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REVIEW ARTICLE

A Review on Recent Advances in Assessment of Myocardial Toxicity

Prateek Manure*[1], Nimbal S K[2]

[1]*PG Scholar, Department of Pharmacology, KLE College of Pharmacy (A constituent unit of KLE Academy of Higher Education and Research, Belagavi), Hubbali, Karnataka, India*
[2] *Professor, Department of Pharmacology, KLE College of Pharmacy (A constituent unit of KLE Academy of Higher Education and Research, Belagavi), Hubballi, Karnataka, India*

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Abstract: Myocardial toxicity is a significant challenge in drug development, chemotherapy, and environmental exposure assessments. Current techniques to evaluate cardiac damage uses multiple parameters like functional, biochemical, and molecular domains. Traditional markers like cardiac troponins and creatine kinase-MB remain valuable indicators of acute injury, while newer biomarkers including natriuretic peptides, galectin-3, and ST2 provide information about chronic remodeling processes. Advanced imaging techniques such as strain echocardiography and cardiac magnetic resonance provide detailed structural and functional information. *In vitro* platforms utilizing human induced pluripotent stem cell-derived cardiomyocytes and organ-on-chip technologies enable high-throughput screening and mechanistic studies. Animal models, particularly rodent systems, continue to offer irreplaceable insights into integrated cardiovascular responses. The combination of oxidative stress markers, inflammatory mediators, and tissue-specific molecular signatures enhances our ability to detect subclinical injury and predict long-term outcomes. Recent developments in telemetry systems and real-time monitoring have improved temporal resolution in toxicity assessment. Usage of these parameters has led to more sensitive and specific evaluation strategies, crucial for early detection and intervention in cardiac injury. The aim of this review is to outline the main parameters and methodologies in myocardial toxicity assessment, emphasizing their complementary roles in providing information about mechanisms involved in cardiac damage.

Keywords: Myocardial toxicity; Cardiac biomarkers; Cardiotoxicity models; Cardiac imaging; Oxidative stress.

1. Introduction

Myocardial toxicity emerges as a critical concern in modern medicine, particularly given the rising incidence of cardiovascular diseases and their impact on global health. Recent epidemiological data indicate that cardiovascular diseases affect approximately 17.9 million people worldwide, with coronary artery disease alone impacting 1.72% of the global population [1]. The World Health Organization reports approximately 100 million cases of acute myocardial infarction annually, resulting in 9 million deaths [2]. The spectrum of cardiac toxicity extends beyond traditional risk factors, encompassing pharmaceutical compounds, environmental toxins, and metabolic disorders. The heart's unique characteristics - high metabolic demands, limited regenerative capacity, and constant contractile activity - make it particularly susceptible to toxic insults [3]. This vulnerability manifests through various pathological mechanisms, including oxidative stress, mitochondrial dysfunction, calcium handling abnormalities, and inflammatory responses [4]. Recent advances in molecular biology and imaging technologies have revolutionized our ability to detect and characterize cardiac injury. While conventional markers like troponins and creatine kinase-MB remain valuable, newer biomarkers offer insights into subtle cardiac dysfunction and early-stage remodeling [5]. The development of high-sensitivity assays has enhanced our capability to detect subclinical cardiac injury, crucial for preventive interventions [6].

The complexity of cardiac responses to toxic insults necessitates multiple experimental approaches. Animal models, particularly rodent systems, provide essential platforms for studying integrated cardiovascular responses [7]. These models enable the evaluation of complex interactions between cardiac tissue and systemic factors, including neurohormonal and immune responses [8]. Complementing these *in vivo* systems, advanced *in vitro* platforms utilizing human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) offer controlled environments for mechanistic studies and high-throughput drug screening [9].

