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IMAGING, MOLECULAR MECHANISMS, PHARMACOTHERAPY, AND SURGICAL PROTECTION

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PREFACE

Cardiovascular medicine has undergone a profound transformation in recent years, both in terms of fundamental science and clinical practice. When the rapid advances in imaging technology, discoveries in molecular biology, pharmacological innovations, and surgical techniques are considered together, it becomes clear that the modern approach to cardiac disease demands a multidimensional, integrated, and evidence-based perspective.

This book has been prepared to comprehensively address four closely related and clinically vital areas of cardiology and cardiac surgery. Beginning with phenotype-based multimodality imaging in cardiomyopathies and its diagnostic and prognostic contributions, the journey continues through the role of miRNAs in myocardial ischemia-reperfusion injury, current approaches to the use of SGLT2 inhibitors in heart failure, and concludes with the present status of myocardial protection in cardiac surgery. Together, these chapters aim to provide both a solid scientific foundation and a practical guide for the reader.

Each section of this work stands as an independent reference in its own right; yet when considered as a whole, the four chapters offer a unified perspective on cardiovascular disease. The phenotyping of cardiomyopathies through advanced imaging provides a comprehensive framework for diagnosis and risk stratification, while an understanding of the molecular mechanisms underlying ischemia-reperfusion injury opens new avenues for therapeutic targets. The chapter on SGLT2 inhibitors reflects the growing importance of this drug class in the management of heart failure and addresses the practical questions that clinicians most frequently encounter. The chapter on myocardial protection examines an indispensable dimension of cardiac surgery in the light of current evidence.

We sincerely thank all contributing authors for their scholarly dedication and intellectual efforts in the preparation of this book. It is our hope that this work will serve as a valuable reference for cardiologists, cardiac surgeons, cardiology residents, and all healthcare professionals working in this field.

Editor: Assoc. Prof. Dr. Kayıhan KARAMAN

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CHAPTER 1

PHENOTYPE-BASED MULTIMODALITY IMAGING IN CARDIOMYOPATHIES: DIAGNOSTIC AND PROGNOSTIC PERSPECTIVES

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Introduction

Cardiomyopathies represent a heterogeneous group of myocardial disorders characterized by structural and/or functional abnormalities of the myocardium that cannot be explained solely by coronary artery disease, hypertension, valvular heart disease, or congenital heart disease (Elliott, 2008). In clinical practice, cardiomyopathies encompass dilated, hypertrophic, and restrictive phenotypes, as well as arrhythmogenic cardiomyopathy and left ventricular non-compaction. Although this phenotype-based classification provides a standardized diagnostic framework, the fact that similar phenotypes may arise from diverse genetic, inflammatory, infiltrative, or metabolic mechanisms renders the diagnostic process complex (Arbelo et al., 2023; Pinto et al., 2016).

The clinical spectrum of cardiomyopathies is broad, ranging from an asymptomatic course to advanced heart failure, thromboembolic events, malignant ventricular arrhythmias, and sudden cardiac death. Even among patients sharing the same phenotypic diagnosis, disease progression and prognosis may vary considerably. Consequently, reliance on clinical findings alone is often insufficient for accurate risk stratification, prompting current guidelines to recommend a systematic and integrated imaging-based evaluation (Arbelo et al., 2023).

Cardiovascular imaging techniques have undergone substantial evolution over the past decades. Transthoracic echocardiography (TTE) remains the first-line imaging modality in cardiomyopathies owing to its wide availability, real-time hemodynamic assessment, and versatility. In particular, speckle-tracking echocardiography and the assessment of global longitudinal strain have enabled the detection of subclinical myocardial dysfunction, even in patients with preserved left ventricular ejection fraction (Voigt et al., 2015).

Cardiac magnetic resonance imaging (CMR) has become an indispensable component of the diagnostic algorithm in cardiomyopathies due to its high spatial resolution and unique capability for myocardial tissue characterization. Late gadolinium enhancement allows the identification of focal myocardial fibrosis, while T1 and T2 mapping techniques and extracellular volume quantification facilitate the assessment of diffuse fibrosis, inflammation, and infiltrative processes (Messroghli et al., 2017). In selected patient populations, cardiac computed tomography (CCT) and nuclear imaging techniques provide complementary diagnostic information, particularly in the etiological work-up and risk stratification. The establishment of noninvasive diagnostic criteria for transthyretin cardiac amyloidosis using bone-avid radiotracer scintigraphy exemplifies the clinical impact of a multimodality imaging approach (Gillmore et al., 2016).

Despite major advances in cardiovascular imaging and the availability of comprehensive international guidelines, the practical application of multimodality imaging in cardiomyopathies remains challenging. Clinicians are frequently confronted with an expanding array of imaging techniques, parameters, and disease-specific recommendations, which may lead to uncertainty regarding the optimal sequencing and clinical relevance of each modality. In this context, an imaging strategy focused solely on individual techniques risks fragmentation and limited clinical utility. Therefore, the aim of this narrative review is to summarize the diagnostic and prognostic contributions of the main imaging modalities in cardiomyopathies and to propose a phenotype-oriented, integrated multimodality imaging approach that may support clinical decision-making in routine practice.

Imaging Modalities in Cardiomyopathies

Cardiomyopathies require a comprehensive imaging-based evaluation owing to their heterogeneous structural, functional, and tissue-level manifestations. No single imaging technique is sufficient to address all diagnostic and prognostic aspects of these disorders. Therefore, contemporary clinical practice relies on the complementary use of multiple imaging modalities, each contributing distinct and incremental information. The following sections outline the roles of the principal imaging techniques used in cardiomyopathies, with emphasis on their strengths, limitations, and integration within a multimodality diagnostic framework.

Transthoracic Echocardiography

TTE remains the cornerstone and first-line imaging modality in the evaluation of patients with suspected or established cardiomyopathies. Its widespread availability, bedside applicability, lack of ionizing radiation, and ability to provide real-time hemodynamic assessment make echocardiography indispensable in daily clinical practice (Lang et al., 2015). In most patients, TTE represents the initial diagnostic step and plays a pivotal role in guiding further diagnostic work-up and the need for advanced imaging modalities.

Two-dimensional echocardiography allows comprehensive assessment of cardiac chamber size, wall thickness, ventricular geometry, and global systolic function. Standardized measurements of left ventricular volumes and ejection fraction using the biplane Simpson method, as well as right ventricular dimensions and functional indices such as tricuspid annular plane systolic excursion, are essential for phenotypic classification and longitudinal follow-up in cardiomyopathies. Current recommendations emphasize indexed measurements and standardized imaging planes to improve reproducibility and interobserver agreement, which is particularly important in serial evaluations (Lang et al., 2015).

Doppler echocardiography plays a central role in the assessment of intracardiac hemodynamics and diastolic function. Pulsed-wave and continuous-wave Doppler enable evaluation of transmitral and transtricuspid flow patterns, pulmonary venous flow, and valvular gradients, while tissue Doppler imaging provides insight into myocardial relaxation and filling pressures. The integrated diastolic function algorithm proposed by the American Society of Echocardiography and the European Association of Cardiovascular Imaging has improved diagnostic consistency, especially in patients with preserved or mildly reduced left ventricular ejection fraction, a frequent scenario in several cardiomyopathy phenotypes (Nagueh et al., 2016).

Speckle-tracking echocardiography has substantially expanded the diagnostic and prognostic capabilities of TTE. Global longitudinal strain (GLS) provides a sensitive and reproducible measure of myocardial deformation and enables detection of subclinical systolic dysfunction that may not be apparent using conventional ejection fraction assessment (Voigt et al., 2015). GLS has demonstrated incremental prognostic value in dilated, hypertrophic, and infiltrative cardiomyopathies and may aid in risk stratification. In addition, disease-specific strain patterns, such as relative apical sparing in cardiac amyloidosis, may offer valuable etiological clues.

Three-dimensional echocardiography further enhances volumetric assessment by reducing geometric assumptions inherent to two-dimensional imaging. Three-dimensional measurements of ventricular volumes and ejection fraction have shown improved accuracy and closer agreement with cardiac magnetic resonance imaging, particularly in patients with distorted ventricular geometry, such as those with dilated cardiomyopathy or left ventricular non-compaction (Lang et al., 2012; Mor-Avi et al., 2008). This improved accuracy is especially relevant for follow-up and treatment response assessment.

Despite its many strengths, echocardiography has limitations, including dependency on acoustic window quality, operator expertise, and limited ability for direct myocardial tissue characterization. Consequently, echocardiographic findings should often be interpreted within a multimodality imaging framework, integrating complementary information from CMR or other advanced techniques when clinically indicated. Standardized reporting of TTE is therefore essential to ensure consistent communication and optimal integration into multimodality diagnostic pathways (Galderisi et al., 2017).

Cardiac Magnetic Resonance Imaging

CMR is a central component of the multimodality imaging approach in cardiomyopathies, as it provides highly accurate assessment of ventricular volumes and function while uniquely enabling noninvasive myocardial tissue characterization. Its high spatial resolution, excellent reproducibility, and independence from geometric assumptions render CMR particularly valuable in cardiomyopathies with complex ventricular geometry (Kramer et al., 2013).

CMR allows precise quantification of left and right ventricular volumes, ejection fraction, and myocardial mass. This capability is especially advantageous in conditions such as dilated cardiomyopathy, arrhythmogenic cardiomyopathy, and left ventricular non-compaction, where echocardiographic assessment may be limited. In addition, CMR is considered the reference standard for right ventricular volumetric and functional assessment (Kramer et al., 2013; Petersen et al., 2005).

Late gadolinium enhancement (LGE) imaging represents a cornerstone technique for the detection of focal myocardial fibrosis in cardiomyopathies. The presence and distribution pattern of LGE are critical for differentiating ischemic from non-ischemic etiologies and for phenotypic characterization. In non-ischemic dilated cardiomyopathy, mid-wall septal LGE is commonly observed, whereas hypertrophic cardiomyopathy typically demonstrates patchy LGE within hypertrophied segments. Histopathological correlation studies have confirmed that LGE corresponds to areas of replacement fibrosis (Assomull et al., 2006; Moon et al., 2004).

Parametric mapping techniques, including native T1 and T2 mapping and extracellular volume (ECV) quantification, have expanded the diagnostic capabilities of CMR by enabling the assessment of diffuse myocardial processes that may not be detected by LGE imaging. Increased native T1 and ECV values are indicative of diffuse fibrosis or infiltrative disease, while T2 mapping is particularly useful for identifying myocardial edema and active inflammation (Messroghli et al., 2017). These techniques have proven especially valuable in the evaluation of cardiac amyloidosis, early-stage dilated cardiomyopathy, and myocarditis.

