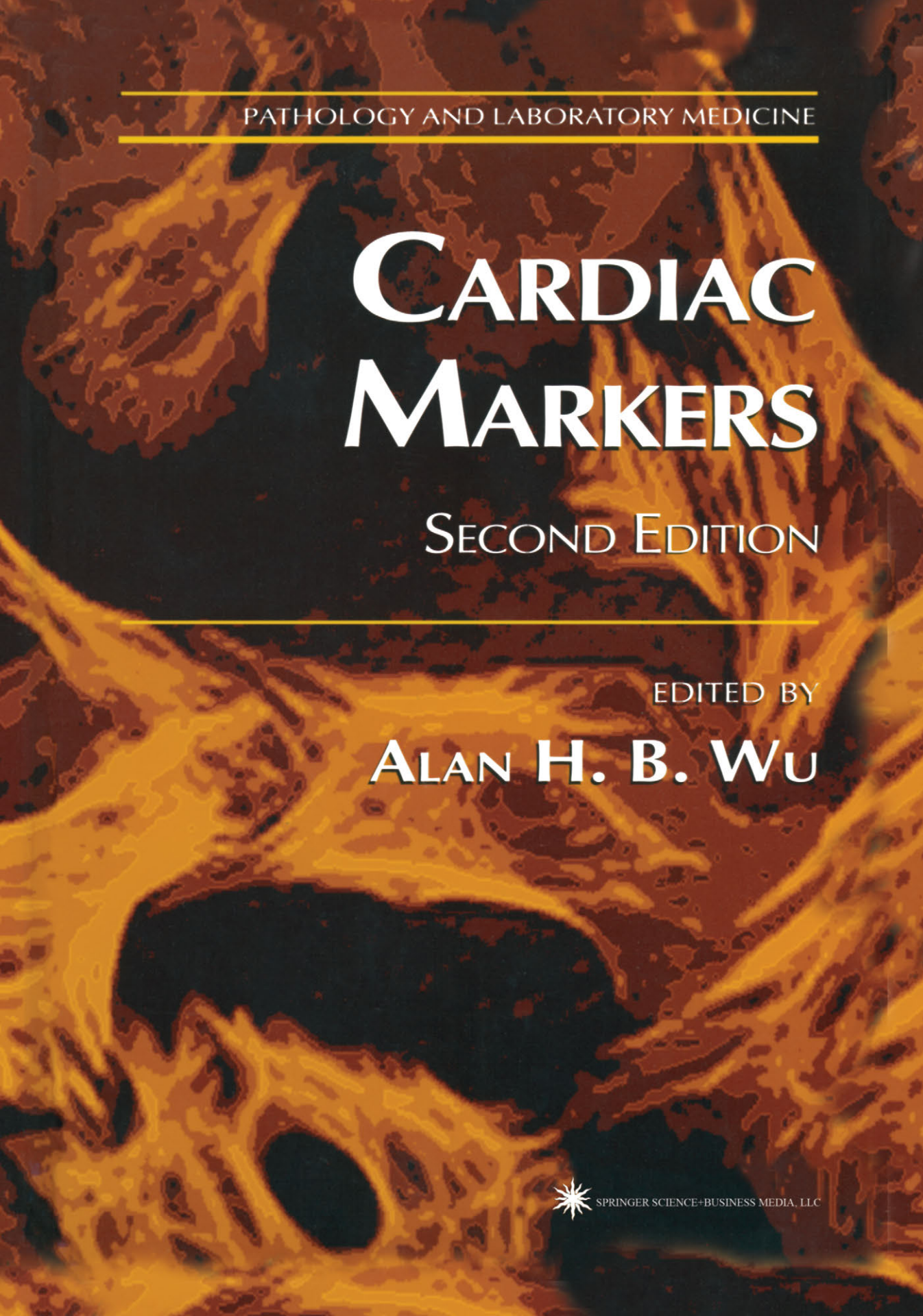
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Cardiac Markers

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Cardiac Markers

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Dedication

This book is dedicated to my parents, my loving wife, Pam, and to our children Ed, Marc, and Kim, whose career journals have only just begun.

Foreword

The management of patients with acute coronary syndromes (ACS) has evolved dramatically over the past decade and, in many respects, represents a rapidly moving target for the cardiologist, internist, emergency medicine specialist, intensivist, and clinical pathologist—all of whom seek to integrate these recent advances into contemporary clinical practice.

