Coronary and Cerebral Thromboses

Richard G. Lynch, MD
Originally published in The ASIP Bulletin, Volume 9, Issue 1 - February 2006

MILESTONES

Constantinides, P: **Plaque fissures in human coronary thrombosis.** *Journal of Atherosclerosis Research* 1966, 6:1-17

Constantinides, P: **Pathogenesis of cerebral artery thrombosis in man.** *Archives of Pathology* 1967, 83:422-428

Paris Constantinides

Until these meticulous studies by Paris Constantinides were published, the pathogenesis of arterial thrombosis was a subject of considerable controversy and speculation. It had long been known that thrombotic occlusion of a coronary artery was a common autopsy finding in patients dying from myocardial infarction (heart attack), and that cerebral artery blockage by a recently formed clot was a typical finding in patients with a cerebral infarction (stroke). While there was strong consensus that advanced atherosclerosis predisposed coronary and cerebral arteries to thrombosis, the mechanisms underlying these events had remained obscure.

The hallmark lesion of atherosclerosis is the atheromatous plaque, or atheroma, a term derived from the Greek word for gruel. An atheroma is a raised focal plaque within the arterial intima that is composed of a pasty, cholesterol-rich core covered by a fibrous cap. With time, atheromas become calcified and acquire the brittleness of an egg shell.

In a minority of patients with coronary or cerebral thrombosis, the clot forms over an ulcerated atherosclerotic plaque. This was readily explained because the collagen, calcium and phospholipoproteins exposed in a denuded plaque were well known aggregators of platelets and activators of thromboplastin. However, in the majority of patients with coronary or cerebral thrombosis, the clot formed over seemingly intact, hemorrhagic plaques. The pathogenesis of these clots remained unexplained until the milestone investigations of Constantinides.

Several mechanisms had been proposed to account for coronary and cerebral thrombosis, but each was conceptual, speculative and unproven. The consistency of finding hemorrhage within seemingly intact plaques at the site of thrombosis spawned a novel concept – the capillary hemorrhage theory, which proposed that capillaries from the arterial lumen invaded the plaque and then ruptured, triggering a retrograde thrombosis that expanded to occlude the artery. This theory ignored the fact that capillary invasion of plaques usually occurs from the adventitia – the outside of the artery – not from the lumen.

The *stasis theory* proposed that diminished blood flow caused by atherosclerotic narrowing of the vessel resulted in thrombus formation, while the *turbulence theory* envisioned thrombosis as the result of eddying-induced platelet aggregation at sites of atherosclerotic narrowing. The enormous morbidities and mortalities associated with coronary and cerebral thrombosis, disorders highly prevalent in developed nations, fostered major research efforts in North America and Europe. However, progress was stymied by the lack of a relevant experimental model and by a reductionist research approach to the overwhelmingly complex process of atherogenesis. Although the list of predisposing conditions, such as hypertension, hyperlipidemia, diabetes, obesity and cigarette smoking, continued to grow, real progress towards identifying pathogenic mechanisms proved elusive.

A popular concept held that thrombus formation in an atherosclerotic coronary or cerebral artery was a result of systemic hypercoagulability. Support for this idea came from clinical trials in which anticoagulants appeared to improve survival in selected patients. A major criticism of the *hypercoagulability theory* was its failure to account for the exclusive formation of only a single clot, at a single site, in a single artery, in spite of numerous atherosclerotic lesions present in the same and other arteries of the patient.

The *tiny fissure hypothesis* of Constantinides proposed that the thrombi that form over seemingly intact hemorrhagic plaques are caused by microscopic cracks in the collagenous caps of the plaques – cracks so small that they are rarely detected by routine histological examination. To test his idea, Constantinides conducted a monumental

examination of serial seven-micron-thick paraffin sections cut through the entire length of occluded coronary arteries. This meticulous study of thrombosed segments from 20 consecutive autopsy cases of coronary thrombosis[1] involved more than 40,000 microscopic sections!

Constantinides observed that in every case the thrombi were anchored in fissures of the caps of atherosclerotic plaques. The fissures were about 300 to 400 microns in length, a size where fissures would likely be missed if one or only a few random histological sections of the thrombus were examined. The fissures tended to occur at the margins of plaques, where the edge of the cap attached to the uninvolved arterial wall. The adherence of the thrombus to the fissure occurred in the platelet-rich zone of the thrombus, the region where clotting is initiated. He concluded that almost all plaque hemorrhages were caused by tiny cracks in the cap that triggered thrombus formation when blood came in contact with the thrombogenic material contained inside of plaques.

In another massive undertaking, Constantinides employed the same approach to examine 10 consecutive autopsy cases of cerebral artery thrombosis[2]. He observed that all thrombi were attached by their platelet-rich zones to tiny cracks in the caps of atherosclerotic plaques.

Subsequent studies by other investigators confirmed the observations of Constantinides, and it became accepted that thrombosis in atherosclerotic coronary and cerebral arteries is practically always initiated by local breaks in the surface of atherosclerotic plaques. By the early 1960's a rabbit model of human atherosclerosis had been developed. Using this model Constantinides showed that the induction of breaks in the experimentally induced atherosclerotic plaques resulted in the formation of overlying thrombi. In rabbits with experimental atherosclerosis, but not in control rabbits, an induced burst of hypertension caused plaque fissures and overlying thrombosis.

An interesting characteristic of scientific progress is the frequency with which competing hypotheses are eventually found to contain valid elements. In the instance of arterial thrombosis research, there are elements of truth in most of the hypotheses that had been put forward. This likely reflects both the complexity of atherogenesis and the multiplicity of its complications.

Hypercoagulability remains an important detail of coronary and cerebral thrombosis and underlies the recommendation of daily intake of small doses of aspirin for individuals at risk for myocardial infarction or strokes. Where the hypercoagulability theory envisioned a systemic clotting disorder, Constantinides' findings pointed to localized clotting that occurred when a fissure allowed blood to come in contact with thrombogenic materials contained within a plaque.

Constantinides later suggested[3] that plaque fissures might occur all the time, but the rate at which thrombi grow, the size they attain, and their clinical consequences might depend on systemic factors, such as hypercoagulability and fibrinolysis, and local factors, such as stasis and turbulence. He further proposed that mechanical factors, such as bursts of hypertension, or the constant bending and torsion of coronary arteries with each ventricular contraction, could result in the formation of cracks in brittle atherosclerotic plaques.

The milestone research of Constantinides is a sterling example of the vital role of the individual investigator in advancing biomedical knowledge. The research enterprise of Paris Constantinides consisted of himself, who conducted some of the autopsies, a histology technician, the secretary who typed the manuscripts, and colleagues who provided some of the specimens. The research was supported by a small NIH grant.

References

1. Constantinides, P: *J Athero Res* 1966, 6:1-17
2. Constantinides, P: *Arch Path* 1967, 83:422-428
3. Constantinides P: *Ultrastructural Pathobiology,* Elsevier Science Publishers, Amsterdam, 1984, p.115