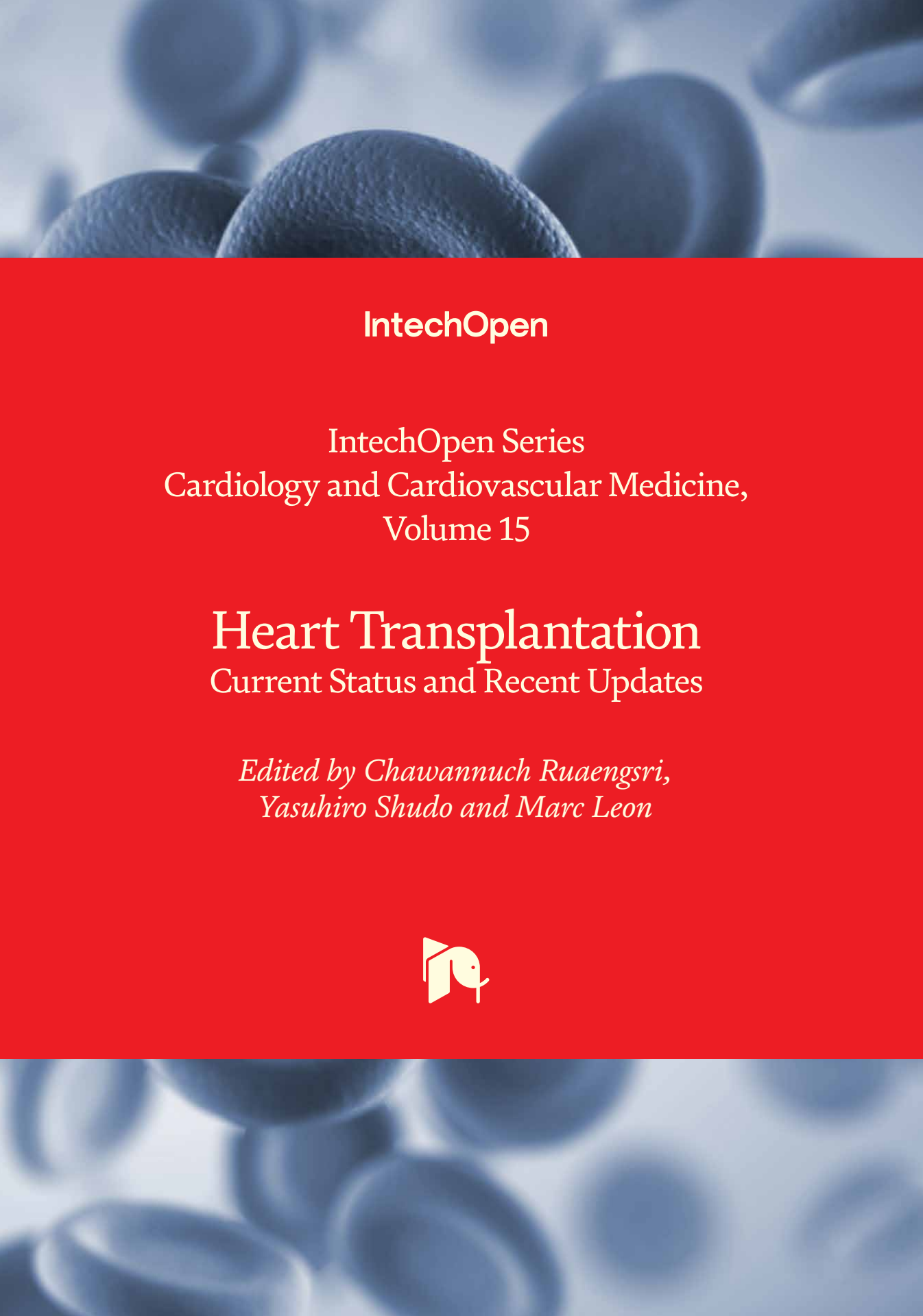


The background of the book cover features a microscopic view of red blood cells, which are biconcave discs. The top and bottom portions of the cover show these cells in a light blue, out-of-focus environment. The central portion of the cover is a solid red band containing the text.

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Heart Transplantation

Current Status and Recent Updates

*Edited by Chawannuch Ruaengsri,
Yasuhiro Shudo and Marc Leon*



Heart Transplantation - Current Status and Recent Updates

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Yasuhiro Shudo and Marc Leon*

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Volume 15

Aims and Scope of the Series

Today, since molecular science on structural causes of oncological pathologies and their molecular treatments are developing at an unbelievable rate, the primary medical cause of death in the twenty-first century will be cardiovascular disease. Neither pandemics that threaten all humanity nor deterioration in the ecosystem will be able to change this fact. Especially, this century seems poised to witness an incredible struggle against atherosclerotic disease, which develops in the arterial walls and results in narrowing and occlusion of the arterial lumen. In addition to this disease, there has been an increasing prevalence of heart rhythm problems, deterioration of heart valves due to aging, and heart failure. Serious vascular pathologies such as stenosis and occlusion, dissection and rupture, and aneurysmal enlargement are also major concerns. Medical and invasive treatment methods may work to save human lives, but they will never provide a real solution. All kinds of medical, technological, and genetic engineering developments obtained in these processes have not yet been sufficient to alleviate or eliminate cardiovascular disease. This book series, Cardiology and Cardiovascular Medicine, includes three topics. The first, Cardiovascular Diseases and Health, reviews important cardiovascular diseases and the developments in their prognosis. The second topic, Cardiovascular Electrophysiology, illuminates the abnormal functioning of the cardiac conduction system, which is caused by all heart pathologies and negatively affects prognosis. The third topic in this series, Cardiovascular Surgery, details treatment for cardiovascular pathologies and how to regulate normal physiological functions with percutaneous or extracorporeal interventions.

Meet the Series Editor



After completing his studies at the Medicine Faculty of Istanbul University in 1990, Prof. Kaan Kırallı fulfilled his mandatory medical service and commenced his residency training at Koşuyolu Heart and Research Hospital in 1992. Following five years of assistant education, he pursued further training in England and the USA in 1998. Specializing in laparoscopic and minimally invasive cardiac surgery, he earned the titles of consultant cardiovascular surgeon in 1998, Assistant Professor in 1999, Associate Professor in 2002, and Chief in 2005 at the same hospital. Prof. Kırallı also developed an interest in preventive medicine, obtaining an MSc in Public Health from Istanbul University in 2000. Over the past two decades, he has concentrated his scientific pursuits on cardiovascular repairs requiring specialized experience. With his expertise in coronary artery surgery, minimally invasive cardiac surgery, valve repair, and aortic root surgery, he has established new methods for awake coronary bypass revascularization, a new surgical approach for AVR during first and re-operations, aortic valve-sparing procedure, and radiofrequency ablation. Notably, he pioneered awake complete coronary artery bypass grafting (CABG) with bilateral internal mammary arteries (BIMA) and played a crucial role in advancing aortic root surgery with a new aortotomy incision, simplifying aortic valve interventions. Since the year 2000, Prof. Kırallı has expanded his interests to heart transplantation, and in recent years, to left ventricular assist devices. He has served as the head of the transplantation department since 2015 and currently continues his work as the director of Koşuyolu High Specialization Education and Research Hospital in Istanbul, Turkey. In his prolific career, he has authored numerous papers in SCI journals, contributed to various book chapters, and served as an editor and reviewer for multiple academic journals. Additionally, he has edited several international books in the field of cardiovascular medicine.

Meet the Volume Editor



Dr. Chawannuch Ruaengsri is a Clinical Assistant Professor in the Division of Cardiothoracic Surgery at Stanford University and serves as Director of the Transplant Procurement Surgery Program. She earned her MD from Mahidol University in Bangkok, Thailand, and completed residency and fellowship training in adult cardiac surgery at the same institution. She further specialized in atrial fibrillation surgery as a postdoctoral fellow at Washington University in St. Louis, followed by extensive training in mechanical circulatory support and minimally invasive adult cardiac surgery at Emory University. Since joining Stanford in 2021, Dr. Ruaengsri has made significant contributions to the development of novel techniques for heart and lung transplantation, including the first beating-heart transplant from a donor after circulatory death at Stanford. Her research focuses on organ preservation, transplant innovation, and expanding donor pools through the use of advanced surgical approaches.



Dr. Yasuhiro Shudo is a Clinical Associate Professor of Cardiothoracic Surgery at Stanford University School of Medicine and a Collaborative Professor at Osaka University Graduate School of Medicine. He earned his MD and Ph.D. in Cardiovascular Surgery from Osaka University, Japan, and completed advanced training in transplant surgery and mechanical circulatory support at Stanford and the University of Pennsylvania. With extensive expertise in heart and lung transplantation, his research focuses on organ preservation, innovative surgical techniques, and mechanical circulatory support systems. Dr. Shudo has published over 120 peer-reviewed articles, contributed to numerous book chapters, and delivered invited presentations worldwide. His leadership includes serving as the Surgical Director of ECMO at Stanford, where he actively shapes the future of transplantation and advanced cardiac therapies.



Dr. Marc Leon is a Clinical Assistant Professor of Cardiothoracic Surgery at Stanford University. He earned his MD and Ph.D. from the Fourth Military Medical University in China, where he conducted pioneering translational research on immunomodulatory therapies for heart transplantation and developed innovative pharmacological treatments for heart failure. Dr. Leon has also explored the application of large language models to enhance self-care in patients with heart failure, demonstrating a commitment to integrating digital health into cardiovascular care. His research focuses on stem cell therapies for ischemic heart disease, with a particular emphasis on mechanisms to enhance cell efficacy and promote cardiac repair. An active contributor to the scientific community, Dr. Leon has published extensively, holds multiple patents, and is dedicated to advancing surgical and regenerative therapies for cardiovascular diseases.

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Preface

Since the landmark first human heart transplantation performed by Dr. Christiaan Barnard in 1967, the field of heart transplantation has experienced remarkable growth and transformation. Advances across various domains, including donor and recipient selection, surgical techniques, perioperative management, immunosuppressive therapies, and mechanical circulatory support, have collectively contributed to substantial improvements in patient outcomes.

This book aims to provide a comprehensive overview of the current state of heart transplantation, highlighting recent updates and emerging trends that continue to shape the future of this life-saving specialty. As the field evolves, so too do the strategies for optimizing long-term survival and quality of life for transplant recipients, alongside novel techniques and technologies that enhance donor organ utilization and recipient care.

In addition to conventional approaches, innovative therapies such as personalized immunosuppression protocols and advancements in mechanical circulatory support devices are expanding the therapeutic landscape, offering hope to more patients with advanced heart failure.

I would also like to express my sincere gratitude to our co-editors, Yasuhiro Shudo and Marc Leon, for their invaluable contributions to the editorial process. Their expertise and dedication were instrumental in shaping this publication.

I hope that this compilation of expert insights, recent research, and clinical advancements serves as a valuable resource for clinicians, researchers, and healthcare professionals committed to improving the care of patients undergoing heart transplantation. Together, we aim to continue pushing the boundaries of knowledge and innovation in this vital field.

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Section 1

Advances in Mechanical
Support and Surgical
Techniques

Pushing the Boundaries: The Revolutionary Role of Mechanical Circulatory Support in Advanced Heart Failure

Özgür Çoban

Abstract

Mechanical circulatory support (MCS) has revolutionized the management of advanced heart failure, providing both temporary and long-term solutions for patients' ineligible for heart transplantation. This chapter explores the historical evolution, classification, and clinical applications of MCS devices, including intra-aortic balloon pumps (IABP), ventricular assist devices (VADs), and total artificial hearts (TAHs). Recent technological advancements, such as miniaturization, biocompatible materials, and remote monitoring, have significantly improved patient outcomes by reducing complications like thrombosis, infection, and hemolysis. Furthermore, MCS plays a crucial role in heart transplantation as a bridge to transplant (BTT), bridge to recovery (BTR), and destination therapy (DT). Ethical considerations, cost implications, and quality-of-life impacts are also discussed. The chapter concludes by highlighting future research directions, including fully implantable systems and bioengineered solutions, positioning MCS as a cornerstone in the evolving field of heart failure management.

Keywords: mechanical circulatory support, ventricular assist devices, heart failure, transplant, destination therapy

1. Introduction

Heart failure remains a leading cause of morbidity and mortality worldwide, imposing a significant burden on healthcare systems and patient quality of life. It is characterized by the heart's inability to pump sufficient blood to meet the body's metabolic demands, resulting in symptoms such as dyspnea, fatigue, fluid retention, and exercise intolerance. The etiology of heart failure is diverse, including ischemic heart disease, hypertension, valvular disorders, and cardiomyopathies, with many patients progressing to advanced stages despite optimal medical therapy.

While pharmacological treatment and lifestyle modifications play a fundamental role in managing early-stage heart failure, they often fail to provide adequate relief in end-stage cases. Cardiac resynchronization therapy (CRT) and implantable

cardioverter defibrillators (ICDs) can delay disease progression, but a subset of patients continues to deteriorate, requiring more aggressive interventions. Heart transplantation remains the gold standard for end-stage heart failure, offering superior long-term survival and quality of life improvements. However, the scarcity of donor organs, immunological challenges, and surgical risks limit its applicability, creating an urgent need for alternative treatment strategies.

Mechanical circulatory support (MCS) has emerged as a transformative solution for patients with advanced heart failure, either serving as a bridge to transplantation (BTT) or as a destination therapy (DT) for those who are ineligible for transplantation. The evolution of MCS technology has dramatically changed the treatment paradigm for end-stage heart failure, allowing patients to achieve prolonged survival with improved functional capacity. From early-generation pulsatile-flow devices to modern continuous-flow systems, MCS has demonstrated substantial improvements in device durability, hemodynamic performance, and patient outcomes [1].

The application of MCS has expanded significantly over the past two decades, driven by advancements in miniaturization, biocompatible materials, and remote monitoring capabilities. With an increasing number of patients benefiting from left ventricular assist devices (LVADs) and total artificial hearts (TAHs), understanding the indications, patient selection criteria, and long-term management of these devices has become crucial for healthcare providers. Additionally, the integration of artificial intelligence and telemedicine has introduced novel possibilities for personalized care and real-time monitoring, enhancing patient safety and clinical outcomes.

Despite these remarkable advancements, challenges remain in optimizing MCS therapy. Issues such as infection risk, thrombogenicity, bleeding complications, and device malfunction necessitate ongoing research and innovation. Ethical considerations related to patient autonomy, economic burden, and quality of life must also be addressed to ensure equitable access and responsible utilization of these life-saving technologies.

This chapter delves into the classification, indications, and future potential of MCS in contemporary cardiac care. By exploring recent breakthroughs in device engineering, patient management strategies, and emerging trends, we aim to provide a comprehensive overview of the evolving landscape of MCS and its role in shaping the future of heart failure treatment.

2. Mechanical circulatory support systems: Current applications and future perspectives

Mechanical circulatory support (MCS) systems play a crucial role in the management of advanced heart failure, providing both short-term and long-term solutions for patients awaiting heart transplantation or those who are ineligible for transplant (**Table 1**). This section explores the classification, indications, recent technological advancements, and the evolving future landscape of MCS.

2.1 Classification of MCS devices

MCS devices are broadly classified based on their intended duration of use and support mechanism. These include:

Device type	Usage duration	Indications	Advantages	Disadvantages
IABP	Short-term	Cardiogenic shock, AMI, supportive therapy	Minimally invasive, easy placement	Low support capacity
ECMO	Short to Medium-term	Acute respiratory and heart failure	Full cardiopulmonary support	High thrombosis and infection risk
pVADs	Short to Medium-term	High-risk PCI, cardiogenic shock	Better hemodynamic support	Risk of vascular injury and thrombosis
LVAD	Long-term	End-stage heart failure	Bridge to transplant or permanent therapy	Requires anticoagulation, infection risk
TAH	Long-term	Advanced heart failure	Complete heart replacement	Major surgery, high complication rates

Table 1.
Comparison of MCS devices. This table compares different mechanical circulatory support devices based on their key characteristics.

2.1.1 Short-term support devices

- Intra-aortic balloon pumps (IABP): Used to enhance coronary perfusion and reduce myocardial oxygen demand in acute decompensated heart failure.
- Extracorporeal membrane oxygenation (ECMO): Provides full cardiopulmonary support in cases of severe cardiac and respiratory failure.
- Percutaneous ventricular assist devices (pVADs): Temporary mechanical support for patients in cardiogenic shock or undergoing high-risk procedures.

2.1.2 Long-term support devices

- Ventricular assist devices (VADs): Provide continuous mechanical support for left (LVAD), right (RVAD), or both ventricles (BiVAD), with the latest generations showing enhanced durability and biocompatibility.
- Total artificial hearts (TAHs): Fully replace the function of the native heart, serving as a permanent alternative for patients who are ineligible for transplant.

2.2 Indications and patient selection

The selection of candidates for MCS requires a comprehensive evaluation of heart failure severity, comorbidities, and eligibility for heart transplantation. Key indications include:

- Bridge to transplantation (BTT): MCS stabilizes patients awaiting a donor heart, improving their survival and transplant outcomes. Patients with refractory heart failure, despite optimal medical therapy, are primary candidates for BTT. Studies have demonstrated that LVADs as BTT can significantly improve hemodynamics and organ function, thereby enhancing post-transplantation survival rates.

- Bridge to recovery (BTR): Temporary use of MCS allows myocardial function to recover, potentially eliminating the need for transplantation. Patients with acute myocarditis, peripartum cardiomyopathy, or post-cardiotomy shock may benefit from this approach. The ability of MCS to offload the failing ventricle and provide myocardial rest is critical in reversing heart failure in reversible conditions. Longitudinal studies indicate that a subset of patients weaned from VADs after recovery continues to demonstrate stable cardiac function without recurrence of heart failure.
- Destination therapy (DT): For patients ineligible for transplant, MCS serves as a long-term solution, improving survival and quality of life. DT is indicated for patients with end-stage heart failure who do not meet the criteria for transplantation due to age, comorbidities, or contraindications such as pulmonary hypertension or malignancy. Advances in DT-LVADs have significantly improved survival rates, with recent data showing that patients with contemporary LVADs achieve two-year survival rates comparable to selected transplant recipients. Additionally, advancements in battery life, wearable components, and remote monitoring have contributed to improved patient autonomy and long-term outcomes.

Beyond these primary indications, patient selection for MCS requires a multidisciplinary approach, including cardiologists, cardiac surgeons, and intensivists. Several risk stratification tools, such as the INTERMACS classification system, help predict outcomes and guide patient selection [2]. Proper preoperative evaluation, including right heart catheterization, echocardiography, and end-organ function assessment, is crucial to optimizing outcomes in MCS candidates.

2.3 Comparative analysis: MCS vs. other heart failure treatments

MCS represents one of several therapeutic options for advanced heart failure. It is crucial to compare its effectiveness, benefits, and risks with alternative treatments such as medical therapy, cardiac resynchronization therapy (CRT), and heart transplantation.

Pharmacological treatment remains the first-line approach for heart failure management. Medications such as beta-blockers, ACE inhibitors, and aldosterone antagonists have been shown to reduce mortality and hospitalizations. However, in patients with refractory heart failure, medical therapy alone is insufficient to halt disease progression, necessitating mechanical support.

Cardiac resynchronization therapy (CRT) and implantable cardioverter defibrillators (ICD) improve cardiac function and reduce arrhythmic events in select heart failure patients. CRT has been associated with a reduction in mortality and an improvement in left ventricular function. However, CRT is ineffective in non-responders, highlighting the need for MCS in select cases.

Heart transplantation offers the best long-term survival for end-stage heart failure, with a median survival of 12 years post-transplant. However, due to limited donor availability and strict eligibility criteria, many patients require alternative therapies such as MCS.