* Corresponding author: Prateek Manure

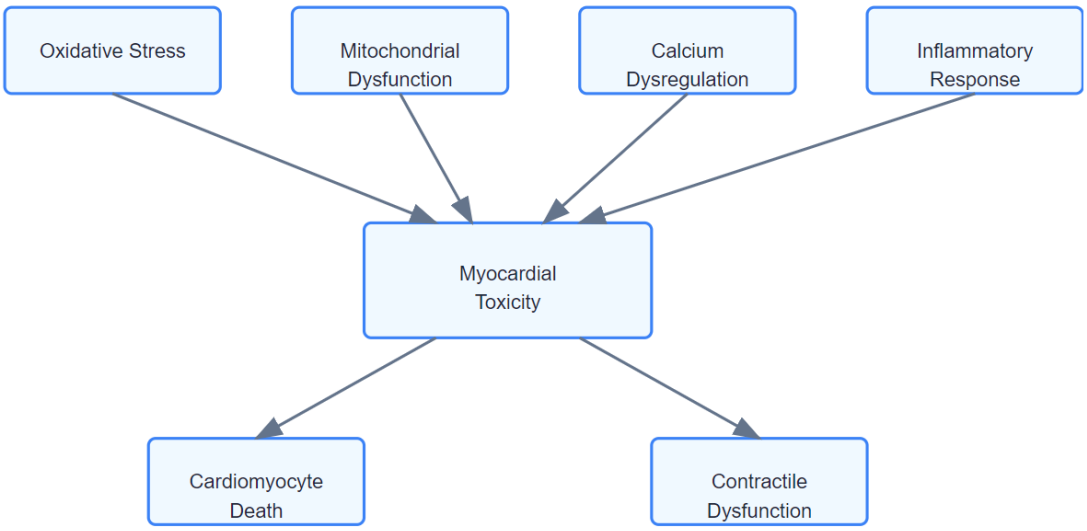

Figure 1. Pathways for Myocardial Toxicity

2. Experimental Models in Myocardial Toxicity

2.1. *In vivo* Models

In vivo models serve as fundamental tools for investigating cardiac responses to toxic agents. These models, predominantly utilizing rodents, enable the study of complex physiological interactions and systemic responses that cannot be replicated in simpler systems [10].

2.1.1. Chemical Induction Models

Several chemical agents are employed to induce cardiac damage in experimental settings. Doxorubicin, an anthracycline antibiotic, generates reactive oxygen species and causes mitochondrial dysfunction, leading to dose-dependent cardiotoxicity [11]. Isoproterenol, a synthetic β-adrenergic agonist, induces myocardial infarction-like lesions through excessive sympathetic stimulation and calcium overload [12]. Trastuzumab affects cardiac function by disrupting HER2-mediated survival signaling in cardiomyocytes [13]. 5-Fluorouracil causes cardiotoxicity through coronary vasospasm and direct myocardial damage [14].

2.1.2. Administration Routes and Protocols

The selection of administration routes significantly influences the model's outcomes. Intravenous administration provides rapid and predictable drug delivery but requires technical expertise. Intraperitoneal injection offers easier handling and consistent absorption. Subcutaneous administration enables sustained drug release and reduces peak concentrations [15].

2.2. *In vitro* Models

In vitro systems have revolutionized cardiotoxicity research by offering controlled environments for mechanistic investigations and high-throughput screening applications [16].

2.2.1. Cell-Based Systems-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs)

These are a significant advancement in cardiac toxicity testing. These cells recapitulate human cardiac physiology and enable patient-specific responses to be studied. They express relevant ion channels, contractile proteins, and metabolic enzymes, making them valuable for investigating drug-induced functional and structural changes [17].

H9c2 cells, derived from embryonic rat heart tissue, provide a reliable platform for studying basic cellular mechanisms of cardiotoxicity. Though lacking some features of mature cardiomyocytes, these cells maintain cardiac-specific biochemical properties and respond consistently to cardiotoxic stimuli [18].

2.2.2. Culture Systems

Three-dimensional cardiac spheroids better mimic the native myocardial environment compared to traditional monolayer cultures. These systems facilitate cell-cell interactions and extracellular matrix development, providing more physiologically relevant responses to toxic agents [19].

Engineered heart tissues (EHTs) incorporate mechanical and electrical stimulation, enabling the assessment of contractile function under various conditions. These systems can detect subtle changes in force generation and rhythm disturbances induced by cardiotoxic compounds [20]

Table 1. Common Experimental Models for Myocardial Toxicity Assessment

Model Type	Examples	Features	Advantages	Limitations
In Vivo Models	Rat/Mouse models Rabbit models Dog models	Intact physiological systems Systemic responses Chronic studies possible	Full physiological response Multiple parameter assessment Clinical relevance	Species differences High cost Ethical considerations
Cell Lines	H9c2 cells HL-1 cells Primary cardiomyocytes	Controlled conditions High reproducibility Cost-effective	- High throughput Mechanistic studies Standardization	Lack of systemic effects Limited maturity Simplified responses
iPSC-derived Cardiomyocytes	Commercial lines Patient-specific cells	Human origin Disease modeling Genetic manipulation possible	Patient-specific response Disease modeling Genetic studies	Immature phenotype High cost Technical complexity
3D Models	Cardiac spheroids Engineered heart tissue Organoids	3D architecture Cell-cell interactions ECM development	Physiological structure Complex interactions Better prediction	Technical challenges Limited throughput Cost considerations