From a prognostic perspective, the presence and extent of LGE have been consistently associated with adverse clinical outcomes. In patients with non-ischemic dilated cardiomyopathy, myocardial fibrosis detected by LGE is independently associated with increased risks of all-cause mortality, ventricular arrhythmias, and sudden cardiac death (Assomull et al., 2006; Gulati et al., 2013). Consequently, CMR findings are increasingly incorporated into risk stratification strategies and may inform decisions regarding implantable cardioverter-defibrillator implantation.

CMR also plays a pivotal role in the assessment of inflammatory cardiomyopathies. In myocarditis, a multiparametric CMR approach combining T2-weighted imaging, parametric mapping, and LGE allows noninvasive detection of myocardial inflammation and injury. This strategy is supported by international consensus documents and has become integral to contemporary diagnostic algorithms (Friedrich et al., 2009).

Despite its many strengths, CMR has certain limitations, including contraindications related to non–MRI-compatible devices, restricted use of gadolinium-based contrast agents in advanced renal dysfunction, claustrophobia, and limited availability in some centers. Therefore, CMR should be applied judiciously and interpreted within an integrated multimodality imaging framework in conjunction with echocardiography and other imaging techniques (Kramer et al., 2013).

Cardiac Computed Tomography

CCT plays a complementary yet strategically important role within the multimodality imaging approach to cardiomyopathies. In particular, the ability of noninvasive coronary CT angiography to reliably exclude coronary artery disease with a high negative predictive value substantially facilitates the diagnostic process. In patients with suspected cardiomyopathy, accurate exclusion of an ischemic etiology is a critical step for correct phenotypic classification and for guiding appropriate therapeutic strategies (Knuuti et al., 2020; Budoff et al., 2008).

Owing to its high spatial resolution, CCT allows detailed assessment of cardiac anatomy and morphological structures. Ventricular cavity dimensions, myocardial wall thickness, geometric relationships of cardiac chambers, and the anatomy of the great vessels can be visualized with high accuracy. These characteristics make CCT especially valuable in the evaluation of complex anatomical variants, associated vascular abnormalities, and congenital heart disease. In addition, CCT provides an excellent anatomical roadmap for surgical or interventional planning when detailed structural information is required (Budoff et al., 2008).

In patients in whom CMR is contraindicated or yields suboptimal image quality, CCT may serve as an alternative imaging modality for structural and limited functional assessment. With current multidetector CT technology, measurements of left and right ventricular volumes and ejection fraction can be obtained, and these parameters have been shown to correlate well with CMR-derived measurements. Nevertheless, the ability of CCT to characterize myocardial tissue is limited, and therefore it should not be considered a substitute for CMR but rather a complementary option in selected clinical scenarios (Maffei et al., 2012).

CCT has a distinct role in the evaluation of pericardial disease. Pericardial thickening, calcification, and the anatomical relationship between the pericardium and adjacent structures can be clearly delineated by CT imaging. In patients with suspected constrictive pericarditis, the identification of pericardial calcification provides important diagnostic support and may have implications for surgical decision-making. In this context, CCT complements echocardiography and CMR by offering superior visualization of pericardial anatomy and calcific involvement (Syed, Schaff, & Oh, 2014).

Despite its clinical utility, the use of CCT requires careful consideration of potential limitations, including exposure to ionizing radiation and the risk of contrast-induced nephrotoxicity associated with iodinated contrast agents. Although advances in scanner technology, dose-reduction algorithms, and prospective ECG-gating have markedly reduced radiation exposure, prudent patient selection remains essential, particularly in younger patients and in those requiring serial imaging. Consequently, in cardiomyopathies, CCT should be applied in a targeted manner to address specific clinical questions (Knuuti et al., 2020; Maffei et al., 2012).

Nuclear Imaging and Positron Emission Tomography

Nuclear imaging techniques and positron emission tomography (PET) provide unique functional and metabolic information that complements structural imaging modalities in the evaluation of cardiomyopathies. Unlike echocardiography, CMR, or CCT, nuclear imaging enables direct assessment of myocardial perfusion, metabolism, and inflammatory activity, thereby contributing to etiological differentiation and disease activity evaluation within a multimodality imaging framework.

Myocardial perfusion imaging, most commonly performed using single-photon emission computed tomography (SPECT), remains an established tool for the assessment of concomitant coronary artery disease and ischemic burden in patients with cardiomyopathies. Standardized protocols for stress testing, radiotracer selection, and image acquisition are well defined in contemporary nuclear cardiology guidelines. In selected patients, perfusion imaging may assist in distinguishing ischemic from non-ischemic mechanisms contributing to left ventricular dysfunction and symptoms (Henzlova et al., 2016).

PET imaging offers important advantages over SPECT by enabling absolute quantification of myocardial blood flow and coronary flow reserve (CFR). Reduced CFR reflects not only epicardial coronary artery disease but also coronary microvascular dysfunction, which is increasingly recognized as a key pathophysiological mechanism in several cardiomyopathy phenotypes. Noninvasive assessment of CFR by PET has been shown to provide incremental prognostic value beyond conventional risk markers and to improve risk stratification in patients with cardiomyopathy and left ventricular dysfunction (Murthy et al., 2011; Taqueti & Di Carli, 2018).

Bone-avid radiotracer scintigraphy represents one of the most impactful clinical applications of nuclear imaging in cardiomyopathies, particularly in the diagnosis of transthyretin (ATTR) cardiac amyloidosis. In the appropriate clinical context and after exclusion of light-chain amyloidosis, cardiac uptake of bone-seeking tracers enables a non-biopsy diagnosis of ATTR cardiac amyloidosis. This approach has fundamentally altered the diagnostic pathway of infiltrative cardiomyopathies and has significant implications for early diagnosis and disease-specific therapy (Gillmore et al., 2016).

Fluorodeoxyglucose (FDG) PET plays a central role in the evaluation of inflammatory cardiomyopathies, most notably cardiac sarcoidosis. FDG-PET allows visualization of active myocardial inflammation, assessment of disease extent, and monitoring of response to immunosuppressive therapy. Given the heterogeneous clinical presentation of cardiac sarcoidosis, integration of FDG-PET findings with clinical data and other imaging modalities is essential. International consensus documents provide detailed recommendations regarding patient preparation, imaging protocols, and standardized reporting to ensure accurate interpretation (Birnie et al., 2016; Chareonthaitawee et al., 2017).

Despite their clinical value, nuclear imaging techniques have inherent limitations, including exposure to ionizing radiation, limited availability, higher cost, and the need for meticulous patient preparation, particularly for FDG-PET studies. Consequently, nuclear imaging and PET should be applied in a targeted manner to address specific clinical questions and should be interpreted within an integrated multimodality imaging strategy rather than as standalone diagnostic tools (Henzlova et al., 2016; Birnie et al., 2016). The complementary diagnostic and prognostic roles of the principal imaging modalities used in cardiomyopathies are summarized in Table 1.

Table 1. *Role of Imaging Modalities in Cardiomyopathies: Diagnostic and Prognostic Contributions*

Imaging modality	Main diagnostic role	Unique strengths	Key prognostic information	Main limitations
Transthoracic echocardiography (TTE)	First-line phenotypic assessment; chamber size, systolic/diastolic function	Widely available; real-time hemodynamics; GLS for subclinical dysfunction	GLS associated with outcomes in DCM, HCM, infiltrative CMP	Limited tissue characterization; operator and acoustic window dependency
Cardiac magnetic resonance (CMR)	Gold standard for ventricular volumes and function; tissue characterization	LGE, T1/T2 mapping, ECV quantification	Myocardial fibrosis strongly associated with mortality and arrhythmic risk	Contraindications; limited availability; gadolinium use
Cardiac computed tomography (CCT)	Exclusion of ischemic etiology; anatomical assessment	High negative predictive value for CAD; excellent spatial resolution	Indirect prognostic value via etiology clarification	Ionizing radiation; limited tissue characterization
SPECT myocardial perfusion imaging	Detection of ischemia and CAD burden	Established protocols; wide availability	Ischemic burden related to outcomes	Limited spatial resolution; radiation exposure
PET imaging	Quantification of myocardial blood flow, CFR, inflammation	Absolute flow quantification; assessment of microvascular dysfunction	Reduced CFR and active inflammation predict adverse outcomes	Limited availability; cost; radiation
Bone-avid scintigraphy	Noninvasive diagnosis of ATTR cardiac amyloidosis	Disease-specific diagnostic accuracy	Early diagnosis enables prognostic stratification and targeted therapy	Limited to amyloidosis; requires exclusion of AL

Abbreviations: *TTE, transthoracic echocardiography; GLS, global longitudinal strain; CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; ECV, extracellular volume; CCT, cardiac computed tomography; CAD, coronary artery disease; SPECT, single-photon emission computed tomography; PET, positron emission tomography; CFR, coronary flow reserve; ATTR, transthyretin; AL, amyloid light-chain; CMP, cardiomyopathy.*

Disease-Specific Multimodality Imaging Strategies

Cardiomyopathies represent a heterogeneous group of myocardial disorders characterized by diverse phenotypes, pathophysiological mechanisms, and clinical outcomes. As no single imaging modality can fully capture this complexity, disease-specific multimodality imaging strategies are essential for accurate diagnosis, risk stratification, and informed clinical decision-making. Contemporary guidelines and expert consensus documents emphasize the complementary use of multiple imaging techniques tailored to the underlying cardiomyopathy phenotype (Elliott et al., 2014; Casas & Rodríguez-Palomares, 2022).

Dilated Cardiomyopathy

In dilated cardiomyopathy, TTE serves as the first-line imaging modality for the assessment of left ventricular dilatation, systolic dysfunction, and valvular abnormalities. CMR provides more accurate quantification of ventricular volumes and function and enables myocardial tissue characterization through LGE. The presence of myocardial fibrosis detected by LGE has important prognostic implications and is strongly associated with arrhythmic risk and adverse clinical outcomes (Assomull et al., 2006). In patients in whom an ischemic etiology must be excluded, cardiac computed tomography plays a complementary role. This multimodality approach directly influences therapeutic decisions, particularly regarding implantable cardioverter-defibrillator implantation and advanced heart failure therapies (Ponikowski et al., 2016; Casas & Rodríguez-Palomares, 2022). A phenotype-based multimodality imaging strategy integrating first-line and complementary imaging modalities for the major cardiomyopathy subtypes, together with their key diagnostic and prognostic imaging markers, is summarized in Table 2.