Recent clinical trials indicate that modern continuous-flow LVADs provide a two-year survival rate of approximately 80%, which is comparable to carefully selected heart transplant recipients. This highlights the effectiveness of MCS as a viable

alternative for patients who are either ineligible for heart transplantation due to age, comorbidities, or contraindications such as pulmonary hypertension or malignancy, or those who face prolonged waiting periods due to organ scarcity.

Furthermore, LVAD technology has undergone significant advancements in recent years, improving patient outcomes by addressing key complications such as infection risk, thrombogenicity, and hemocompatibility. The introduction of fully magnetically levitated pumps, as seen in the HeartMate 3 device, has led to a substantial reduction in pump-related thrombosis and adverse events, making long-term support safer and more reliable. Studies have also shown improvements in patients' functional status, with many achieving enhanced exercise tolerance, better quality of life, and reduced hospitalization rates compared to earlier LVAD models.

A pivotal study by Mehra et al. [3], demonstrated that the HeartMate 3 LVAD, featuring full magnetic levitation, resulted in a significantly lower rate of pump thrombosis compared to previous continuous-flow devices, further solidifying LVADs as a robust alternative to transplantation. Additionally, ongoing research in artificial intelligence-driven monitoring and remote management is expected to further enhance patient safety and optimize long-term outcomes in MCS therapy.

2.4 Clinical outcomes and recent data

Several studies have evaluated the impact of MCS on patient survival and quality of life:

- The INTERMACS registry reports that patients with contemporary LVADs achieve a two-year survival rate of approximately 80%, comparable to heart transplantation in selected cases [2].
- Studies indicate that MCS improves exercise capacity, functional status, and overall quality of life, with significant reductions in rehospitalization rates.
- Miniaturized devices and remote monitoring have decreased major adverse event rates, improving long-term patient adherence and satisfaction.

Despite these advancements, challenges such as infection risk, device thrombosis, and bleeding complications remain areas for continued innovation.

2.5 Accessibility of MCS in low- and middle-income countries

While MCS has revolutionized heart failure treatment in high-income nations, its accessibility in low-to-middle-income countries (LMICs) remains limited [4]. Barriers include high costs, infrastructure challenges, and lack of government support. The implantation and maintenance of MCS devices are expensive, often exceeding the financial capacity of healthcare systems in LMICs. Additionally, advanced cardiac centers with expertise in MCS management are scarce, and many health insurance systems do not cover the costs of MCS therapy.

Efforts to improve access include cost-reduction strategies, international collaboration, and enhancements in battery technology for MCS to support patients in areas with inconsistent electricity supplies. Addressing these disparities is essential to ensuring equitable access to life-saving technologies worldwide.

2.6 Technological advances and future directions

Recent advancements in MCS technology have significantly improved the efficacy, safety, and longevity of these life-saving devices. One major breakthrough is the miniaturization of VADs, reducing the need for invasive surgical procedures and allowing for better patient mobility. Smaller devices mean fewer complications related to implantation and a faster recovery period, which enhances the quality of life for patients. Additionally, the development of biocompatible materials has minimized adverse reactions, reducing clot formation and inflammation, two of the most significant challenges associated with MCS use. Researchers are now focusing on fully implantable devices, which eliminate percutaneous driveline connections, drastically decreasing the risk of infections and improving patient comfort.

Another critical area of advancement is thrombogenicity and infection control. The integration of novel surface coatings and improved biomaterials has significantly decreased the incidence of thrombosis and infections, which are common complications with MCS. Antithrombotic coatings and enhanced hemodynamic designs have reduced clot formation and the need for long-term anticoagulation therapy, thereby minimizing bleeding risks. Ongoing research aims to develop self-regulating devices capable of dynamically adapting to physiological demands while reducing the need for extensive pharmacologic intervention.

The integration of artificial intelligence (AI) and remote monitoring has further enhanced the safety and effectiveness of MCS. Smart algorithms analyze real-time physiological data, allowing devices to self-regulate and make micro-adjustments to optimize cardiac output. This real-time adaptation improves hemodynamic performance and reduces hospital readmissions by enabling early detection of complications. Furthermore, remote monitoring capabilities provide physicians with continuous insights into patient status, allowing for proactive interventions and personalized treatment adjustments. This development is particularly crucial for patients in remote or underserved areas, where frequent hospital visits may not be feasible. As these technologies continue to evolve, the future of MCS holds the promise of even greater reliability, safety, and patient autonomy, ultimately reshaping the landscape of advanced heart failure treatment.

3. Conclusion

Mechanical circulatory support (MCS) has become a vital component in the management of advanced heart failure, offering both short-term and long-term solutions for patients with limited therapeutic options. The rapid advancements in MCS technology have expanded its role beyond a temporary measure to a more sustainable alternative for those ineligible for heart transplantation [5]. From the early days of pulsatile-flow devices to the current generation of continuous-flow ventricular assist devices (VADs) and total artificial hearts (TAHs), significant improvements in durability, biocompatibility, and patient outcomes have been achieved.

The integration of miniaturization, biocompatible materials, and remote monitoring has addressed some of the major challenges associated with MCS, significantly improving patient outcomes and long-term device performance. Smaller, more efficient devices have led to reduced surgical invasiveness, making implantation procedures safer and more accessible for a broader range of patients, including those who may not have previously been eligible due to anatomical or comorbid constraints.

Additionally, these compact designs contribute to improved patient mobility, allowing individuals to engage in daily activities with greater ease and independence, which is crucial for enhancing their overall quality of life.

The development of novel biomaterials has played a key role in minimizing risks related to thrombosis, bleeding, and infection—three of the most serious complications associated with MCS. Modern LVADs now incorporate advanced coatings and surface modifications that reduce platelet activation and clot formation, thereby decreasing the need for intensive anticoagulation therapy and lowering the risk of hemorrhagic complications. Moreover, improvements in biocompatibility have enhanced the durability and longevity of these devices, leading to fewer mechanical failures and revisions over time.

Simultaneously, the integration of remote monitoring and artificial intelligence has introduced a new era of personalized, data-driven care. AI-enhanced algorithms can analyze real-time physiological data from MCS patients, detecting subtle changes that may indicate early signs of device malfunction, infection, or hemodynamic instability [6]. This enables clinicians to make proactive adjustments, optimize pump performance, and prevent complications before they become severe, ultimately reducing hospital readmissions and improving long-term survival. As research continues to evolve, the combination of these technological advancements is expected to further revolutionize the field of MCS, making these life-saving devices more effective, reliable, and patient-friendly.

Despite these remarkable advancements, several challenges remain in optimizing MCS therapy. One of the most significant concerns is infection risk, particularly in devices requiring percutaneous driveline connections. Fully implantable systems are being actively researched as a solution to eliminate external components and reduce infection rates. Additionally, lifelong anticoagulation therapy remains necessary for many MCS patients, increasing the risk of bleeding complications. Further advancements in antithrombotic coatings, hemodynamic designs, and adaptive anticoagulation strategies may help address this issue.

Another crucial consideration is the economic and ethical impact of MCS therapy. The high cost of device implantation, postoperative care, and lifelong maintenance poses financial challenges for healthcare systems, insurance providers, and patients. Equitable access to MCS remains a concern, particularly in resource-limited settings. Ethical dilemmas also arise in end-of-life decision-making, device explantation, and long-term management of patients with irreversible complications. A multidisciplinary approach, incorporating cardiologists, cardiac surgeons, bioengineers, ethicists, and policymakers, is necessary to ensure responsible and fair utilization of MCS technologies.

Looking to the future, MCS is poised to undergo further evolution, with several promising advancements on the horizon. Fully implantable VADs and wireless energy transfer systems aim to eliminate external driveline components, significantly reducing infection risks and improving patient comfort. Hybrid bioengineered solutions, including tissue-engineered heart components and bioartificial hearts, may offer a more physiological alternative to mechanical support, bridging the gap between traditional transplantation and synthetic devices. Artificial intelligence and machine learning algorithms are expected to play a crucial role in personalizing MCS therapy by optimizing pump performance, predicting complications, and enhancing patient-specific treatment strategies.

As the burden of heart failure continues to rise worldwide, MCS will remain a cornerstone in the evolving landscape of cardiovascular medicine. By continuously

improving device design, enhancing patient safety, and addressing ethical and economic concerns, MCS has the potential to redefine heart failure management further, offering hope and extending survival for thousands of patients who would otherwise have limited options. Through continued interdisciplinary collaboration, clinical research, and technological innovation, MCS will not only enhance longevity but also revolutionize the quality of life for end-stage heart failure patients, marking a new era in mechanical heart support.

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Conflict of interest

The authors declare no conflict of interest.

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Mechanical Circulatory Support in Adult and Pediatric Populations with Advanced Heart Failure

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Abstract

The prevalence of heart failure (HF) has increased, coinciding with the increase in the prevalence of cardiovascular risk factors such as diabetes, hypertension, and obesity. With the improvement in corrective surgeries for congenital heart disease (CHD), patients are living longer, and around 40% of the CHD population will develop HF later in life. Cardiomyopathies in adults and pediatrics are becoming recognized with advancements in cardiac imaging and family screening. However, HF remains a progressive disease, and a portion of these patients will reach end-stage HF that will require advanced HF therapies, including implanting left ventricle assist devices (LVAD) and heart transplantation (HT). The evolving mechanical circulatory support (MCS) technology, including LVADs, has helped manage patients with advanced HF and acute HF in adults and pediatric patients. The MCS registries have shown improved survival over the past two decades with reduced risk of adverse events. Moreover, emerging experiences are arising for unique uses of LVADs in hypertrophic and restrictive cardiomyopathies, CHD, and small children. The following chapter will highlight the importance of timely patient selection for LVAD therapies in adult and pediatric populations. Further, the challenges associated with the long-term management of these patients will be discussed.

Keywords: advanced heart failure, left ventricle assist device, Berlin heart, single ventricle, transplant

1. Introduction

There is a significant increase in the number of patients living with HF [1]. There is a high rate of hospitalization and mortality related to HF [1]. Recent estimations of deaths related to HF per year have reached more than 300,000 deaths [1]. The rate of HF hospitalization has increased to 26% [1]. Population-based studies have shown an increase in the prevalence of HF in the younger population [2]. HF has diverse phenotypes and etiologies [1]. The most common etiology of HF remains ischemic heart disease, with increasing epidemics of diabetes and obesity [1]. There is an increased awareness of familial, restrictive, and hypertrophic cardiomyopathies with advanced imaging techniques and genetic testing [1]. Moreover, in the pediatric population, HF

diagnosis is difficult to define as the presentation is variable between the neonate and adolescent populations [3].

HF is a progressive disease; some patients present with advanced HF (stage D) despite optimal medical therapy [1, 4]. These patients are at risk of mortality at 1-year from 25–75% [4]. The therapeutic options for advanced HF patients are limited to either LVAD support or HT [5]. The introduction of LVAD has shown an improvement in HF survival rate of >80% in 2 years [1]. In pediatrics, there is a lack of clinical trials and evidence on advanced HF therapies [6]. The Organ Procurement and Transplant Network (OPTN) reported an increase in the number of adult patients listed for HT by 32.3% from 2010 to 2016 and an increase in pediatric patients by 39.8% since 2010 [7]. The number of patients on the HT wait list is 4373 adult patients and 1146 pediatric patients in 2021 [7]. These numbers highlight the extent of the advanced HF patient population.

The long-term outcome data for patients on LVAD support are reported in adults from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) [8]. In children, the Pediatric Interagency Registry for Mechanical Circulatory Support (Pedimacs) and the Paedi-European Registry for Patients with Mechanical Circulatory Support (Paedi-EUROMACS) have reported survival rates for device type and intended implant strategy [9, 10]. The survival rate free of major events has improved with the centrifugal continuous-flow LVAD. The 1-year survival rate in the MagLev technology in patients undergoing mechanical circulatory support therapy with HeartMate 3 (MOMENTUM 3) reached 76.9% [11]. However, LVAD-related infection is the most common adverse event and is associated with mortality, morbidity, and increased rehospitalization [12].

2. Case presentation

The following case series includes patients with advanced HF who underwent LVAD support. Each case highlights the decision-making process for LVAD support.

2.1 Case I

A 12-year-old girl, a student weighing 48 kg, height 157 cm, and blood group O+, presented to the emergency department with abdominal pain, nausea, and vomiting. She was initially treated for gastrointestinal viral illness. She had persistent symptoms, worsening fatigue, and shortness of breath with activity. She had presented to the emergency department again with hypotension and tachycardia. Her clinical examination was consistent with pulmonary congestion and high jugular venous pressure. Her electrocardiogram showed sinus tachycardia. Her laboratory results were significant for an increased natriuretic peptide (BNP) level. The echocardiogram (ECHO) showed severe left ventricle dysfunction (LV) and severe ventricular dilatation with an LV ejection fraction (LVEF) of 25% (**Figure 1**).

She was referred to the advanced HF Centre, where she was started on guideline-directed medical therapy (GDMT). She was on valsartan 40 mg daily, metoprolol tartrate 50 mg twice daily, and spironolactone 25 mg daily with diuretics. She was not tolerating higher doses of medication due to hypotension. Over a six-month follow-up, she reported declining physical activity at school and increased fatigue. The decision was made to proceed with right heart catheterization that showed low cardiac output (CO) of 2.5 L, high pulmonary capillary wedge pressure (PCWP) of 23 mmHg, pulmonary artery pressure (PAP) 51/15 mmHg with a mean PAP of 33 mmHg, and right atrial pressure (RAP)

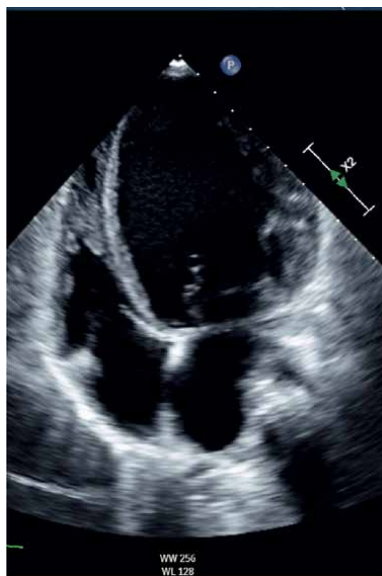


Figure 1.
Case 1: Echocardiography in Apical 4-chamber view at presentation.

14 mmHg. The patient was listed for HT, while on the list, she had ventricular tachycardia (VT), and the decision was made to proceed with LVAD implantation with HeartMate 3 (HM3) as a bridge to HT. Given her body surface is (BSA) 1.45 m², she had a computed tomography (CT) chest to assess her chest cavity for LVAD implant (**Figure 2**).

She had a successful HM3 LVAD implant and an uneventful recovery. Her LVAD speed was set to provide a 3.5–3.7 L flow. She was optimized with low-dose valsartan, metoprolol, and anticoagulation with warfarin. She was discharged home and went back to school with regular clinic follow-up. Six months post-LVAD, she had one episode of localized driveline exit site infection. Driveline exit site swab culture was positive for gram-negative pseudomonas aeruginosa. She had negative blood cultures.

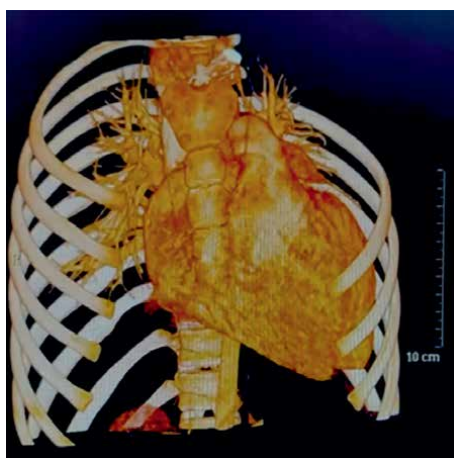


Figure 2.
Case 1: Computed tomography (CT) chest; 3-D reconstruction view for surgical planning.

CT scan did not reveal a deep seeding infection. She was treated with local wound care and intravenous piperacillin-tazobactam for 6 weeks. She remained on VAD support for 1 year and then had a successful HT.

2.2 Case II

A 7-month-old baby girl presented with failure to thrive, respiratory distress, and seizures at a peripheral hospital. She was only 5.4 kg with blood group O+. Her history was significant for two siblings having dilated cardiomyopathy diagnosed at less than 1 year of age. Both siblings had died of advanced HF. On assessment, the patient was lethargic, tachypneic, and tachycardic. She was intubated and started on inotropic support with dobutamine. The patient was transferred to an advanced HF Centre, where further evaluation showed severe biventricular failure with severe mitral and tricuspid valve regurgitation (**Figure 3**). She had hepatic congestion with high bilirubin and had a high urea level and low urine output.

The patient was maintained on inotropic support and diuresis; despite this, she continued to have high lactate levels. Since she was in INTERMACS level II, the heart team decided to proceed with Excor Berlin Heart (BH) support as a biventricular support. The BH pump sizes were 15 cc for the LV and RV and set in synchronous mode (**Figure 4**). The pump rate was set for optimal LV unloading and end-organ perfusion. The patient showed improvement in urine output and resolution of hepatic congestion. The patient was extubated post-BH implant and weaned off inotropic support. She was shifted to the ward and optimized on medical therapy, including enalapril and metoprolol. She had recurrent atrial tachycardia, which did not impair BH pump function, and it was treated medically with amiodarone. On the ward, she received nutritional and physiotherapy support. She gained weight and showed good intellectual growth as well. She was maintained on BH for 9 months and then successfully had an HT.

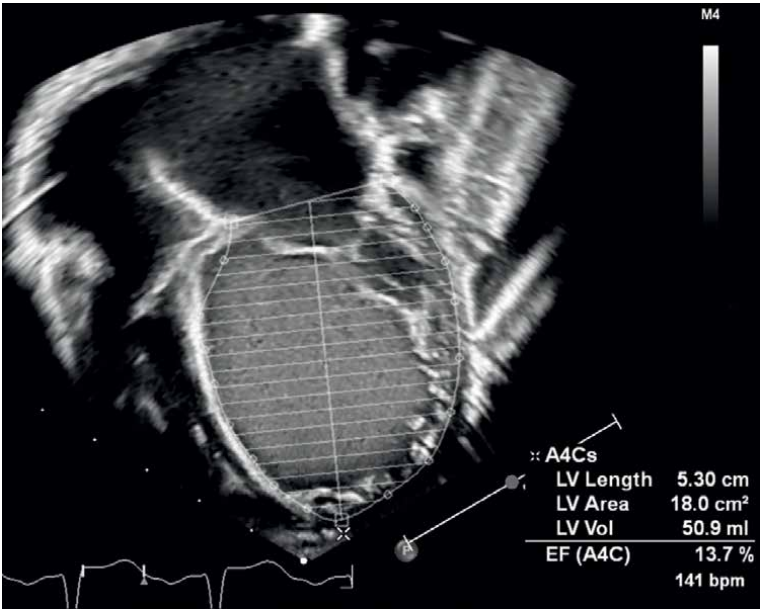


Figure 3.
Case 2: Echocardiography in Apical 4-chamber view at presentation.



Figure 4.
Case 2: Post-implant of Berlin heart biventricular device.

2.3 Case III

An 18-year-old girl, a student, weighs 45 kg and has an O+ blood group. She was known to have dilated cardiomyopathy (DCM) since the age of 5 years. She was following up with a pediatric cardiologist at a secondary hospital. She no longer tolerated medical therapy, had recurrent admission for HF, and needed ascitic fluid drainage. She was referred to an advanced HF center for HT evaluation. On admission, she had shortness of breath, orthopnea, and ascites; she had severe cardiac cachexia. She was in a low cardiac output state and volume overload, requiring inotropic support with milrinone and non-invasive ventilation. Her liver enzymes were elevated, with hepatomegaly without liver cirrhosis. Her ECHO revealed severe biventricular dysfunction with LVEF 20% with severe dilatation of both LV and right ventricle (RV), with severe functional mitral and tricuspid regurgitation (**Figure 5**).