3. Parameters for Evaluating Myocardial Toxicity

3.1. Functional and Hemodynamic Assessment

3.1.1. Heart Rate and Blood Pressure Monitoring

Continuous monitoring of heart rate and blood pressure provides crucial information about cardiovascular function and autonomic regulation. Non-invasive techniques like tail-cuff plethysmography offer practical solutions for routine measurements, while implanted telemetry systems enable long-term data collection in freely moving animals [21]. Advanced pressure-volume catheterization provides detailed hemodynamic parameters, including contractility indices and ventricular filling characteristics [22].

3.1.2. Electrocardiography

ECG analysis reveals crucial information about cardiac electrical activity and potential arrhythmogenic effects of toxic compounds. The main parameters include:

- QT interval measurements for detecting repolarization abnormalities
- QRS complex analysis for assessing ventricular conduction
- ST-segment changes indicating ischemic events
- T-wave morphology reflecting repolarization patterns [23]

3.2. Biochemical Markers

3.2.1. Cardiac-Specific Troponins

Cardiac troponins (cTnI and cTnT) serve as highly specific indicators of cardiomyocyte injury. Their release patterns correlate with the extent of myocardial damage, and high-sensitivity assays can detect subclinical cardiac injury. The kinetics of troponin release provide valuable information about the timing and progression of cardiac damage [24].

3.2.2. Creatine Kinase-MB

Creatine Kinase-MB (CK-MB) maintains its significance in cardiac injury assessment despite newer biomarkers. Its rapid release kinetics, peaking within 12-24 hours of injury, make it valuable for detecting acute cardiac damage. The CK-MB/total CK ratio enhances specificity for cardiac injury versus skeletal muscle damage [25]. The enzyme's relatively short half-life enables effective monitoring of recurrent injury and recovery patterns [26].

Table 2. Biomarkers for Myocardial Toxicity Detection

Category	Biomarker	Time to Peak	Half-life	Clinical Significance
Cardiac Injury	Troponin I	12-24 hours	24 hours	High specificity for cardiac damage
	Troponin T	12-48 hours	48 hours	Early marker of cardiotoxicity
	CK-MB	18-24 hours	12 hours	Acute injury assessment
Cardiac Stress	BNP	24-48 hours	20 minutes	Ventricle wall stress
	NT-proBNP	24-48 hours	120 minutes	Heart failure indication
Inflammation	CRP	24-48 hours	19 hours	Systemic inflammation
	IL-6	6-12 hours	2-4 hours	Acute phase response
Oxidative Stress	MDA	Variable	Variable	Lipid peroxidation
	GSH/GSSG ratio	Real-time	Variable	Oxidative balance

3.2.3. Lactate Dehydrogenase and Aspartate Transaminase

Lactate Dehydrogenase (LDH) release patterns, particularly the LDH1/LDH2 ratio, indicate cardiac tissue damage. The enzyme remains elevated for extended periods, providing a wider window for damage assessment. Aspartate Transaminase (AST) elevations, when considered alongside other cardiac markers, strengthen the evidence of myocardial injury. The combined analysis of LDH and AST profiles aids in determining the extent and progression of cardiac damage [27].