Unstable angina and non-ST-segment elevation myocardial infarction (MI) comprise a growing percentage of patients with ACS and is emerging as a major public health problem worldwide, especially in Western countries, despite significant improvements and refinements in management over the past 20 years. In the United States alone, over 2.3 million people are admitted to coronary care units annually with either unstable angina or acute MI, the great majority of whom now present with non-ST-segment elevation ACS. Consequently, much attention has been directed toward optimizing the diagnosis and management of such patients, where risk stratification remains a pivotal component to sound clinical decision-making. The clinical spectrum of ischemic heart disease is diverse, ranging from silent ischemia to acute MI to congestive heart failure. Fundamental initial components of assessing a patient with ischemic heart disease—and properly gauging risk—include the clinical history, physical examination, 12-lead electrocardiography, and, increasingly, the measurement of biochemical markers.

Over the past decade, however, there has been a progressive evolution of cardiac marker testing in patients with ACS, MI, and CHF. Not only has this resulted in a dramatic shift in how we view the diagnosis of these clinical conditions, but it has also extended the role of cardiac marker testing into risk stratification and guidance of treatment decisions. By the year 2000, the development of highly sensitive and cardiac-specific troponin assays had resulted in a consensus change in the definition of acute MI, placing increased emphasis on cardiac marker testing with troponins as the new "gold standard." Furthermore, and perhaps more importantly, the role of the troponins as superior markers of subsequent cardiac risk in acute coronary syndrome patients has now become firmly established.

But, with so much attention directed at troponin as the dominant cardiac marker, it has likewise become increasingly clear that, for both diagnostic and risk stratification purposes, cardiac troponin testing alone may only quantify risk incompletely for many subsets of ACS, MI, and CHF patients. For example, the use of high-sensitivity (hs) C-reactive protein (CRP) and other novel inflammatory markers may add significantly to our ability to correctly identify patients presenting with ACS who are at high risk for future cardiovascular events. The predictive value of CRP appears to be independent of, and additive to, troponin. Individuals with evidence of heightened inflammation may benefit most from aggressive life-style modification and intensification of proven preventive therapies such as aspirin and statins. Moreover, the benefits of an early invasive strategy may also be greatest among those with elevated levels of inflammatory biomarkers.

In addition, other novel cardiac markers, including B-type natriuretic peptide (BNP) and pro-BNP, have become important determinants of risk and prognosis in both patients with CHF and ACS. Thus, as increasingly more sophisticated biochemical testing modalities become available clinically, there will be an even greater ability to delineate various risk strata for patients with ACS, MI, and CHF who present to emergency departments and coronary care units and, equally importantly, to direct, or tailor, the magnitude and extent of therapy to the level or severity of risk. Such an approach holds great promise to optimize event-free survival among all subsets of patients by balancing the benefits and risks of various treatment strategies.

Against this swiftly evolving landscape, Dr. Alan Wu has once again assembled a distinguished cadre of opinion leaders and subject matter experts to update the expanding field of cardiac markers. In *Cardiac Markers*, *Second Edition*, Dr. Wu expands our applications of biomarkers beyond the general analytic and clinical use of troponins in ACS patients and provides a much-needed, lucid, and more comprehensive assessment of the role of early cardiac marker use in myocardial ischemia and risk stratification. Both the diagnostic and prognostic roles of troponins, as well as novel, emerging markers (such as BNP, ischemia-modified albumin, free fatty acids, glycogen phosphorylase BB, among others) as well as hs-CRP are discussed in detail for their application to patients with ACS, MI, and CHF.

As we seek ever-improving technologies and pharmacologic approaches to enhance clinical outcomes in patients with cardiac disease, so too, do we seek concomitant, sophisticated diagnostic modalities that provide clinicians with greater precision in delineating various strata of risk that will permit the more timely, efficient, and cost-effective application of event-reducing therapies. Without question, the future of diagnostic testing will evolve increasingly toward a more refined approach to using multiple cardiac markers to better and more reliably identify which patients with ACS, MI, and CHF will benefit from an increasingly wide array of aggressive or conservative treatment strategies, and Dr. Wu has helped significantly to elucidate the critical role such cardiac markers play today in arming physicians with the tools they need to achieve these goals.

Thus, *Cardiac Markers*, *Second Edition*, is a valuable resource for both clinicians and laboratory medicine specialists who require a thorough understanding of this exciting and important diagnostic area, and is must reading for all healthcare professionals who want to keep abreast of this rapidly evolving field in cardiovascular medicine.