The right heart catheterization showed low CO 2.4 L, high PCWP 31 mmHg, PAP 54/26 mmHg with a mean PAP 41 mmHg and RAP 24 mmHg. The pulmonary artery

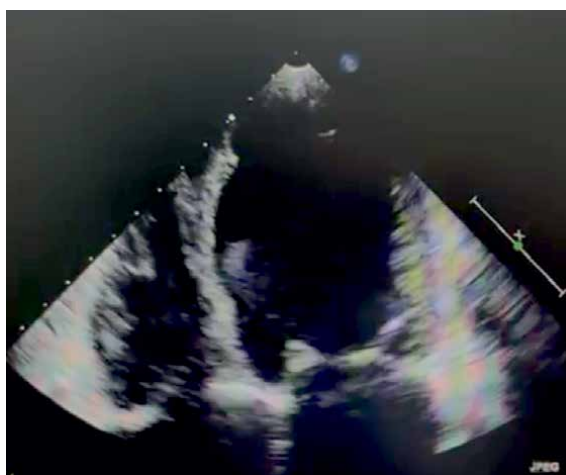


Figure 5.
Case 3: Echocardiography in Apical 4-chamber view at presentation.

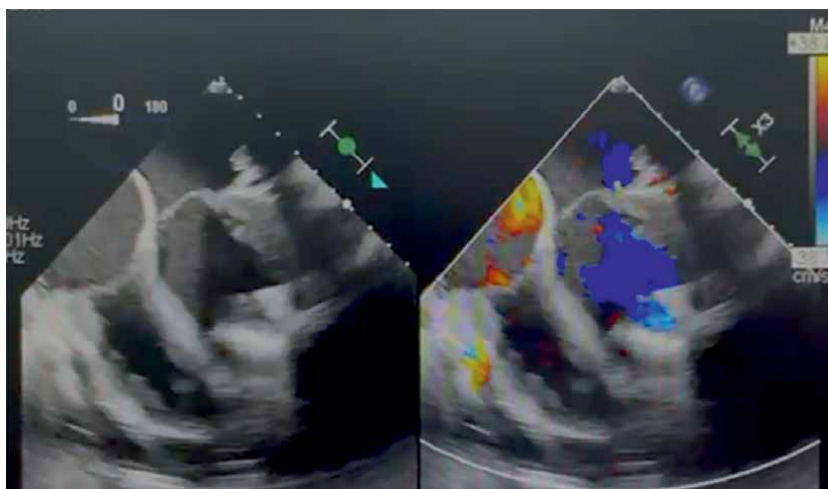


Figure 6.
Case 3: Intraoperative transesophageal echo.

pulsatility index (PAPi) was only 1.4, and pulmonary vascular resistance (PVR) was 4 woods. She continued to decline hemodynamically, requiring higher inotropic support and elective mechanical ventilation. The patient was in INTERMACS level II on the increasing requirement of milrinone, dobutamine, and epinephrine. Given her critical condition, the decision was made to pursue BiVAD support. A durable HM3 LVAD supported her LV, and a temporary RVAD supported the RV (**Figure 6**). Postoperatively, she was maintained on milrinone, epinephrine, and NO inhalation for RV contractility and unloading. The HM3 was set at a low speed to maintain a 3–3.2 L flow. The RVAD flow was set at around 2–2.5 L flow, and it was reduced gradually over 1 week and successfully explanted.

The patient was listed for HT 3 months after the implant. She is following up in the outpatient unit with GDMT therapy. Her recent right heart catheterization showed improved PCWP 6 mmHg, PAP 19/9 mmHg with a mean PAP 14 mmHg, and RAP 7 mmHg. Her RV on ECHO remains dilated, and her contractility has improved after LV unloading. She is currently waiting at home for HT.

3. Heart failure in the adult population

3.1 Identifying advanced heart failure patients; timing matters

GDMT has improved survival in HF patients [1, 4]. As the disease progresses, HF patients do not tolerate GDMT due to hypotension or renal impairment, which leads to frequent episodes of decompensation and hospitalization [1]. It is estimated that around 10–15% of HF patients are living with New York Heart Association (NYHA) class III–IV symptoms [5]. The median survival declines with each HF readmission [13]. At this stage, patients should be offered advanced therapies [4]. The advanced HF criteria can be categorized as clinical, functional, and invasive hemodynamic criteria [1, 4, 14]. The clinical criteria include symptoms of HF at rest or with minimal NYHA class III–IV, episodes of fluid retention requiring increasing diuretics, hospitalization for volume overload or low cardiac output at least once within 6 months,

	REMATCH [15]	HM II BTT [16]	HM II DT [17]	MOMENTUM3 [11]
Age (Years)	> 18	> 18	Age > 18 years	Age > 18 years
BSA (m ²)	> 1.5	> 1.2	BSA > 1.5 m ²	BSA > 1.2 m ²
NYHA class	NYHA IV IV > 60 days	NYHA IV	NYHA IIIB - IV	NYHA III -IV, Advanced HF > 14 days
LVEF	LVEF <25%		LVEF <25%	LVEF <25%
Functional test	pVO ₂ < 14 ml/kg/min		pVO ₂ < 14 ml/kg/min or < 50% of predicted VO ₂	
Hemodynamics		PCWP or PADP >20 mmHg, and Cardiac Index <2.2 L/min/m ² or SBP < 90 mmHg		CI <2.2
Inotrope	inotrope-dependent		inotropes > 14 days	Inotrope-dependent
Temporary MCS	IABP >14 days		IABP >7 days	IABP >7 days
Clinical	Transplant ineligible	Transplant listed as: Status 1A or Status 1B	Transplant ineligible On OMM for >45 days and failing to respond, intolerant of ACEi or BB > 30 days	On OMM for at least 45 out of the last 60 days and are failing to respond

Table 1.
 LVAD selection criteria in landmark clinical trials.

intolerance to GDMT, and ventricular arrhythmia leading to intracardiac defibrillator shock [14]. Functional testing provides an objective assessment of symptoms and correlates strongly with prognosis [14]. The HF patients who are able to exercise are assessed by a 6-minute walk distance <300 m and by cardiopulmonary test, a peak $\text{VO}_2 \leq 12\text{--}14$ ml/kg/min [14]. The hemodynamic criteria for the invasive study are PCWP >16 mmHg and RAP >12 mmHg [14]. The criteria of LVEF <30% is limited to the dilated and ischemic phenotype of HF. The invasive hemodynamic criteria can be applied to restrictive phenotypes as well. Other criteria include high serum urea and BNP levels and hyponatremia <133 meq/L [1, 14].

Clinical trials for implantable durable LVAD, HeartMate (HM), had variable inclusion criteria summarized in (**Table 1**). In the multicenter study MOMENTUM 3, the enrollment criteria were age > 18 years, body surface area (BSA) > 1.2 m², NYHA class III-IV, LVEF <25%, inotrope-dependent, cardiac index (CI) <2.2 L/min/m² [11, 18]. The main exclusion criteria in the LVAD trials were obesity with body mass index (BMI) > 40, active infection, thrombocytopenia and coagulopathy, aortic valve prosthesis, aortic aneurysm >5 cm, post-myocardial infarction <15 days, stroke <90 days, severe psychological illness, and end-organ damage including severe chronic obstructive airway disease, and high PVR > 5–8 woods, chronic kidney disease stage IV or hemodialysis, intrinsic liver disease, carotid stenosis >80% [11, 15, 16, 19, 20].

Frailty is a marker of mortality and morbidity in the cardiovascular disease population [21]. Frail patients undergoing cardiac intervention experience a prolonged length of stay, readmission, disability, and a higher rate of mortality post-intervention [21]. Patients undergoing LVAD as destination therapy who were older than 70 years of age had similar outcomes compared to patients below the age of 70 years [21]. Frailty can be a result of long-standing HF, which can improve with LVAD therapy [21]. A formal assessment of frailty with multidimensional evaluation can help differentiate HF-related frailty from age-related frailty [21].

3.2 Role of INTERMACS profile in the selection of patients for an assist device

The advanced HF patients in the INTERMACS profiles 4–7 were evaluated in the Medical Arm of Mechanically Assisted Circulatory Support (MedaMACS) study [22]. The prospective study followed advanced HF patients on medical therapy for 1 year. The study highlighted the trajectory of HF by reporting the primary outcome as the need for LVAD or HT and mortality. The patients enrolled were in the following INTERMACS profiles: 4, 5, 6, and 7 (12, 32, 49, and 7%), respectively [22]. The primary outcome at 1 year was for mortality of 17%, 8% LVAD, and 9% HT [22]. The 2-year follow-up showed 24% mortality [22]. The survival analysis favored LVAD therapy for INTERMACS profile 4 and 5 patients compared to medical treatment (p -value 0.0092); however, no difference was noted for INTERMACS profiles 6 and 7 compared to medical treatment [22].

4. The challenges of managing advanced HF in the pediatric population

The pediatric patient population has a diverse etiology and clinical presentation for HF [3, 6]. Compared to the adult population, there is limited data on HF clinical trials for medical or interventional therapies [3, 6]. Pediatric HF registry data showed that HF was the admission diagnosis in 10–33% of cardiac admissions [3]. HF due to CHD accounted for 6–24% of these patients, while cardiomyopathy accounted for 5–19%

[3]. Similarly, a report on the prevalence of HF in pediatrics showed an increase in HF hospitalization between 2012 and 2016 [23]. The hospitalized pediatric patients had a mean age of 7 years; the most common diagnoses were CHD (62.7%) and cardiomyopathy (13.7%) [23]. HF hospitalization was associated with arrhythmia (22.2%) and acute kidney failure (14%) [23]. The pediatric HF clinical presentation and etiology differ between neonates and adolescents. The cornerstones for the HF presentation are growth failure, respiratory distress, and exercise intolerance [6]. Older children present with abdominal pain and poor appetite; the diagnosis of HF is delayed due to

	Adult [4, 14]	Pediatric [3]
Etiologies	Ischemic heart disease Valvular heart disease Cardiomyopathies Dilated Restrictive/infiltrative Hypertrophic Arrhythmogenic Myocarditis Peripartum cardiomyopathy Congenital heart disease chemotherapy induced	<i>Congenital heart disease: (6-24%)</i> Single ventricle physiology Systemic right ventricle Left sided obstructive lesions Right sided obstructive lesions Atrioventricular valve regurgitations Shunt disease <i>Cardiomyopathies: (5-19%)</i> Dilated 54%, arrhythmogenic, restrictive 5.4%, hypertrophic 1.2% <i>Acquired:</i> Myocarditis 16%, chemotherapy induced
Clinical presentation	Shortness of breath Orthopnea Paroxysmal nocturnal dyspnea Reduced exercise tolerance Fatigue Lower limb swelling Loss of appetite Palpitation Dizziness Syncope	Modified Ross HF symptoms: Class I asymptomatic Class II: Infants: Mild tachypnea or diaphoresis with feeding Children: Dyspnea on exertion Class III: Infants: Marked tachypnea or diaphoresis with feeding, prolonged feeding times with growth failure Children: Marked dyspnea on exertion Class IV: Tachypnea, chest muscle retractions, grunting, or diaphoresis at rest Other symptoms: Abdominal pain, loss of appetite, fatigue
Advance HF criteria	NYHA class III-IV Hospitalization for volume overload or low cardiac output > 1 in 6 months Intolerance to GDMT ICD shock 6-minute walk <300 m cardiopulmonary test peak VO ₂ ≤12–14 ml/kg/min PCWP) > 16 mmHg RAP > 12 mmHg LVEF < 30%	<i>Vary by age groups:</i> NYHA class for age > 5 years Growth percentile Natriuretic peptide Invasive hemodynamics Cardiopulmonary test Number of hospitalizations per year <i>For congenital heart disease:</i> Refractory arrhythmia Reactive pulmonary HTN Protein losing enteropathy
Outcome	HF hospitalization 28% 1-year HF mortality 20% 5-year HF mortality 53%	Overall mortality HF hospitalization increase death by 20 folds [25]. In hospital mortality 7-10% [25].

Table 2.
The similarities and differences in advanced HF between adult and pediatric populations.

atypical presentation [24]. The HF etiology can be divided by pathophysiology into volume overload, pressure overload, or cardiomyopathies [3]. The differences in etiology and clinical presentation between adults and pediatrics are shown in **Table 2**.

Advanced HF pediatric patients have a more complex profile compared to adults. Their profile includes age, weight, anatomy in CHD cases, severity of illness, and end-organ involvement [24]. Pediatric patients are relatively ill when considered for VAD therapy, with 45% of patients intubated and 94% on inotropes [24]. End organ hypoperfusion can present as intolerance to oral intake, nausea, and vomiting. Nasogastric feeding or total parenteral nutrition was found in 64% of patients during VAD support [24]. Renal dysfunction is associated with worse outcomes post-VAD [24]. The definition is variable based on the patient's age and weight. Renal dysfunction with glomerular filtration rate (GFR) < 60 ml/min was found in 30% of pre-VAD implants [24]. Liver impairment is common due to congestive hepatopathy found in 40% of the pediatric VAD population at the time of LVAD [24]. Hyperbilirubinemia carries a higher rate of mortality and morbidity, especially in children with weights lower than 10 kg [24]. Amdani et al. proposed staging criteria for HF in pediatric patients [26]. The requirements are divided into four stages, 1–4, categorized based on NYHA class for age > 5 years, growth percentile, natriuretic peptide, invasive hemodynamics, cardiopulmonary test, and number of hospitalizations per year [26]. Stage 4 represents severe HF patients who need evaluation for advanced therapies [26].

The percentage of pediatric patients with LVAD implants increased from 11–24% from 2005 to 2016 [25]. Most LVAD implants in pediatrics, either fully implantable or paracorporeal, are implanted in INTERMACS I profile 21–33% [24]. At the time of LVAD, most pediatric patients are inotrope-dependent 81.3% and mechanically ventilated 25.3% [27]. The patients in the Paedi-EUROMACS were from ages 0–19 years [27]. Patients in the INTERMACS I, II, and III profiles were 21%, 49.6% and 19.3%, respectively [27]. The role of LVAD is increasingly recognized; however, most advanced HF centers implant <10 LVADs in children per year [24].

5. Criteria for advanced heart failure in the unique congenital population

The patients with CHD have bi-ventricle physiology, including systemic RV or single ventricle physiology [24, 26]. Classification of advanced HF varies significantly between both physiologies. Currently, > 88% of CHD patients reach adulthood due to the advancement of congenital cardiac surgeries [28]. A Finnish registry reported that the development of HF is around 40% among CHD patients followed up to 20 years post corrective congenital surgeries [26]. Standard GDMT does not have strong evidence in the CHD population. HF medication is required in 20% of patients with CHD [26]. Patients with adult CHD who have advanced HF need early evaluation for advanced therapies [24]. In the Paedi-Euromacs, the mean age of pediatric patients with CHD was 2.5 years, and around 73.5% had a pulsatile flow device [10]. Mortality was higher in the CHD group, at 30.8% [10].

Systemic RV failure is seen in patients with transposition of the great arteries (TGA), congenitally corrected CC-TGA or (L-TGA), and D-TGA after Mustard or Senning surgeries [28, 29]. The single ventricle morphology can be either LV morphology or RV morphology. Patients with RV morphology carry a worse outcome [29]. HF in CHD patients may occur due to arrhythmia, atrioventricular valve regurgitation, thrombosis, or narrowing in the conduit in the Fontan circulation or

in patients with RV-pulmonary artery (PA) conduit [29]. These causes should be corrected before advanced HF therapies are considered [29].

Patients with CHD should be listed for an HT or considered for advanced VAD therapies to improve survival and quality of life. Refractory atrial or ventricular arrhythmia and reactive pulmonary hypertension in CHD patients should prompt evaluation for LVAD or HT [25]. Patients with falling Fontan physiology present with reduced ventricular systolic function, abnormal diastolic function, protein-losing enteropathy, or plastic bronchitis due to abnormal lymphatic drainage and liver and kidney dysfunction due to congestion [25].

6. Implant strategy of mechanical support for heart failure

6.1 Durable LVAD support as destination therapy

The durable LVAD devices are improving long-term survival [30]. The 1-year survival for HM XVE in REMATCH was 52%, compared to 25% survival with optimal GDMT [15]. The HM II destination therapy (DT) showed 1-year and 2-year survival at 46% and 58% [17, 31]. The MOMENTUM3 showed event-free survival at 1-year and 2-year survival rates of 76.9% and 79% [11]. At 5 years, 50% of patients were still on LVAD support, and the event-free survival for DT was 54.8% [18, 30]. Outcomes of LVAD support as a DT did not significantly differ between transplant and non-transplant centers [32]. The 1-year survival of patients on LVAD as DT was 71.3% in a non-transplant center compared to 76.4% in a transplant center [32].

The DT can be provided in a non-transplant center. A study reported a non-significant difference in survival post-DT LVAD in a transplant center compared to a non-transplant center [33]. The freedom of death or major adverse event was similar at 1 year, 76.4% vs. 71.3% in transplant vs. non-transplant centers [33]. For a successful LVAD-DT program, multidisciplinary team availability is key for decision-making [33]. The post-implant care plan must include cardiac rehabilitation, a psychologist, and a social support team [33].

6.2 Devices type and function

The device selection is based on the patient's clinical presentation and INTERMACS score, size, weight, cardiac anatomy, and the intended support duration. The implant strategy is either a bridge therapy to transplant, candidacy, or decision and as a DT. The MCS devices can be subcategorized according to their intended use as short-term and long-term, based on implant technique to percutaneous or surgical devices, and as paracorporeal or intracorporeal devices. They are also described based on pump function to pulsatile or non-pulsatile devices. The devices mentioned in this article are the most recent and commonly reported in the MCS registries (**Table 3**).

The surgically implanted LVAD pumps in the HM XVE, the Thoratec VAD, the Berlin Heart, and the total artificial heart function as pulsatile devices. The continuous-flow VADs are either the axial pump HMII, the Jarvik, or the centrifugal pump HVAD, HMIII. Pulsatile devices tend to be larger pumps implanted extracorporeally or intracorporeally. They are asynchronous with the heart and have intermittent ventricle unloading, thus preserving arterial pulsatility. Pulsatile LVADs have a fixed rate and stroke volumes and are preload-dependent [34].

	Adult registry [8]	Pediatric registry [9, 26]	
Age (years)	57.3 ± 13	7.6 ± 6.4	
Age group			
< 1 year		26.9%	
1–5 years		21.3%	
6–10 years		14.8%	
11–18 years		37.1%	
>18 years			
Gender	Women 21.9%		
Weight (Kg)		32.5 ± 30.5	
Body mass index (KG/m ²)	28.7 ± 7.3		
Body surface area (m ²)		1.07 ± 0.58	
Implant strategy:			
Bridge to recovery		9.2%	
Bridge to candidacy	26.9%	35.5%	
Bridge to transplant	21.9%	49.9%	
Destination	50.4%	1.8%	
Type of device:			
Fully implantable	98.1%*	DCM	55%
Continuous flow		CHD	27.8%
Paracorporeal		DCM	12.9%
Continuous flow		CHD	36.1%
Paracorporeal		DCM	27.2%
Pulsatile flow		CHD	27.8%
Mode of support	LVAD** 93.7% Concomitant RVAD 4.4%	LVAD DCM CHD BiVAD DCM CHD	 84.8% 88% 14% 10.2%
Duration of support		4.6 month	
Adverse events:			
Infection	14.2%	21%	
GI bleeding	13.1%	5%	
CVA	8%	7%	
Survival rate	83% at 1-year	75% at 6-month	
Rate of transplant	20.9%*** at 1-year	56.1% at 6-month**** 65.6% at 1-year****	

BiVAD; Biventricular Assist Device, CHD; Congenital Heart Disease, DCM; Dilated Cardiomyopathy, LVAD; Left Ventricle Assist Device, RVAD; Right Ventricular Assist Device

*The patients with pulsatile flow device were excluded from the registry's final report

**The patients with biventricular or isolated right ventricle assist device were excluded from the registry's final report

***After change of allocation system for patients on HearMate3 support as bridge to transplant

****For all pediatric patients enrolled in Pedimacs

Table 3.