Table 2. *Phenotype-Based Multimodality Imaging Strategies in Cardiomyopathies*

Cardiomyopathy phenotype	**First-line imaging**	**Second-line / complementary imaging**	**Key imaging markers**	**Clinical implications**
Dilated cardiomyopathy	TTE	CMR ± CCT	LGE (mid-wall), LV volumes, GLS	ICD decision, prognosis, HF progression
Hypertrophic cardiomyopathy	TTE	CMR ± PET	Max wall thickness, LGE extent, microvascular dysfunction	Sudden cardiac death risk stratification
Restrictive / infiltrative CMP	TTE	CMR + nuclear imaging	Diffuse LGE, elevated native T1/ECV, tracer uptake	Etiologic diagnosis, targeted therapy
Arrhythmogenic cardiomyopathy	TTE	CMR	RV volumes, regional wall motion abnormalities, fibro-fatty replacement	Arrhythmic risk, ICD indication
Left ventricular non-compaction	TTE	CMR	Non-compacted/compacted ratio, fibrosis	Diagnostic confirmation, thromboembolic risk
Inflammatory CMP (myocarditis, sarcoidosis)	TTE	CMR + FDG-PET	Edema, LGE, active inflammation	Disease activity, therapy monitoring

Abbreviations: *TTE, transthoracic echocardiography; CMR, cardiac magnetic resonance; CCT, cardiac computed tomography; PET, positron emission tomography; FDG, fluorodeoxyglucose; LGE, late gadolinium enhancement; ECV, extracellular volume; LV, left ventricle/left ventricular; RV, right ventricle/right ventricular; GLS, global longitudinal strain; ICD, implantable cardioverter-defibrillator; HF, heart failure; CMP, cardiomyopathy.*

Hypertrophic Cardiomyopathy

Echocardiography remains the cornerstone of imaging in hypertrophic cardiomyopathy, allowing evaluation of hypertrophy distribution, left ventricular outflow tract obstruction, and diastolic function. CMR is indispensable for precise measurement of maximal wall thickness, detection of apical involvement, and assessment of myocardial fibrosis using LGE. The extent of myocardial fibrosis has emerged as a key marker for sudden cardiac death risk stratification and contributes to individualized risk assessment. In selected patients, nuclear imaging and PET may provide additional insights into myocardial perfusion abnormalities and microvascular dysfunction, further refining clinical evaluation (Elliott et al., 2014; Casas & Rodríguez-Palomares, 2022).

Restrictive and Infiltrative Cardiomyopathies

In restrictive and infiltrative cardiomyopathies, echocardiography is useful for identifying restrictive filling patterns and biatrial enlargement but lacks specificity. CMR plays a central role by enabling detailed myocardial tissue characterization, which is critical for differential diagnosis. In cardiac amyloidosis, characteristic LGE patterns and parametric mapping techniques support diagnosis and disease staging. When integrated with nuclear imaging, particularly bone-avid tracer scintigraphy, a noninvasive diagnosis of transthyretin cardiac amyloidosis can be established, significantly reducing the need for endomyocardial biopsy and facilitating early initiation of disease-specific therapy (Habib et al., 2017; Gillmore, et al., 2016).

Arrhythmogenic Cardiomyopathy

In arrhythmogenic cardiomyopathy, echocardiography may demonstrate right ventricular dilatation and systolic dysfunction but has limited sensitivity in early disease stages. CMR is the reference standard for the evaluation of right ventricular volumes, regional wall motion abnormalities, and fibro-fatty myocardial replacement. Imaging findings constitute a key component of international diagnostic criteria and play a pivotal role in arrhythmic risk assessment. Multimodality imaging is therefore fundamental in identifying high-risk patients and guiding decisions regarding implantable cardioverter-defibrillator therapy (Marcus et al., 2010; Casas & Rodríguez-Palomares, 2022).

Left Ventricular Non-Compaction

In left ventricular non-compaction, echocardiography allows initial detection of excessive trabeculation and deep intertrabecular recesses. CMR provides more robust diagnostic confirmation by accurately quantifying the ratio between non-compacted and compacted myocardium and by identifying associated myocardial fibrosis. A multimodality imaging approach reduces diagnostic uncertainty and contributes to improved assessment of heart failure progression and thromboembolic risk, thereby optimizing patient management (Petersen et al., 2005).

Prognostic and Therapuetic Implications

Multimodality imaging plays a pivotal role in cardiomyopathies not only for diagnosis but also for prognostic stratification and therapeutic decision-making. Imaging-derived markers provide incremental information beyond conventional clinical parameters, enabling a more individualized approach to patient management.

Among available imaging techniques, CMR has emerged as a key modality for prognostic assessment owing to its ability to characterize myocardial tissue. The presence of myocardial fibrosis detected by LGE is strongly associated with adverse outcomes in both dilated and hypertrophic cardiomyopathies. Importantly, myocardial fibrosis confers prognostic value independent of left ventricular ejection fraction and is closely linked to an increased risk of ventricular arrhythmias and mortality (Assomull et al., 2006; Chan et al., 2014).

Myocardial fibrosis represents the structural substrate for electrical heterogeneity and re-entrant arrhythmias. In hypertrophic cardiomyopathy, quantitative assessment of LGE burden has been shown to improve sudden cardiac death risk stratification, supplementing established clinical risk models. This has important clinical implications, as imaging findings increasingly inform decisions regarding primary prevention strategies (Chan et al., 2014).

Advanced imaging findings also influence therapeutic decision-making, particularly with respect to implantable cardioverter-defibrillator (ICD) implantation. Contemporary European Society of Cardiology (ESC) guidelines emphasize that, in selected patients, imaging markers such as the extent of myocardial fibrosis may complement traditional risk factors when evaluating the indication for ICD therapy. This integrated approach aims to optimize patient selection, reducing both under-treatment of high-risk individuals and unnecessary device implantation in low-risk patients (Priori & Blomström-Lundqvist, 2015; Zeppenfeld et al., 2022).

Beyond risk stratification, multimodality imaging plays a crucial role in longitudinal patient management and therapy monitoring. Serial imaging enables assessment of ventricular remodeling, evaluation of treatment response, and detection of disease progression. Standardized CMR acquisition and reporting protocols are particularly important to ensure reproducibility and consistency during follow-up, thereby facilitating reliable comparison over time and across centers (Kramer et al., 2020).

Overall, the integration of multimodality imaging findings into prognostic evaluation and therapeutic planning represents a cornerstone of contemporary cardiomyopathy management, supporting precision medicine and improved clinical outcomes.

Future Directions

The field of cardiovascular imaging in cardiomyopathies is undergoing a rapid transformation driven by advances in artificial intelligence (AI), quantitative imaging, and data integration. AI-based algorithms, particularly deep learning models, are increasingly being applied to echocardiography and CMR imaging to enable automated image acquisition, segmentation, and functional assessment. These technologies have the potential to reduce interobserver variability, improve workflow efficiency, and enhance diagnostic accuracy in routine clinical practice (Topol, 2019).

Radiomics and quantitative imaging biomarkers represent another promising frontier in cardiomyopathy imaging. By extracting high-dimensional quantitative features from conventional imaging data, radiomics enables a more detailed characterization of myocardial tissue beyond visual assessment. When combined with machine learning techniques, these approaches may facilitate improved phenotypic classification, early disease detection, and more accurate risk stratification in patients with cardiomyopathies (Lambin et al., 2012).

The future of cardiovascular imaging also lies in integrated multimodality reporting. Standardized acquisition protocols and structured reporting systems allow comprehensive synthesis of data derived from echocardiography, CMR, computed tomography, and nuclear imaging. Such integration supports more consistent interpretation, improves communication among multidisciplinary teams, and enhances longitudinal patient follow-up (Kramer et al., 2020).

Ultimately, these technological developments are paving the way for personalized imaging strategies. Tailoring imaging protocols to individual patient characteristics, disease stage, and clinical questions will enable more targeted diagnostic pathways and optimized therapeutic decision-making. In this context, advanced imaging techniques will play a central role in precision medicine approaches for cardiomyopathies (Ferreira et al., 2018).

Conclusion

Multimodality imaging has become an indispensable component in the diagnosis, risk stratification, and therapeutic management of cardiomyopathies. The complementary use of TTE, CMR, CCT, and nuclear imaging enables a comprehensive assessment of myocardial structure, function, and tissue characteristics. This integrated approach provides clinically meaningful diagnostic and prognostic information that cannot be achieved by any single imaging modality alone and allows a more precise characterization of disease mechanisms across different cardiomyopathy phenotypes.

A phenotype-oriented imaging strategy represents the cornerstone of contemporary clinical practice, reflecting the heterogeneous nature of cardiomyopathies. Selecting the most appropriate imaging modality according to disease subtype, stage, and the specific clinical question improves diagnostic accuracy while minimizing unnecessary investigations. In particular, the detection of myocardial fibrosis, inflammation, and infiltration has major implications for prognostic evaluation and therapeutic decision-making. In routine practice, standardized imaging protocols, integrated reporting, and the increasing incorporation of digital technologies support individualized patient management and longitudinal follow-up, reinforcing the central role of phenotype-driven multimodality imaging strategies in cardiomyopathy care.

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CHAPTER 2

MiRNAs AND MYOCARDIAL ISCHEMIA REPERFUSION INJURY

KORAY AK [1]

Pathophysiology of Myocardial Ischemia/Reperfusion Injury

Ischemia-reperfusion (IR) injury is described as the cellular damage secondary to the period of ischemia and reperfusion. Production of inflammatory cytokines and reactive oxygen species (ROS) cause microvascular abnormalities in the already ischemic tissues in reperfusion [Anaya-Prado et al., 2002]. Myocardial IR injury has been regarded as one of the most devastating consequences of coronary artery disease and it continues to be one of the leading issues in cardiac surgery and cardiology [Sánchez-Hernández et al, 2020 & Maeda and Ruel, 2015]. Reperfusion of acutely or chronically ischemic myocardium is the inevitable result of percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) [Dhalla et al., 2000]. Therefore, severity of myocardial IR injury has been the main factor dictating the early outcome seen after PCI and CABG [Turer and Hill, 2010].

