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Preface: Cardiac Markers xi

Kent B. Lewandrowski

Overview of Cardiac Markers in Heart Disease 1

Petr Jarolim

Cardiac troponins I and T have been the cornerstone of diagnostics of acute coronary syndrome for almost 20 years. Natriuretic peptides have established themselves in heart failure during the last decade. These and additional promising biomarkers, such as ST-2, galectin-3, GDF-15, copeptin, midregional proadrenomedullin, and the markers of glomerular filtration rate and kidney injury, are reviewed in groups corresponding to the pathophysiological processes they probe—cardiomyocyte injury, myocyte stress, inflammation, oxidative stress, plaque instability, extracellular-matrix remodeling, or those markers grouped in the neurohormone category. Biomarkers linking the renal and cardiac functions and microRNAs and metabolomic markers are addressed as well.

Clinical Features of Heart Failure and Acute Coronary Syndromes 15

Ravi B. Patel and Eric A. Secemsky

This article provides a brief overview of the clinical presentation, laboratory and radiologic features, and basic management principles in patients with congestive heart failure (CHF) and acute coronary syndromes (ACS). CHF is a clinical syndrome that typically results in symptoms of congestion and hypoperfusion. A thorough physical examination complemented by cardiac biomarkers and imaging are essential in making the diagnosis. Medical and device therapies for CHF target improvement in survival as well as control of symptoms. The management of ACS involves making a prompt diagnosis through the use of a focused history and physical examination, electrocardiogram assessment, and cardiac biomarker evaluation. Timely revascularization along with optimal medical management have helped to improve patient outcomes and mortality.

Cardiac Markers of Myocardial Necrosis: A History and Discussion of Milestones and Emerging New Trends 31

Kent B. Lewandrowski

Laboratory testing for blood-based biomarkers of myocardial injury has steadily evolved over the past 60 years. Initial assays were cumbersome and were neither sensitive nor specific for myocardial necrosis. Major improvements have included the development of more cardiospecific markers, the introduction of random access immunoassays that facilitated near real-time reporting of results, the development of rapid whole-blood point-of-care testing, and progressive improvements in assay design leading to modern high-sensitivity troponin assays that are now being introduced to the market. These new high-sensitivity assays will dramatically change the approach to patients presenting with acute coronary syndromes.

- Natriuretic Peptides in Heart Failure and Acute Coronary Syndrome** 43
Hanna K. Gaggin and James L. Januzzi Jr
- B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are the gold standard biomarkers in determining heart failure (HF) diagnosis and prognosis. These natriuretic peptides may also be useful in guiding HF management, but further studies are needed before they can be routinely recommended for that purpose. A novel natriuretic peptide biomarker, mid-regional pro atrial natriuretic peptide (MR-proANP), shows promise in determining diagnosis and prognosis in HF patients. BNP and NT-proBNP may be of use in excluding myocardial infarction and to assist in determining prognosis in acute coronary syndrome (ACS). Therapeutic implication of natriuretic peptides in ACS is unclear.
- Cardiac Troponins and High-sensitivity Cardiac Troponin Assays** 59
Michael J. Conrad and Petr Jarolim
- Measurement of circulating cardiac troponins I and T has become integral to the diagnosis of myocardial infarction. This article discusses the structure and function of the troponin complex and the release of cardiac troponin molecules from the injured cardiomyocyte into the circulation. An overview of current cardiac troponin assays and their classification according to sensitivity is presented. The diagnostic criteria, role, and usefulness of cardiac troponin for myocardial infarction are discussed. In addition, several examples are given of the usefulness of high-sensitivity cardiac troponin assays for short-term and long-term prediction of adverse events.
- The Benefits of a Rapid, Point-of-Care “TnI-Only” Zero and 2-Hour Protocol for the Evaluation of Chest Pain Patients in the Emergency Department** 75
Kenneth E. Blick
- Delays in diagnosis and treatment of cardiac patients presenting in the Emergency Department with symptoms of acute coronary syndromes are associated with poorer patient outcomes; hence, the timely and accurate diagnosis in the Emergency Department now requires the 24/7 availability of real-time, rapid testing for cardiac markers. Cardiac troponin (cTnI) has emerged as the biomarker of choice to aid physicians in the diagnosis of acute myocardial infarction and moreover current guidelines call for cTnI results to be available to clinicians within 60 minutes of blood draw each and every time a cTnI is ordered.
- Soluble ST2 and Galectin-3 in Heart Failure** 87
Ravi V. Shah and James L. Januzzi Jr
- Circulating biomarkers that directly reflect disease progression, hemodynamics, and ventricular remodeling at a molecular level are critical to risk stratification in heart failure (HF), affording unique insights into pathophysiology not fully captured by traditional risk markers. Despite the wealth of data confirming the importance of natriuretic peptides in HF diagnosis and prognosis, residual clinical risk in HF suggests that additional biomarkers complementary to natriuretic peptides may be useful.