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Preface

The incidence of cardiovascular disease has decreased in the last several years with a better understanding of the pathophysiology of acute coronary syndromes (ACS), widespread implementation of lipid lowering drugs, improved surgical treatments such as stent placements, and new therapeutic regimens such as the statins, low molecular weight heparins, and platelet glycoprotein IIb/IIIa receptor inhibitors. Nevertheless, it remains today as the leading cause of morbidity and mortality in the Western world.

Serologic markers of cardiac disease continues to grow in importance in the diagnosis and management of patients with ACS, as witnessed by the recent incorporation of cardiac troponin into new international guidelines for patients with acute coronary syndromes *(1–5)*. Of paramount importance to the field of cardiac markers is the redefinition of myocardial infarction, putting emphasis on cardiac troponin *(4)*.

Cardiac troponin are not only useful for diagnosis and risk stratification of ACS patients, but also in the optimum selection of therapies. Technical advances continue to be developed at a rapid pace, especially in the implementation of point-of-care testing (POCT) devices. Evidence for the efficacy of POCT has accumulated in the last few years.

Despite the success of cardiac troponin, there is still a need for development of early markers that can reliably rule out acute cardiac disease from the emergency room at presentation. The American College of Emergency Physicians concluded that none of the existing markers are reliably in early rule out reversible coronary ischemia *(5)*. This second edition of *Cardiac Markers* documents the importance of early rule out, and the research markers that have been studies to date in this regard. With the population getting older, and more patients are surviving episodes of acute coronary disease, the incidence of congestive heart failure is growing at a dramatic rate. The second edition details discussion of cardiac markers for diagnosis and management of patients with heart failure, an area where biochemical tests have traditionally not played any role. With the characterization of the natriuretic peptides, this promises to be an emerging field of laboratory medicine.

As with the first edition, *Cardiac Markers* is intended for clinicians and laboratorians working in the fields of cardiology, pathology and laboratory medicine, and emergency medicine. With the emergence of the natriuretic peptides, this book also has relevance to critical care, geriatrics, and family practice medicine. This book is appropriate to clinical and research scientists, and sales, marketing and product support personnel who work in the in vitro worldwide diagnostics industry.

Alan H. B. Wu

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Part I
Cardiac Markers in Clinical Practice

1

Early Detection of Myocardial Necrosis in the Emergency Setting and Utility of Serum Biomarkers in Chest Pain Unit Protocols

Andra L. Blomkalns and W. Brian Gibler

INTRODUCTION

Chest pain accounts for nearly 8 million Emergency Department (ED) patient visits each year and represents the second most common emergency complaint *(1)*. Although nearly half of these patients are admitted to inpatient units for further evaluation and treatment, only one third of these individuals are ultimately found to have the diagnosis of an acute coronary syndrome (ACS) *(2)*. The cost to society is large, approx 3–6 billion dollars per year in the United States for admissions involving "noncardiac" chest pain 3–6 *(3)*. With continued economic constraints discouraging unnecessary or preventable inpatient admissions, EDs and physicians have developed various strategies for identifying and "ruling out" low- to moderate-risk patients with chest pain. Emergency physicians are challenged with the task of sifting through this high cost, high volume, and high morbidity complaint to distill an appropriate evaluation of a dynamic process within the first few hours of symptom onset. Cardiac markers are an integral part of these strategies. They serve not only to identify patients with acute myocardial infarction (AMI), but also to provide risk stratification to help dictate initial patient treatment as well as in-hospital disposition.

Chest pain units (CPUs) and ED observation units using various cardiac marker protocols have been successful in identifying patients with or at risk for adverse cardiac events in a timely and cost-efficient manner. Point-of-care testing (POCT) or bedside testing of cardiac markers at the patient's bedside allows for even more timely determination.

This chapter outlines the use of cardiac markers in heterogeneous patients presenting to EDs with chest discomfort. Specific cardiac marker strategies are reviewed along with their contribution to CPU protocols. We discuss the impact of POCT on marker determination and briefly discuss ED treatment modalities based on marker results.

CARDIAC MARKER PROTOCOLS IN THE ED

Initial assessment of ED patients with chest pain begins with a careful history, physical examination, and initial electrocardiogram (ECG). Each of these components contributes to an initial chest pain risk stratification impression. A fourth component, cardiac

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markers, helps to complete the picture and more appropriately identify patients at high risk. While the initial aim of the emergency physician is to "rule out MI," an equally important goal of ACS risk assessment is aided by these markers as well.