Myocardial IR injury is a complicated phenomenon that occurs after blood flow restoration. During ischemia, depletion of adenosine triphosphate (ATP) stores, deviation of metabolic pathways from aerobic to anaerobic metabolism, intracellular acidosis, and intracellular overload of Na^+ and Ca^{2+} cause intracellular edema and mitochondrial dysfunction. The most devastating part of the injury happens during reperfusion. The abrupt infflux of oxygen triggers excessive generation of ROS, which disturbs the body's own antioxidant defenses and ends up with lipid peroxidation, protein degradation, and DNA fragmentations/damage. Concomitantly, normalization of intracellular pH in an expeditious fashion further promotes Ca^{2+} influx and hypercontracture. Mitochondrial damage is the cornerstone in the pathogenesis of IR injury. Indeed, mitochondrial permeability transition pore (mPTP) opening during early reperfusion is a pivotal event, leading to loss of the membrane potential, loss of ATP stores, and initiation of apoptotic pathways leading to cell daeth [Hausenloy and Yellon, 2003 & Turer and Hill, 2010].

Upon reperfusion, leukocytes target extracellular Ca^+ and ATP released by necrotic cell bodies and this starts the activation of many Toll-like receptor (TLR) pathways to launch an inflammatory reaction. A rapidly induced reaction caused by T helper-1 lymphocyte (Th1) response removes the necrotic debris. However, this sort of immune response expands MI-

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associated damage [Yellon & Hausenloy, 2007]. As the stage progresses, the reaction induced by Th1 cells lessens and Th 2 lymphocytes take an active role to start tissue remodeling and scarring [Ong et al., 2018].

Myocardial IR injury as an unsolved issue in cardiology and cardiac surgery

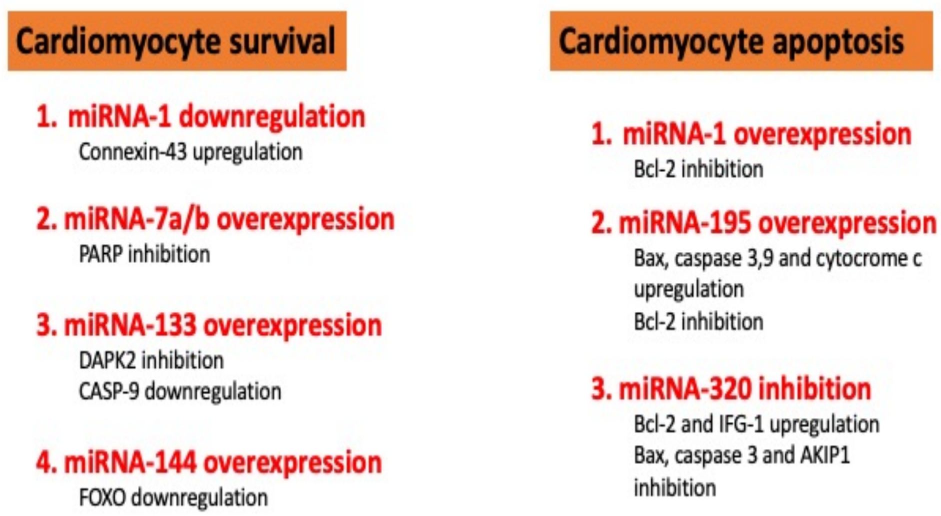
Despite on on-going research over the last 50 years, myocardial IR injury has remained as unresolved and partially understood issue in cardiovascular medicine [Buja and Weerasinghe, 2010]. Although the basic underlying mechanisms of myocardial IR injury have been extensively explained, significant elements of ischemic damage and the consequences of reperfusion remain incompletely understood. In this regard, incorporating genetic research and genetically informed therapies may help address existing gaps in our understanding [Wang et al., 2021].

There are several reasons dictating the necessity of genetic research in myocardial IR injury. First, current studies underestimate the role of interpersonal variability in myocardial IR injury. Taking patients undergoing CABG, despite similar aortic cross clamp durations, systemic temperatures and reperfusion strategies, patients show significant variabilities in the extent of perioperative myocardial infarction, myocyte stunning, incidence of rhythm problems, and low cardiac output postoperatively. These differences may be better explained by taking the underlying genetic contributions into account. Being stuck on conventional variables such as the type of cardioplegic solution, the use of several additive substances in cardioplegia, and altering the level of cooling during cardiopulmonary bypass could mask the real reasons under myocardial IR injury in cardiac surgical patients. [Xiang et al., 2024]. Second, cardioplegic solutions with different electrolyte and pharmacological compositions that are effective in experimental models have failed to translate into consistent clinical benefit. Genetic heterogeneity may underlie these discrepancies. [Alsadder and Hamadah, 2025]. Third, IR promote rapid alterations in gene expression through DNA methylation, histone modification, and microRNA regulation. Understanding these regulatory networks may uncover reversible molecular switches that dictate cell survival versus death, offering novel therapeutic targets beyond conventional pharmacology [Tang and Zhuang, 2019 & Boovarahan, 2022]. Fourth, from the ultrastructural point of view, mitochondrial dysfunction has been shown to be the most important part of myocardial IR injury through the mitochondrial permeability transition pore (mPTP) opening, production of ROS, and depleted ATP stores. Genetic regulation of mitochondrial function may critically determine the threshold for irreversible injury during reperfusion [Ge et al., 2024]. Therefore, genetic studies such as single-cell ribonucleic acid (RNA) sequencing can identify unidentified mechanisms involved in IR injury. Moreover, these new findings may pave the way for new innovative approaches in the treatment of myocardial IR injury [Guan et al, 2020].

MiRNAs: novel markers of myocardial ischemia reperfusion injury

Micro-RNAs (miRNAs) are small non-coding RNAs, and they are transcribed from DNA sequences into primary miRNAs (pri-miRNAs). miRNAs interact with the 3′ untranslated region (UTR), the 5′ UTR, coding sequence, and gene promoters. It was reported that interaction of miRNAs with the 3′ untranslated region (UTR) of target mRNAs suppresses genetic expression [Ha and Kim ,2014]. They were also claimed to be important in the regulation of genetic expression [Majoros and Ohler, 2007]. Recently, it was suggested that miRNAs are transferred among several intracellular organelles and different compartments to regulate the rate of translation, and transcription [Makarova et al, 2018]. Six miRNAs, namely miRNA-1, miRNA-7a/b, miRNA-133, miRNA-144, miRNA-195 and miRNA-320, have been shown to have a significant role in the pathogenesis of myocardial IR injury and apoptosis. Figure 1 demonstrates the summary of miRNA expressions and their relationship with cardiomyocyte survival/apoptosis.

Figure 1: *The relationship between downregulation/overexpression of different miRNAs and cardiomyocyte survival/apoptosis (PARP (Poly (ADPribose) polymerase); DAPK2 (Death-associated protein kinase 2); CASP9 (Caspase 9); FOXO (Forkhead box O); BCl2 (B-cell lymphoma 2); Bax (BCL2 associated X); IGF-1 (insulin-like growth factor 1); AKIP1 (A kinase interacting protein 1))*



Reference: [Song et al., 2026].

miRNA-1

Recently, several investigators have focused on the promising therapeutic role of miRNAs in coronary artery disease. miRNA-1 has been one of the most important miRNAs involved in the pathogenesis of IR injury of cardiomyocytes. Inhibition of miR-1 using a locked nucleic acid modified oligonucleotide against miRNA-1 (LNA-antimiR-1) was shown to exert a protective effect on the myocardium upon IR injury [Pan et al., 2012]. The level of miRNA-1 was found to suppress the expression of B-cell lymphoma 2 (Bcl2) protein, fostering survival by inhibiting apoptosis of rat cardiac myocytes in an experimental IR setting [Tang et al., 2009]. Connexin 43 (Cx43) is a protein essential to the formation of gap junctions of cardiomyocytes. In an in-vitro experimental model, down-regulation of miRNA-1 was shown to avert the redistribution of Cx43, which will protect the myocardium from IR injury.

Ischemic postconditioning has been proposed a method to tackle myocardial IR injury. It was shown that by inhibiting miR-1 expression, it preserves Cx43 levels and localization, thereby maintaining proper gap junction formation in cardiomyocytes. [Bian et al, 2017]. Another detrimental impact of miRNA-1 overexpression was shown to be exacerbated myocardial IR injury thorough inhibition of protein kinase C epsilon and heat shock protein 60 and 90 [Pan et al., 2012 & Zhu et al., 2016]. Downregulation of miRNA-1 was also shown to control the symptoms better in patients with systolic heart failure [Sygitowicz et al., 2015]. ın another study, it was stated that even

miRNA-7a/b

MiR-7a/b was shown to be involved in myocardial IR injury and is upregulated during ischemia/reperfusion. It was shown that miR-7a/b could be regarded as a valuable marker of IR injury and it protects cardiomyocytes against IR-induced apoptosis by negatively regulating poly (ADP-ribose) polymerase (PARP) expression [Li et al., 2014]. Furthermore, miRNA-7a/b mimics reduce poly (ADP-ribose) polymerase (PARP) expression, a principal mediator involved in the initiation of apoptotic pathways (D'Amours et al., 2001).

miRNA-126a-5p

In an experimental model, it was shown that transfection of mesenchymal stem cells with miR-126 can support angiogenesis and cardiac contraction in the infarcted area of the heart [Chen and Zhou, 2011]. Evidence indicates that heat shock protein B8 (Hspb8), which exerts protective effects in myocardial tissue, is targeted by miRNA-126a-5p [Hu et al., 2017]. miRNA-126a-5p exacerbated ischemia–reperfusion (I/R) injury by suppressing Hspb8 expression, suggesting a potential therapeutic target for I/R injury. [Jiang et al., 2017]. On the other hand, it was stated that among diabetes patients, miRNA-126 expression was a strong independent predictor of long-term all-cause mortality [Pordzik et al., 2021].

miRNA-133

Post IR transfection of cardiomyocytes with miR-133 suppressed apoptotic pathways through direct inhibition of Death-Associated Protein Kinase 2 (DAPK2) [Li et al., 2015]. Caspase-9 (CASP9) was known to be another target of miR-133. CASP9 was upregulated after myocardial IR injury, attenuated by ischemic postconditioning, and suppressed by miR-133 mimic treatment, highlighting its potential therapeutic relevance in IR injury [He et al., 2011]. miRNA-133 conferred protection against oxidative stress by negatively regulating caspase-3 and caspase-9. From a therapeutic perspective, carvedilol protected cardiomyocytes by upregulating miRNA-133 expression and inhibiting caspase-9–mediated apoptotic pathways. [Xu et al., 2014].

miRNA-144

miRNA-144 targets several transcription factors like Forkhead box O1 (FOXO1)—transcription factor which mediates apoptosis of cardiac myocytes via inducing the expression of inducible nitric oxide synthase. The authors suggested that it These miR-144 may be exploited as a novel molecular marker or therapeutic target for myocardial IR injury [E et al., 2019]. It was shown that bone marrow mesenchymal stem cell derived exosomes containing miRNA-144 protects cardiomyocytes against apoptosis after hypoxia [Wen et al., 2020].

