NO). Various vasoactive substances, when present intravascularly, bind to endothelial surface receptors, thereby inducing a Ca^{2+}-dependent luminal and abluminal release of NO. This causes an increase in cGMP levels in vascular smooth muscle cells, leading to relaxation, and in platelets, increasing their antiaggregatory potential (for further details, see text)

smooth muscle cells and thus vasodilatation is brought about. EDRF released into the vascular space similarly activates guanylate cyclase in platelets, and here the elevation of cGMP is a powerful antiaggregatory signal. Owing to the short half-life of the EDRF, which is in the order of seconds in blood, the antiplatelet action of EDRF is obviously restricted in vivo to the close vicinity of the endothelial production site (for details of EDRF actions, see reviews [1, 21]).

A localized action is also expected for the nucleoside adenosine, a strong inhibitor of platelet aggregation [4], which we have shown to be continuously formed and released by the endothelium, and which can be additionally generated at the vessel wall through dephosphorylation of adenine nucleotides by means of endothelial ectonucleotidases [18, 19, 26]. However, as mentioned above in the context of the metabolic barrier function, adenosine is also avidly taken up and metabolized by endothelial cells. This seemingly discrepant capability of endothelial cells for both uptake and release of adenosine raises the intriguing question of which process prevails.

Since under physiological conditions the adenosine concentration is known to be almost identical in the arterial and venous blood [40], the regulatory

mechanisms outlined in Fig. 2 appear important. In the upper part of Fig. 2 the normal steady-state situation is shown. As indicated by the arrows, adenosine must be continuously released from the endothelium in excess of the amount that is taken up because also red blood cells incorporate adenosine. As a consequence of these dynamic processes a concentration gradient of adenosine is presumably established across the vessel lumen, the highest concentration existing close to the endothelial surface. Thus, it is mainly in this border zone where, already under normal conditions, adenosine can augment the antiplatelet actions of EDRF and PGI_2.

As depicted in the lower part of Fig. 2, the adenosine concentration can be locally enhanced when adenine nucleotides become stepwise dephosphorylated at the endothelial surface through the ectonucleotidase cascade, which consists of an ATPase, ADPase, and 5′-nucleotidase [18, 33]. Such a condition actually exists close downstream from a vascular lesion, where adenine nucleotides are liberated from injured cells and from aggregating platelets. It is easy to appreciate that the increased adenosine concentration must result in a much stronger antiplatelet action, thus preventing a spreading of platelet aggregation beyond the primary lesion. In this context it is important that the ecto-ADPase is thus not only involved in the extracellular formation of antiaggregatory adenosine but also in the rapid removal of the potent aggregatory stimulant ADP.

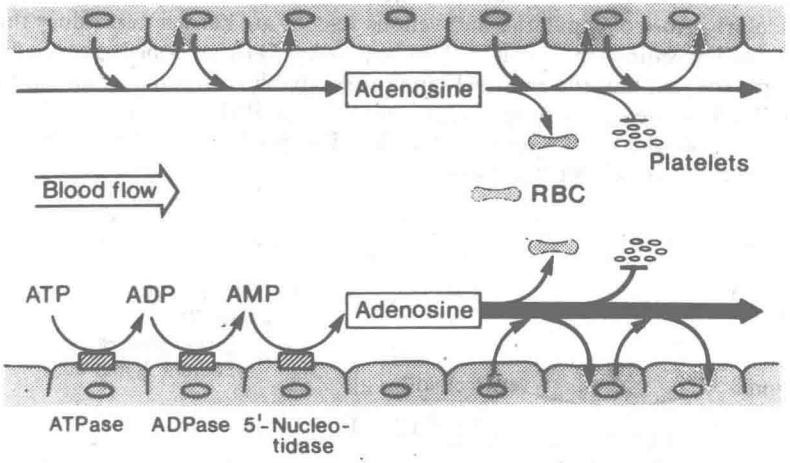

Fig. 2. Adenosine homeostasis in streaming blood under normal conditions (*above*) and after release of adenine nucleotides from damaged tissue or from platelets (*below*). Normally, formation and release of adenosine prevails over uptake by endothelial cells and red blood cells (*RBC*), thus establishing an antiaggregatory adenosine concentration in the plasma layer adjacent to the endothelium. This condition becomes greatly enhanced if adenine nucleotides occur intravascularly and become degraded by the ectonucleotidases (*thick arrow*)

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