EDITORIAL COMMENT
Thrombogenesis and Fibrinolysis in Acute Coronary Syndromes
Important Facets of a Prothrombotic or Hypercoagulable State?

Gregory Y.H. Lip, MD, FACC, Andrew D. Blann, PhD, MRCPATH
Birmingham, United Kingdom

Over 150 years ago, Virchow (1) first postulated that a triad of conditions predispose to thrombus formation, these three factors being abnormalities in blood flow, blood constituents and the vessel wall. While Virchow was referring to venous thrombosis, the same processes have been applied to arterial thrombosis. A contemporary viewpoint of Virchow’s triad considers abnormalities of hemorheology and turbulence at bifurcations and stenotic regions (i.e., abnormal blood flow), abnormalities in platelet function and the coagulation and fibrinolytic pathways (abnormal blood constituents) and finally, abnormalities in the endothelium (abnormal vessel wall). As the processes of thrombogenesis and atherogenesis are intimately related, there is perhaps little surprise that thrombogenesis has been studied extensively in cardiovascular disease.

Improvements in laboratory techniques have allowed us to quantify various components of Virchow’s triad, which, if abnormally elevated, confer the presence of a so-called “prothrombotic” or “hypercoagulable” state. Such abnormalities in certain indexes of hypercoagulability (such as fibrinogen) have been found in cardiovascular diseases as diverse as coronary artery disease (CAD), atrial fibrillation and heart failure (2–5). This prothrombotic state has been related to target organ damage and cardiovascular risk as well as prognosis, and it can be modified by interventions such as antithrombotic and antiplatelet therapy (6–10).

Myocardial infarction is often associated with mural thrombus and/or associated heart failure or atrial fibrillation (4,5), which can alter markers of thrombogenesis and can perhaps be further confounding factors. Indeed, the greater myocardial damage in MI compared with unstable angina may release several cytokine mediators, such as interleukin-6, resulting in a more marked acute phase response with different effects on thrombogenesis and fibrinolysis—perhaps explaining some of the observations in this article (14). Many drugs, such as the angiotensin-converting enzyme inhibitors and heparin, as well as contrast media from the subset undergoing cardiac catheterization or angioplasty, can also influence the measured parameters.

As apparent in the article by Figueras et al. (14), the use of thrombolytic therapy during the treatment of acute MI results in further generation of fibrin degradation products, including fibrin D-dimer (which they measure). Previous
reports have suggested that the maximum rise in fibrin D-dimer is seen between 1 and 4 h, but importantly, elevations in fibrin D-dimer levels do not appear to be predictive of coronary patency (15,16). However, it is important to note that only a fraction of the elevation in fibrin D-dimer is actually due to lysis of coronary thrombi, and most derive from other types of intravascular fibrin (17) for example, the lysis of cross-linked circulating fibrin polymers. Measurement of peripheral fibrin D-dimer levels after thrombolytic therapy for acute MI therefore does not distinguish between these two potential sources of D-dimer, and as the article from Figueras et al. (14) suggests, there is little role for the routine measurement of fibrin D-dimer after thrombolytic therapy for acute MI. The increase in fibrin D-dimer levels also appears to be independent of the type of thrombolytic agent used and of the clinical course following the infarct (18).

The observations linking the prothrombotic state and cardiovascular disease are nevertheless important in view of the relationship between these markers and both short- and long-term cardiovascular outcomes. For example, hypertensive subjects with plasma fibrinogen levels >3.5 g/liter had a 12-fold higher cardiovascular risk than those with plasma fibrinogen levels <2.9 g/liter in the Leigh general practice study (19). In a study of 617 patients with claudication, the Edinburgh Artery Study reported that baseline fibrin D-dimer levels were closely related to future coronary events (both fatal and nonfatal, with a relative risk of 4.4 between upper and lower quintiles) and also with hemodynamic progression of peripheral arterial disease (6). Indeed, higher plasma levels of fibrin degradation products have been found in patients suffering thrombotic reocclusion following femoropopliteal artery angioplasty, when compared with patients with maintained patency of the dilated arterial segment (20). Indeed, indexes of a prothrombotic or hypercoagulable state, even within the "normal" laboratory range, can predict both arterial thrombotic events and postoperative thrombosis (6,10,21), suggesting that there may be a continuum between health, a "statistical" increase in (say) fibrin turnover as a prethrombotic state, and "overtly" increased fibrin turnover in acute thrombosis (or sometimes in acute extravascular fibrin formation, as follows injury or surgery) (10). Importantly, increased thrombogenesis appears to contribute to the progression of both coronary and peripheral atherosclerosis, which is consistent with the hypothesis that markers such as fibrin D-dimer may be a useful index of intravascular fibrin turnover and the contribution of thrombosis to arterial disease (6,10–13).

Figueras et al. (14) also report that levels of the various indexes measured were "significantly higher" than "controls," which comprised 25 healthy individuals with a mean age of 47 years, compared with a mean age of 57.8 years in the patient group. As the authors rightly point out, some caution is needed in interpreting this statement in view of the association between some of the measured indexes and age. Furthermore, their use of symptomatic assessments (i.e., angina vs. no angina) have some limitations, and evaluations using measures of high risk such as troponins would perhaps have been more valuable (22), especially if they could be correlated with the indexes of thrombogenesis. Another question that may be raised is whether subgroup analyses (e.g., 12 patients with unstable angina who are compared with the 11 who did not develop angina [14]) are adequately powered. Some parameters such as D-dimer and thrombin-antithrombin are highly skewed so that median (rather than mean) values would be more representative of what is actually going on.

Would thrombogenesis or fibrinolysis represent a cause, or an effect, in acute coronary syndromes or MI? Since the processes of thrombogenesis and atherogenesis have many similarities to inflammatory disease, the elevations in various indexes may simply reflect the severity of the underlying vascular disorders as a secondary phenomenon rather than act as a true prognostic factor. Indeed, it has been suggested that the associations between cardiovascular disease and the prothrombotic state may be explained by a reactive or secondary rise in plasma hemostatic factors, either as an acute phase response or as a vascular disease-related "hematological stress syndrome" (23). There is increasing recognition of the parallel changes in the inflammatory response in the pathogenesis of CAD, including the prediction of subsequent cardiac events in patients with both unstable and chronic coronary disease (24,25). Furthermore, in view of possible relationships between C. pneumoniae and Helicobacter pylori (26) with CAD, including acute coronary syndromes, the role of potential pathogenic infections needs to be defined. For example, some studies have suggested that interventions with antibiotics to eradicate C. pneumoniae in patients with acute coronary syndromes may be beneficial, although some of the antibiotics used have anti-inflammatory effects (27,28). There is also the possibility that thrombolytic therapy for acute MI may be related to an increase in oxidative stress, platelet activation and endothelial cell damage (29). Despite the diverse nature of (possible) stimuli, the final common pathway linking abnormal thrombogenesis and cardiovascular disease may well be cytokine mediated (30), which opens the possibility of a target for intervention.

The identification of ongoing thrombogenesis and fibrinolysis in patients with MI or acute coronary syndromes represents facets of a prothrombotic or hypercoagulable state and may possibly identify a high-risk subset of patients who may develop complications. Large prospective studies are required to carefully document the precise interactions between the many components of Virchow's triad and clinical outcomes in cardiovascular disease.

Acknowledgments

We acknowledge the support of the City Hospital NHS Trust Research and Development Programme for the Haemostasis Thrombosis and Vascular Biology Unit.
REFERENCES