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miRNA-195

It was shown that miR-195 expression level is increased in myocardial IRI. In a study, it was stated that myocardial I/R injury upregulates the expression of miR-195 which promote cardiomyocyte apoptosis by targeting Bcl-2 and inducing mitochondrial apoptotic pathway. [Gao et al., 2016]. Another study found increased levels of miR-195 in failing cardiomyocytes. Moreover, the increased expression of miRNA-195 suppressed mitochondrial deacetylase sirtuin 3 (SIRT3) and enzymatic inhibition of pyruvate dehydrogenase (PDH) and ATP synthase that have pivotal roles in myocardial energy metabolism [Zhang et al., 2016]. In dilated cardiomyopathy, suppressing miR-195-5p reduced EndMT and myocardial fibrosis in DCM by interfering with transforming growth factor beta-1 (TGF-β1) signaling [Ding et al., 2021].

miRNA-320

While overexpression of miRNA-320 facilitated cardiomyocyte death and apoptosis, knockdown was found to be cytoprotective in an experimental model. Heat-shock protein 20 (Hsp20), a known cardioprotective protein, was found to be an important candidate target for miRNA-320 [Ren et al., 2009]. Inhibition of miR-320 increased insulin like growth factor-1 (IGF-1) mRNA and protein expression, reduced early cardiomyocyte apoptosis during IR injury, and suppressed the ASK1–JNK/p38 signaling pathway, identifying a potential therapeutic target for IR injury [Tian et al., 2018]. Furthermore, inhibition of miR-320 suppresses proapoptotic markers (Bax, caspase-3), upregulates Bcl-2 and IGF-1, and exerts pro-survival effects in cardiomyocytes [Song et al., 2026].

Conclusion

Myocardial IR injury has remained the leading issue in patients with ischemic heart disease. Our current understanding and knowledge about the pathophysiology of this challenging issue have become insufficient to tackle the issue effectively. In cardiac surgery, recent advancements in cardioplegic solutions have subtly changed the mortality and morbidity of myocardial IR injury compared to those in 40 years ago. With this regard, circulating miRNA in patients exposed to the IR injury would provide more insights into both the pathophysiology and treatment of such a challanging condition.

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CHAPTER 3

KALP YETMEZLİĞİNDE SGLT2 İNHİBİTÖRLERİNİN KULLANIMINDA GÜNCEL YAKLAŞIMLAR

MEHMET ÖZYAŞAR[1]

Giriş

Kalp yetmezliği (KY), küresel ve ulusal düzeyde önemli bir sağlık sorunu oluşturmaya devam etmektedir. Dünya genelinde yaklaşık 64 milyon kişiyi etkileyen bu sendrom, yüksek mortalite, morbidite ve sağlık harcamalarıyla ilişkilidir (Groenewegen & ark., 2020: 1342-1356). Türkiye'de de KY prevalansı yaşla birlikte artmakta olup, hastane yatışlarının ve kardiyovasküler mortalitenin başlıca nedenlerinden biridir (Türkiye Halk Sağlığı Kurumu, 2015).

Son on yılda KY tedavisinde önemli ilerlemeler kaydedilmiştir. 2021 Avrupa Kardiyoloji Derneği (ESC) KY kılavuzları ve 2022 AHA/ACC/HFSA kılavuzları ile ortaya konan "dört temel ilaç" (quadruple therapy) yaklaşımının – ARNI/ACEI/ARB, beta-blokerler, mineralokortikoid reseptör antagonistleri (MRA) ve sodyum-glukoz ko-transporter 2 inhibitörleri (SGLT2i) – mortaliteyi ve hastane yatışlarını anlamlı derecede azalttığı görülmektedir

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(McDonagh & ark., 2023: 3627-3639), (Heidenreich & ark., 2022: e895-e1032).

SGLT2i (dapagliflozin ve empagliflozin başta olmak üzere), başlangıçta tip 2 diyabet tedavisinde kullanılan bir ilaç sınıfı olmasına rağmen, kardiyovasküler sonlanım noktalarını gösteren çalışmalarda (EMPA-REG OUTCOME, DECLARE-TIMI 58) beklenmedik kardiyo-renal yararlar göstermiştir (Zinman & ark., 2015: 2117-2128), (Wiviott & ark., 2019: 347-357). Bu bulgular, DAPA-HF (dapagliflozin, azalmış ejeksiyon fraksiyonlu kalp yetmezliğinde-HFrEF) (McMurray & ark., 2019: 1995-2008), EMPEROR-Reduced (empagliflozin, HFrEF) (Liuzzo & Patrono, 2020: 3881-3882), EMPEROR-Preserved (empagliflozin, korunmuş ejeksiyon fraksiyonlu kalp yetmezliğinde-HFpEF) (Anker & ark., 2021: 1451-1461) ve DELIVER (dapagliflozin, hafif azalmış ve korunmuş ejeksiyon fraksiyonlu kalp yetmezliğinde-HFmrEF/HFpEF) (Peikert & ark., 2022: e010080) gibi büyük randomize kontrollü çalışmalarla doğrulanmış ve SGLT2i'nin KY tedavisinde diyabet hastalığından bağımsız bir rolü olduğunu kanıtlamıştır.

2023 ESC KY odaklı güncellemesinde SGLT2i (dapagliflozin veya empagliflozin), sol ventrikül ejeksiyon fraksiyonu (LVEF) spektrumunun tamamında – HFrEF (≤%40), HFmrEF (%41-49) ve HFpEF (≥%50) – Sınıf I, Kanıt Düzeyi A öneri haline gelmiştir; bu öneri, KY hastane yatışı veya kardiyovasküler ölüm riskini azaltmak amacıyla yapılmıştır (McDonagh & ark., 2023: 3627-3639). 2025 ESC verileri özellikle hastanede yatış sırasında SGLT2i ile tedaviye erken başlanılmasının, erken dönemde kardiyovasküler ölüm veya KY kötüleşmesi riskini azalttığını göstermiştir (Metra & ark., 2025: 3806–3825).

Bu bölümde, klinisyenlere SGLT2i’nin kalp yetmezliğindeki pratik kullanımı, etki mekanizması, uygun hasta seçimi, tedavi yönetimi, potansiyel yan etkiler, özel popülasyonlar ve izlem stratejileri ile ilgili güncel, kılavuz temelli bilgiler sunulması amaçlanmıştır.

SGLT2 İnhibitörlerinin Etki Mekanizması

SGLT2i'nin KY'ndeki yararlı etkileri, renal proksimal tübüller üzerinden başlar; SGLT2 inhibisyonu, glukoz ve sodyum reabsorpsiyonunu baskılayarak glukozüri ve natriüreze yol açar. Bu etki, osmotik diürezi tetikler ve intravasküler/interstisyel volümde azalmaya neden olur, böylece kalp preload'ı azalır, pulmoner konjesyon ve sistemik ödem geriler (McDonagh & ark., 2023: 3627-3639). Bu volüm azaltıcı ("konjestif dekompresyon") etki, SGLT2i'nin en erken gözlenen yararıdır ve geleneksel loop diüretiklere kıyasla daha az elektrolit kaybı ve hipotansiyon riski ile ilişkilidir; interstisyel sıvıyı intravasküler bölgeye tercihli mobilize eder (McMurray & ark., 2019: 1995-2008).

SGLT2i ayrıca, glomerüler hiperfiltrasyonu baskılayarak uzun vadede renal koruma sağlar (eGFR düşüş hızını yavaşlatır) ve afferent arteriol vazokonstriksiyonu yoluyla intraglomerüler basıncı stabilize eder. Diyabetten bağımsız kardiyoprotektif etkiler ise multifaktöriyeldir ve tam olarak aydınlatılamamıştır (McDonagh & ark., 2023: 3627-3639), (Cherbi & ark., 2025: e039105).

Kardiyoprotektif etkileri açıklayan klinik mekanizmalar şöyle özetlenebilir:

- **Miyokardiyal enerji metabolizmasında iyileşme:** Glukozüriye bağlı hafif hipoglisemi ve keton cisimlerinin artışı, ketonların daha verimli enerji substratı olarak kullanımını teşvik eder; mitokondriyal fonksiyon optimize olur, oksidatif stres azalır (McMurray & ark., 2019: 1995-2008).
- **İnflamasyon ve oksidatif stres baskılanması:** Proinflamatuar sitokinlerde azalır, NF-κB yolakları down-

regüle olur ve antioksidan kapasite artar (Metra & ark., 2025: 3806–3825).

- **Kardiyak iyon homeostazı ve remodeling düzelmesi:** Kardiyak Na+/H+ exchanger (NHE-1) inhibisyonu yoluyla intraselüler sodyum ve kalsiyum dengesi iyileşir; sarkoplazmik retikulum kalsiyum kaçakları azalır, kontraktilite artar ve fibrozis baskılanır (Chung & ark., 2023: 27).
- **Diğer pleiotropik etkiler:** Epikardiyal yağ dokusu azalması, sempatik aktivite baskılanması ve NHE3 ile sinerjik sodyum atılımı olarak sıralanabilir (Theofilis & ark., 2022: 109927).

Bu mekanizmaların kombinasyonu, SGLT2i'nin tüm KY spektrumunda (HFrEF, HFmrEF, HFpEF) mortalite ve hastane yatışını azalttığını ve yararların büyük kısmının erken dönemde (günler-haftalar) başladığını açıklamaktadır. SGLT2i'nin klinik pratikteki başlıca yararları, volüm yönetimine yönelik hızlı semptomatik iyileşme sağlaması ve diyabetten bağımsız ek klinik faydalar sunmasıdır (Metra & ark., 2025: 3806–3825).

