The Search for a Biomarker of Cardiac Ischemia

With ~8 million patients arriving with nontraumatic chest pain to emergency departments in the US each year, the clinical evaluation, triage, and management of patients with possible acute coronary syndromes (ACS) presents a substantial medical and fiscal challenge (1). Although 2–5% of patients with myocardial infarction (MI) are inadvertently discharged from the emergency department and are a leading reason for malpractice claims, more than 50% of patients hospitalized for evaluation of chest pain are discharged with diagnoses other than ACS (1). Among those patients with definite ACS, early treatment may reduce the extent of myocardial injury, and thus rapid diagnosis and initiation of therapy is a central tenet of management (2). In addition, given the increasing array of treatments for the heterogeneous population of patients admitted with definite ACS, effective risk stratification and targeting of therapy have become a focus of contemporary management of ACS (2, 3). As such, the objectives of the initial assessment are twofold: (a) to assess the probability that the patient's symptoms are related to acute coronary ischemia; and (b) to assess the patient's risk of recurrent cardiac events, including death and recurrent ischemia (2). In the ideal circumstance, physicians could reliably identify patients with definite ACS and begin appropriate therapy as early as possible, as well as distinguish those without acute coronary ischemia who may be candidates for early discharge without extended observation in the emergency department, chest pain unit, or inpatient wards.

Unfortunately, other than in the ~15% of patients with ACS who present with diagnostic ST-segment elevation, our basic clinical tools (history, physical exam, and electrocardiogram) for making the diagnosis of ACS offer limited sensitivity and specificity. Biomarkers of myocardial necrosis add importantly to these other clinical tools and are a critical component of the assessment of suspected ACS (4). In particular, cardiac troponins have emerged as powerful tools for triage, as well as for targeting the use of more aggressive (and often costly) antiplatelet, anticoagulant, and invasive therapies to those patients who are likely to benefit most (2, 3, 5). Nevertheless, despite the ability to detect quantitatively smaller degrees of myocardial necrosis, cardiac troponins exhibit a time course for release and detection in the peripheral circulation that is similar to creatine kinase-MB and necessitates measurement at least 6 h after symptom onset to exclude MI with high accuracy (5).

Approximately 40–60% of patients with likely/definite ACS will present with initial troponin concentrations below the clinical decision limit for the assay (6). These patients fall into two major categories: (a) those presenting early after onset of an acute MI in whom cardiac troponin I/T or creatine kinase-MB is not yet detectable by serum/plasma testing; and (b) those presenting with acute myocardial ischemia without necrosis (i.e., unstable angina). Differentiating these two groups from patients with chest pain syndrome of an etiology other than coronary ischemia is the major clinical challenge.

Although multimarker strategies (7, 8), myocardial perfusion imaging (9), and carefully developed clinical pathways that integrate all of the above elements (10) improve overall diagnostic performance, they are also limited by obligatory time for observation. "Rapid rule-out MI" protocols incorporating myoglobin do not identify patients with unstable angina and are limited by diminished specificity for MI (11). Thus, a biomarker that reliably detects myocardial ischemia in the absence of necrosis or before cardiac troponins are increased would add substantially to our current clinical tools. In this issue of *Clinical Chemistry*, Bhagavan et al. (12) take an additional step in the evaluation of albumin cobalt binding, one of a few proposed biomarkers of myocardial ischemia under investigation for diagnostic use in suspected ACS (13–15).

ATTRIBUTES OF AN IDEAL BIOMARKER FOR MYOCARDIAL ISCHEMIA

The properties of an ideal biomarker for myocardial ischemia follow from the unmet clinical needs. Foremost, the biomarker must detect myocardial ischemia regardless of whether irreversible myocyte injury is present and should not be increased in healthy individuals or during ischemia, inflammation, or injury of other organs. For optimal clinical usefulness, the biomarker should be detectable early during myocardial ischemia and increase in proportion to the extent of myocardium involved. The marker should persist in a detectable (stable) form for a sufficient duration to provide a convenient diagnostic time window but, ideally, fall within a period of ~24 h so that recurrent ischemia can be detected and confounding by stable coronary disease with exertional ischemia is minimized. Optimally, the assay should be simple to perform with a turnaround time of 30–60 min or less and have reliable analytic performance and a reasonable cost.

