Cardiac Biomarkers

Case Studies and Clinical Correlations

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Dedicated to Dr. Burton E. Sobel, whose pioneering work on creatine kinase and tireless mentoring were instrumental in helping us understand the importance of biomarkers, and my partner in crime at Washington University where we validated the initial assay for cTnI, Dr. Jack Ladenson.

Allan S. Jaffe, MD

Preface

Biomarkers now play an integral role in the treatment and management of patients with congestive heart failure and acute ischemic heart disease because of the important information the values provide. All of us in the field are terribly interested in how to optimally use these biomarkers and particularly to understand when values provide actionable information. However, extrapolating a large compendium of information to the average clinician is difficult because many do not have the underlying basic science, laboratory, and/or clinical expertise about the use of these markers.

Accordingly, it seemed to us that there was a need to develop a case-based compendium of learning. For that reason, we asked our most knowledgeable colleagues to help us generate a book that hopefully comprehensively informs clinicians about how to optimally deploy the major clinically utilized biomarkers in a case-based manner. From scrutinizing the chapters, it appears we have succeeded. We hope you will enjoy and learn from the case studies as much as we have.

La Jolla, CA, USA — Alan S. Maisel, MD
Rochester, MN, USA — Allan S. Jaffe, MD

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Part I
Ischemic Heart Disease

Chapter 1
Pre-analytical Factors and Analytical Issues Affecting Interpretation of Cardiovascular Biomarkers

Amy K. Saenger

Abstract The Universal Definition of Myocardial Infarction globally endorses cardiac troponin (T and I; cTnT, cTnI) as the biomarker of choice for the diagnosis and assessment of acute coronary syndrome (ACS) and should be utilized routinely in patients with symptoms suggestive of acute myocardial infarction (AMI) [1]. Despite the widespread use of troponin in clinical practice there remain a number of pre-analytical, analytical and interpretive issues which can confound clinical interpretation and will likely be magnified with high-sensitivity troponin assays. The following case studies and discussion highlight some of these issues and nuances associated with troponin assays.

Keywords Troponin • High-sensitivity troponin • Myocardial infarction • Acute coronary syndrome • Chest pain • Biomarker • Hemolysis • Interferences • Heterophile • Antibody

The Universal Definition of Myocardial Infarction globally endorses cardiac troponin (T and I; cTnT, cTnI) as the biomarker of choice for the diagnosis and assessment of acute coronary syndrome (ACS) and should be utilized routinely in patients with symptoms suggestive of acute myocardial infarction (AMI) [1]. Despite the widespread use of troponin in clinical practice there remain a number of pre-analytical, analytical and interpretive issues which can confound clinical interpretation and are likely magnified with high-sensitivity troponin assays. The following case studies and discussion highlight some of these issues and nuances associated with troponin assays.

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Case 1

A 68-year-old African-American male presents to the emergency room with complaints of indigestion, mild chest pain and shortness of breath. The onset of pain began approximately 4 h prior and would last intermittently for 15 min. He has no previous history of overt coronary heart disease but was overweight with a body mass index of 28 and new onset of mild hypertension. His initial electrocardiogram (ECG) shows mild T-wave flattening in the lateral leads along with other non-specific changes. A cardiac chest pain protocol was ordered which included serial cardiac troponin testing. The baseline plasma cTnT was 0.04 ng/mL (99th percentile: <0.01 ng/mL) and the patient was placed in the chest pain observation area where he was given nitroglycerin to assist with his chest and abdominal discomfort. Three hours later nursing staff in the emergency department drew another sample for cTnT testing. The laboratory called approximately 30 min later to inform ED staff that the 3-h sample was hemolyzed and recommended the patient be redrawn. There was insistence that the result be released and the technologist reported the 3-h cTnT result of 0.02 ng/mL. The patient's pain appeared to be resolving, his TIMI score was 1 and he was deemed low-risk and discharged. Ten hours post-discharge his wife found him unconscious and called 911. She was able to rouse him and he was transported to the same emergency department via ambulance. Upon arrival it was noted that his ECG remained non-diagnostic but cTnT was now 0.12 ng/mL. He was admitted for coronary catheterization and ultimately diagnosed with NSTEMI. Further investigation into the laboratory results reveal the patient's first cTnT specimen was deemed "mildly hemolyzed but acceptable" and the second cTnT specimen was "grossly hemolyzed" but released per physician request.