The MCS strategies and outcome in adult and pediatric ventricle assist device registry; INTERMACS and Pedimacs.

In contrast, continuous-flow LVADs are smaller, fully implantable, intracardiac or sub-diaphragmatic pumps. They depend on both preload and afterload; flow is related to the set speed of the pump. Pulsatile LVADs have a higher rate of pump

thrombosis and thromboembolic events; the patients on pulsatile flow devices are not dischargeable. Thus, it is used as a bridge therapy [34].

6.3 Short-term support

Short-term devices in adult or pediatric patients are implanted in patients with low cardiac output and end-organ hypoperfusion when not responding to the inotropic support. The aim is cardiac unloading, improving end-organ perfusion and recovery. The short-term devices can be implanted as a bridge to transplant (BTT) or bridge to bridge for a durable LVAD. However, a multicenter study's transition from extracorporeal life support extracorporeal membrane oxygenation machine (ECMO) to durable VAD remains low, with 30-day survival post-VAD at 77% and 1-year survival at 53% [35]. Short-term continuous-flow devices such as an Impella device are approved for pediatrics with BSA > 1.0 m² for Impella CP 2.5 L, while BSA > 1.5 m² for Impella [24].

6.4 Long-term support

The decision of LVAD is either BTT, to Candidacy (BTC), or DT. This decision may change during the follow-up; the transplant in patients with BTT was 30.4%, BTC was 15.9%, and DT was 4.7% at 1 year of implant [8, 25]. Currently, implantable continuous-flow devices are used for long-term support. The durable devices are used in both adult and pediatric populations.

The Berlin Heart (BH) is considered durable support for intermediate duration and is mainly used for smaller children who are not candidates for HM3. It is a paracorporeal pulsatile device. It has versatile support for either single ventricle or biventricular support as a bridge therapy. In children, the most reported device used in the VAD registry was BH, 51.6%, as LVAD, RVAD, or BiVAD for short-intermediate support duration. A French multicenter study evaluating children on BH support showed a survival rate of 73% [36]. The median duration of support for pediatrics is 4.2 months (0–36 months) as a BT or recovery [27].

7. Mechanical support in the pediatric population

7.1 Size matters

There is limited data on the use of implantable LVAD in pediatrics [37]. Pediatric patients vary in weight and body surface area. Those on the lower end of the spectrum present a unique challenge. The FDA approved the HM3 and HeartWare devices with flows ranging between 2 and 10 L/min [24]. Meanwhile, the BH can provide a flow of 0.6–8 L/min [24]. The Advanced Cardiac Therapies Improving Outcomes Network (ACTION) has published data for pediatric patients who underwent LVAD using HM3 from 2017 to 2022 [38]. The study included 170 patients with a median age of 15.3 years and BSA of 1.68 m² [38]. The inclusion criteria in MOMENTUM 3 were BSA > 1.2 m², while the smallest patient in the ACTION database for HM3 had a BSA of 0.73 m² [11, 38]. The outcomes were promising, with <8% mortality. However, a higher rate of adverse events was noted in patients with BSA < 1.4 m² [38].

In the Paedi-EUROMACS, the 1-year post-VAD survival rate is 81.5% [27]. However, it was less in the patients younger than 1 year and lower weight < 20 kg [27]. A retrospective analysis of the EUROMACS registry for children <19 years of age included 142

patients on continuous-flow LVAD; 28 were HM3 recipients [39]. The HM3 patients had a median age of 14.5 years, a median BSA of 1.6 m^2 (range 1.1–2.1), and a median weight of 60 kg (range 32–86 Kg) [39]. The four-year survival rate was more than 70% [39]. In Pedimacs, the mean age for patients with durable implantable LVAD was 13 ± 3.9 years, and the mean weight was 55.1 ± 28.7 Kg [9]. Meanwhile, the patients receiving pulsatile devices' mean age is 2.7 ± 3.5 years with a mean weight of 11.9 ± 12.2 Kg [9]. In the prospective multicenter feasibility study, Pumps for Kids, Infants, and Neonates (PumpKIN), Jarvik 2015, a miniaturized continuous-flow LVAD was implanted as BT [40]. There were seven patients with a median age of 2.2 years, weight of 10 kg, and BSA of 0.5 m^2 . All patients were successfully transitioned to recovery or transplant [40].

7.2 Implant challenges

When evaluating pediatric patients for implantable continuous-flow LVAD, the approach should consider that the pediatric patient population is not a group of “small adults”. The HM3 device dimensions based on the manufacturer user manual are as follows: height of 55.8 mm including the inflow cannula, 33.8 mm excluding the inflow cannula, and the outer diameter of the pump body 50.3 mm, which may be too large to implant in certain patients [41]. Therefore, when evaluating patients for HM3 implantation, the following parameters should be examined: thoracic cavity, apex size and thickness, distance between LV apex and the mitral valve, presence of apical trabeculations, position of papillary muscles, presence of patches on the ascending aorta, presence of shunts on the ascending aorta, and presence of retrosternal structures that may complicate sternal re-entry [42]. Computed tomography (CT), ECHO, and a “dummy device” are used for better preimplant assessment of the LV and thoracic cavity [43]. In addition, virtual simulated implantation through segmented cardiac CT images was used to reconstruct the patient's anatomy [44].

8. Mechanical support in the congenital heart disease population

In the Pedimacs population between 2012 and 2017, the CHD patients accounted for 108 (24%) of the VAD-supported population [45]. The CHD disease patients with biventricular physiology were 45 patients, while the single ventricle physiology patients were 63 patients [45]. The CHD patients were more often supported with paracorporeal devices and had higher mortality on VAD and lower rates of transplant [45]. The CHD patients compared to cardiomyopathy patients are younger with a mean age of 5.7 ± 5.7 years (32% were < 1 yr) and smaller with a BSA of 0.8 ± 0.5 [45]. The sixth Pedimacs report showed increased utilization of VAD in the CHD cohort $>60\%$ [9]. In the UNOS registry looking at patients <18 years of age, the utilization of BH was implanted in 233 patients with CHD, while patients with cardiomyopathy were 573 patients [46]. The CHD patients supported with BH had an LVAD support of 70.4%, RVAD support of 9.9%, and biventricular support of 19.7% [46].

8.1 Systemic ventricle

Patients with cc-TGA or d-TGA post Mustard or Senning develop systemic RV dysfunction due to high afterload and systemic atrioventricular valve regurgitation [28]. These patients have a higher risk of developing pre- and post-capillary pulmonary hypertension (PHTN) [28]. They usually present in the 3rd or 5th decade with

advanced HF warranting VAD or HT [28]. A case series including five patients with systemic RV underwent VAD implants [28]. Their median age was 39, in the range of 19–49 years [28]. These patients had PHTN with high PVR, median 7.3 woods, in the range 2–9.5 woods [28]. The implant challenge was described due to the moderator band and hypertrophied trabeculae [28]. All five patients had successful transplants [28]. There were no subpulmonic ventricle failures, possibly due to the morphological LV with higher contractile reserve [28].

8.2 Single ventricle

The single ventricle patient population is comprised of three groups depending on their stage of palliation: Stage 1 (Norwood or hybrid), Stage 2 (Bidirectional Glenn shunt), and Stage 3 (Fontan circulation) [45, 47]. Consequently, the implantation of LVADs in each group carries its unique considerations. The patients with a single ventricle physiology in Pedimacs were younger, with a mean age of 3.8 ± 4.6 years compared to biventricular physiology patients of 8.2 ± 6.2 years [45]. The patients with single ventricle have a BSA of 0.6 ± 0.4 m² and worse renal function [45]. Stage 3 single ventricle patients had a higher rate of surviving LVAD support than stages 1 and 2 [45].

A Fontan circulation patient has previously undergone at least two surgeries, making sternal re-entry more difficult. Due to previous ascending aorta augmentation, the ascending aorta may not have enough space for an outflow graft [47]. They are also liable to get complications associated with hepatic congestion such as liver dysfunction and protein-losing enteropathy. consequently, the International Society of Heart and lung Transplantation (ISHLT) mechanical circulatory support guidelines designated the indication for LVAD insertion in the patient with a single ventricle physiology as a class IIb indication.

9. Long-term challenges of MCS

9.1 The impact of rehospitalization post-LVAD

Patients with LVAD implants are a high-risk population. The most common adverse events leading to rehospitalization are VAD-related or unrelated infection, gastrointestinal bleeding (GI), HF-related hospitalization, and thrombotic events [48]. In a 2-year follow-up of HM3 study patients, the rehospitalization rate for all-cause was 90.7% vs. 93.2% in the HMII group. The HF-related hospitalization rate was 19.2% in HM3 vs. 13.8% in the HMII group. The rate of GI bleeding was 20.6% in HM3 vs. 24.4% in HMII, while major driveline infection was 15.9% in HM3 vs. 13% in HMII [48]. The rehospitalization due to HF-related causes and GI bleeding were associated with lower long-term survival. The higher-risk patients for HF readmission are patients with high RA pressure preimplant, renal impairment, obesity, use of ICD or cardiac resynchronization therapy device (CRTD), and older age [48].

9.2 Right ventricle dysfunction

9.2.1 Survival in patients with early and late RV dysfunction

The right ventricle (RV) dysfunction can occur acutely post-LVAD implant or late after LVAD implant [25]. RV failure is defined by the presence of elevated

right-sided filling pressure with right atrial pressure (RAP) > 16 mmHg, or ECHO finding of dilated inferior vena cava with lack or respiratory variation, clinical finding of edema and worsening hepatic and renal function requiring prolonged use of inotropes, or the use of an RVAD [34, 49]. RV failure post-LVAD is associated with higher mortality and morbidity, including bleeding, renal failure, and prolonged length of stay [34]. In the HeartMate II (HMII) BTT trial, the incidence of RV failure was 20% [34, 50]. In the HMII DT trial, RVAD was used in 4% of patients post-LVAD implant [34, 50]. Acute RV failure requiring prolonged RVAD support post-implant should be listed for heart transplant [25]. The progressive RV failure post-implant should also be considered for a heart transplant [25]. Late RV failure can occur in 10% of patients and is associated with a higher rate of rehospitalization, bleeding, stroke, and infection [49]. Patients who developed mild or moderate RV failure within 3 months post-LVAD had lower survival compared to patients with no RV failure [49]. 1-year mortality for patients with mild RV failure was 16.7%, and for moderate RV failure was 28.1%, compared to patients without RV dysfunction, 6.9% [49]. Risk assessment for RV failure is crucial when evaluating candidates for LVAD implants [51].

9.2.2 Predictors of RV failure post-LVAD; a reminder

Several studies have reported predictors for RV failure post-LVAD. The risks of RV failure include preimplant inotrope and vasopressor requirement, invasive ventilation, high bilirubin, increased liver enzymes, coagulopathy, hypoalbuminemia <3.3 g/dl, high urea >51 mg/dl, thrombocytopenia, and low hematocrit <34% [34]. Invasive hemodynamics predictors include central venous pressure (CVP) > 15 mmHg and systolic pulmonary artery pressure (PAP) < 50 mmHg. The calculated right ventricle stroke volume index (RVSWI) < 600 has been shown to predict RV failure by 38% [34]. Pulmonary artery pulsatility index (PAPi), defined as [(systolic PAP – diastolic PAP)/CVP] [52]. The PAPi score of 2.0 has a sensitivity (74%) and specificity (67%) for predicting RV failure post-LVAD implant, with an odds ratio (OR) of 0.49 [52]. The multivariable risk score, including destination LVAD strategy, use of IABP, inotropes, GDMT, obesity, and pulmonary vascular resistance (PVR), correlates with the incidence of RV failure [53]. A score of <5 has a probability of RV failure of 11%, while a high score of >12.5 has an 83% probability of RV failure post-LVAD implant [53]. Echocardiography (ECHO) is the cornerstone of RV assessment before LVAD implants. The ECHO assessment for RV size and systolic function evaluation using the following parameters: RV end-diastolic dimension (RVEDD) and the RV to LV end-diastolic dimension (LVEDD) ratio, tricuspid annular plane systolic excursion (TAPSE), RV systolic wave velocity (S'), fractional area change (FAC), and degree of tricuspid regurgitation [54, 55]. The TAPSE <12.5 mm has a sensitivity (84%) and specificity (75%) for predicting RV failure post-LVAD implant [56]. Severe tricuspid valve regurgitation is associated with early RV failure post-LVAD [34].

9.3 Role of neurohormonal blockade in LVAD patients

The role of neurohormonal therapy and ongoing HF management is vital post-LVAD implant. The data from the INTERMACS registry showed that 16.2% of LVAD patients were on triple therapy (beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers and mineralocorticoids at 6-month post-LVAD) [57]. In comparison, 14.2% of patients were not receiving any neurohormonal

blockade [57]. This study had shown a higher survival rate in patients on neurohormonal blockade compared to patients who did not receive neurohormonal blockade (56.0%; 95% CI, 54.5%–57.5% vs. 43.9%; 95% CI, 40.5%–47.7%) [57].

9.4 Infection in VAD patients, prevention, and management challenges

9.4.1 Incidence and risk factors

Infection is the leading cause of mortality and rehospitalization in adult LVAD patients. The rate of LVAD infection is 22.4% within 90 days of implant and 31.5% after 90 days of implant [12]. The LVAD infection accounts for 13.5% of rehospitalizations [12]. There is an improvement in the survival rate for pediatric patients post-VAD implants, with fewer adverse events except for infection [9]. The incidence of infection within 2 weeks of the implant was 12%, and after 2 weeks, it increased to 21% in the Pedimacs registry [9]. The infection rate for pediatric patients supported with continuous-flow implantable devices was 28% [9]. The infection rate within 90 days of implanting a pulsatile paracorporeal device is 17%, and beyond 90 days, it is 14.5% [12]. Similarly, patients with continuous-flow devices had an infection rate within 90 days of 16%, and beyond 90 days, it was 18%. In the pediatric Euromacs registry, the mortality related to infection was 6% [12]. In Pedimacs, infection accounted for 17% of the reported adverse events, mainly non-VAD-related infection [58].

The clinical risk factors associated with VAD-related infection are age, obesity or malnutrition, renal disease, diabetes, and smoking [59, 60]. Prolonged length of stay in the intensive care unit post-implant, invasive central or arterial lines, and delayed sternal closure increase the risk of infection [60]. The duration of LVAD support as DT increases the risk of infection. Patients with the HM3 devices compared to HMII had a higher rate of readmission due to DLI infection, 21.7% vs. 8.7% in a single-center study [59]. In the MOMENTUM3 trial final report, DLI in HM3 patients was 23.3% compared to HMII 19.4% [59]. This is explained by the size of the HM3 driveline diameter, the rigid composition of the driveline (polyurethane + silicone), and the connection to the system monitor may cause additional load and traction of the driveline, leading to trauma [59].

The Driveline Expert Staging and Care (DESTINE) recommended standardized surveillance and procedures related to driveline exit site dressing [60]. This recommendation aims to prevent driveline infection (DLI) by standardizing the driveline fixation technique, dressing change steps, and the required equipment [60]. A multidisciplinary LVAD team with trained nurses in exit site dressing and DLI monitoring ensures compliance with the standard of care [60]. In addition, training patients and caregivers on self-care improves quality of life and patient satisfaction [60].

9.4.2 Classification of infections in VAD patients

VAD-specific infections include infections specific to patients with VADs, related to the device hardware, and not occurring in non-VAD patients [61]. Examples include pump and cannula infections, pocket infections, and percutaneous DLI [61]. VAD-related infection also includes central line-associated bloodstream infections, mediastinitis or sternal wound infections. DLI staging presented in the DESTINE paper includes local assessment for erythema, discharge, or presence of pus around the driveline exit site, with or without positive cultures [60]. Deep DLI, when there is tenderness or bleeding with significant pus collection and discharge, can be

associated with dehiscence and abscesses around the driveline [60]. Severe infections include fever, bacteremia, and systemic infection [60].

In deep VAD-related infection involving the pocket, pump, and cannula infection, a heart transplant listing is recommended [25]. Patients who have resistant VAD-related infection without severe systemic infection or sepsis should be listed for heart transplant [25]. However, meta-analysis shows 30% post-transplant mortality in patients with LVAD infection [25].

9.5 Hemocompatibility

9.5.1 Bleeding-related adverse event

Gastrointestinal (GI) bleeding occurs in 15–30% of patients with LVADs [25]. The MOMENTUM 3 trial demonstrated an equally high rate of GI bleeding (27%) in patients with the centrifugal flow HM3 or an axial flow HM2 device [11]. Less strict inclusion criteria in the real world and utilization of LVADs across a broader range of patients for a longer duration could translate into rates of GI bleeding of up to 40% [62]. GI bleeds are associated with significant morbidity related to recurrent hospitalizations, prolonged length of stay, the need for transfusions, and possibly higher sensitization [62].

Several factors predispose to GI bleeding among patients with LVADs. Aside from the anticoagulant and antiplatelet regimens that inherently increase the risk of bleeding, factors related to the design and operational elements of LVADs are postulated to contribute directly to the risk of bleeding. For example, acquired von Willebrand syndrome is common among patients who experience bleeding with continuous-flow LVADs [63]. The syndrome may arise due to sheer stress that unravels the protein and predisposes it to breakdown by ADAMTS13. Alterations in angiogenic signals may also directly contribute to the development of angiodysplasias [64]. The most common source of GI bleeding is the upper GI tract. However, bleeds from the midgut (ligament of Treitz to the ileocecal valve) or an unknown source could account for 45% of all GI bleeds [62]. Notably, between 30% and 40% of bleeds are due to arteriovenous malformations (AVMs) that typically develop in the midgut [62].

After ensuring hemodynamic stabilization, controlling the source of bleeding requires upper and/or lower GI endoscopy. The overall yield of conventional endoscopy to identify a source for bleeding in patients with LVADs is 50% [65]. Therefore, if no lesion is identified, push enteroscopy could be considered to assess the midgut where AVMs are common. An alternative option is capsule endoscopy or a tagged red blood cell scan in the case of rapid bleeding. The specific treatment strategy can be tailored based on the results of these investigations.

The intensity of the antithrombotic regimen could be reduced while remaining aligned with the latest recommendations discussed later. Octreotide, a somatostatin analogue, is associated with reduced portal pressures, enhanced platelet aggregation, decreased angiogenesis, and a 40% reduction in GI bleeding rates [66]. Therefore, it is a first-line agent among many therapies examined to reduce the recurrence of GI bleeding in patients with LVADs.

9.5.2 Thrombosis-related adverse events

Pump thrombosis and embolism have been among the most feared complications of LVAD therapy. To reduce the risk of these complications, guidelines from

the International Society of Heart and Lung Transplantation (ISHLT) have recommended using aspirin and warfarin with a target International Normalized Ratio (INR) between 2.0 and 3.0 [67]. Before LVAD implantation, patients with heart failure can have several factors that predispose to bleeding, such as hepatic and renal dysfunction, poor nutrition, and stress ulcers. The implantation procedure itself is associated with a substantial risk of bleeding, and the long-term post-implantation risk of bleeding remains elevated. All these factors complicate the post-operative initiation and maintenance of antithrombotic regimen to reduce the risks of thrombosis and embolism.

