variance, such as intense physical exercise, advanced heart failure or diabetic neuropathy. Spectral analysis of RR variability does not measure tonic nerve activity of any of the two autonomic outflows, but only provides an estimate of the continuous interaction between sympathetic and vagal modulatory activities with the sino-atrial node function, examined in closed loop conditions.

Large scale normative studies are still not available, and it will be important to titrate the results in a clinical setting. In spite of the remaining difficulties and uncertainties, the introduction of portable equipment with more user-friendly standardized procedures, will prove essential to open the door between the computer room and the clinical ward.

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References

Non-invasive markers of coronary reperfusion in acute myocardial infarction

A sufficient number of controlled clinical trials have convincingly demonstrated that thrombolytic therapy reduces short-term and long-term mortality after acute myocardial infarction[11]. However, there are limitations to intravenous thrombolytic therapy. It has been shown that in approximately 30% to 35% of patients, intravenous thrombolysis fails to restore coronary artery patency[21]. Patients who fail to reperfuse do worse compared to patients with a patent infarct-related artery and furthermore there are also differences among reperfused arteries. For example, patients achieving an angiographic TIMI 3 score have a better outcome than those achieving only a TIMI 2 score.

Since different therapies are available to improve or to restore infarct-related coronary patency once thrombolysis has failed, and since time is usually a limiting and prognostic related factor, we are in need of reliable markers to determine whether successful reperfusion has occurred. Undoubtedly coronary angiography is the gold standard to determine reperfusion; however, for clinical practice it is impractical and not recommended. Non-invasive markers have been evaluated in order to distinguish between patients with successful and failed reperfusion and therefore to allow further treatment to those patients who failed to reperfuse following intravenous thrombolytic therapy.

Clinical symptoms (resolution of chest pain), electrocardiographic monitoring (reduction of ST segment elevation and appearance of accelerated idioventricular rhythm) and cardiac enzymes have all been used as non-invasive markers of reperfusion.

Shah et al.[31] conducted an angiographic validation study of bedside markers of reperfusion.
following thrombolytic therapy. They showed that a rapid and progressive decrease in ST segment elevation is a reliable marker of reperfusion (sensitivity, specificity, positive and negative predictive accuracy of 100%, 69%, 94% and 100% respectively). Using the four bedside variables (time to 50% ST segment decrease, time to relief of chest pain, occurrence of accelerated idioventricular rhythm and reflex bradycardia) for multivariate analysis, they found only the first two variables as univariate predictors and only the ST segment as a significant predictor in the multivariate model.

Similar to Shah's report, other studies have evaluated different methods of ST segment monitoring, including the performance of serial 12-lead ECGs or of continuous ECG monitoring. The latter method has been performed either with Holter recording or with sophisticated computer assisted continuous multilead ECG recordings which allows on-line analysis of the 12-lead ECG.

A variety of serum cardiac markers have also been evaluated for determining reperfusion. All these studies are based on the notion that cardiac enzymes are more rapidly released into the peripheral circulation once reperfusion has occurred. Creatine kinase with its isoenzymes (creatine kinase-MB) and more recently with its isoforms have been continuously tested regarding predictability of reperfusion.

Myoglobin is a low molecular weight, cytoplasmic, heme-protein. The advantage offered by myoglobin as a sensitive serum marker for myocardial injury is that it is released earlier from necrotic cells compared to creatine kinase. Serum concentration of myoglobin increase above the normal range as early as 1 h after myocardial infarction, with peak activity in the range of 4 to 12 h, suggests that serum myoglobin reflects the early course of myocardial necrosis. Although myoglobin lacks specificity for early diagnosis of infarction, its kinetics make it appear promising for distinguishing patients with successful from unsuccessful reperfusion and for detecting reocclusions. Experimentally, plasma myoglobin peaks within 30 min of reperfusion.

In patients undergoing reperfusion therapy, myoglobin after documented reperfusion peaks within approximately 2 h compared with 4 to 6 h for patients who failed to reperfuse. Ellis et al. found that a 4-6-fold increase in myoglobin concentration over the first 2 h can be calculated rapidly and has an even greater predictive accuracy for reperfusion than does the time to peak value (correctly identified 85% of the reperfused patients and 100% of the non-reperfused patients).