In this article, the current literature addressing the role of these biomarkers in the clinical diagnosis and risk stratification in HF is summarized.

Cardiac Markers Following Cardiac Surgery and Percutaneous Coronary Intervention 99

Remco B. Grobбен, Hendrik M. Nathoe, James L. Januzzi Jr, and Roland R.J. van Kimmenade

Differentiation between procedure-related necrosis and postprocedural myocardial infarction (MI) is challenging because of the inherent association of these procedures to varying levels of myocardial injury. To improve risk stratification of patients at risk of an acute MI, the universal definition of MI implemented cardiac biomarker thresholds. The cutoff points for these thresholds, however, are largely arbitrary and lack therapeutic implications. Measurement of cardiac marker concentrations after percutaneous coronary intervention and cardiac surgery should, therefore, be used as a marker of baseline risk, atherosclerosis burden, and procedural complexity rather than a conclusive marker to diagnose acute MI.

Cholesterol, Lipoproteins, High-sensitivity C-reactive Protein, and Other Risk Factors for Atherosclerosis 113

Joseph Rudolf and Kent B. Lewandrowski

Coronary heart disease is a common and costly epidemic in the Western world. Intensive study has led to a deeper understanding of the pathogenesis of coronary disease and risk stratification. Traditional risk factor assessment has focused on parameters derived from the Framingham Heart Study (age, hypertension, cholesterol, family history, and cigarette smoking). New emerging risk factors, both biological and genetic, are reshaping the understanding of heart disease and the approach to risk stratification. As these emerging assays become more standardized, automated, and inexpensive to perform, they are becoming increasingly important tools in the assessment and treatment of coronary heart disease.

Special Topics: Cardiac Markers in Myocarditis: Cardiac Transplant Rejection and Conditions Other than Acute Coronary Syndrome 129

Kent B. Lewandrowski

The utility of blood biomarkers of cardiac myocyte damage such as troponin T and I in the evaluation of acute coronary syndromes and heart failure is well established. However, some of these markers may also be elevated in other conditions, such as myocarditis, cardiac transplant rejection, and several other conditions. Recognizing this phenomenon is essential to avoid misdiagnosis of acute coronary syndromes. Furthermore, identifying an elevated troponin level in patients without acute coronary syndrome or heart failure may often have diagnostic or prognostic significance.

New Molecular Genetic Tests in the Diagnosis of Heart Disease 137

Matthew S. Lebo and Samantha M. Baxter

With the increasing use of next-generation sequencing applications, there has been an increase in identification of genetic causes of cardiac disease.

This technology has also enabled the transition of these genes into the clinical setting and the rapid growth of large gene tests for the diagnosis of heart disorders. The ability to combine tests to include similar, but distinct, diseases has shown that many genes can be responsible for a wide variety of both syndromic and nonsyndromic disorders. This article discusses the current state of molecular genetic diagnosis for cardiac disorders, focusing on diseases with mendelian inheritance.

**Biomarkers for Cholesterol Absorption and Synthesis in Hyperlipidemic Patients:
Role for Therapeutic Selection**

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Alan H.B. Wu

Increased total serum cholesterol and low-density lipoprotein cholesterol concentrations are associated with atherosclerosis and risk for myocardial infarction and stroke. Those who have high cholesterol with other factors that predispose them to cardiovascular disease should be treated with cholesterol-lowering medications. The pathophysiology of hyperlipidemia is important in the proper selection of drug therapy. Patients who have increased cholesterol synthesis should be medicated with drugs that reduce in vivo cholesterol production, whereas those who have increased dietary absorption of cholesterol should be treated with drugs that inhibit dietary absorption. Sterol-based biomarkers are available to assess the cause of hypercholesterolemia and may have an impact on therapeutic selection.

Methodologies for Measurement of Cardiac Markers

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Patrick M. Sluss

Antibody-based tests are the primary technology used for clinical measurement of cardiac biomarkers in peripheral circulation. This article focuses on the principles of immunometric methods that have been applied to cardiac biomarkers of widespread clinical utility (CKMB, Troponins, and B-type natriuretic proteins) and of more recent clinical testing (ST2, Galectin-2, and myosin binding protein C). How these principles are applied in the design of immunometric assays and how they influence assay performance in quantifying cardiac biomarkers in biologic fluids (serum or plasma) is discussed.

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