Discussion of Case 1

This scenario illustrates how pre-analytical variables such as hemolysis can drastically affect the analytical results and potentially result in serious patient safety risks. Reliability of the cTn measurement depends on the quality and integrity of the blood specimen collected, as with all analytes measured using central laboratory or point-of-care (POC) assays. Pre-analytical variables have significant potential to confound cTn measurement and can produce falsely elevated or falsely decreased results. Serious risk exists if a rise and/or fall in cTn values is masked or falsely detected by the presence of interfering substances in patient specimens and can adversely impact medical decision-making and patient care. Understanding about the pre-analytical factors and interferences that can influence cTn measurements is critical in order to establish strategies to assure collection of quality specimens, prevent reporting erroneous results, and identify scenarios when cautious interpretation of cTn results is warranted.

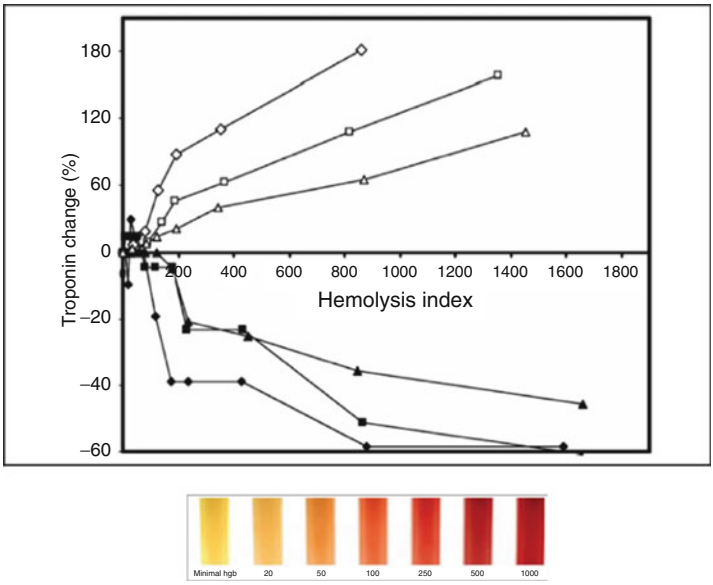

Fig. 1.1 Effect of increasing hemolysis on the Ortho Clinical Diagnostics TnI ES assay (*open symbols*) and the Roche hs-cTnT assay (*closed symbols*). *Note that the negative and positive scales are not equal (From Bais [4], reproduced with permission from the American Association for Clinical Chemistry)

Hemolysis is defined as the breakdown of erythrocytes with subsequent release of intracellular contents and is a known interference of a majority of cTnI and cTnT immunoassays [2–4]. Specimens collected from patients in the Emergency Department have high rates (up to 20 %) of contamination due to hemolysis [5]. Hemolyzed specimens can cause either a positive or negative bias in troponin measurements, and although the bias is assay-specific in general hemolysis causes false-negative results in cTnT assays and false-positives in cTnI assays (Fig. 1.1) [4]. Florkowski *et al.* illustrated that specimens with cTnT concentrations near the 99th percentile reference interval (<14 ng/L) exhibited up to a 50 % negative interference with increasing hemolysis in the Roche high-sensitivity cTnT (hs-cTnT) assay, whereas the Vitros ECi cTnI assay demonstrated a positive interference up to 576 % with increasing hemolysis [2]. The mechanism of hemolysis interference remains unclear; it has been suggested that the release of hemoglobin and proteases from erythrocytes upon lysis may cause interference with the detection method or anti-cTn antibody recognition of degraded cTn fragments [3, 6, 7]. Plasma specimens are also more sensitive to hemolysis compared to serum which is unfortunate since plasma is the primary specimen type used in the emergency room and critical care patient areas [8].

The presence of hemolysis can be visually detected as a pink to red color when hemoglobin concentrations are > 0.2 g/dL [9]. However, visual examination of specimen color is extremely subjective. Central laboratory analyzers are typically

capable of performing automated spectrophotometric detection of hemoglobin to reliably detect hemolysis and aid in defining acceptable specimen rejection criteria. Unfortunately, there is no way to detect hemolysis in whole blood samples which is the primary specimen type used for POC cTn testing. Laboratories must implement acceptance/rejection criteria for hemolyzed specimens to assure accurate troponin results are reported, as well as monitor hemolysis rates originating from areas such as the emergency department where specimens are often not collected by phlebotomy staff.