Such a marker would provide clinical utility complementary to that of cardiac troponins. An early-increasing biomarker of ischemia would be used for the initial identification of the patient with ACS, with subsequent confirmation of the diagnosis of MI (vs unstable angina) by a sensitive and specific test for myocardial necrosis. For this purpose, a test with high early sensitivity for ischemia with specificity comparable to our traditional clinical tools would provide an advantage over present care. A specific biomarker of myocardial ischemia could also be valuable in distinguishing acute MI from the increasing number of identified nonischemic causes of myocardial injury (16) that lead to increases in cardiac troponin. Moreover, distinguishing whether repeated episodes of chest pain after a MI (when markers of necrosis remain increased) represent ischemia is a particularly frequent and vexing problem for cardiologists that could

be addressed by a rapidly increasing and decreasing biomarker of ischemia.

RESEARCH CHALLENGES

The challenges of identifying a novel biomarker of myocardial ischemia should not be underestimated. Foremost, testing the specificity of such a marker presents a formidable task to investigators as there is no "gold standard" for myocardial ischemia. Comparison with cardiac troponins for this purpose will be inherently misleading, as it is expected that a perfectly specific biomarker of myocardial ischemia would be increased in patients with unstable angina, who by definition have no detectable increase in a cardiac troponin. In the study by Bhagavan et al. (12), the sensitivity and specificity of albumin cobalt binding for a clinical diagnosis of ischemia were good; it is not surprising, and is in fact reassuring, that the test differentiated poorly between unstable angina and MI. Similar challenges were faced in the development and integration of troponins into clinical care (5). As in the case for troponins, laboratory and translational research establishing a plausible pathobiologic basis for considering the proposed biomarker as a new gold standard will be vital to achieving clinical acceptance of the biomarker.

ALBUMIN COBALT BINDING AS A TEST FOR MYOCARDIAL ISCHEMIA

The report by Bhagavan et al. (12) adds to a growing body of investigation supporting the potential of albumin cobalt binding as a measure of myocardial ischemia (13, 17, 18). This test is based on the observation that the affinity of the NH_2 terminus of human albumin for cobalt is reduced in patients with myocardial ischemia. Detectable changes in albumin cobalt binding have been documented to occur minutes after transient occlusion and reperfusion of a coronary artery during angioplasty and to return toward baseline within 6 h (17). Bhagavan et al. (12) and others (13, 18) have shown reduced albumin cobalt binding in patients with spontaneous coronary ischemia, with abnormal values detectable before subsequent increases in cardiac troponin (18). The precise mechanisms for production of ischemia-modified albumin (IMA) during coronary ischemia are not known, but have been localized to modifications of the N-Asp-Ala-His-Lys sequence of human albumin and are proposed to be related to production of free radicals during ischemia and/or reperfusion, reduced oxygen tension, acidosis, and cellular alterations such as disruption of sodium- and calcium-pump function (17, 19).

Why modification of a ubiquitous circulating protein such as albumin would be specific for the local phenomenon of myocardial ischemia is unknown and warrants additional exploration. Increases in IMA could, in theory, be observed during ischemia in any vascular bed, or could be attributable to oxidative processes related to other organ injury. Increased concentrations of IMA have been demonstrated 24–48 h after endurance exercise and have been postulated to relate to delayed gastrointestinal ischemia (20). Bhagavan et al. (12) have now also documented a deletion defect of the NH_2 terminus that was responsible for reduced cobalt binding (a "false positive" test for ischemia) and for which the overall prevalence is unknown.

Evaluation of these structural variants and other mechanisms for reduced albumin cobalt binding that may impact the diagnostic performance of IMA is ongoing and will be important to assessing its clinical utility. Nevertheless, if the clinical situations, other than coronary ischemia, in which IMA is detectable are rare and/or easily distinguishable from ACS on other clinical grounds, testing of albumin cobalt binding could still be valuable for evaluation of chest pain. Carefully planned additional studies of patients presenting with possible ACS that incorporate blinded expert reviews of each case on the basis of the clinical history, electrocardiogram, and myocardial perfusion data will be informative. In addition, to convince cardiologists of the added value from this and other proposed tests for ischemia, investigators will need to demonstrate that the results are associated with prognosis and/or response to specific therapies. IMA appears to have passed the first litmus tests for sensitivity among patients with induced or spontaneous coronary ischemia and warrants additional study as a promising marker of myocardial ischemia.

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