Hasta Seçimi ve Endikasyonlar

SGLT2i, KY'nin tüm fenotiplerinde mortalite ve hastane yatış riskini azaltan temel bir tedavi haline gelmiştir. Hasta seçimi kriterleri oldukça geniştir ve diyabet varlığı artık zorunlu değildir; yarar diyabet bağımsızdır (McDonagh & ark., 2023: 3627-3639). Pratik klinik endikasyonlar şöyle özetlenebilir:

- **Temel Endikasyonlar:**

1. Semptomatik KY (NYHA II-IV) tanısı konmuş tüm hastalar, LVEF bağımsız olarak (McDonagh & ark., 2023: 3627-3639).
2. Hastane yatışı sırasında (akut dekompanse KY) erken tedavi başlanması güvenlidir ve önerilir; meta-analizler

SGLT2i'nin erken dönemde (2 ay içinde) KY kötüleşmesi veya kardiyovasküler ölüm riskinde anlamlı azalmaya neden olduğu göstermiştir (Cherbi & ark., 2025: e039105).

3. Tip 2 diyabet + kronik böbrek hastalığı (KBH) varlığında, KY gelişiminin önlenmesi veya tedavisi amacıyla Sınıf I endikasyonla önerilir (Metra & ark., 2025: 3806–3825).

- **SGLT2i başlanması için eGFR sınırları:**

1. Dapagliflozin: eGFR ≥25 mL/dk/1.73 m² (DAPA-HF/DELIVER kriterleri); bazı kılavuzlarda ≥20 mL/dk kabul edilebilir (McMurray & ark., 2019: 1995-2008), (Peikert & ark., 2022: e010080).
2. Empagliflozin: eGFR ≥20 mL/dk/1.73 m² (EMPEROR çalışmaları) (Liuzzo & Patrono, 2020: 3881-3882), (Anker & ark., 2021: 1451-1461).
3. Başlangıçta hafif eGFR düşüşü (%10-15, ilk 2-4 hafta) beklenir ve genellikle geçicidir; renal koruma uzun vadede sağlanır (McMurray & ark., 2019: 1995-2008), (Peikert & ark., 2022: e010080), (Liuzzo & Patrono, 2020: 3881-3882), (Anker & ark., 2021: 1451-1461).

- **Kontrendikasyonlar ve Dikkat Edilecek Durumlar** (McMurray & ark., 2019: 1995-2008)**,** (Peikert & ark., 2022: e010080)**,** (Liuzzo & Patrono, 2020: 3881-3882)**,** (Anker & ark., 2021: 1451-1461)**:**

1. Tip 1 diyabet (diyabetik ketoasidoz riski).
2. Ciddi dehidratasyon veya hipotansiyon (sistolik kan basıncı <90-95 mmHg).
3. Tekrarlayan genital mikotik enfeksiyon öyküsü olanlarda önlem alınarak başlanabilir.

4. eGFR <20 mL/dk/1.73 m² (başlama önerilmez, ancak devam edilebilir).
5. Gebelik/emzirme (veri yetersiz).

SGLT2i Başlama Zamanı ve Doz Ayarlanması

SGLT2i KY'nde temel tedavi olarak erken başlanmalıdır. Tedavinin sağladığı yararların, tanı anından itibaren ve özellikle hastane yatışı sırasında başlatılarak en üst düzeye çıkarılması beklenmektedir. 2023 ESC KY Odaklı Tedavi güncellemesi dapagliflozin veya empagliflozin'i tüm LVEF spektrumunda (HFrEF, HFmrEF, HFpEF) Sınıf IA öneri olarak konumlandırır; başlama için diyabet zorunlu değildir ve KY'nin diğer tedavilerine (ARNI/ACEI/ARB + beta-bloker + MRA + SGLT2i) mümkün olan en erken zamanda eklenmesini önermektedir (McDonagh & ark., 2023: 3627-3639).

- **Başlama zamanı, doz ayarlanması ve izlem:**
    1. **Ambulatuvar (Ayaktan) hastalar:** Tanı konur konmaz başlanması önerilir, gecikme mortalite yararını azaltabilmektedir (McDonagh & ark., 2023: 3627-3639).
    2. **Hastanede yatış (Akut Dekompanse KY):** Klinik stabilizasyonun sağlanmasını takiben (genellikle 24 saat ile 14 gün içinde, tercihen daha erken) tedavinin başlatılması güvenli ve uygun kabul edilmektedir (Cherbi & ark., 2025: e039105).
    3. **Doz artışı:** Dapagliflozin için sabit 10 mg/gün (artış yok); empagliflozin için 10 mg başlangıç, tolere edilirse (KB, volüm ve elektrolitlerin durumu iyi ise) 25 mg'a çıkılabilir (ancak KY'de genellikle 10 mg yeterli) (McMurray & ark., 2019: 1995-2008), (Peikert & ark., 2022: e010080), (Liuzzo & Patrono, 2020: 3881-3882), (Anker & ark., 2021: 1451-1461).

4. **Başlangıç izlemi:** İlk 1-4 hafta eGFR, potasyum, KB ve volüm durumu izlenir; geçici eGFR düşüşü (%10-15) beklenir ve doz kesintisi gerektirmez. Hastanede başlama, taburculuk sonrası uyumu artırır ve erken fayda sağlar. Volüm durumu kötü olanlarda düşük doz diüretikle eş zamanlı başlama önerilir; hipotansiyon riski düşük olsa da KB izlemi şarttır (Cherbi & ark., 2025: e039105).

Potansiyel Yan Etkiler ve Yönetimi

SGLT2i KY'nde genel olarak iyi tolere edilir; büyük randomize çalışmalar (DAPA-HF, EMPEROR-Reduced/Preserved, DELIVER) ve gerçek dünya verileri (geriatrik kohortlar dahil) düşük tedavi kesilme oranları gösterir (%2-3) (McMurray & ark., 2019: 1995-2008), (Peikert & ark., 2022: e010080), (Liuzzo & Patrono, 2020: 3881-3882), (Anker & ark., 2021: 1451-1461). Yan etkiler genellikle hafif-orta şiddette olup, çoğu önlenebilir veya yönetilebilir niteliktedir. En sık görülenler genital mikotik enfeksiyonlar, dehidratasyon/hipotansiyon ve geçici renal fonksiyon değişiklikleridir; ciddi advers olaylar (diabetik ketoasidoz, fournier gangreni, amputasyon) nadir olup, KY popülasyonunda belirgin artış göstermez (McDonagh & ark., 2023: 3627-3639).

- **En Sık Yan Etkiler ve Yönetim Stratejileri:**

1. **Genital mikotik enfeksiyon (vulvovajinit, balanit):** En yaygın yan etki olarak görülebilir (%5-10, kadınlarda %10-15, önceki öykü varsa risk yüksektir). Sünnetsiz erkeklerde daha sık izlenir. Genellikle Candida spp. kaynaklıdır, hafif-orta şiddette görülebilir (Metra & ark., 2025: 3806–3825).

   Yönetim: Topikal antifungal (klotrimazol, mikonazol) veya oral flukonazol (150 mg tek doz) ve hijyen önlemleri (pamuklu iç çamaşırı, idrar sonrası temizlik) önerilir. Tekrarlayan enfeksiyonlarda proflaksi düşünülebilir. Tedavi kesilmesi nadiren gerekir (%<1) (Metra & ark., 2025: 3806–3825).

2. **Dehidratasyon ve hipotansiyon:** Osmotik diürez nedeniyle volüm kaybı; semptomatik hipotansiyon %2-4, özellikle başlangıçta veya diüretik doz yüksekse görülebilir (McDonagh & ark., 2023: 3627-3639).

   Yönetim: Hastaya yeterli sıvı alımının teşvik edilmesi (susama hissiyle uyumlu), varsa diüretik dozunun azaltılması yararlı olabilir (loop diüretik %20-30 azaltılabilir). Sistolik KB <90-95 mmHg ise geçici olarak doz kesilmesi veya azaltılması yararlı olabilir; genellikle geçicidir (McDonagh & ark., 2023: 3627-3639).

3. **Renal fonksiyon değişiklikleri:** Başlangıçta eGFR'de geçici düşüş görülebilir (%10-15, ilk 2-4 hafta); uzun vadede renal koruma sağlar (eGFR düşüş hızı yavaşlar) (Metra & ark., 2025: 3806–3825).

   Yönetim: İzlem (başlangıç + 1-2 hafta + 3 ay); akut böbrek hasarı riski düşüktür (%<2). eGFR <20 mL/dk'ya düşerse doz kesilebilir, ama hafif düşüşlerde devam edilmesi önerilir (yarar > risk) (McDonagh & ark., 2023: 3627-3639).

4. **Diğer nadir/önemli yan etkiler:**

   a. Diyabetik ketoasidoz (DKA): Çok nadir olup (%<0.1), cerrahi ve akut hastalıkta risk artmıştır. SGLT2i'lerinin kullanımı Tip 1 DM'de kontrendikedir. Şüpheli durumlarda keton testi; önleme için hasta eğitimi (hastalıkta insülin devamı, sıvı alımı) yarar sağlar (Garg & ark., 2025: 437-442).

   b. Fournier gangreni/amputasyon: Çok nadir olup, diyabetik ayak öyküsü varsa dikkat edilmesi gerekir;

KY'de belirgin artış yoktur (Metra & ark., 2025: 3806–3825).

c. Kemik Fraktür etkileri: Bazı çalışmalarda hafif artış gösterilmiştir, ancak KY meta-analizlerinde anlamlı bulunmamıştır (Metra & ark., 2025: 3806–3825).

Pratikte yan etkiler nadiren tedaviyi sınırlayıcıdır; hasta eğitimi (hijyen, sıvı alımı, semptom takibi) ve erken izlem kesilme oranını minimize eder. Yaşlı/geriatrik hastalarda bile tolere edilebilirlik yüksektir (enfeksiyon artışı hafif artsa da düşük kesilme oranı) (Hacil & ark., 2025: e012794).

Özel Popülasyonlar

SGLT2i kalp yetmezliğinde (KY) geniş bir hasta yelpazesinde yarar sağlar; yaşlı, kırılgan, kronik böbrek hastalığı komorbiditesi olan veya hipotansif hastalar gibi özel popülasyonlarda da mortalite ve hastane yatış riskini azaltır (McDonagh & ark., 2023: 3627-3639). Post-hoc analizler (DAPA-HF, EMPEROR-Reduced/Preserved, DELIVER) ve gerçek dünya verileri (AGING-HF kohortu, kırılganlık derlemeleri 2025-2026) bu gruplarda tutarlı yararlı etkileri destekler; advers olaylar (volüm kaybı, enfeksiyon) artabilir ama genel tolere edilebilirlik yüksektir ve tedavi kesilme oranı düşüktür (%2-3) (McMurray & ark., 2019: 1995-2008), (Peikert & ark., 2022: e010080), (Liuzzo & Patrono, 2020: 3881-3882), (Anker & ark., 2021: 1451-1461).