Therefore, a key focus in designing the latest generation and only currently approved centrifugal pump, the HM3, was to reduce the risk of thrombosis. This was achieved by engineering a frictionless design that uses magnetic levitation, an intrinsic pulse that reduces stasis, and wide blood flow passages that minimize shear stress. In the MOMENTUM 3 trial, only two patients had suspected or confirmed pump thrombosis with HM3, accounting for 1.1% of patients in the HM3 arm of the study [11]. This compared to 27 patients (15.7%) who had similar events with the HM2, translating to a hazard ratio (HR) of 0.06 (95% confidence interval 0.06–0.26) [11]. While 21 patients (12.2%) with HM2 required reoperation or device removal for thrombosis, none with HM3 reoperation needed for a similar indication [11].

The risk of ischemic stroke was also lower (6.3%) in patients with HM3 compared with HM2 (13.4%), HR 0.44 (95% CI 0.22–0.88) [11]. Although the risk of thromboembolism has been reduced with HM3, there remains a residual risk. Additionally, patients who were implanted with other LVAD devices (e.g., HeartWare, HM2) and are currently alive have a higher risk of thromboembolic complications. Therefore, routine monitoring for pump thrombosis is necessary by assessing for power elevations, isolated increase in lactate dehydrogenase (LDH), evidence of overt hemolysis, and new onset HF. If sustained (> 24 hours) power elevations or an isolated increase in LDH (> $\times 3$ upper limit of normal) is encountered without overt hemolysis or HF, further workup includes ECHO to assess whether the unloading of the LV is suboptimal. LV dilatation, ventricular septal deviation to the right, frequent opening of the aortic valve, worsening mitral regurgitation, left atrial dilatation, higher PAP, RV dilatation, and worsening tricuspid regurgitation could indicate suboptimal pump function. A ramp study that assesses the response of LV size to pump speed changes may be more sensitive for pump malfunction. Should these investigations lead to a higher suspicion of pump thrombosis, or if the patient presents with unexplained overt hemolysis or HF, a chest CT angiogram is advised to assess the inflow cannula and outflow graft for malposition or obstruction.

Subclinical thrombosis may be managed with intensifying the antithrombotic regimen as an initial measure, followed by direct thrombin inhibitors. Thrombosis with hemodynamic compromise or end-organ dysfunction requires an urgent evaluation for the possibility of pump exchange or urgent heart transplantation. Patients who are not surgical candidates could be considered for thrombolytic therapy [68].

9.5.3 Newer evidence of anticoagulation

Given the decrease in the risk of thrombosis with the newest generation of LVAD therapy, there has been an ongoing effort to re-evaluate the traditional antithrombotic regimen that combines an antiplatelet (e.g., aspirin) agent with an anticoagulant (e.g., warfarin) to reduce the risk of bleeding. In the ARIES-HM3 trial, patients that underwent implantation of the HeartMate 3 LVAD were randomized to aspirin 100 mg daily

(n = 314) versus avoidance of aspirin (n = 314) [69]. All patients were treated with warfarin. After a median follow-up of 14 months, avoidance of aspirin was associated with a 34% decreased risk of major nonsurgical bleeding without an increase in thromboembolic risk, even among those with prior vascular disease, coronary artery disease, obesity, or diabetes [69]. The study strongly suggested that aspirin is not required to maintain outcomes with the HM3 LVAD.

Direct oral anticoagulants (DOACs) were evaluated in the DOAC LVAD study [70]. In this phase 2 trial of 30 subjects, 14 patients were randomized to warfarin and 16 patients to apixaban on background therapy with aspirin. The study evaluated the primary composite outcome of freedom from death, stroke, device thrombosis, major bleeding, aortic root thrombosis, and arterial non-central nervous system thrombosis. After a follow-up period of 24 weeks, the primary composite outcome occurred in no patients receiving apixaban and two patients receiving warfarin (14%), both of whom experienced major GI bleeding [70]. This study paves the way for future pivotal phase 3 trials.

10. The importance of multi-disciplinary teams in advanced HF programs

The “Heart Team”, multidisciplinary cardiovascular team, has significantly facilitated patient selection and post-intervention care for revascularization and aortic stenosis interventional programs [71]. The team members in LVAD or MCS programs include a cardiologist, a cardiac surgeon, an LVAD coordinator, a nurse practitioner, a clinical pharmacist, a psychologist, and a social worker [51, 71].

In LVAD programs, the role of the heart team involves patient selection from medical, surgical, and psychosocial readiness for LVAD. In addition, the healthcare team education around implant and post-implant care. Most importantly, outpatient follow-up for anticoagulation, exit site care, psychosocial support, and HT assessment. The multidisciplinary team approach has been shown to improve survival and reduce long-term complications [71]. The standard of care of driveline exit site management emphasizes the VAD team’s role in lowering DLI. The VAD team includes surgeons, cardiologists, nurses, home health care, cardiac rehab centers, and caregivers [22].

11. Emerging technologies in MCS

Despite the advancement in the LVAD therapy, further innovations are required to improve the device’s longevity and meet the demands of the diverse HF population. The unmet needs in LVAD therapies are related to pump design, driveline, and external charging batteries. Emerging technologies address novel designs that can support patients with small BSA and biventricular failure, transcutaneous energy transfer and improve device hemocompatibility [72]. In addition, the emerging artificial intelligence (AI) can improve patient selection, surgical planning for LVAD implants, and prediction models of RV failure post-implant [72]. Finally, long-term management of patients post-LVAD with remote-monitoring can improve health and quality of life of these patients [72].

12. Conclusion

The VAD therapy is a cornerstone of advanced HF management. The benefits have been reported in clinical trials and registries across adult and pediatric populations,

with variability in patients' size and LV morphology. There is a need to develop consensus pathways for managing young children and CHD patients presenting with advanced HF. Creating a multidisciplinary team for VAD patient care will enhance clinical outcomes for these patients.

Conflict of interest

There are no conflicts of interest related to this publication.

Nomenclature

ACTION	advanced cardiac therapies improving outcomes network
ARIES-HM3	antiplatelet removal and hemocompatibility events with the HeartMate 3 pump
BH	Berlin heart
BMI	body mass index
BNP	brain natriuretic peptide
BSA	body surface area
BTC	bridge to candidacy
BTT	bridge to transplant
CHD	congenital heart disease
CRTD	cardiac resynchronization therapy device
DCM	dilated cardiomyopathy
DESTINE	driveline expert staging and care
DLI	driveline infection
DOAC	direct oral anticoagulants
DT	destination therapy
ECHO	echocardiography
ECMO	extracorporeal membrane oxygenation machine
EUROMACS	Paedi-European Registry for patients with mechanical circulatory support
FAC	fractional area change
GDMT	guideline-directed medical therapies
GI	gastrointestinal
HF	heart failure
HM	HeartMate
HT	heart transplant
ICD	Intracardiac Defibrillator
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
ISHLT	International Society of Heart and Lung Transplantation
LV	left ventricle
LVAD	left ventricle assist device
LVEF	left ventricle ejection fraction
LVEDD	LV end-diastolic dimension
MedaMACS	Medical Arm of Mechanically Assisted Circulatory Support study
MCS	mechanical circulatory support
MOMENTUM3	MagLev technology in patients undergoing mechanical circulatory support therapy with HeartMate 3

NYHA	New York Heart Association
OPTN	The Organ Procurement and Transplant Network
PCWP	pulmonary capillary wedge pressure
Pedimacs	Interagency Registry for Mechanical Circulatory Support
PumpKIN	Pumps for Kids, Infants, and Neonates
PVR	pulmonary vascular resistance
RAP	right atrial pressure
REMATCH	The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure
RV	right ventricle
RVAD	right ventricle assist device
RVEDD	right ventricle end-diastolic dimension
RVSWI	right ventricle stroke volume index (RVSWI)
S'	RV systolic wave velocity
TAPSE	tricuspid annular plane systolic excursion
VAD	Ventricle Assist Device

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Section 2

Innovations in Heart Transplantation

Cardiac Transplantation: Echocardiographic Approach

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Abstract

Heart transplantation, predominantly orthotopic heart transplantation (OHT), serves as a critical intervention for end-stage heart failure. Post-transplant complications, including rejection, cardiac allograft vasculopathy (CAV), and primary graft dysfunction (PGD), pose significant challenges requiring meticulous monitoring. Echocardiography emerges as an indispensable tool in this context, facilitating early detection of complications and guiding clinical management. This document, aligned with ISHLT and ASE guidelines, outlines a structured echocardiographic surveillance strategy for transplant recipients. It underscores the importance of clinicians adeptly requesting and interpreting echocardiographic data to inform decision-making. Real-world clinical cases illustrate the application of key parameters—such as TAPSE, RV free-wall strain, LV global longitudinal strain (GLS), and mechanical dispersion—in risk stratification across scenarios like right ventricular dysfunction, subclinical rejection, and arrhythmic risk. The semaforization system categorizes patients into low, moderate, or high risk, aiding tailored interventions. Furthermore, the document explores future directions, notably the integration of artificial intelligence, which promises to enhance echocardiographic precision. It aims to empower clinicians to translate imaging findings into actionable clinical strategies, improving patient outcomes. Ultimately, it reaffirms echocardiography's pivotal role in post-transplant care and emphasizes the value of interdisciplinary collaboration in optimizing heart transplant success.

Keywords: echocardiography, heart transplantation, graft rejection, cardiac allograft vasculopathy, mechanical dispersion, complications

1. Introduction

Heart transplantation remains, even today, the definitive option for patients with end-stage heart failure when conventional treatments no longer provide relief. Since the first successful clinical experiences, survival and long-term outcomes have consistently improved, establishing transplantation as the gold standard for advanced heart failure [1–13]. It offers survival and quality of life that no other therapy can match [14].

Of the different transplant techniques described—orthotopic, heterotopic, domino, donation after circulatory death (DCD), and even the experimental xenotransplant—the orthotopic heart transplant (OHT) is by far the most widely performed and the one with the most robust evidence to guide daily practice [14]. For this reason,

this chapter will focus mainly on OHT, while occasionally highlighting specific nuances of other techniques where clinically relevant [4].

Echocardiography has become the central imaging tool in the follow-up of these patients. It not only allows monitoring of graft function, but also facilitates the early detection of complications such as rejection, cardiac allograft vasculopathy (CAV), or primary graft dysfunction (PGD) [15, 16]. For the transplant cardiologist, echocardiography is not just a complementary test; it is often the first window into the functional state of the allograft, guiding decisions on immunosuppression, the need for biopsy, or advanced therapies [15]. Beyond the ventricular assessment, parameters such as atrial strain have also shown growing prognostic value in transplant recipients.

The clinical problems we face in follow-up are diverse. Acute rejection can present silently or with sudden hemodynamic deterioration. CAV progresses insidiously and is frequently under-recognized until advanced stages. PGD, on the other hand, remains a dreaded complication in the early postoperative period [17]. Each of these entities requires timely recognition, and echocardiography—especially when integrated with biomarkers and hemodynamic data—offers the possibility of anticipating adverse outcomes [18].

This chapter has a very practical purpose: to provide clinicians with tools to ask the right questions of echocardiography and to interpret its findings in a way that translates directly into the patient management. It is not only about measuring dimensions or calculating gradients; it is about knowing what to do with those results in the real-world transplant clinic [4].

To make it useful for the reader, the following sections are organized around clinical cases. Each case presents a problem commonly encountered in practice and is analyzed with a risk-stratification system (“traffic-light risk stratification system”), including interpretation, plan of action, and level of evidence. In this way, the text avoids staying at the theoretical level and instead provides concrete decision-making tools [19].

2. Case 1: The right ventricle in distress

Scenario: A 45-year-old male, 1 month post-transplant, presenting with worsening dyspnea (**Table 1**).

Clinical question: How can echocardiography identify right ventricular dysfunction?

Parameter	 Low risk	 Moderate risk	 High risk	LOE/references
TAPSE (mm)	>15	12–15	<12	I, B [16, 20]
RV free-wall strain (%)	> –20	–17 to –20	< –17	I, B [21, 22]
Pulmonary vascular resistance (WU)	<2	2–3	>3	I, A [15, 16]
BNP/NT-proBNP (pg/mL)	<1000	1000–2000	>2000	I, A [15, 23]

Table 1.
Risk stratification (traffic light table).

2.1 Clinical interpretation

- Low risk: routine follow-up, echo every 6 months, monitor strain and TAPSE (IIa, B, [16, 20]).
- Moderate risk: optimize pulmonary vasodilators, adjust diuretics (I, B, [15, 16]).
- High risk: right heart catheterization and consider ECMO or RVAD (I, A, [15, 23]).

2.2 Plan of action

1. Immediate right heart catheterization if pulmonary hypertension is suspected.
2. Adjust immunosuppression and vasodilators.
3. Evaluate for ECMO or RVAD if severe dysfunction persists.

Clinical pearl: TAPSE alone can miss early dysfunction; RV strain is more sensitive in transplant patients.

3. Case 2: Silent rejection - What you cannot see might hurt you

Scenario: A 55-year-old female, 3 months post-transplant, completely asymptomatic.

Clinical question: What is the role of strain imaging in detecting subclinical rejection? (Table 2).

Parameter	● Low risk	● Moderate risk	● High risk	LOE/references
LV Global Longitudinal Strain (GLS, %)	> -18	-16 to -18	< -16	I, A [21, 22, 24, 25]
LVEF (%)	>55	50-55	<50	I, A [20]
BNP/NT-proBNP (pg/mL)	<1000	1000-2000	>2000	IIa, B [15, 23]
Troponin	Normal	Slightly ↑	Markedly ↑	IIa, B [15]

Table 2.
Strain-based risk stratification for silent rejection.

3.1 Clinical interpretation

- Low risk: continue routine follow-up, echo every 6 months (IIa, B, [20-22]).
- Moderate risk: repeat strain in 1-2 weeks, add biomarkers (I, B, [15, 21-25]).
- High risk: immediate biopsy and immunosuppression adjustment (I, A, [15, 26, 27]).

3.2 Plan of action

1. Strain imaging every 3 months.
2. Use biomarkers (BNP, troponin) to guide therapy.
3. Biopsy if GLS worsens or biomarkers increase.

Clinical pearl: A declining GLS, even with preserved EF, is often the earliest signal of acute rejection.

4. Case 3: Predicting sudden death

Scenario: A 52-year-old male, 2 years post-transplant, with unexplained syncope and normal ECG.

Clinical question: Can echocardiography predict life-threatening arrhythmic events? (**Table 3**)

Parameter	● Low risk	● Moderate risk	● High risk	LOE/references
GLS (%)	> -18	-16 to -18	< -16	I, A [21, 22, 24, 25]
Mechanical dispersion (ms)	<40	40–50	>50	I, B [19]
LVEF (%)	>55	40–55	<40	I, A [20]
Late gadolinium enhancement (CMR)	Absent	Mild	Extensive	I, A [18, 28]
NSVT (Holter, episodes/day)	<1	1–5	>5	IIa, B [14, 29]

Table 3.
Arrhythmic risk stratification after transplantation.

4.1 Clinical interpretation

- ● Low risk: annual Holter + strain imaging (IIa, B, [29]) [14, 29].
- ● Moderate risk: Holter every 6 months + CMR (I, B, [28]) [14, 18, 29].
- ● High risk: EP study and consider ICD implantation (I, A, [19]).

4.2 Plan of action

1. Serial Holter and strain monitoring.
2. Perform CMR for fibrosis detection.
3. ICD in patients with significant mechanical dispersion or recurrent NSVT.

Clinical pearl: Mechanical dispersion, more than EF, reveals the arrhythmic substrate after transplant.

5. Case 4: Advanced mechanical dispersion and arrhythmia risk

Scenario: A 60-year-old male, 5 years post-transplant, presenting with palpitations and a history of ventricular arrhythmias.

Clinical question: What role does mechanical dispersion play in arrhythmia risk assessment post-transplant? (**Table 4**).

Parameter	● Low risk	● Moderate risk	● High risk	LOE/references
Mechanical dispersion (ms)	<40	40–50	>50	I, A [19, 30]
GLS (%)	> -18	-16 to -18	< -16	I, B [21, 22, 24]
LVEF (%)	>55	40–55	<40	I, A [20]
NSVT (Holter, episodes/day)	<1	1–5	>5	IIa, B [14, 29]
QTc prolongation	None	Mild	Severe	IIa, B

Table 4.
Mechanical dispersion risk stratification.

5.1 Clinical interpretation

- Low risk: annual Holter and strain monitoring (IIa, B, [29]) [14, 29].
- Moderate risk: Holter every 6 months, consider EP study (I, B, [30])
- High risk: urgent referral for ICD implantation (I, A, [23]).

5.2 Plan of action

1. Holter + strain monitoring.
2. Consider electrophysiology study in moderate risk.
3. ICD if NSVT or dispersion abnormalities confirmed.

Clinical pearl: Mechanical dispersion is more reliable than EF alone to identify arrhythmia-prone grafts.

6. Case 5: Right ventricular dysfunction post-transplant

Scenario: A 58-year-old male, 1-year post-transplant, presenting with exertional dyspnea and signs of right heart failure.

Clinical question: How can echocardiography help differentiate primary graft dysfunction from pulmonary hypertension-related RV failure? (**Table 5**).

Parameter	● Low risk	● Moderate risk	● High risk	LOE/ references
TAPSE (mm)	>15	12–15	<12	I, A [16, 20]
RV Free-Wall Strain (%)	> -20	-17 to -20	< -17	I, B [21, 22]
Pulmonary Artery Pressure (mmHg)	<25	25–35	>35	I, A [15, 16]
BNP/NT-proBNP (pg/mL)	<1000	1000–2000	>2000	Ia, B [15, 23]

Table 5.
Right ventricular dysfunction risk stratification.

6.1 Clinical interpretation

- Low risk: optimize volume status, routine follow-up (IIa, B, [15]).
- Moderate risk: cardiac MRI for fibrosis, serial echo follow-up (I, B, [18, 23]).
- High risk: right heart cath and advanced therapies (I, A, [15, 16]).

6.2 Plan of action

1. Optimize diuretics and preload.
2. Perform echo follow-up with strain every 3–6 months.
3. RHC for advanced therapies if high risk.

Clinical pearl: RV strain and hemodynamic confirmation distinguish graft dysfunction from pulmonary hypertension.

7. Case 6: The electrical storm - Ventricular arrhythmias post-transplant

Scenario: A 50-year-old male, 3 years post-transplant, presenting with sustained ventricular tachycardia and syncope.

Clinical question: What echocardiographic markers can predict arrhythmogenic risk post-transplant? (Table 6).

Parameter	● Low risk	● Moderate risk	● High risk	LOE/references
GLS (%)	> -18	-16 to -18	< -16	I, A [21, 22, 24]
Mechanical Dispersion (ms)	<40	40–50	>50	I, B [19, 30]
LVEF (%)	>55	40–55	<40	I, A [20]
NSVT (Holter, episodes/day)	<1	1–5	>5	Ia, B [14, 29]

Table 6.
Electrical storm risk stratification.

7.1 Clinical interpretation

- Low risk: routine annual Holter and echo follow-up (IIa, B, [14, 29]).
- Moderate risk: Holter every 6 months, consider EP study (I, B, [14, 29, 30]).
- High risk: immediate ICD placement and antiarrhythmic therapy (I, A, [14, 19, 29]).

7.2 Plan of action

1. Serial Holter + strain imaging.
2. EP study in moderate risk.
3. ICD for recurrent NSVT or high dispersion

Clinical pearl: Arrhythmic storms post-transplant demand aggressive risk-based stratification dispersion and GLS guide decisions beyond EF.

8. Case 7: The hidden right atrium - Unmasking a subtle player

Scenario: A 57-year-old female, 2 years post-transplant, with persistent fatigue and mild exertional dyspnea.

Clinical Question: Can echocardiographic assessment of the right atrium provide insight into graft dysfunction? (Table 7).