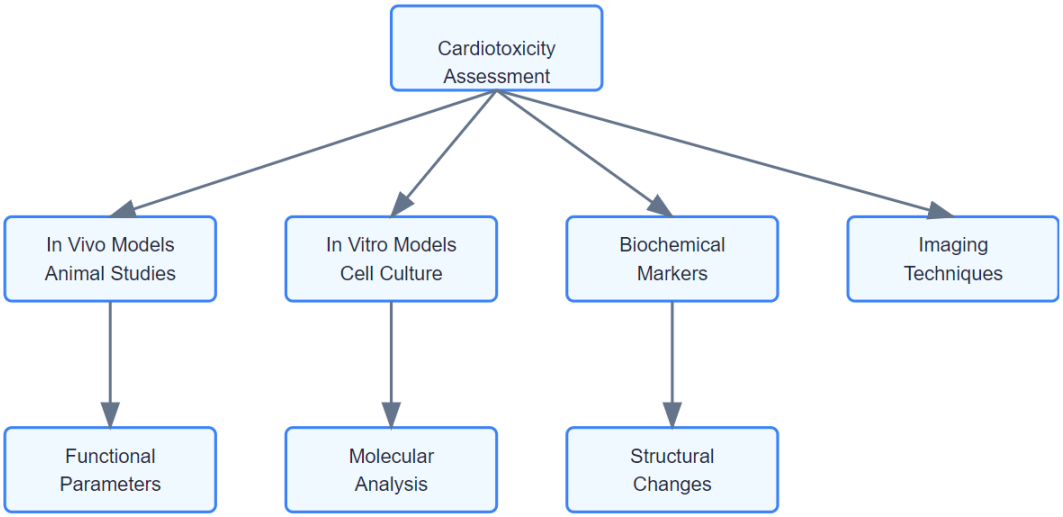

Figure 2. Assessment of Myocardial Toxicity

3.3. Molecular Markers of Cardiac Stress and Remodeling

3.3.1. Natriuretic Peptides

B-type Natriuretic Peptide (BNP) and its N-terminal fragment (NT-proBNP) serve as sensitive indicators of ventricular wall stress and cardiac remodeling. These peptides increase in response to volume overload and pressure changes, reflecting early stages of cardiac dysfunction. Their levels correlate with the severity of cardiac stress and predict adverse outcomes [28].

3.3.2. Tissue Remodeling Markers

Galectin-3 expression indicates active cardiac fibrosis and adverse remodeling processes. Soluble ST2 (sST2) levels reflect myocardial strain and inflammatory responses. The ratio of matrix metalloproteinases to their tissue inhibitors provides insights into extracellular matrix turnover and structural remodeling [29].

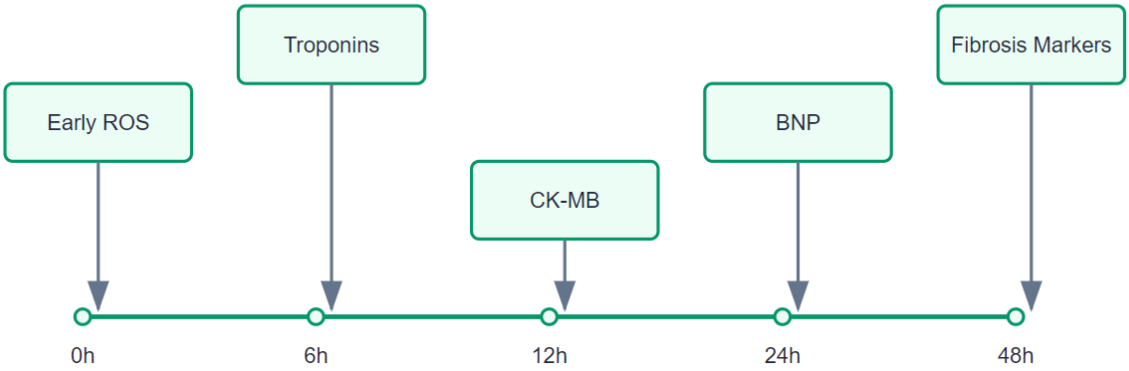

Figure 3. Temporal Sequence of Release of Biomarkers

3.4. Inflammatory and Oxidative Stress Parameters

3.4.1. Inflammatory Mediators

Tumor Necrosis Factor-alpha (TNF-α) and Interleukin-6 (IL-6) levels reflect the inflammatory component of cardiac injury. These cytokines participate in both damage mechanisms and repair processes. C-reactive protein levels indicate systemic inflammatory responses to cardiac injury. The temporal profile of inflammatory markers helps distinguish acute from chronic cardiac damage [30].

3.4.2. Oxidative Stress Indicators

Malondialdehyde (MDA) levels serve as markers of lipid peroxidation and oxidative damage. Reduced glutathione (GSH) depletion indicates compromised antioxidant defenses. Superoxide dismutase (SOD) and catalase activity changes reflect cellular responses to oxidative stress. The balance between oxidant production and antioxidant defenses provides crucial information about ongoing cellular damage [31].

4. Imaging Techniques

4.1. Echocardiographic Evaluation

4.1.1. Conventional Parameters

Left ventricular ejection fraction (LVEF) remains a fundamental measure of cardiac function. Wall motion analysis provides regional contractility information. Diastolic function parameters, including E/A ratio and deceleration time, indicate filling abnormalities. These measurements enable sequential monitoring of cardiac function during toxicity studies [32].