- **Yaşlı ve Kırılgan Hastalar** (≥75-80 yaş, Klinik Kırılganlık Skoru-Clinical Frailty Scale ≥5):

    a. Yaşlı populasyonda KY prevalansı yüksek olup, kırılgan hasta oranı %30-50'ye ulaşır; bu grupta SGLT2i başlama tereddüdü yaygındır (dehidratasyon, hipotansiyon, düşme riski endişesi) (Hacil & ark., 2025: e012794).

b. Yarar: DAPA-HF/DELIVER post-hoc analizlerinde kırılgan gruplarda kardiyovasküler ölüm/KY kötüleşmesi riskinde azalma gösterilmiş olup (HR 0.71-0.77, en kırılgan hastalarda mutlak yarar daha büyüktür); AGING-HF gerçek dünya kohortu (ortalama yaş 90, yüksek komorbidite) SGLT2i ile tüm neden mortalite (HR 0.67) ve KY yatışı (HR 0.64) azalması gösterilmiştir (McMurray & ark., 2019: 1995-2008), (Peikert & ark., 2022: e010080), (Hacil & ark., 2025: e012794).

c. Güvenlik: Enfeksiyon ve volüm kaybı riski artmıştır, ancak plaseboya göre anlamlı fark yoktur; kesilme düşüktür. Kırılgan hastalarda yaşam kalitesi iyileşmesi daha belirgindir (Hacil & ark., 2025: e012794).

d. Pratik öneri: Başlangıç dozunun düşük tutulması (empagliflozin 10 mg), diüretik dozunun %20-30 azaltılması, yakın izlem (KB, volüm, elektrolitler, düşme riski); hasta eğitimi kritiktir (Hacil & ark., 2025: e012794).

- **Kronik Böbrek Hastalığı (KBH) Komorbiditesi (eGFR <60 mL/dk/1.73 m²):**

a. SGLT2i renal koruma sağlar (eGFR düşüş hızı yavaşlar, albuminüri azalır); DAPA-CKD/EMPA-KIDNEY çalışmaları KBH'da KY'ni önleme/tedavi yararını doğrular (Metra & ark., 2025: 3806–3825).

b. KY spektrumunda mortalite/KY nedenli yatış azalması KBH'lı hastalarda da tutarlıdır (HR ~0.6-0.7); düşük eGFR'de bile uzun vadeli renal fayda ağır basmaktadır (Metra & ark., 2025: 3806–3825).

c. Güvenlik: Başlangıçta geçici eGFR düşüşü daha belirgin olabilir ama kalıcı hasar yoktur; eGFR ≥20-25 mL/dk başlama önerilir, <20 mL/dk'da başlanmamalıdır (ancak devam edilebilir) (Metra & ark., 2025: 3806–3825).

d. Pratik öneri: Başlangıç + 1-2 hafta eGFR izlem; RAAS inhibitörleriyle kombinasyonda hiperkalemi riskine dikkat edilmelidir (McDonagh & ark., 2023: 3627-3639).

- **Hipotansif veya Düşük Kan Basınçlı (KB) Hastalar: (sistolik KB <95-100 mmHg):**

a. SGLT2i hafif antihipertansif etki gösterir (sistolik KB azalması 1-3 mmHg) ama düşük KB'lı hastalarda bile iyi tolere edilir; EMPEROR-Reduced/DAPA-HF analizleri düşük KB grubunda benzer yarar gösterilmiş olup, hipotansiyon riski artışı minimal bulunmuştur (McMurray & ark., 2019: 1995-2008), (Liuzzo & Patrono, 2020: 3881-3882).

b. Düşük KB, KY'nin kötü prognostik belirteci olsa da SGLT2i mutlak faydayı artırır (McMurray & ark., 2019: 1995-2008), (Metra & ark., 2025: 3806–3825).

c. Güvenlik: Semptomatik hipotansiyon nadirdir (%2-4); volüm durumu kötü veya diüretik dozu yüksekse risk artar (Metra & ark., 2025: 3806–3825).

d. Pratik öneri: Başlangıçta diüretik/RAAS dozunu optimize ettikten sonra, KB >90-95 mmHg ise başlamak; ilk haftalarda yakın izlem önerilmiştir (McDonagh & ark., 2023: 3627-3639).

Bu gruplarda SGLT2i'nin yarar/risk dengesi yarar yönünde olup, erken başlama ve dikkatli izlemle (KB, eGFR, volüm, elektrolitler, semptom) çoğu hastada güvenli kullanım sağlanır (McDonagh & ark., 2023: 3627-3639), (Metra & ark., 2025: 3806–3825). Kırılgan/çok yaşlı hastalarda bireysel karar verme (yaşam beklentisi, hasta tercihi) önemlidir (Hacil & ark., 2025: e012794).

Takip ve İzlem

SGLT2i, KY'nde başlandıktan sonra takip, yan etki yönetimi ve devamlılık için kritik olup, erken dönemde (ilk 1-4 hafta) yoğun, uzun vadede rutin olmalıdır. 2023 ESC KY Odaklı Güncellemesinde; eGFR, potasyum, KB ve volüm durumunun izlenmesini vurgulanmaktadır; geçici değişiklikler (eGFR düşüşü %10-15, hafif KB azalması) tedaviyi kesmeyi gerektirmez, çünkü uzun vadeli renal ve kardiyovasküler koruma daha önemlidir (McDonagh & ark., 2023: 3627-3639).

a. **İlk 1-2 hafta (kritik dönem):** eGFR, serum potasyum, KB, volüm durumu (kilo, ödem, dispne), semptomlar (genital enfeksiyon, dehidratasyon belirtileri) değerlendirilmelidir. Geçici eGFR düşüşü beklenir; hiperkalemi riski RAAS inhibitörü/MRA kombinasyonunda daha fazladır (Metra & ark., 2025: 3806–3825).

b. **1-3 ay:** Rutin laboratuvar (eGFR, potasyum, kreatinin), KB, semptom/KY sınıfı (NYHA), kilo takibi önerilir. İyileşmenin değerlendirilmesi için KCCQ skoru veya NT-proBNP (opsiyonel) yararlı olabilir (Metra & ark., 2025: 3806–3825).

c. **3-6 ay ve sonrası:** Her 3-6 ayda bir rutin kontroller; yıllık renal fonksiyon izlemi yapılmalıdır. Uzun vadede eGFR düşüş hızının yavaşlaması beklenmektedir (renal koruma kanıtı) (Metra & ark., 2025: 3806–3825).

d. **Ek izlem:** Hastaya semptom eğitimi verilir (susama, idrar artışı, genital kaşıntı, halsizlik); tele-tıp veya ev KB/kilo takibi önerilebilir (özellikle yaşlı/kırılgan hastalarda) (Metra & ark., 2025: 3806–3825), (Hacil & ark., 2025: e012794).

Sonuç ve Öneriler:

SGLT2i, KY tedavisinde devrim niteliğinde bir ilerleme sağlamıştır. Diyabet varlığı zorunlu olmaksızın, LVEF spektrumunun tamamında (HFrEF, HFmrEF, HFpEF) mortaliteyi, KY nedenli hastane yatışlarını ve kardiyovasküler olayları anlamlı derecede azaltır; yararlar erken dönemde (günler-haftalar) başlar ve uzun vadede renal koruma ile bağlantılıdır. 2023 ESC KY Odaklı Güncellemesinde Sınıf IA öneri haline gelen bu ajanlar, ARNI/ACE/ARB + Beta Blokerler + MRA'lar ile birlikte, KY tedavisinin vazgeçilmez bir parçası haline gelmiştir (McDonagh & ark., 2023: 3627-3639).

- **Erken tedavi başlanması:** Tanı anında veya hastane yatışında (stabilizasyon sonrası) mümkün olan en erken zamanda eklenmelidir; gecikme mortalite yararını azaltır. Hastanede başlama güvenli ve erken fayda sağlar (Metra & ark., 2025: 3806–3825).
- **Hasta seçimi:** Diyabet olsun/olmasın, yaşlı/kırılgan, KBH olan veya hipotansif hastalarda bile yarar ağır basar; eGFR ≥20-25 mL/dk/1.73 m² başlama için yeterlidir (Metra & ark., 2025: 3806–3825).
- **Doz seçimi:** Dapagliflozin 10 mg/gün sabit; empagliflozin 10 mg başlanır, tolere edilirse 25 mg'a kadar çıkılabilir (Metra & ark., 2025: 3806–3825).
- **Yan etki yönetimi:** En sık genital enfeksiyon (hijyen + antifungal), dehidratasyon (sıvı alımını artır, diüretik azalt) ve geçici eGFR düşüşü (devam et); kesilme nadir (%2-3) (Metra & ark., 2025: 3806–3825).

- **Takip ve izlem:** İlk 1-2 hafta eGFR/potasyum/KB/volüm izlenmelidir; sonra 3-6 ay rutin. Hasta eğitimi (susama, enfeksiyon belirtileri) uyumu artırır (McDonagh & ark., 2023: 3627-3639).
- **KY tedavisinin optimizasyonu:** SGLT2i'ni ARNI/ACEI/ARB + Beta-bloker + MRA ile kombine etmek ve erken entegrasyon mortaliteyi önemli oranda azaltması beklenmektedir (McDonagh & ark., 2023: 3627-3639).

Kaynakça

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CHAPTER 4
CURRENT STATUS OF MYOCARDIAL PROTECTION IN CARDIAC SURGERY

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Cardioplegic solutions

The chief aim behind cardioplegic myocardial arrest is to eliminate the spontaneous generation and the propagation of electrical impulses that elicit myocardial contraction. When electrical excitation of the contractile apparatus is blocked, no propagation of electrical signals is possible anymore. Cardioplegic solutions can be classified by solvent (crystalloid, blood or mixture of both), ionic composition (extracellular versus intracellular) and mechanism of arrest (hyperpolarizing versus depolarizing), temperature (cold versus warm), route of delivery (antegrade versus retrograde) and dosing strategy (single dose versus intermittent versus continuous). Cardioplegic solutions with low Na^+ concentrations (e.g. Bretschneider-HTK solution) eliminate the fast sodium influx and arrest the action potential in a hyperpolarized state. Solutions with high potassium concentrations inhibit the potassium efflux during repolarization and arrest the action potential in a depolarized state (Ali et al., 2018). Some solutions act by interfering with both Na^+ influx and K^+ efflux. The Del Nido solution for instance inhibits both potassium efflux by high concentration of K+, thereby achieving rapid depolarized arrest, and sodium influx with Lidocaine acting as sodium channel blocker polarizing the membrane to some degree. Moreover, modification of Ca^{2+} and Mg^{2+} concentrations directly interferes with excitation-contraction coupling by blocking the mechanisms that induce actin-myosin interaction leading to contraction (Calafiore et al, 1995).

