patients are best treated with parenteral cobalamin, although large oral doses (1000 μg daily) can be used if necessary. A failure to split cobalamin from its binders in food (food-cobalamin malabsorption), a disorder due to various types of gastric dysfunction including atrophic gastritis and most forms of gastric surgery, is more common than pernicious anemia and has been identified in 30–40% of patients with low cobalamin levels. Such patients can probably be treated with small oral doses of cobalamin (1–10 μg daily), as can patients with nonmalabsorptive causes of deficiency. Treatment of patients with mild cobalamin deficiency may take on added importance as folate supplementation becomes more widespread in the United States.

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Cardiac Troponins in Patients with Chest Pain

BECAUSE THE ELECTROCARDIOGRAM is not diagnostic in almost 50% of patients with acute myocardial infarction (MI), biochemical methods have been crucial for detection of MI in this group. Important characteristics of a reliable serum marker of cardiac necrosis include high concentration in the myocardium, absence in noncardiac tissues, rapid release from injured cells and sufficient persistence in the serum to allow detection after an extended interval from the onset of symptoms. For more than two decades, these criteria have been best met by the myocardial band (MB) isoenzyme of creatine kinase (CK), establishing it as the most widely used serum marker of acute MI. Although CK-MB has been useful, its limitations include lack of specificity due to its presence in noncardiac tissues such as small intestine, skeletal muscle, diaphragm, uterus and prostate and its elevation in renal failure, as well as a pattern of elevation that begins three hours after onset of acute MI and takes up to 12 hours for diagnostic values in many patients. Because CK-MB levels usually return to normal in less than three days in most patients, increased isoenzyme-1 of lactate dehydrogenase (LDH), which also has imperfect specificity but persists for 10–14 days, has been utilized for delayed diagnosis of MI. The limitations of these current biochemical methods have spurred recent interest in new serum markers, much of which has focused on the troponins.

The troponins comprise a protein complex of three subunits that regulates the interaction of actin and myosin in cardiac and skeletal muscle. The subunits are troponin T (cTnT), I (cTnI) and C (cTnC). The amino acid sequences of cTnT and cTnI (but not cTnC) in cardiac and skeletal muscle differ, allowing for a highly specific monoclonal antibody-based assay for their measurement in serum. Early clinical studies of the troponins in the diagnosis of acute MI have revealed a number of advantages over CK-MB. Serum levels of cTnT and cTnI are very low in normal individuals and have greater relative magnitudes of increase in serum after MI than current markers, facilitating the distinction between normal and abnormal data. The sensitivity of cTnT and cTnI for diagnosing acute MI has been equivalent to or higher than that of CK-MB in most studies. Although the time of initial release of the troponins after MI is similar to that of CK-MB, they remain elevated for up to two weeks. The persistence of troponin elevation after infarction will likely render measurement of LDH-1 obsolete for late detection of MI.

A major advantage of the troponins is their superior specificity over CK-MB, reflected in their lack of elevation by injury of noncardiac tissues. This is well demonstrated by normal cardiac troponin levels in marathon runners, in whom CK-MB levels can be elevated. Specificity of cTnI in acute MI is 85–95%. Although the specificity of cTnT has been reported to be as low as 80% in some studies, this may be due to its ability to detect minimal cardiac damage in some patients currently categorized as having unstable angina. Exclusion of the latter group from these studies has resulted in a marked improvement in specificity of cTnT to 95%. One difference between the two cardiac troponins is elevation of cTnT in uremia, which may be related to its detection of uremic myocardial damage.

A growing role for the cardiac troponins has been in the assessment of patients who present to the emergency department without ST-segment elevation on their electrocardiograms. This group includes patients with non-Q MI, unstable angina and chest pain of noncardiac origin. Both cTnI and cTnT obtained in the emergency department have been accurate in identifying those patients in whom acute MI was subsequently diagnosed after admission. Furthermore, elevations of the cardiac troponins in patients with unstable angina have been strong predictors of late cardiac events. The availability of rapid, bedside assays for both cTnT and cTnI have made the troponins an important component of the decision-making process for managing the large group of patients presenting to the emergency department with chest pain of uncertain origin. These early studies must be extended to determine whether the troponins provide additional data beyond the clinical evaluation and electrocardiogram in this important patient population.

The troponins possess superior characteristics as serum markers of myocardial damage compared with current methods. They combine a high degree of sensitivity with greater specificity, more sustained elevation and better prognostic value than current markers and they can be measured by a rapid assay. These factors justify their emerging status as the serum markers of choice

for assessment of patients presenting with chest pain of possible cardiac origin.