Low- to moderate-risk patients can now typically be evaluated in the ED setting or CPU. CPUs arose from the necessity for decreasing inpatient admissions to reduce costs and minimizing inappropriate ED discharge by providing efficient care to those patients presenting with chest pain. Early CPUs and other accelerated diagnostic protocols have proved to be efficient, safe, and cost effective for the evaluation of patients in the ED with low- to moderate-risk chest pain *(4–6)*. Their popularity continues to grow in a variety of settings. Many CPUs and ED chest pain evaluation protocols utilize a system of cardiac marker determination combined with serial ECG determination, perfusion imaging, and/or provocative testing. These combination marker strategies include several variations over several different time courses ranging from 3 to 24 h. Ideally a CPU will evaluate patients for evolving myocardial necrosis and ongoing myocardial ischemia not detected initially on presentation to the hospital.

Cardiac markers have undergone an amazing transformation from aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) to the three cardiac marker families available at present for routine use in ED for the evaluation of the chest discomfort: myoglobin, creatine kinase (CK) and the MB isoenzyme of CK (CK-MB), and the troponins I and T (cTnI and cTnT). Each of these has well known kinetics of release from dying myocardial cells and should be carefully applied to each patient as directed by timing of symptoms and presentation *(7)*. Myoglobin has been touted as an early marker with a high negative predictive value but low specificity. CK and CK-MB represent the "gold standard" for the diagnosis of MI as defined by the World Health Organization criteria. The troponins are cardiac-specific proteins with high degrees of both sensitivity and specificity for myocardial necrosis. These serum markers of necrosis have been well studied in high-risk groups with a high prevalence of AMI. Promising research has also proven benefit in lower-risk patients in the CPU setting *(8)*.

Inflammatory markers such as C-reactive protein (CRP) and markers of platelet activation such as P-selectin are currently being studied but have not yet been accepted for widespread use, particularly in the setting of CPUs.

CK-MB Protocols

Early myocardial necrosis "rule-out" protocols challenged the traditional notion of a 24-h period required to detect AMI. Lee and colleagues' multicenter trial validated a 12-h algorithm using CK and CK-MB in patients identified as "low risk" through assessment of clinical characteristics in the ED. "Low risk" was defined as the probability of AMI <7%. Among patients with CK-MB levels <5% of the total CK without recurrent chest pain after 12 h, there was a 0.5% missed AMI rate while 94% of AMI patients were identified *(9)*. Farkouh et al. demonstrated the utility of a CPU protocol and CK-MB measurements for patients identified as intermediate risk for adverse cardiac events. In this study, patients underwent 6 h of observation followed by provocative testing. This protocol identified all patients with short- and long-term cardiac events while using fewer resources over a 6-mo time period *(10)*.

Symptom onset to patient presentation is a crucial factor in the use of cardiac marker protocols. Marker release kinetics vary with time and as time to ED presentation may

be as short as 90 min or as long as several days, no single marker determination is suitable for adequately "ruling out" ACS *(4,11,12).* In one of the first studies with CPU protocols, Gibler et al. used a 9-h protocol with serial CK-MB at 0, 3, 6, and 9 h along with continuous ECG monitoring, echocardiography, and exercise testing. They found that serial markers alone had a sensitivity and specificity for AMI of 100% and 98%, respectively *(4).* The American Heart Association currently recommends serial cardiac marker determinations to increase sensitivity for detecting necrosis, rather than a single determination on ED presentation.

Several other studies have examined the value of cardiac markers in the risk stratification of heterogeneous patients with chest pain presenting to the ED. In a multicenter study of more than 5000 patients in 53 EDs, the relative risk of ischemic complications and death for ED patients with positive CK-MB at 0 or 2 h was 16.1 and 25.4, respectively *(13).* Serial CK-MB results have also proved to be sensitive in MI detection when collected at 0 and 3 h after ED presentation. Young et al. found a 93% and 95% sensitivity and specificity when combining 0, 3, and net change in CK-MB level. As expected, this sensitivity improved with increased time from symptom onset *(14).* Serial marker measurements and comparison of marker elevation over 3–6 h also improved sensitivity for MI *(15–17).* Even minor elevations of CK-MB as small as twice the upper limit of normal are associated with an increased 6-mo mortality when compared to those with normal levels *(18).*