Parameter	● Low risk	● Moderate risk	● High risk	LOE/references
RA area (cm ²)	<18	18–22	>22	I, A [16, 20]
RA pressure (mmHg)	<8	8–12	>12	I, B [16, 20]
IVC collapsibility (%)	>50	30–50	<30	IIa, B [16, 20]
TR gradient (mmHg)	<25	25–35	>35	IIa, B [16, 20]

Table 7.
Right atrial involvement risk stratification.

8.1 Clinical interpretation

- Low risk: routine follow-up with RA and IVC monitoring (IIa, B, [16, 20]).
- Moderate risk: consider right heart cath to confirm pressures (I, B, [15, 16]).
- High risk: evaluate for rejection or progressive graft failure with biopsy (I, A, [15]).

8.2 Plan of action

1. Echo follow-up with RA metrics every 6 months.
2. RHC in moderate-risk patients.
3. In high risk, biopsy and adjust immunosuppression accordingly.

Clinical pearl: RA enlargement and pressure rise often precede overt RV dysfunction — do not ignore “the silent atrium.”

9. Case 8: The silent saboteur—Cardiac allograft vasculopathy (CAV)

Scenario: A 63-year-old male, 6 years post-transplant, presenting with exertional dyspnea, prior normal coronary angiography 1 year ago.

Clinical question: Can echocardiography detect early signs of CAV before angiographic evidence? (Table 8).

Parameter	● Low risk	● Moderate risk	● High risk	LOE/references
Coronary flow reserve (CFR)	>2.5	2.0–2.5	<2.0	I, A [31, 32]
Myocardial perfusion (CMR)	Normal	Mild defect	Severe defect	I, B [33, 34]
GLS (%)	> –18	–16 to –18	< –16	I, A [21, 22, 24, 25]
Diastolic function (E/e')	<8	8–14	>14	IIa, B [23, 35–37]
E-wave deceleration (ms)	>200	150–200	≤150	I, A [35, 36]

Table 8.
Cardiac allograft vasculopathy risk stratification.

9.1 Clinical interpretation

- ● Low risk: annual echo, risk factor control (IIa, B, [15, 31, 32, 38]).
- ● Moderate risk: stress echo, evaluate CFR (I, B, [15, 31–34, 39]).
- ● High risk: invasive coronary assessment, therapy adjustment (I, A, [15, 40, 41]).

9.2 Plan of action

1. Monitor GLS and diastolic indices annually.
2. Stress echo and CFR testing in moderate risk.
3. Coronary angiography for high-risk cases.

Clinical pearl: CAV is often invisible to angiography early on—strain and CFR unmask the disease earlier.

10. Case 9: The electrical storm—Tackling ventricular arrhythmias

Scenario: A 55-year-old male, 4 years post-transplant, with recurrent NSVT and occasional syncope.

Clinical question: How can echocardiography stratify ventricular arrhythmia risk post-transplant? (**Table 9**).

Parameter	● Low risk	● Moderate risk	● High risk	LOE/references
GLS (%)	> -18	-16 to -18	< -16	I, A [21, 22, 24, 25]
Mechanical dispersion (ms)	< 40	40–50	> 50	I, B [19, 30]
LVEF (%)	> 55	40–55	< 40	I, A [20]
NSVT (Holter)	< 1 episode/day	1–5	> 5	IIa, B [14, 29]
QTc prolongation	None	Mild	Severe	IIa, B

Table 9.
Post-transplant ventricular arrhythmia risk stratification.

10.1 Clinical interpretation

- Low risk: annual Holter + echo (IIa, B, [14, 29]).
- Moderate risk: Holter q6 months, consider EP study (I, B, [14, 29, 30]).
- High risk: ICD + antiarrhythmics (I, A, [14, 19, 29]).

10.2 Plan of action

1. Serial Holter and strain.
2. EP study in moderate risk.
3. ICD in recurrent NSVT or abnormal dispersion.

Clinical pearl: *Post-transplant arrhythmias may reflect subtle fibrosis or dispersion — never rely on EF alone.*

11. Case 10: The long road—Chronic surveillance in a stable but fragile patient

Scenario: A 60-year-old female, 8 years post-transplant, presenting with progressive exercise intolerance and mild right heart failure.

Clinical question: How can echocardiography help guide long-term management in stable transplant recipients with progressive symptoms? (**Table 10**).

Parameter	● Low risk	● Moderate risk	● High risk	LOE/References
LVEF (%)	>55	45–55	<45	I, A [20]
RV function (TAPSE, mm)	>15	12–15	<12	I, B [16, 20]
Diastolic dysfunction (E/e')	<8	8–14	>14	IIa, B [23, 35, 36]
BNP/NT-proBNP (pg/mL)	<1000	1000–2000	>2000	IIa, B [15, 23]

Table 10.
Long-term surveillance echocardiographic risk stratification.

11.1 Clinical interpretation

- Low risk: routine annual echo and BNP (IIa, B, [15, 20, 23]).
- Moderate risk: RHC + extra imaging (I, B, [15, 16, 18]).
- High risk: biopsy, advanced imaging, therapy adjustment (I, A, [15, 18, 28]).

11.2 Plan of action

1. Serial BNP and echo.
2. RHC in moderate risk with unclear physiology.
3. Intensify therapy or biopsy in high-risk patients.

✓ *Clinical pearl: A normal EF is not reassuring in a transplant heart—diastolic indices and BNP often tell the true story.*

12. Case 11: Vasculopathy detection through diastolic dysfunction

Scenario: A 60-year-old male, 4 years post-transplant, presenting with exertional dyspnea.

Clinical question: How can diastolic dysfunction parameters unmask cardiac allograft vasculopathy (CAV)? (**Table 11**).

Parameter	● Low risk	● Moderate risk	● High risk	LOE/references
E-wave deceleration (ms)	>200	150–200	≤150	I, A [35, 36]
LV GLS (%)	> –18	–16 to –18	< –16	I, B [21, 22, 24, 25]
E/e' ratio	<8	8–14	>14	IIa, B [23, 35–37]
LVEF (%)	>55	50–55	<50	I, A [20]

Table 11.
Diastolic function–based CAV risk stratification.

12.1 Clinical interpretation

- Low risk: annual echo (IIa, B, [15, 20, 23]).
- Moderate risk: stress echo, CFR (I, B, [15, 31, 32]).
- High risk: invasive coronary angiography (I, A, [15, 40]).

12.2 Plan of action

1. Evaluate E-wave deceleration and GLS.
2. Use CFR/stress echo for moderate risk.
3. Coronary angiography for high risk.

Clinical pearl: In transplant patients, diastolic dysfunction is often the first red flag of vasculopathy, even before angiography shows disease.

13. Case 12: Acute rejection with hemodynamic instability

Scenario: A 50-year-old female, 2 months post-transplant, presenting with hypotension and fatigue.

Clinical question: What echocardiographic parameters can suggest acute rejection in unstable patients? (Table 12).

Parameter	● Low risk	● Moderate risk	● High risk	LOE/references
LV GLS (%)	> -18	-16 to -18	< -16	I, A [21, 22, 24, 25]
LVEF (%)	>55	40–55	<40	I, A [20]
Pericardial effusion	Absent	Mild	Moderate/severe	I, B [15]
LV ejection time (ms)	Normal	Slightly reduced	Severely reduced	IIa, B [21, 25]
LV twist/torsion	Normal	Borderline	Abnormal (>25% ↓)	IIa, B [24, 25]

Table 12.
Hemodynamically unstable acute rejection risk stratification.

13.1 Clinical interpretation

- Low risk: adjust immunosuppression, follow-up echo (IIa, B, [21, 22, 24, 25]).
- Moderate risk: increase corticosteroids, monitor closely (I, B, [15, 23]).
- High risk: urgent biopsy, escalate immunosuppressive therapy (I, A, [15, 24–27, 42]).

13.2 Plan of action

1. Focused transthoracic echo with GLS and effusion.
2. Rule out sepsis or drug toxicity in parallel.
3. Immediate biopsy if high risk; treat with augmented immunosuppression.

Clinical pearl: GLS often declines before LVEF—compare with patient’s baseline, not population norms.

14. Case 13: Chronic rejection with progressive graft dysfunction

Scenario: A 65-year-old male, 7 years post-transplant, presenting with worsening exercise intolerance and fatigue.

Clinical question: How can echocardiography follow chronic rejection progression? (Table 13).

Parameter	● Low risk	● Moderate risk	● High risk	LOE/references
LV GLS (%)	> −18	−16 to −18	< −16	I, A [21, 22, 24, 25]
Coronary flow reserve (CFR)	>2.5	2.0–2.5	<2.0	I, B [31, 32]
LVEF (%)	>55	40–55	<40	I, A [20]
BNP/NT-proBNP (pg/mL)	<1000	1000–2000	>2000	IIa, B [15, 23]

Table 13.
Chronic rejection progression risk stratification.

14.1 Clinical interpretation

- ● Low risk: annual echo + biomarkers (IIa, B, [15, 20, 23, 38, 43]).
- ● Moderate risk: stress echo, monitor for CAV (I, B, [15, 31–34, 39]).
- ● High risk: invasive coronary imaging, escalate therapy (I, A, [15, 18, 40, 41]).

14.2 Plan of action

1. Serial LV GLS and CFR to monitor progression.
2. BNP/NT-proBNP surveillance in moderate risk.
3. Coronary imaging + therapy intensification in high risk.

Clinical pearl: In chronic rejection, subtle strain decline may precede both EF reduction and angiographic CAV—do not wait for EF to fall.

15. Conclusions

Echocardiography remains the most accessible, versatile, and indispensable imaging tool in the care of heart transplant recipients. Since the earliest transplant experiences, survival and diagnostic strategies have evolved substantially, but echocardiography has remained central in both research and clinical practice [1–5].

Beyond its traditional role in measuring left ventricular systolic function, modern echocardiography allows for earlier recognition of rejection, allograft vasculopathy, and graft dysfunction through advanced indices such as global longitudinal strain, right ventricular deformation, and atrial mechanics.

By presenting a case-based structure with practical risk tables, this chapter emphasizes not only what can be measured but how these measurements should influence clinical decision-making. The lesson across all cases is simple: In transplantation, timing is everything. Detecting dysfunction early—sometimes before symptoms arise—can change the patient's trajectory, improving both survival and quality of life. Furthermore, long-term outcomes continue to depend not only on imaging but also on donor-recipient compatibility and immunological factors, which remain critical challenges in transplantation medicine [44].

16. Future perspectives

The future of echocardiography in transplantation is evolving rapidly. Strain imaging and myocardial work indices are transitioning from research tools into standard practice. Coronary flow reserve and diastolic indices may soon be embedded in routine follow-up. Even more disruptive, artificial intelligence and automation are approaching a level where acquisition and interpretation can be standardized worldwide, democratizing access to high-quality echo assessment.

Still, technology alone is not the solution. Clinical judgment, cultural context, and human experience remain irreplaceable. As Latin American and global transplant programs continue to grow, collaboration and data sharing will be critical. The integration of multiparametric imaging with biomarkers, hemodynamic assessment, and clinical acumen is the path toward personalized transplant surveillance.

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Cardiac Transplantation and ECMO: A Synergistic Approach

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Abstract

Cardiac transplantation is the gold standard treatment for end-stage heart failure, offering definitive therapy for patients unresponsive to advanced medical management. Extracorporeal membrane oxygenation (ECMO) plays a pivotal role in critically supporting ill patients as a bridge to transplant, providing temporary hemodynamic and respiratory stabilization. ECMO is particularly effective in patients with cardiogenic shock or multi-organ dysfunction, improving tissue oxygenation and perfusion while awaiting a suitable donor organ. Despite its life-saving potential, ECMO is associated with significant risks, including hemorrhage, thromboembolism, infection, and prolonged organ dysfunction. Careful candidate selection, meticulous anticoagulation management, and a multidisciplinary team approach are essential to mitigate these complications and optimize outcomes. Emerging evidence highlights the potential of ECMO to expand the transplant candidate pool and improve survival rates. As an integral part of advanced heart failure treatment, ECMO continues to evolve, offering hope to patients in critical need of a heart transplant. Refractory cardiogenic shock has a high mortality rate despite optimal medical management. Cardiogenic shock is one of the main causes of in-hospital mortality, with significant variations in incidence depending on access to advanced therapies such as the use of venoarterial extracorporeal membrane oxygenation (VA-ECMO), which is a vitally important therapy. Its implementation as part of the treatment of patients with refractory cardiogenic shock is necessary.

Keywords: heart transplant, graft heart, oxygen consumption, venoarterial extracorporeal membrane oxygenation, intra-aortic balloon pump

1. Introduction

Venoarterial (VA) ECMO is an invasive procedure that improves the survival of patients who receive a heart transplant, so it is widely used as it provides support during severe illness or after surgery; it serves as a short- and long-term rescue therapy, which justifies the review chapter on management in the intensive care unit.

VA-ECMO is a cardiocirculatory support therapy used for the management of refractory cardiogenic shock characterized by heart failure accompanied by sustained hypotension with decreased cardiac output <2.2 L/min/m²; need for high-dose inotropic or vasopressor drugs such as dopamine >10 µg/kg/min, norepinephrine >0.5 µg/kg/min, adrenaline >0.1 µg/kg/min, dobutamine >10 µg/kg/min, or milrinone >0.5 µg/kg/min; and signs of hypoperfusion plus elevated serum lactate >2.0 mmol/l [1].

ECMO has become a crucial tool in the treatment of refractory cardiogenic shock or end-stage heart failure; its implementation in critically ill patients has evolved significantly, especially as a bridge strategy to heart transplantation. However, the use of ECMO presents significant challenges, including the risk of thrombotic, infectious, and hemorrhagic complications, which may affect post-transplant survival. The justification is based on the need to assess the indications, strategies of use, and complications to optimize outcomes in patients requiring advanced mechanical circulatory support [2].

Emerging evidence highlights the potential of ECMO to expand the transplant candidate pool and improve survival rates, and as an integral part of advanced heart failure care, this therapy continues to evolve, offering hope to patients in need of a heart transplant [3]. Heart transplantation is the gold standard for end-stage heart failure, offering definitive therapy for patients who fail to respond to advanced medical treatment [4].

ECMO is a perfusion technique that works as a type of extracorporeal life support that allows maintaining and improving oxygenation and perfusion in severe cases such as respiratory distress syndrome with refractory hypoxemia or heart failure with hypoperfusion. There are two modes of clinical and therapeutic application; venovenous (VV ECMO) is used in cases of respiratory failure [5].

Venoarterial (VA) perfusion with extracorporeal life support, in which blood drains through a catheter placed in the internal jugular vein and returns to the circulation through the aorta via a catheter placed in the axillary, carotid, or femoral artery or by direct cannulation through the chest.

Extracorporeal membrane oxygenation (ECMO) plays a pivotal role in critically supporting ill patients as a bridge to transplantation, providing temporary hemodynamic and respiratory stabilization. ECMO is particularly effective in patients with cardiogenic shock or multi-organ dysfunction, improving tissue oxygenation and perfusion while awaiting a suitable donor organ. Despite its life-saving potential, ECMO is associated with significant risks, such as hemorrhage, thromboembolism, and infection, and thus, careful candidate selection, meticulous anticoagulation management, and a multidisciplinary team approach are essential to mitigate these complications and optimize outcomes [6].

Key aspects for ECMO implementation vary depending on hospital infrastructure, implementation time, and complications.

Devices and equipment: ECMO is a circuit consisting of a drainage cannula that circulates through the machine and oxygenators and then returns to the patient through a return cannula (**Figure 1**) [7].



Figure 1.
Heart transplant patient on ECMO with nursing care and continuous hemodynamic monitoring.

The intensive care unit (ICU) stay for ECMO patients represents high costs; the care of critical cardiogenic shock represents a challenge for the ICU staff; a specialized team is required, including perfusionists, intensivists, and cardiovascular surgeons. Post-ECMO rehabilitation: Recovery, including physical therapy and cardiac rehabilitation. ECMO has been shown to be effective in selected patients, particularly those awaiting cardiac transplantation [8].

Classification of cardiogenic shock [9].

Before considering the use of ECMO, it is essential to risk-stratify patients with cardiogenic shock. The Society of Cardiovascular Angiography and Interventions (SCAI) developed a five-stage classification for shock:

Stage A (risk): Patients at risk of developing cardiogenic shock but without evidence of hypoperfusion.

Stage B (onset): Initial hypoperfusion with mild signs of organ dysfunction.

Stage C (classic): Manifest cardiogenic shock, with hypoperfusion requiring inotropic or vasopressor support.

Stage D (deterioration): Progressive cardiogenic shock despite pharmacological support, requiring emergency mechanical assistance.

Stage E (extremis): Refractory cardiogenic shock with multi-organ dysfunction and high mortality.

The SCAI classification is essential to guide therapy selection, including ECMO, and improve clinical outcomes in patients with advanced cardiogenic shock. The SCAI classification showed a higher risk estimate of death than Killip and Kimball [10].

2. Methodology

A review of medical articles published in PubMed, Google Scholar, Latindex, and Embase databases was conducted on a research question: What is the usefulness

of VA ECMO in heart transplantation? What are the indications and contraindications of extracorporeal membrane oxygenation for heart transplantation? Cardiac transplantation and ECMO were used as search words; publications that clearly and precisely addressed the issue with results available for analysis were used, and articles published more than 5 years ago that did not address the research topic were excluded.

3. Timing of ECMO initiation and its importance

Implementing when to initiate ECMO is critical in determining patient outcomes. The decision should be based on a careful assessment of the severity of cardiogenic shock, the patient's eligibility for transplant, and anticipated complications. Critical factors in ECMO decision-making include [11]:

1. Hemodynamic instability: Persistent hypotension and end-organ hypoperfusion despite maximal inotropic support.
2. Lactate levels: An elevated lactate level (>4 mmol/L) may indicate worsening perfusion and warrant initiation of ECMO.
3. Right ventricular dysfunction: Signs of right ventricular failure may warrant early consideration of ECMO.
4. Multi-organ dysfunction assessed by APACHE III or SAPS II.

These patients need to be evaluated by a multidisciplinary team with experience in the selection, implantation, and management of mechanical circulatory support devices [11].

The optimal timing for ECMO application is before irreversible end-organ damage occurs [12]. Studies have shown that early initiation of ECMO, within the first 6 hours of refractory shock, is associated with improved survival rates, as a 12-hour increase in refractory shock dramatically increases mortality. Sustained severe hemodynamic instability and ECMO delay beyond 12 hours were correlated with increased mortality and complications, according to an international American Heart Association study of 8619 adult patients with cardiogenic shock receiving venoarterial ECMO from the international Extracorporeal Life Support Organization (ELSO) registry (adjusted odds ratio, 1.06 [95% CI, 1.03–1.10]; $P < .001$) [13].

The most frequent complications of ECMO include major bleeding in 17.9% to 38.4%, ischemia of the vascular access site in 12.3–21.6%, abdominal compartment syndrome in 3.7–9.4%, and need for renal replacement therapy with cardiorenal syndrome in 39.1–58.5% [14].

4. Indications for the use of ECMO in heart transplantation

ECMO therapy is used in various clinical situations for patients with heart failure requiring transplantation:

4.1 Refractory cardiogenic shock

Patients with severe ventricular dysfunction who do not respond to inotropes or minor mechanical support devices, always as a bridge to a goal: recovery, heart transplant, therapeutic decision-making, or change to another type of long-term assistance [15].

4.2 Primary post-transplant graft failure

Severe dysfunction of the transplanted organ within the first few hours or days after surgery.

4.3 Fulminant myocarditis

Patients with severe hemodynamic deterioration who require support until recovery or transplantation [16].

4.4 Acute decompensation of chronic heart failure

ECMO as a bridge to heart transplantation.

