Mirror, mirror on the wall: the quest for the earliest marker of myocardial ischaemia

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This editorial refers to "Serum deoxyribonuclease I activity can be used as a sensitive marker for detection of transient myocardial ischaemia induced by percutaneous coronary intervention"1 by K. Arakawa et al., on page 2375

In patients with acute ST-segment elevation myocardial infarction (STEMI), the diagnosis and immediate initiation of reperfusion therapy is based on the standard 12-lead ECG. Owing to the fact that cardiac markers appear in the blood a substantial time after the onset of symptoms, cardiac markers are neither helpful for early diagnosis of patients with STEMI nor should results be awaited before initiation of recanalization therapy.

Unfortunately, at least 40% of all patients with confirmed acute myocardial infarction (AMI) show no diagnostic ECG changes on admission.1 In these patients with suspected acute coronary syndrome (ACS), cardiac troponins have become the biochemical gold standard for classification, risk stratification, and guidance of therapy.1 Cardiac troponins owe their exclusive superiority to their cardiосpecificity, which indicates myocardial necrosis, and to their higher sensitivity compared with creatine kinase. However, obviously myocardial necrosis is a prerequisite for appearance of troponins in the blood, and the inflicting event needs to have occurred a few hours earlier.2

Novel cardiac markers ideally should improve these limitations by appearing earlier in the blood in case of an AMI, or by allowing identification of myocardial ischaemia in advance, or even in the absence of myocardial infarction. Needless to say that markers suitable in clinical routine should not be increased in healthy individuals or during endurance exercise, such as marathon race, after radiofrequency catheter ablation, after skeletal muscle ischaemia, or in patients with peripheral vascular disease, as well as in diseases associated with oxidative stress such as systemic sclerosis.3,4 Impaired cobalt binding has been related to structural changes of the NH2 terminus of albumin occurring during hypoxia, acidosis, or free radical damage. Findings in patients with systemic sclerosis and experimental data indicate that serum albumin may be modified more likely by reperfusion after an ischaemic event than by ischaemia itself.4

In essence, IMA does not appear to fulfil the criteria of an ideal marker of myocardial ischaemia and its results must be interpreted cautiously, taking into consideration clinical circumstances and comorbidity.

Arakawa et al.5 introduce serum DNase I activity, measured with a novel rapid assay, as a new marker for early and sensitive detection of myocardial ischaemia. In the present report, the authors were able to show that serum DNase I activity rose significantly after elective percutaneous coronary intervention (PCI) of single vessel disease in patients with stable angina. DNase I activity increased much earlier than cardiac troponin-T or CK-MB, and the number of patients with abnormal DNase activity exceeded the number of subjects with detectable cardiac troponin-T levels. On the basis of these findings, the authors claimed that serum DNase I activity might serve as an earlier and more sensitive biochemical marker of reversible myocardial ischaemia.

In a recent publication, the same authors reported an increased DNase I activity in AMI patients.6 DNase I activity was elevated within 3 h after the onset of pain, suggesting that DNase I might also be useful for earlier diagnosis of AMI. This time gap of 3 h from onset of symptoms to elevation in the blood is not different for myoglobin or troponins measured by sensitive assays and lower diagnostic cut-off values. Furthermore, in that earlier study the same authors found that DNase I activity in patients with stable or unstable angina or in patients with stroke, trauma, renal failure, or chronic heart failure was not different from serum DNase I activity in healthy controls.6

How can serum DNase be a sensitive and early marker of myocardial ischaemia in patients undergoing elective PCI but not in symptomatic patients with stable or unstable angina?
The exact pathomechanism responsible for DNase I elevation is still unknown. DNase I is not a cardiospecific enzyme, as it is present in biological fluids and is ubiquitously expressed in mammalian tissues. DNase I is an endonuclease that preferentially degrades double-stranded DNA in a Ca²⁺-dependent manner to produce oligonucleotides with 5′-phospho and 3′-hydroxy termini.

There is also a consistent body of evidence suggesting that DNase I is involved in DNA breakdown during apoptosis in patients with cardiomyopathy.⁷

In the present publication, balloon angioplasty and provisional coronary stenting were used as a model to induce reversible myocardial ischaemia. However, PCI has several shortcomings and is not an ideal model to evaluate the effects of myocardial ischaeemia. First, a substantial proportion of patients undergoing elective coronary interventions develop peri-interventional myocardial infarction because of side branch occlusion, major coronary dissection, dislodgement of visible thrombus, or distal embolization of platelet microaggregates. Secondly, brisk repetitive inflations of the balloon at high pressures and coronary stenting will cause endothelial injury or plaque disruption, resulting in release of plaque debris that might represent a target for reactive oxygen species.⁸

Thirdly, short episodes of myocardial ischaemia during PCI have been shown to induce reperfusion injury as suggested by sustained oxidative stress detectable in the venous effluent of reperfused myocardium.⁹ Priming of neutrophils and induction of oxidative stress after elective PCI, however, are not necessarily associated with myocardial ischaemia.¹⁰

In summary, the potential applicability of DNase I activity for non-invasive detection of myocardial ischaemia remains to be defined. Up to now, there is very little and inconsistent evidence that increased endonuclease activity is specific either for myocardial infarction or even for myocardial ischaemia. Conversely, it is tempting to speculate that the same mechanisms involved in the structural modification of albumin during balloon angioplasty may also affect activity of DNase I in the blood. Thus, whether DNase activity results exclusively from myocardial ischaemia marker or is rather the result of a complex mechanism involving acidosis, reperfusion injury, or oxidative stress remains to be determined.

Further studies are required to characterize precisely the characteristics of this marker and to test the predictive power in unselected clinical cohorts of chest pain patients before DNase I activity can become a diagnostic tool for patients with suspected ACS.

Conflict of interest: H.A.K. has developed the cardiac troponin T assay and holds a patent jointly with Roche Diagnostics. E.G. and H.A.K. have received honoraria for lectures from MSD, Roche Diagnostics, Novartis, AstraZeneca, Sanofi and Bayer.

References