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Factor V Leiden and the Prothrombin Gene Mutation: Two Common Genetic Defects Associated with Thrombosis

MORE THAN 50% OF PATIENTS who develop a spontaneous deep vein thrombosis (DVT) will be found to have one or more thrombophilic disorders. The majority of these defects are inherited rather than acquired, in most cases due to a mutation in the genes coding for either factor V or factor II (prothrombin). The most well known defect, factor V Leiden, causes resistance to the action of activated protein C (APC), one of our most potent natural anticoagulant proteins. This disorder, which involves Caucasians almost exclusively, is thought to have arisen as a single mutation approximately 30,000 years ago. The prothrombin gene mutation was reported in 1996 as a result of ambitious DNA sequencing of the bulk of the prothrombin gene in search of a prothrombotic polymorphism. The mechanism by which the mutation causes thrombosis is under current investigation.

Both of these inherited defects can be easily identified in patients with thrombotic disease. There are two diagnostic tests for factor V Leiden. The best test for screening is the APC resistance ratio, which is available in most Hemostasis and Thrombosis reference laboratories, and costs approximately $60. In the "second generation" assay, the patients plasma is diluted in factor V-deficient plasma before determination of the clotting time with and without APC. The current assay is highly sensitive and specific, and importantly, can be performed in patients on anticoagulation (both heparin and warfarin), and is not affected by low titer lupus inhibitors. The PCR-based DNA test for the specific factor V Leiden mutation will identify heterozygotes and homozygotes, but is more expensive (e.g. $100-150). It should be reserved for patients in whom the screening test is uninformative, or to confirm that patients with low APC resistance ratios (e.g. < or= 1.3) are homozygous for the defect. Unfortunately, prothrombin activity assays cannot reliably be used to screen for the prothrombin gene mutation, making DNA testing mandatory.

Both thrombophilic disorders are exceedingly common. Factor V Leiden occurs in 3–8% of European populations and is found in approximately 15–20% of patients with a first DVT, and in up to 50% of patients with recurrent venous thromboembolism or women with estrogen-related thromboses. The prothrombin gene mutation is present in 2% of the general population, 6% of patients presenting with a single DVT and up to 18% of patients with a personal and family history of thrombosis.

Because these disorders are so prevalent, they frequently coexist with other hypercoagulable states, greatly magnifying the risks of thrombosis. For example, many cases of factor V Leiden or the prothrombin gene mutation occurring together with hyperhomocysteinemia, antiphospholipid antibodies, or protein C deficiency have been reported, and combined defects are frequently encountered in clinical practice. In general, the risks of future thromboembolism increase exponentially when patients have multiple defects. For example, in the Physicians Health Study, subjects with either factor V Leiden or hyperhomocysteinemia had a 3–4-fold increased risk of idiopathic thrombosis. However, when both defects were present, the relative risk soared to 22. There is also a striking increase in thrombotic risk when factor V Leiden is combined with other circumstantial risk factors such as surgery, trauma, or immobilization, or high estrogen states associated with oral contraceptives or pregnancy. There appears to be a synergistic interaction with estrogens, reflected in the greater than 30-fold increase relative risk in factor V Leiden carriers who also use oral contraceptives.

Although both the factor V Leiden and prothrombin gene mutations have been primarily linked to venous thromboembolism, two recent studies reported a nearly 4-fold increased risk of MI in young women with other cardiovascular risk factors, particularly smoking. Arterial thromboembolism may also occur in patients with venous thrombosis via a right to left shunt through a patent foramen ovale or other cardiac defect.

What are the implications of these disorders for clinical practice?

Both the factor V Leiden and prothrombin gene mutations, by themselves, are relatively "mild" hypercoagulable disorders. This is illustrated by the observation that many carriers do not experience their first thrombotic episode until an advanced age, and some never develop thrombosis. In the absence of a history of thrombosis, long term anticoagulation is not routinely recommended since the 1–2%/ year risk of major bleeding from warfarin is greater than the estimated < 1%/year risk of thrombosis in asymptomatic carriers. However, if other circumstantial or hormonal risk factors or other persistent hemostatic defects are present, then the potential benefits from long term anticoagulation may outweigh the bleeding risks. Ultimately, in the future, identification of one or more hereditary or acquired prothrombotic states will allow accurate prediction of the risk of future thrombosis, making the