Serial CK/CK-MB protocols have largely become the diagnostic standard for AMI in the CPU setting. Almost all of the studied protocols use a specific threshold, levels above which are diagnostic for AMI or ACS. Fesmire et al. studied a promising novel approach of change in CK-MB levels within the normal range over the course of ED evaluation. In his population of 710 CPU patients, a CK-MB increase or delta of 1.6 ng/mL over 2 h was more sensitive for AMI than a second CK-MB drawn 2 h after patient arrival (93.8% vs 75.2%) *(17).* Validation of these novel protocols will add to the utility of markers in the CPU setting.

CK-MB ($CK\text{-}MB_1$ and $CK\text{-}MB_2$) isoforms are additional markers with promising results in the CPU setting. A small study of 100 patients with AMI prevalence of 41% found that CK-MB isoform were equal or more sensitive than CK-MB and myoglobin when measured >2 h after symptom onset *(19).* In the Diagnostic Marker Cooperative Study, 955 ED chest pain patients were evaluated using a 24-h marker protocol utilizing CK-MB isoform, CK-MB, myoglobin, cTnI, and cTnT. CK-MB isoforms were found to be most sensitive and specific (91% and 89%) for AMI within 6 h of symptom onset. In addition, CK-MB isoforms were elevated in 29.5% of unstable angina patients as compared to myoglobin (23.7%), cTnI (19.7%), and cTnT (14.8%). This study concluded that protocols utilizing CK-MB isoforms could reliably triage chest pain patients, thereby improving treatment and reducing costs *(20).* Puleo et al. demonstrated CK-MB isoform sensitivity for AMI of 95.7% 6 h after symptom onset in a population whose prevalence of AMI was 18% as compared to 48% for the conventional CK-MB assay. The specificity of this marker protocol was 93.9% and 96.2% among hospitalized and discharged patients, respectively *(21).*

Myoglobin Protocols

Myoglobin is a small cytosolic protein found in striated muscle. The diagnostic strength of myoglobin lies in its early release kinetics and sensitivity, while its primary weakness

is a lack of specificity. Davis et al. showed that serial myoglobin levels were 93% sensitive and 79% specific in detecting MI in patients within 2 h of arrival *(22)*. Similarly, Tucker et al. showed a myoglobin sensitivity of 89% in patients with nondiagnostic ECGs within 2 h of ED presentation *(7)*. Myoglobin appears to achieve maximal diagnostic accuracy within 5 h of symptom onset *(23)*.

Therefore, it is reasonable and recommended that myoglobin should be combined with other more specific cardiac markers when used in CPU protocols. Brogan et al. found that a combination of carbonic anhydrase III and serum myoglobin was more sensitive and equally specific as CK-MB in patients presenting early, within 3 h of symptom onset *(24)*. Contrastingly, Kontos et al. reported less encouraging results from a study of 2093 patients combining CK, CK-MB, and myoglobin obtained at 0, 3, 6, and 8 h. A CK-MB level >8.0 ng/mL at 3 h was 93% sensitive and 98% specific for AMI, adding myoglobin decreased the sensitivity to 86% with no significant increase in sensitivity *(25)*.

Much like the other cardiac markers, myoglobin levels also increase in utility when used in a serial fashion. In a study of 133 consecutive admitted chest pain patients, myoglobin levels were obtained at 2, 3, 4, and 6 h after symptom onset. This regimen was found to be 86% sensitive for AMI at 6 h. The negative predictive value in patients with negative myoglobin levels during 6 h of evaluation and without doubling over any 2-h period was 97% *(26)*.

Data from protocols using myoglobin measurements in patients with lower risk for AMI are sometimes conflicting. In a study of 3075 low-risk CPU patients with AMI prevalence of 1.4%, a 4-h serial myoglobin protocol was reported as 100% sensitive for AMI *(27)*. Conversely, in a study of 368 patients whose MI prevalence was 11%, the sensitivity and specificity of myoglobin at 0 and 2–3 h were only 61% and 68%. Myoglobin change or increase did not improve diagnostic performance either *(16)*.

Myoglobin in the ED setting is probably best used in a serial fashion along with another cardiac marker of necrosis. It is most valuable when used in patients presenting very early in the time course of symptoms and less so for remote events.