4.1.2. Advanced Echocardiographic Techniques

Speckle tracking echocardiography measures myocardial strain and strain rate, detecting subtle contractility changes before evident LVEF reduction. Tissue Doppler imaging quantifies myocardial velocities and timing intervals. Three-dimensional echocardiography provides accurate volumetric measurements and enhanced visualization of structural changes [33].

4.2. Cardiac Magnetic Resonance Imaging

4.2.1. Functional Assessment

Cardiac magnetic resonance (CMR) provides precise measurements of ventricular volumes and ejection fraction. Myocardial tagging techniques enable detailed strain analysis. First-pass perfusion imaging detects microvascular dysfunction. These techniques offer superior tissue characterization compared to conventional imaging [34].

4.2.2. Tissue Characterization

T1 and T2 mapping techniques identify myocardial edema and fibrosis. Late gadolinium enhancement reveals areas of myocardial scarring. T2* imaging detects iron overload in chemotherapy-induced cardiotoxicity. These parameters enable early detection of tissue-level changes before functional decline [35].

Table 3. Imaging Techniques for Cardiotoxicity Assessment

Imaging Technique	Parameters Measured	Advantages	Clinical Applications	Detection Timing
Echocardiography	LVEF Global longitudinal strain E/A ratio Wall motion	Non-invasive Real-time Cost-effective	Routine monitoring Acute changes Follow-up	Early to late
Cardiac MRI	Tissue characterization T1/T2 mapping Late gadolinium enhancement	High resolution Tissue detail No radiation	Fibrosis detection Edema assessment Structural changes	Early to late
Nuclear Imaging	Perfusion Metabolism Viability	Functional assessment Metabolic imaging	Perfusion defects Metabolic changes	Intermediate to late
CT Imaging	Coronary anatomy Calcium scoring Tissue density	High resolution Fast acquisition 3D reconstruction	Anatomical changes Structural assessment	Late

5. Histopathological Evaluation

5.1. Light Microscopy

Hematoxylin and eosin staining reveals cellular architecture and inflammatory infiltrates. Masson's trichrome staining quantifies collagen deposition and fibrosis. Periodic acid-Schiff staining identifies glycogen accumulation. These techniques provide direct evidence of structural cardiac damage [36].

5.2. Immunohistochemistry

Specific antibody staining identifies cellular markers of injury and repair. TUNEL assay detects apoptotic cells. CD68 staining reveals macrophage infiltration. These methods enable detailed analysis of cellular responses to toxic injury [37].

5.3. Electron Microscopy

Transmission electron microscopy reveals ultrastructural changes in cellular organelles. Mitochondrial morphology changes indicate energetic dysfunction. Sarcomere organization assessment reveals contractile apparatus integrity. These observations provide mechanistic insights into cellular damage [38].

6. Combined Methods

6.1. Multiparametric Assessment

The combination of functional, biochemical, and structural parameters enhances the sensitivity and specificity of cardiotoxicity detection. Early molecular markers often precede functional changes, while imaging parameters confirm structural alterations. Temporal relationships between different parameters provide insights into damage progression and recovery patterns [39].

6.2. Model-Specific parameters

In vivo models require careful selection of parameters based on technical feasibility and physiological relevance. Cell-based systems benefit from high-throughput biochemical and molecular assessments. The integration of multiple parameters compensates for individual marker limitations and provides comprehensive toxicity profiles [40].

Microfluidic devices enable real-time monitoring of cellular responses. Novel biosensors detect subtle changes in cardiac function. Advanced imaging techniques provide increased spatial and temporal resolution. These technological advances enhance our ability to detect and characterize cardiac injury [41].

6.3. Biomarkers

Novel circulating microRNAs show promise as cardiac-specific markers. Proteomics approaches identify new protein signatures of cardiac injury. Metabolomic profiling reveals alterations in cardiac energy metabolism. These developments expand the range of available toxicity markers [42].

7. Conclusion

The myocardial toxicity assessment requires combined evaluation of multiple parameters across different experimental models. Traditional biomarkers maintain their utility while newer molecular markers and imaging techniques provide additional insights. The combination of *in vivo* and *in vitro* techniques, supported by advanced imaging and molecular techniques, enables detailed evaluation of cardiac injury mechanisms. Recent developments in technology and biomarker discovery will further enhance our ability to detect and characterize myocardial toxicity. The combined use of these parameters strengthens the predictive value of preclinical studies and improves translation to clinical applications.

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