There are three main strategies for using ECMO in this setting:

4.4.1 Bridge to decision

Allows clinical evaluation before determining eligibility for transplant [17].

4.4.2 Bridge to device

Stabilizes the patient until implantation of a ventricular assist device [18].

4.4.3 Direct bridge to transplant

Maintains perfusion until a suitable organ is available [19].

5. Catheterization techniques for VA ECMO

Catheterization can be performed surgically by surgical dissection and percutaneously using the Seldinger technique. The cannulas are made of polyurethane reinforced with stainless steel rings; they are flexible and resistant to kinking, they are radiopaque and allow high flows, the venous lines are the patient's output, long and large, connected to a circuit with the system (blue color), and the arterial lines entering the patient are red and are connected to a circuit of tubes that come out of the device, short and small. The sizes of the arterial cannulas vary between 15 and 21 French (Fr).

Peripheral cannulation is indicated in critically ill patients who are difficult to transfer to the operating room. This approach should be considered in cases of cardiogenic shock refractory to catecholamines and/or intra-aortic balloon pump (IABP) in the immediate postoperative period of cardiac surgery, cardiogenic shock (acute coronary syndrome, myocarditis, exacerbation of chronic heart failure), or in cases

of primary heart/lung graft failure. The common femoral artery is usually used as a percutaneous approach for peripheral cannulation.

Central cannulation is mostly used in cardiogenic shock (post-cardiotomy) and postoperative cardiac arrest. This technique involves a sternotomy, which is then tunneled to allow closure of the sternotomy. This type of cannulation allows for more adequate drainage and greater cardiac decompression than peripheral cannulation. Furthermore, since blood enters the ascending aorta, there is less retrograde flow and better oxygenation of the upper body. This approach requires a sternotomy, which poses a greater risk of bleeding and mediastinitis.

6. Hemodynamic monitoring in VA-ECMO

Hemodynamic monitoring in patients on venoarterial (VA) ECMO is essential to assess support effectiveness, prevent cardiovascular complications, and guide therapeutic decisions. Since VA-ECMO partially replaces cardiac function, continuous monitoring of parameters such as mean arterial pressure (MAP), central venous pressure (CVP), arterial pulsatility, and mixed venous saturation (SvO₂) is essential. These indicators allow assessment of systemic perfusion and detection of signs of hypovolemia, left ventricular overload, or inadequate native heart discharge.

A key tool in this context is echocardiography, both transthoracic and transesophageal, which allows monitoring of ventricular function, aortic valve opening, and the presence of intracavitary thrombi. Absence of valve opening or left ventricular distension may indicate harmful overload requiring strategies such as intra-aortic balloon pump, Impella, or surgical drainage. Likewise, the use of pulmonary artery

Author	Population	Intervention	Results	Level of evidence
Levy et al. [21]	334 patients with cardiogenic shock	Patients endotracheally intubated with venoarterial ECMO for cardiogenic shock for <6 hours	Moderate hypothermia for 24 hours did not improve survival	Randomized clinical trial in 20 French cardiac shock care centers
Schrage et al. [22]	686 patients with cardiogenic shock treated with VA-ECMO with or without left ventricular unloading	Left ventricular unloading using Impella in patients with venoarterial ECMO	The Impella microaxial flow pump is associated with lower mortality in patients with cardiogenic shock treated with venoarterial extracorporeal membrane oxygenation with statistical significance P = 0.03	International and multicenter cohort study conducted in 16 centers in 4 countries
Park et al. [23]	60 patients randomized to early left atrial ventilation versus conventional treatment for left ventricular decompression during	Early left ventricular unloading at the time of VA-ECMO insertion	survival to discharge (53.3% vs. 50.0%, p = 0.796)	Randomized clinical trial

Table 1.
Summary of clinical trials with results on the implementation of ECMO in cardiogenic shock.

Proof	Measurement frequency and normal range	Objective
Activated partial thromboplastin time (TTaP)	6–12 h, Normal range 26–36 s	1.5–2.5 times the baseline value equivalent to 40–60 s in patients at risk of bleeding and 60–90 s as the target of therapeutic anticoagulation
Activated clotting time (ACT)	1–2 h	180–240 s therapeutic anticoagulation
Anti-Xa	6–12 h normal range 0.3–0.5 U/mL	0.3–0.7 U/mL therapeutic anticoagulation
Platelets	6–12 h	100,000/ μ L
Fibrinogen	12–24 h, normal range 1.5–4.5 g/L	>1.5 g/L if there is bleeding
Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are viscoelastic tests used in patients with ECMO TEG/ROTEM	Daily or as needed	Evaluate complex coagulopathies

Table 2.
Coagulation tests required for ECMO monitoring.

Parameter/tool	Objective/meaning
Mean Arterial Pressure (MAP)	Goal: >65 mmHg. Determines systemic perfusion.
Systolic pressure	Desirable >90 mmHg. Also reflects residual contractility.
Cardiac index (CI)	Target: >2.2 L/min/m ² (if a pulmonary artery catheter is used). Reflects native flow.
Pulmonary artery wedge pressure (PCWP)	<15 mmHg to avoid pulmonary congestion.
Central Venous Pressure (CVP)	Evaluate blood volume, although it can be misleading if there is nearby venous drainage.
SvO ₂ (Mixed Venous Saturation)	Ideal >65–70%. Used for calculating cardiac output with the Fick formula.
ETCO ₂ (end-tidal CO ₂)	<14 mmHg suggests native GC <1 L/min.
Arterial pulsatility	Reflects native cardiac flow. Absence: possible LV failure or excessive ECMO support.
Serum lactate	Its decrease indicates improvement in tissue perfusion. Goal: normalization within 24–48 h.
Temperature	Controlled, except in hypothermia protocol.

Table 3.
Key parameters for hemodynamic monitoring of ECMO.

catheters allows calculation of cardiac index and filling pressures, which are useful for assessing myocardial recovery or the need for support adjustment.

Monitoring should be complemented with measures such as cerebral regional oximetry (NIRS), frequent blood gas analysis, and lactate monitoring as a marker of tissue perfusion. Together, these parameters provide a comprehensive view of the patient's hemodynamic status, allowing for adjustment of ECMO flow, inotropic use, ventilatory strategy, and eventual transition to another type of support. Adequate

hemodynamic monitoring not only optimizes therapy but can prevent serious complications such as Harlequin syndrome, cardiac tamponade, or hypoperfusion of vital organs (**Tables 1 and 2**).

Hemodynamic monitoring seeks to ensure adequate systemic perfusion, prevent left ventricular overload, assess cardiac recovery, and detect complications such as hypovolemia, differential hypoxemia, thrombosis, or pump dysfunction (**Table 3**).

Transthoracic and transesophageal color Doppler echocardiography is essential for assessing biventricular function, geometry, and valves; confirming cannula position; diagnosing cardiac tamponade and left-sided cardiac overload; and visualizing aortic valve opening to prevent thrombosis. In VA-ECMO, retrograde flow can overload the left ventricle, so ventricular filling and valve opening should be monitored. Therefore, daily evaluation is recommended, especially in the absence of pulses or differential hypoxemia.

A pulmonary artery catheter (Swan-Ganz) is used in VA-ECMO to measure pulmonary pressures, calculate native cardiac output (by subtracting ECMO flow), and guide decisions about fluid therapy and the use of vasopressors or inotropes.

Transcranial Doppler (TCD) and NIRS are of great relevance in brain evaluation, and NIRS (near-infrared spectroscopy) detects differential hypoxemia in the carotid territory, and Doppler can identify acute changes that indicate neurological damage.

7. Mechanical ventilation during ECMO

Ventilatory management in patients on ECMO aims to minimize ventilator-induced lung injury (VILI) while ensuring adequate oxygenation and CO₂ removal. In the setting of venoarterial ECMO, the lung may receive decreased blood flow due to partial cardiac unloading, requiring carefully balanced ventilation. Therefore, a “protective ventilation” or “lung rest” strategy is employed, characterized by low tidal volumes (4–6 mL/kg of ideal body weight), plateau pressure (P_{plat}) less than 25 cmH₂O, a low respiratory rate (4–10 bpm), and moderate Positive End Expiration Pressure (PEEP) levels (10 cmH₂O), with reduced fractions of inspired oxygen (FiO₂) (<50%) to avoid oxygen toxicity.

In patients on VA-ECMO, ventilatory management is challenging due to the potential for differential hypoxemia (Harlequin syndrome). In these cases, the native heart expels desaturated blood into the cephalic circulation while the ECMO oxygenates the distal body. Mitigating this risk requires close coordination between ventilator settings, ECMO flow, and modification of support configuration (e.g., switching to a V-to-VA configuration). Furthermore, careful management of PEEP can help prevent alveolar collapse without compromising venous return or hemodynamic function.

As lung function improves, gradual weaning from ECMO and mechanical ventilation is considered. This process includes monitoring the patient’s ventilatory capacity and performing diagnostic tests like a Spontaneous Breathing Trial (SBT), in which membrane oxygenation support is discontinued to assess respiratory autonomy. During this phase, it is essential to ensure stable oxygenation (PaO₂ >60 mmHg), ventilation (PaCO₂ <60 mmHg), PEEP ≤10 cmH₂O, FiO₂ <60%, and adequate ventilatory mechanics.

Successful weaning from ECMO depends not only on blood gas values but also on the patient’s general condition, respiratory effort, and the absence of complications that compromise lung function. Strategies during ECMO (“lung rest” mode): tidal volume: 4–6 mL/kg (PBW), PEEP: 10 cmH₂O, P_{plat}: <25 cmH₂O, respiratory rate: 4–15 rpm, FiO₂: <60% or lower if possible.

8. Contraindications of ECMO

Despite its benefits, ECMO is contraindicated in certain scenarios, including [20]:

Severe comorbidities that limit the possibility of transplantation or recovery.

Irreversible neurological damage due to prolonged cardiac arrest.

Uncontrolled bleeding or severe coagulopathy.

Active systemic infection that could compromise transplant results.

Other absolute and relative contraindications include refusal of extracorporeal techniques, advanced neoplasia, cerebral hemorrhage, cerebral herniation, intracranial hypertension, contraindications to transplantation, advanced age, immunosuppressed patients, SAPS II score ≥ 60 points, Sequential Organ Failure Assessment (SOFA) score > 12 points, and do not resuscitate order [20].

Necessary equipment in an intensive care unit for the management of a patient assisted with VA-ECMO with immediate transplant due to cardiogenic shock (**Figure 1**). A critical patient receiving ECMO in an intensive care unit (**Figure 2**). Mechanical ECMO pump at the foot of the bed as a bridge to receive a heart transplant



Figure 2.
Distribution of the console used for short-term assistance management (pumping system).



Figure 3.
Oxygenation membrane (gas exchange device), thrombus is observed in the membrane.



Figure 4.
ECMO circuit with silicone venous line and thrombus formation in a three-way stopcock.

(**Figure 3**). The membrane oxygenator for support with heparin coating serves as a heat exchanger and door for sampling (**Figure 4**). Venous access cannula and arterial infusion cannula.

Table 1 shows the implementation of ECMO in therapeutic hypothermia and ventricular discharge, which constitute new lines of research [21–23].

An anticoagulation strategy is one that manages to prevent thrombotic complications, minimizing the hemorrhagic risk, and maintaining it in an adequate range becomes a therapeutic objective strategy: fine adjustment of anticoagulation, rigorous hemostatic control, use of TEG/ROTEM, fibrinogen, and platelets [24, 25].

9. Early prediction and forecasting

Evaluation with PREDICT VA scores during ECMO use in patients with cardiogenic shock should be evaluated using predictive tools, such as PREDICT VA scores, to help estimate the probability of success.

PREDICT VA Score: Evaluates factors such as age, arterial pH, lactate, and renal function to predict survival in patients with venoarterial ECMO [26]. The REMEMBER scale predicts hospital mortality in adult patients after VA-ECMO for refractory cardiogenic shock [27].

Prognostic factors and predictors of success Simplified Acute Physiology Score II (SAPS II), Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and Sequential Organ Failure Assessment (SOFA) score are used to assess prognosis; duration of ECMO support, presence of multi-organ failure, and renal function on admission have been identified as key predictors of post-transplant success [28].

10. Complications of the ECMO

Unfractionated heparin (UFH) is the standard of care anticoagulant, initially given as an intravenous dose of 75–100 U/kg (max. 5000 U) before cannulation, then continued as a continuous infusion of 25–30 U/kg/h. Other medications include direct thrombin inhibitors such as bivalirudin or argatroban, indicated for heparin-induced thrombocytopenia or heparin resistance.

Anticoagulation is crucial to prevent thrombosis of the circuit through which blood circulates to the extracorporeal oxygenation machine and returns oxygenated blood to the patient. Anticoagulant treatment carries a risk of bleeding when starting ECMO, making the strategies that can be implemented to prevent or manage these complications vitally important.

During extracorporeal life support for the treatment of infarction-related cardiogenic shock, data from a multicenter randomized controlled trial in 417 patients evaluated all-cause mortality; moderate to severe bleeding complications were between 9.6% and 23.4% of complications [29]. According to a pediatric ECMO guideline, in the presence of bleeding complications, recommend maintaining a platelet count of 100,000; plasma transfusion in cases of significant bleeding with aPTT >1.5 times the baseline value, prolonged clotting times, or low fibrinogen in cases of disseminated intravascular coagulation (DIC); consider antifibrinolytic therapy during acute bleeding; and immediately discontinue anticoagulants as the management in the intensive care unit (ICU) [30].

In cases of acute bleeding, it is necessary to determine the site of bleeding, surgical hemostasis, and amount of blood loss; evaluate hemoglobin levels with a target value of 7–9; associated hemodynamic alterations require vasopressor and inotropic drugs; and tranexamic acid in situations of severe bleeding allows for controlling bleeding [31, 32]. The main causes of bleeding are systemic anticoagulation, platelet dysfunction induced by contact with the pump, heparin-induced thrombocytopenia, hypofibrinogenemia, disseminated intravascular coagulation (DIC), recent surgeries, surgical cannulation, or coagulation factor deficiency [33].

Thrombosis is common in patients connected to ECMO; the presence of thrombosis in the circuit is the most reported, with 21.5%, ischemic stroke 2.6%, and pulmonary embolism 11.8% [34].

A strategy to prevent hemorrhagic and thrombotic complications consists of intensive monitoring of coagulation to maintain it within the therapeutic anticoagulation range. Reference controls: activated partial thromboplastin time (aPTT), activated clotting time (ACT), anti-Xa levels, thrombocytometry, and thromboelastography for control of acquired coagulopathies. The objective is to maintain an aPTT 1.5 times greater than the upper limit or an anti-Xa of 0.3–0.7 IU/ml; the objectives of the coagulation test controls are seen in **Table 2** [24, 25].

Mechanical circuit complications are common due to mechanical failures, including air or blood leaks, blood clots in the pump or oxygenator (**Figure 3**), line rupture, and membrane dysfunction requiring urgent replacement of the affected component (oxygenator, pump). Prevention is based on team checks and training.

Specific cardiovascular complications in VA-ECMO are left ventricular overload by retrograde flow preventing the opening of the aortic valve leading to pulmonary edema, stasis and thrombosis of the left ventricle, differential hypoxemia, also known as Harlequin syndrome or North–South syndrome, a condition in which oxygen saturation differs significantly between the upper and lower body; the head receives desaturated blood from the native heart while the body receives oxygenated blood from the ECMO; arrhythmias; or cardiac tamponade [35].

Strategies that can be implemented for the diagnosis and treatment of complications during ECMO.

Hypovolemia: signs on drainage cannula, decreased pump flow, low CVP. Treatment: fluids. Left ventricular overload: caused by aortic retrograde flow and left ventricular failure. Signs: decreased pulses, increased filling pressures, pulmonary

edema, and thrombus in the LV or aortic root. Treatment: reduce ECMO flow and inotropes. Intra-aortic balloon pump (IABP) combined with ECMO may improve survival (OR = 1.58; 95% CI = 1.26–1.98; $p < 0.0001$) [36]; Impella mechanical circulatory support is associated with a lower incidence of in-hospital mortality (RR 0.88 [95% CI: 0.80–0.94], $p = 0.0004$) [37]; left ventricular unloading with Impella or IABP helps to reduce pressure and volume within the left ventricle [38].

Differential hypoxemia: Occurs when the LV pumps poorly oxygenated blood from the lungs to the proximal aorta (head/heart). Detected with pulse oximetry in the right arm or frontal NIRS. Treatment: change to V-VA or central configuration [39]. Cardiac tamponade: To detect this complication during ECMO, it is necessary to keep in mind Beck's triad and loss of pulses with flow maintained by the pump. The final diagnosis is based on serial echocardiography.

Sepsis is a poor prognostic factor; the longer the cannulation time in ECMO, the greater the risk of sepsis. The most frequent infections are due to ventilator-associated pneumonia, catheter-associated infections, or surgical wounds [40]. Although VA-ECMO provides excellent acute hemodynamic support, its prolonged use leads to high rates of renal, infectious, or neurological complications, limiting its application as a long-term support strategy.

11. Future research directions

Long-term mechanical circulatory support in the treatment of advanced heart failure therapies such as ECMO, balloon counterpulsation, ventricular assist devices or the development of a total artificial heart are advances for heart transplantation and will allow a greater number of patients to achieve the goal in the future; for this reason the synergy of ECMO with other methods of treatment of heart failure will successfully increase survival [41].

There is a growing need for the procurement and use of organs or tissues for transplants; these devices will continue to play an important role in the life support of critical patients who are candidates for heart transplants. It is necessary for health personnel to be accustomed to the management and postoperative care of patients who undergo these therapies [42].

Portable ECMO through a pump will allow the native heart to be synchronized for a longer time, focusing on miniaturizing the devices, automating the process, and expanding its use to environments outside the ICU, as well as the promotion of Artificial Intelligence (AI) in interventional cardiology are part of the new lines of current research [43].

12. Conclusions

In the allocation of ECMO in critically ill patients, candidate selection should be based on strict clinical criteria to optimize the benefits of the procedure. ECMO is a valuable tool in the management of patients with end-stage heart failure requiring transplantation, as it provides hemodynamic stability and improves perfusion. The decision to initiate ECMO should be carefully considered, balancing risks and benefits, while ensuring timely implementation to maximize positive outcomes. ECMO remains a life-saving intervention for carefully selected patients, particularly those awaiting heart transplantation.

The optimal window for initiation of ECMO must balance the risks of prolonged mechanical support with the benefits of preventing further clinical deterioration, most importantly allowing time for definitive therapeutic interventions and possible recovery.

Innovations, the future of ECMO, and new technologies such as improved membrane oxygenation systems and safer anticoagulation strategies are optimizing ECMO outcomes, and the development of less invasive cannulation techniques is reducing associated complications.

Despite its benefits, ECMO remains a complex therapy associated with a high burden of complications such as bleeding, infections, thrombosis, and neurological sequelae. Long-term survival has improved thanks to improved patient selection, rigorous clinical protocols, and advances in adverse event management.

In summary, VA-ECMO currently represents an indispensable therapeutic modality in the management of refractory cardiogenic shock and an effective bridge to heart transplantation or long-term ventricular assistance when applied under appropriate clinical criteria.

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Conflict of interest

The authors declare no conflict of interest.

Notes/thanks/other declarations

“Thanks”.