**Present study**

In the present study Jurlander et al. tested the usefulness of serum myoglobin for the early non-invasive detection of coronary reperfusion in patients with acute myocardial infarction. They studied 63 acute myocardial infarction patients of whom 52 received thrombolytic therapy and 11 served as controls. They compared the presence or absence of reperfusion, the level of reperfusion (TIMI flow) and the usefulness of myoglobin and creatine kinase-MB in detecting reperfusion. They found that: (1) as expected, myoglobin levels peaked earlier (both in the reperfused and non-reperfused patients) than creatine kinase-MB; (2) the mean time concentration curve of myoglobin differed significantly between reperfused and non-reperfused patients, the reperfused patients showing higher 'appearance rate', shorter 'time to peak' and a smaller 'area under the curve' (infarct size) than the non-reperfused patients; (3) the patients with delayed reperfusion (such as rescue angioplasty) showed time-concentration curves intermittently between patients with early reperfusion and no reperfusion; (4) a rise in serum myoglobin >2.4-fold within 2 h after onset of thrombolytic therapy identified reperfusion patients with a positive and negative predictive value of 0.94 and 0.44 respectively and that in patients with \( \text{Mb}_2 > 200 \mu g \), the predictive negative value increased to 1.

Based on their observations and considering the fact that newer and rapidly performed assays for quantification of serum myoglobin are now available, the authors constructed an algorithm which allows for the rapid determination of the presence or absence of reperfusion. This in turn provides the possibility of administering further therapy as necessary.

**Conclusions**

The non-invasive accurate determination of the status of the culprit artery following thrombolytic therapy is of major importance in patients with acute myocardial infarction. It seems that the combination of electrocardiographic ST segment monitoring together with serum cardiac enzymes will be our optimal marker for determining absence of vessel patency. Nevertheless, present indexes of reperfusion, including the results of the present study, do not distinguish between patients with TIMI 2 or 3 grade of reperfusion. Furthermore, it has been shown that up to one-third of patients showing TIMI 3 grade flow at 90 min, do not show signs of tissue reperfusion (impaired reperfusion). Therefore, future studies will need to place emphasis not only on successful vessel
reperfusion but also on successful tissue reperfusion. Regarding this aspect, the contribution of further dynamic electrocardiographic patterns\(^6\) and of serum cardiac markers will have to be established.

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Angina, exercise and food

See page 394 for the article to which this Editorial refers

For the normal individual, the cardiovascular challenge of eating is insubstantial. The original observation that angina may be worsened by eating was made more than two centuries ago by William Heberden\(^1\). Classical studies in 1934 suggested that exercise capacity fell by 25% after a meal\(^2\). In addition, Goldstein et al. found 11 of 12 subjects developed angina pain soon after eating\(^3\). Ingestion of even a modest meal increases heart rate and stroke volume, raising cardiac output by around 30% in patients with angina\(^4\) and up to 60% in healthy volunteers\(^5\). Blood pressure remains unchanged as peripheral vascular resistance falls due to gut vasodilatation. A more prolonged elevation of cardiac output may occur with meals of a greater energy content\(^6\). High carbohydrate food results in a rapid haemodynamic response and fat or protein meals result in a delayed response. The increase in cardiac output post-prandially in patients with coronary artery disease represents a substantial proportion of their reduced cardiac reserve and the resulting raised myocardial oxygen demand may lead to anginal symptoms.

As a symptom of coronary artery disease, post-prandial exertional angina may denote the presence of more severe underlying disease than is present in patients without this symptom. Berlinerblau and Shani questioned 408 patients with chest pain who underwent coronary angiography\(^7\). Thirty-five patients (8.6%) had post-prandial angina, at rest and on exertion, most commonly after an evening meal. Post-prandial angina occurred mainly in men, was associated with rest angina and a high incidence of left main and three-vessel coronary artery disease. The ejection fraction was lower in patients with post-prandial angina (0.39 vs 0.47). Post-prandial angina is therefore an indication of severe coronary artery disease and such patients should be considered for coronary angiography.

This issue contains a report concerning the effects of eating meals of differing composition on effort tolerance in patients with angina\(^8\). The authors performed four different pairs of exercise treadmill tests at least one week apart, before and 30 min after meals of mainly fat, mainly carbohydrate, a balanced meal or water alone, in 14 patients with chronic stable angina. Cardiac output was estimated non-invasively using Doppler echocardiography. The authors report improvement of 72 s in the post-prandial exercise time, after a meal consisting mainly of fat in comparison with a balanced meal. Cardiac output increased significantly only following a balanced meal, compared with water alone.

One explanation offered for the lower exercise capacity in patients following food is that of