Case 2

A 58-year-old Caucasian male with type 2 diabetes has been on hemodialysis for approximately a year and currently being evaluated for renal transplantation. He abruptly develops acute dyspnea and is unable to remain ambulatory without mild chest pain, therefore he is transported to the local emergency room. He denies a history of prior cardiovascular events or known coronary disease. His ECG is notable for an ST-segment depression and T waves. A baseline cTnI was measured using a point-of-care (POC) assay which was within normal limits (99th percentile: <0.08 ng/mL). A second POC cTnI result obtained 4 h later was also <0.08 ng/mL. The biomarker protocol at this institution required confirmation of all POC cTnI results with the central laboratory cTnI automated assay. The emergency medicine physician treating the patient received a call from the laboratory that the central lab cTnI results were 0.06 ng/mL for the baseline sample and 0.11 ng/mL for the 4-h sample, which was greater than the automated cTnI assay's 99th percentile (<0.04 ng/mL) and indicated a significant delta (change) over this acute time period. Based on this information, the patient is immediately taken to cardiac catheterization and a diagnosis of NSTEMI is made. The physician was puzzled regarding the lack of concordance between the two cTnI methods and also inquired if the reason was due to the automated "high-sensitivity" cTnI assay.

Discussion of Case 2

This case demonstrates the critical importance of understanding the limitations of the troponin assay used, regardless if the assay is POC or performed in the central laboratory. In addition, it highlights issues related to the lack of standardization between cTnI assays and the heterogeneous nomenclature used to describe assays.

Contemporary POC troponin methods are analytically and clinically less sensitive compared to central lab assays and there are currently no high-sensitivity POC assays available [10, 11]. Therefore, current guidelines recommend use of central laboratory troponin testing as opposed to POC. In a study reported by Apple et al., the ratio of measured 99th percentile to the limit of detection (LoD) across five

different POC cTn test systems demonstrated considerable variability and substantially lower than automated hs-cTn and contemporary cTn assays [12]. Consequently, POC assays often produce undetectable cTn concentrations with lower clinical sensitivity to rule-in AMI or to use for predicting future adverse events in patients presenting to the emergency department with symptoms suggestive of cardiac ischemia [13–17]. This is a major concern in clinical practice as the limited analytical sensitivity of POC assays can lead to missed or delayed diagnosis of patients at-risk for ACS who may benefit from medical intervention. Further improvement in the analytical sensitivity of POC cTn test systems by manufacturers is needed in order to complement the growing utilization and superior diagnostic performance of high-sensitivity assays.

If the central laboratory is unable to meet a 60-min turnaround time (TAT; defined here as time from collection to reporting in the electronic medical record) a majority (>90 % of the time) for cTn testing, then POC testing should be considered although frequently an optimal TAT can be achieved after resolving operational issues and/or inefficiencies. Although use of POC cTn assays clearly improves TAT and availability of results [18, 19], having a more rapid test does not guarantee improved patient outcomes, operational efficiency, or cost effectiveness. Results vary regarding the effect of POC testing in reducing patient length of stay (LOS), patient charges and overall cost effectiveness [18, 20–22]. Whether POC cTn testing improves triage, treatment, and/or discharge of NST-ACS patients largely depends on the effectiveness of integration into the operational workflows and clinical protocols for each hospital or healthcare system.

Standardization and harmonization efforts have focused on cTnI assays, which are available from a wide variety of manufacturers and analytical platforms. Standardization is generally not an issue for cTnT because only one diagnostic company (Roche Diagnostics) holds the patent and antibodies for cTnT, with the caveat that there are known cTnT analytical differences evident between small and large platforms [23]. There are several cTnI diagnostic assays commercially available with variable analytical and clinical performance characteristics and different target antibodies (Table 1.1). The International Federation of Clinical Chemistry (IFCC) website (http://www.ifcc.org/) maintains a collated and updated list of these assays. Anti-cTnI antibody cross-reactivity with cTnI is dependent upon epitope recognition; however, the cTnI complex can also undergo substantial modifications after release into circulation including oxidation, reduction, phosphorylation and proteolytic degradation which can change its interaction with other troponins and anti-cTnI antibodies.

Despite some success with harmonization efforts for cTnI, significant inter-assay differences remain with up to a ten-fold difference in absolute cTnI concentrations [24]. The discordance in numeric cTnI values between assays and methods can largely be attributed to the diversity of different materials utilized for calibrators, as well as the variety of detection and capture antibodies used which have differing antigen epitope specificities (Table 1.1). Current cTnI calibration materials are only traceable to different calibrators selected by each manufacturer; consequently, cTnI results are not interchangeable between different assays and testing platforms.