Troponins Protocols

cTnI and cTnT are the newest commonly available highly specific cardiac markers that have been proven extremely valuable and sensitive in the diagnosis of myocardial necrosis *(28,29)*. In addition to diagnosis of myocardial necrosis in acute ischemic syndromes, the troponins are more valuable in risk stratification of both low- and high-risk patient populations. Troponin release begins about the same time as CK-MB, but persists for days to weeks after AMI.

The main issues surrounding the cardiac troponins include (1) cutoff values for cTnI and (2) appropriately defining the time of chest pain onset in the context of the ED presentation. Although exhaustive time and study have been performed to determine the more superior troponin, most large studies and analyses have determined that cTnI and cTnT can both identify patients at risk for adverse cardiac events *(30,31)*.

Cardiac TnT is detected at slightly lower serum levels than cTnI and has proved valuable in the emergency setting for early identification of myocardial necrosis. Recently, the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO)-II investigators compared cTnI and cTnT in short-term risk stratification of ACS patients. This model compared troponins collected within 3.5 h of ische-

mic symptoms. Ohman and colleagues found that cTnT showed a greater association with 30-d mortality ($\chi^2 = 18.0$, $p < 0.0001$) than cTnI ($\chi^2 = 12.5$, $p = 0.0002$) *(32)*. These authors concluded that cTnT is a strong, independent predictor of short-term outcome in ACS patients, and serial levels were useful in determining the risk of adverse cardiac events *(33)*.

As with all new cardiac markers, initial studies on troponin risk stratification were initially performed on patients with known ACS. Studies using cTnI in ACS patients showed a statistically significant increase in mortality among those patients with levels >0.4 ng/mL *(34)*. Stubbs and colleagues showed that patients with elevated baseline cTnT levels have up to four times higher mortality than ACS patients with normal values *(35,36)*.

Although the increased risk of troponin-positive patients is now well established, the degree of risk varies greatly between studies and patient populations. Meta-analyses have helped consolidate conclusions and clinically useful parameters when using troponins for the evaluation of patients. One such analysis in high-risk patients performed by Wu demonstrated a cumulative odds ratio of a positive cTnT for the development of AMI or death from hospital discharge to 34 mo was 4.3 (2.8–6.8 95% CI) *(37)*. The cumulative odds ratio of a positive cTnT for predicting need for cardiac revascularization within the same period was 4.4 (3.0–6.5 95% CI). Another analysis involving more than 18,000 patients in 21 ACS studies found that troponin-positive patients had an odds ratio of 3.44 for death or MI at 30 d. Troponin-positive patients with no ST-segment elevation and patients with unstable angina carried odds ratios of 4.93 and 9.39 for adverse cardiac outcomes *(31)*.

Benamer et al. compared the prognostic value of cTnI combined with CRP in patients with unstable angina. They found that whereas 23% of patients with elevated cTnI had major in-hospital cardiac events; there was no such prognostic significance associated with CRP *(38)*.

Troponin applications in low- to moderate-risk patients presenting to EDs have shown similar encouraging results. Tucker et al. used a comprehensive marker strategy including myoglobin, CK-MB, cTnI, and cTnT in ED patients over 24 h after arrival. As expected within the first 2 h of presentation, CK-MB and myoglobin maintained better sensitivity. The troponins were useful only when measured 6 h or more after arrival, exhibiting sensitivities and specificities of 82% and 97% for cTnI and 89% and 84% for cTnT *(7)*. Troponin use seems to be more beneficial in later or delayed patient presentations. In a study of 425 patients using serial cTnI and CK-MB over 16 h, Brogan et al. showed no increase in sensitivity or specificity between troponin and CK-MB in patients with symptoms <24 h. However, in patients presenting with >24 h of symptoms, troponin I had a sensitivity of 100% compared to CK-MB (56.5%) *(39)*.

Sayre et al. showed that patients with a cTnT level of 0.2 ng/mL or greater were 3.5 times more likely to have a cardiac complication within 60 d of ED presentation *(40)*. In a CPU population, Newby et al. determined that cTnT-positive patients had angiographically significant lesions (89% vs 49%) and positive stress testing (46% vs 14%) more frequently than cTnT-negative patients. Long-term mortality was also higher in cTnT-positive patients (27% vs 7%) *(41)*. Johnson et al. studied a heterogeneous patient population admitted from an urban teaching hospital and found that cTnT was elevated in 31% of patients without MI who had major short-term complications as compared to CK-MB activity and mass *(29)*.