Cardioplegic solutions may be crystalloid or blood-based formulations. Crystalloid cardioplegia includes extracellular-type solutions, which approximate serum electrolyte composition, and intracellular-type solutions, which mimic the intracellular milieu. On the other hand, blood cardioplegia utilizes the biochemical advantages of oxygenated blood. Intermittent blood cardioplegia combines crystalloid solution with blood in different ratios (usually 1:4 ratio), whereas microplegia uses undiluted oxygenated blood supplemented with additive ions and substances, precluding hemodilution and enhancing physiologic delivery. Cardioplegic arrest can be induced by depolarization and hyperpolarization of the cardiomyocyte membrane. Depolarizing cardioplegia induces arrest by boosting extracellular potassium concentration. On the other hand, hyperpolarizing cardioplegia induces arrest by making the resting membrane potential more negative, through mechanisms such as sodium

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channel blockade (e.g., lidocaine), activation of potassium ATP channels (e.g., adenosine), or reduced extracellular sodium, as in Bretschneider's solution (Oliveira et al, 2005 & Dobson, 2010).

Clinical studies

Despite the immense changes in cardioplegic protocols, the outcomes have remained close to each other. Two randomized controlled studies (RCTs) were performed and the authors compared blood versus crystalloid cardioplegia in patients undergoing coronary artery bypass grafting (CABG) (Øvrum et al, 2004) or aortic valve replacement (Øvrum et al, 2010). They came up with the findings that perioperative outcome like the need and dose of inotropes, ventilation time and spontaneous sinus rhythm after cross-clamping did not show any differences between the groups and even in high-risk patients. In a meta-analysis by Guru et al. (2006) and Sá et al. (2012), similar rates of myocardial infarctions and death were reported. between the same 2 types of cardioplegic strategies.

The ideal temperature of cardioplegic solutions remains as a dilemma. In a meta-analysis by Fan et al. (2010), although lower cardiac enzyme levels and higher postoperative cardiac indices were detected after warm blood cardioplegia, this was reflected as significant differences in mortality and morbidity. Moreover, The Warm Heart Trial randomized CABG patients to taking either warm or cold blood cardioplegia and no significant effect of cardioplegia temperature on survival and perioperative morbidity was observed (Fremes et al, 2000).

Myocardial edema is the histopathological criteria regarding the severity of myocardial damage after cardioplegic myocardial arrest (Foglia et al., 1979). In a study by Mehlhorn et al. (1995), no differences of blood cardioplegia in preventing myocardial oedema compared to crystalloid cardioplegia were shown in an experimental model of myocardial injury. On the other hand, Ak et al. (2024) compared the histopathological effects of intermittent blood and histidine-tryptophan-ketoglutarate (HTK) solution of Bretschneider on myocardium and found that HTK was associated with a higher rate of myocardial edema compared to blood cardioplegia.

There are also conflicts about the delivery route and need for repetition of the cardioplegic solutions. In a small RCT by Dagenais et al. (1999), no differences with either antegrade or retrograde cold blood cardioplegia were detected in survival, stroke, infarction rates and cardiac enzyme release were detected in patients undergoing valve replacement Franke et al. found (2001) found that higher postoperative troponin levels after antegrade cardioplegia delivery in CABG patients. Nonetheless, the exact meaning of such release remains a matter of debate in cardiac surgery (Franke et al., 2001 & Heuts et al., 2023). The comparison of single-shot versus multi-dose cardioplegia administration was evaluated in a meta-analysis by Gambardella et al. (2020), which similarly demonstrated no difference in mortality or myocardial infarction rates.

Current issues with myocardial protection

Myocardial protection strategies currently in use have changed minimally over the past decades. Even the newest approaches, such as del Nido and Calafiore cardioplegia, were introduced in the 1990s, nearly three decades ago, suggesting a decline in sustained clinical and academic focus on this area. As myocardial protection solutions and strategies have remained largely unchanged over these decades, the improvements in clinical outcomes observed during this period cannot be attributed to advances in myocardial protection (Mullan et al., 2020). It was also stressed that though older and more comorbid patients are referred for cardiac surgery, myocardial protection has not changed at all (Mukharyamov et al, 2023).

A cardioprotective strategy with cardioplegia extends myocardial ischemia tolerance in cardiac surgery. However, one should not underestimate the fact that myocardial ischemia occurring during aortic cross clamping is not a harmless situation. It is very well known that prolonged aortic cross clamp times was associated with a high 30-day mortality, which was even most obvious in patients with normal left ventricular function (Banner et al., 2008). Age was shown to be an independent risk factor for early mortality in patients with prolonged aortic cross clap times (Pittams et al., 2022). The necessity for CPB has been shown to be another independent predictor of mortality in high-risk patients (Puskas et al., 2009). In PARTNER 3 trial, patients with severe aortic stenosis were (randomized to either surgical aortic valve replacement (SAVR) or transfemoral aortic valve implantation (TAVI). It was concluded that reduced tricuspid annulus plane systolic excursion was detected early after intervention in the SAVR group, which was not seen in the TAVI group (Pibarot et al., 2020). Consequently, the impact of age and right ventricular dysfunction on myocardial ischemia tolerance during cardioplegic arrest remains insufficiently explored.

There are also several extracardiac issues with cardioplegia. In cardiac surgery with CPB, low systemic vascular resistance (SVR) is a well-known complication, which was shown to be associated with higher morbidity rates and prolonged recovery with longer intensive care unit (ICU) and in-hospital stay (Calafiore et al., 1995). The increasing total volume of cardioplegic solution and specific cardioplegic solutions (HTK and del Nido) were shown to be associated with more severe vasoplegia and require higher vasopressor/inotropic support in the perioperative period than others (Carrel et al., 2000 & Busch et al., 2001). Acute renal dysfunction is another issue that might be associated with cardioplegia. Sanetra et al. (2020) showed less acute renal failure in patients undergoing cardiac surgery with del Nido cardioplegia compared to cold blood cardioplegia. However, this finding was not supported with other studies. Instead of being an independent predictor of acute renal dysfunction, cardioplegic solutions lead to different levels of hemodilution and vasoplegia, which may potentially contribute to the development of acute renal dysfunction (Karkouti et al., 2005). Lastly, Cardioplegia has been claimed to be associated with cerebral dysfunction due to the perioperative alterations in the electrolyte status (e.g. systemic hyponatremia or the induction of hemodilution) (Baraka et al., 2006 & Irqsusi et al., 2022). Some studies demonstrated lower incidences of cerebral inflammation with HTK-N than HTK with cyclosporine-A (Hoyer et al., 2019). However, no generalized consensus has been established on this topic.

Genetic perspectives in myocardial protection

Genetic and molecular studies investigating cardioplegia have primarily concentrated on myocardial gene expression changes associated with ischemia–reperfusion injury and cardioprotective signaling pathways, rather than direct genotype–solution interactions. In-vivo and in-vitro models show that cardioplegic arrest alters the expression of genes involved in apoptosis, oxidative stress, inflammation, and calcium handling. Microarray and transcriptomic analyses have shown that cardioplegia attenuates upregulations of cell cycle, proliferation, apoptosis resistance and response to hypoxia genes (e.g., *HIF1A*, *FOS)* (Ramlawi et al., 2006 & Mamedov et al., 2025).

Different cardioplegic solutions appear to induce characteristic myocardial gene expression profiles. Blood-based cardioplegia has been associated with enhanced expression of vascular endothelial growth factor (VEGF) gene expressions of VEGF protein and the VEGF tyrosine kinase receptor flk-1, suggesting important implications regarding postoperative coronary blood flow regulation, increases in myocardial edema, and vascular remodeling after cardioplegia-reperfusion (Tofukuji et al., 1998). In contrast, crystalloid solutions have been linked to a greater induction of oxidative stress–related genes like Nrf2, although the clinical relevance of these findings remains uncertain (Diao et al., 2023). Elcik et al. (2021) compared the roles of blood cardioplegia (BC) and custodiol cardioplegia (CC) on the expression of total ribonucleic acid and concluded that CC harms the myocardium more than BC at the level of mRNA expression of related markers ().

Recently, expressions of microRNA (miRNA) studies have emerged as a novel area of interest in cardioprotection. Cardioplegic arrest has been shown to change the myocardial expression of cardioprotective miRNAs, including miR-1, miR-133, and miR-21, which control apoptosis, calcium cycling, and fibrosis (Schütte et al., 2023 & Makkos et al., 2021). Alterations in these miRNA profiles may contribute to improved post-ischemic recovery and reduced reperfusion injury. However, data directly comparing specific cardioplegia solutions (e.g., del Nido versus intermittent blood cardioplegia) at the genetic or epigenetic level are still sparse.

Future perspectives

One of the major milestones in the field of myocardial protection has been the development of hyperpolarizing cardiac arrest. In a study by He & Yang (1997), coronary endothelial function was significantly preserved by hyperpolarizing cardioplegia but impaired by depolarizing cardioplegia. Dobson et al. (2013) applied a hyperpolarizing normokalemic solution with adenosine and lidocaine as the cardioprotective agents and described better protection compared to St Thomas' Hospital solution in an experimental model. In the same study, the authors proposed that there several were negative factors associated with depolarizing hyperkalemic cardioplegia such as membrane and cellular ionic imbalance, coronary vasoconstriction and endothelial damage and stunning of cardiomyocytes. In a study by Francica et al. (2022), it was shown that the given theocratical benefits of hyperpolarizing solutions were not translated into clinical applications.

In conclusion, myocardial injury associated with aortic cross-clamping remains a major predictor of mortality in cardiac surgical patients. Despite ongoing efforts, the search for an ideal cardioplegic solution continues. Because the molecular mechanisms underlying ischemia–reperfusion injury have not yet been fully elucidated, myocardial injury remains a leading challenge in patients exposed to aortic cross-clamping. Recently, studies focusing on genetic alterations in myocardial cells induced by cardioplegia have gained increasing attention and may pave the way toward a deeper understanding of the mechanisms of ischemia–reperfusion injury.

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