Acronyms and abbreviations

ECMO	extracorporeal membrane oxygenation
SCAI	society of cardiovascular angiography and interventions
VA-ECMO	venoarterial extracorporeal membrane oxygenation
FiO ₂	fraction inspiratory of oxygen
AI	artificial intelligence
PEEP	positive end expiration pressure

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Biomarkers for Cardiac Graft Assessment in Ex-Vivo Machine Perfusion

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Abstract

Heart transplantation remains the definitive treatment for advanced heart failure. Despite over five decades of advancements in transplantation, the fundamental approach to organ preservation outside the body has remained largely unchanged. Traditionally, the field has relied on static cold storage (SCS) as the clinical standard for preserving hearts from donors after brainstem death. While effective, SCS presents practical limitations, particularly in mitigating ischemic damage, assessing the organ quality in storage and transport, and expanding the donor pool to include extended-criteria donors or donations after circulatory death (DCD). The emergence of ex-vivo machine perfusion, a transformative innovation, offers enhanced preservation by reducing the risk of ischemic damage alongside the ability to assess and optimize grafts from extended-criteria donors and those obtained through DCD. This chapter explores the pivotal role of cardiac biomarkers in graft evaluation within this emerging technology, categorized into functional markers, cell injury and cell death markers, inflammatory markers, omics-based markers, and hormone/pro-hormone markers. By enhancing precision in identifying transplantable hearts, these biomarkers play a crucial role in improving the safety and efficacy of marginal graft utilization, providing reassurance about the advancements in the field. The chapter also includes practical recommendations for integrating these biomarkers into clinical protocols and outlines future research directions to drive innovation in cardiac transplantation.

Keywords: biomarkers, cardiac transplantation, extended-criteria donors, graft assessment, machine perfusion, organ preservation

1. Introduction

Heart failure (HF) is a complex and life-threatening condition associated with high morbidity, mortality, and significant healthcare costs. Affecting over 64 million people globally, HF imposes a substantial burden on healthcare systems and patients alike [1]. For individuals with end-stage HF, heart transplantation remains the gold

standard treatment, offering the best long-term survival and quality of life improvements. However, the success of heart transplantation is heavily dependent on the availability and viability of donor organs, highlighting the need for improved preservation and assessment strategies.

Traditionally, SCS has been the standard technique for preserving donor hearts. This method is simple, cost-effective, and widely used, but it has significant limitations. Prolonged ischemic storage is a known independent risk factor for primary graft dysfunction and post-transplant mortality. Additionally, SCS does not allow for functional assessment of the organ during storage, and conventional clinical parameters do not always correlate well with post-transplant function, causing the rejection of many potentially transplantable hearts [2].

To overcome these challenges, ex-vivo machine perfusion has emerged as a transformative innovation in organ preservation and transportation. Machine perfusion technology enables continuous perfusion of the donor heart with oxygenated blood or preservation solutions, reducing ischemic injury and allowing real-time assessment of organ function. Both normothermic and hypothermic perfusion strategies have shown promise in improving graft preservation, optimizing metabolic conditions, and even resuscitating marginal donor hearts. Experimental and clinical studies suggest that machine perfusion has the potential to significantly improve short- and long-term outcomes in heart transplantation by mitigating ischemia-reperfusion (IR) injury and primary graft failure [2]. Moreover, machine perfusion technologies facilitate the resuscitation of marginal hearts and long-term preservation support extended geometrical radius for transportation, eventually helping in expanding the donor pool [3].

Nevertheless, one of the critical challenges in heart transplantation is the accurate evaluation of donor graft viability in real-time or even before grafting post-SCS. Current donor selection primarily relies on clinical parameters such as hemodynamic stability, inotropic support requirements, electrocardiographic changes, and donor history [4]. However, these criteria alone are insufficient to predict post-transplant function with confidence, leading to the unnecessary discard of potential grafts. There is a pressing need, therefore, to establish reliable markers of good clinical outcomes following heart transplantation to better guide machine perfusion procedures and the selection of viable grafts.

Biomarkers serve as objective indicators of physiological and pathological processes, offering valuable insights into graft viability and potential post-transplant outcomes. The ability to dynamically assess organ quality during machine perfusion presents a unique opportunity to incorporate biomarkers into graft evaluation protocols. While several cardiac biomarkers are routinely used *in-vivo* to assess myocardial injury, their applicability in ex-vivo machine perfusion remains an evolving area of research. With advancements in machine perfusion technology and biomarker research, the field of heart transplantation is on the brink of a paradigm shift. A deeper understanding of biomarker dynamics during ex-vivo perfusion could refine donor selection criteria, improve graft utilization, and ultimately enhance patient outcomes. This chapter provides a comprehensive analysis of the most promising biomarkers for cardiac graft assessment, including functional markers, cell injury/death markers, inflammatory markers, omics-based markers, and hormone/pro-hormone markers. **Figure 1** summarizes these biomarker categories and their respective evaluation targets. By integrating biomarker-based assessment with machine perfusion, this approach aims to optimize organ preservation, reduce early graft failure, and expand the donor heart pool—ultimately improving post-transplant outcomes and patient quality of life.

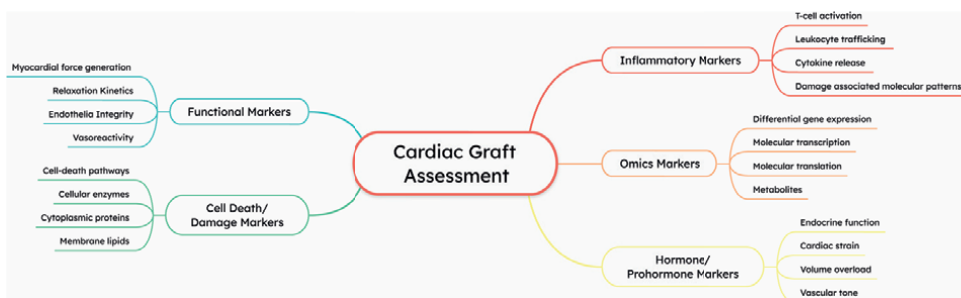


Figure 1.
 A mind map illustrating the assessment of cardiac grafts categorizes key biomarkers used for evaluation, along with their clinical and functional targets.

2. Functional markers

Functional markers serve as indispensable tools for evaluating the viability of cardiac grafts during ex-vivo machine perfusion, offering critical insights into the organ's capacity to resume physiological performance post-transplantation. The heart's ability to sustain systemic circulation post-transplantation hinges on the integrated function of its structural, contractile, and vascular components, necessitating comprehensive monitoring of these systems under perfusion.

At the whole-organ level, functional competence relies on ventricular compliance to accommodate diastolic filling, synchronized contraction to optimize ejection dynamics, and coordinated relaxation to permit efficient refilling. These macroscopic processes are underpinned by cellular mechanisms, including precise coordination of excitation-contraction coupling in cardiomyocytes and intercellular signal propagation to maintain rhythmicity [5]. Continuous assessment of functional parameters during machine perfusion is thus vital to identify grafts capable of post-transplant success. Functional markers are broadly categorized into (i) contractile function metrics, which evaluate myocardial force generation, electromechanical synchrony, and relaxation kinetics, and (ii) vascular and endothelial function markers, which assess coronary flow resistance, endothelial integrity, and vasoreactivity.

2.1 Contractile function

Contractile function metrics are pivotal for evaluating the viability of cardiac grafts during machine perfusion, as they directly reflect the myocardium's capacity to generate force, sustain rhythm, and adapt to hemodynamic demands. To ensure reproducibility and clinical relevance, contractile evaluation requires standardized measurements of key hemodynamic and mechanical variables, including intraventricular pressure, chamber volume, heart rate, and stroke work [6]. These parameters must be acquired under tightly controlled preload, afterload, and inotropic conditions to minimize variability and enhance the reliability of ex-vivo assessments [5, 6].

Central to contractile evaluation are pressure-volume (PV) loop analyses, which quantify systolic function, diastolic compliance, and myocardial work efficiency. These metrics are typically acquired using conductance or impedance catheters inserted into the ventricular chambers, enabling real-time monitoring of pressure and volume dynamics [7]. Notably, conductance catheters remain the gold standard for PV loop analysis due to their ability to simultaneously track pressure and volume

changes with high temporal resolution. Heart rate and rhythm stability are assessed via ECG integrated into perfusion systems, while stroke volume and ejection fraction (EF) are calculated from ventricular volume traces or measured directly using echocardiography [7]. Advanced machine perfusion systems employ multimodal sensors and catheters to maintain physiological loading conditions and ensure measurement accuracy. They are typically calibrated to account for fluid viscosity and temperature variations inherent to perfusion circuits.

The predictive utility of contractile markers hinges on their sensitivity to early myocardial injury and their correlation with post-transplant outcomes. Parameters such as maximal ventricular pressure gradient, ventricular compliance, and stroke work index have demonstrated high specificity for identifying grafts at risk of primary graft dysfunction [8]. For example, impaired diastolic relaxation (elevated end-diastolic pressure) or reduced systolic reserve (low EF) during perfusion may indicate irreversible ischemia or cardiomyocyte dysfunction. **Table 1** provides a comprehensive summary of validated contractile function markers, including their measurement methods and prognostic significance.

Parameter	Measurement Method	Prognostic Significance
CO (Cardiac Output)	Flow probes, thermodilution, or calculated ($HR \times \text{stroke volume}$)	Reflects systemic perfusion capacity; low CO correlates with graft failure.
DP (Developed Pressure)	Pressure catheter in ventricle(s)	Indicates systolic force generation; reduced DP suggests impaired contractility.
dP/dt_{max} (Maximal gradient of left ventricular [LV] pressure)	Pressure catheter (maximal slope of LV pressure rise)	Marker of contractile strength; low gradient predict post-transplant dysfunction.
dP/dt_{min} (Minimal gradient of LV pressure)	Pressure catheter (minimal slope of LV pressure decline)	Reflects diastolic relaxation; impaired relaxation is linked to graft stiffness.
dV/dt_{max} (Maximal gradient of LV volume)	Conductance catheter (maximal rate of LV volume increase during diastole)	Assesses diastolic filling efficiency; abnormal rates suggest compliance deficits.
dV/dt_{min} (Minimal gradient of LV volume)	Conductance catheter (maximal rate of LV volume decrease during systole)	Systolic ejection efficiency; reduced rates indicate outflow obstruction or systolic failure.
EDP (End-Diastolic Pressure)	Pressure catheter in LV at end-diastole	Elevated EDP indicates diastolic dysfunction or volume overload.
EDV (End-Diastolic Volume)	Conductance catheter, volumetric sensors or echocardiography	Elevated EDV suggests ventricular dilation; reduced EDV may indicate restrictive pathology.
EDPV (End-Diastolic Pressure-Volume Relations)	PV loop analysis (slope of EDP versus EDV)	Diastolic stiffness marker; steeper slopes correlate with restrictive physiology.
ESP (End-Systolic Pressure)	Pressure catheter in LV at end-systole	Reflects afterload; elevated ESP indicates increased vascular resistance.
ESV (End-Systolic Volume)	Conductance catheter, volumetric sensors or echocardiography	Elevated ESV correlates with reduced ejection fraction and systolic failure.

Parameter	Measurement Method	Prognostic Significance
ESPV (End-Systolic Pressure-Volume Relations)	PV loop analysis (slope of ESP versus ESV)	The gold standard for contractility; reduced slope indicates systolic impairment.
HR (Heart Rate)	Electrocardiogram (ECG) or pressure waveform analysis	Tachycardia or bradycardia during perfusion may indicate autonomic dysregulation or ischemia.
LVEF (Left Ventricular Ejection Fraction)	Echocardiography, conductance catheter ($EF = [(EDV - ESV) / EDV] \times 100$)	Reduced LVEF predicts a high risk of primary graft dysfunction.
LV-P _{min} (Minimal LV pressure)	Pressure catheter in LV during diastole	Elevated LV-P _{min} suggests impaired ventricular relaxation or compliance.
LV Work (Myocardial work performed by LV)	Calculated from PV loops ($LV\ Work = \int Pressure \times dVolume$)	Reduced LV work indicates poor energy efficiency; correlates with myocardial oxygen consumption.
PRSW (Preload Recrutable Stroke Work)	Echocardiography or PV loop analysis (slope of stroke work versus EDV)	Recrutable stroke work reserve; reduced PRSW predicts poor adaptation to hemodynamic stress.
PSP (Peak Systolic Pressure)	Pressure catheter in LV during systole	Reflects maximal systolic force; low PSP indicates pump failure.
RVSWI (Right Ventricular Stroke Work Index)	Stroke volume $\times 0.0136 \times$ (mean pulmonary artery pressure—mean right atrial pressure)	Workload of the right ventricle; low RVSWI correlates with post-transplant right ventricular failure.

Table 1.
Contractile function markers for cardiac graft viability assessment.

2.2 Vascular and endothelial function

Coronary vascular dysfunction is a major concern in progressive cardiac allograft vasculopathy (CAV), and early assessment of microvascular resistance has been identified as a crucial predictor of post-transplant complications or the need for retransplantation [9]. Endothelial dysfunction, a key factor in graft atherosclerosis, often manifests early and correlates with intimal thickening [10]. Traditional diagnostic approaches, including coronary angiography and intracoronary Doppler flow assessments, have limitations in detecting microvascular dysfunction in ex-vivo machine perfusions, necessitating the development of easy-to-use alternatives. Studies suggest that vascular function parameters, such as coronary flow, hyperemic response, and coronary flow reserve, strongly correlate with cardiac graft recovery in isolated heart preparations [11].

2.2.1 Coronary flow reserve

Coronary flow reserve (CFR) is a key physiological marker used to evaluate coronary circulation and detect early coronary pathology. It is defined as the ratio of maximum coronary blood flow, achieved under maximal vasodilation, to resting coronary blood flow at a given perfusion pressure [12]. In a healthy coronary system, CFR is maintained by the ability of resistance vessels to dilate and compensate for varying myocardial demands. However, in pathological states such as coronary occlusive disease, CFR becomes compromised due to structural and functional impairments in both large and small coronary vessels.

Heart transplant recipients frequently develop transplant-related coronary artery disease, which is characterized by diffuse, concentric narrowing of both large and small coronary vessels. This pathology is often underestimated by traditional coronary angiography, which primarily assesses focal stenoses and fails to capture microvascular dysfunction. Given these limitations, CFR measurements have emerged as a more reliable approach for determining overall coronary circulation. A reduction in CFR indicates impaired coronary perfusion, as vessels lose their ability to dilate adequately to compensate for fluid volume due to upstream stenoses. When these vessels fail to adapt, the ability of the myocardium to meet metabolic demands is compromised, increasing the risk of ischemia and graft failure.

In ex-vivo systems, CFR can be measured using two primary techniques: coronary thermodilution and Doppler flow velocity assessment. The coronary thermodilution method relies on a temperature-sensitive guidewire and calculates CFR based on the mean transit time of three saline boluses during resting and hyperemic (increased blood flow) conditions [13]. While this approach correlates well with absolute coronary flow in research settings, it is susceptible to measurement errors due to the sensitivity of rapid saline injections, which may disrupt basal flow values. In contrast, the Doppler flow velocity technique employs a sensor-equipped guidewire to measure real-time phasic coronary flow velocity [13]. This method not only provides direct feedback on signal quality but also enables advanced physiological assessments of coronary circulation. However, its accuracy depends on the operator's expertise and precise positioning of the guidewire to ensure reliable signal acquisition. Notably, while thermodilution-derived mean transit times reflect absolute coronary flow and are influenced by myocardial mass, Doppler-derived coronary flow velocity is inherently normalized for myocardial perfusion demands based on wall shear stress principles. This distinction makes Doppler-based CFR assessments particularly advantageous in evaluating functional coronary physiology [13].

2.2.2 Fractional flow reserve

Fractional flow reserve (FFR) is a pressure-derived physiological index used to assess the functional significance of coronary stenosis and its impact on myocardial perfusion. Introduced in the early 1990s, FFR is calculated as the ratio of mean distal coronary pressure (P_d) to mean aortic pressure (P_a) during maximal pharmacological vasodilation [14]. The theoretical framework of FFR assumes a linear relationship between coronary pressure and flow during maximal vasodilation, allowing it to estimate the proportion of blood flow available to the myocardium relative to an unobstructed artery. However, this relationship is incrementally linear rather than strictly proportional, making FFR an estimate rather than an absolute measure of coronary flow.

FFR has been extensively validated against non-invasive ischemia tests to determine its optimal cutoff for diagnosing inducible myocardial ischemia in patients with stable coronary artery disease (CAD) and established a threshold of 0.75 [15]. A value below 0.90 soon after transplantation has been identified as an indicator of abnormal epicardial artery physiology and has been linked to adverse clinical outcomes [15]. However, later study reports indicate that an abnormal FFR measured 1 year post-transplantation does not appear to be a significant predictor of long-term prognosis. This discrepancy may be attributed to progressive microvascular dysfunction over

time, which affects coronary flow dynamics. As microvascular function deteriorates, the maximal achievable flow in the vessel decreases, causing FFR values to increase despite no observable changes in intravascular ultrasound-based assessments of epicardial disease [16].

Despite their differences, studies have shown that both CFR and FFR have identical diagnostic accuracy (81%) for detecting inducible myocardial ischemia. While FFR estimates the functional significance of epicardial stenosis by measuring pressure gradients, CFR evaluates the overall coronary circulation, including both the epicardial and microvascular components [14]. However, the clinical adoption of CFR has been limited due to technical challenges, procedural complexity, and its sensitivity to hemodynamic changes. In contrast, FFR, with its simpler pressure-based measurements, has widespread clinical use, including in the ex-vivo perfusion systems.

2.2.3 Edema

Edema in cardiac grafts results from a complex interplay of hemodynamic and neuroendocrine mechanisms that disrupt fluid balance. The hallmark of heart failure with reduced ejection fraction is decreased cardiac output, which the body interprets as a reduction in circulating volume. In ex-vivo machine perfusion, the accumulation of water in a graft increases intragraft pressure, potentially compromising graft function and leading to tissue necrosis and graft rejection [17]. A rapid removal of interstitial fluid immediately upon rejection diagnosis may help mitigate tissue damage and preserve graft viability in an ex-vivo perfusion setup.

3. Cell damage and death markers

Cell death is a fundamental process in biological systems, essential for maintaining tissue homeostasis by removing damaged, senescent, or dysfunctional cells. In the context of cardiac transplantation, cell death plays a pivotal role in determining graft viability and function. The extent of cellular damage within the transplanted heart can influence outcomes, including the risk of primary graft dysfunction (PGD) and long-term survival. Various forms of cell death, including apoptosis, necrosis, and necroptosis, may contribute to graft injury, particularly in response to IR stress and immune-mediated rejection. Recent research has focused on identifying specific markers of cell damage and death that could serve as predictive tools for assessing graft function and survival.

3.1 Cardiac troponins

Cardiac troponins (cTn) are structural proteins essential for cardiac muscle contraction, specifically regulating the calcium-dependent interaction between actin and myosin. These proteins, primarily troponin I (cTnI) and troponin T (cTnT), are highly specific to the heart, making them valuable biomarkers for detecting myocardial damage. When cardiomyocytes undergo necrosis or apoptosis during machine perfusion, cTn is released into the bloodstream or perfusate, with its levels correlating with the extent of myocardial injury. In heart transplantation, cTn has gained attention as a potential marker for graft function, rejection, and the development of CAV. Studies suggest that elevated high-sensitivity troponins (hs-cTnT) levels are

associated with both left and right ventricular dysfunction, demonstrating a sensitivity of 75% and specificity of 87% for detecting PGD [18].

The role of troponins in detecting acute cellular rejection (ACR) remains controversial. A set of studies proposes that cTnT, when used alongside endomyocardial biopsy (EMB), a reference standard technique that has been used for more than 50 years to diagnose cardiac graft rejection, could help confirm rejection. However, the diagnostic utility of troponins alone is inconsistent [19]. Studies also reported a strong association between hs-cTnT and rejection, whereas other studies report varying sensitivity and specificity, suggesting troponins may be more useful in ruling out the probability of rejection rather than confirming it with certainty. Evaluating circulatory cTn in the machine perfusion system can predict the damage that occurred to the graft tissue before transplantation [19]. While cTnI has been studied less extensively than cTnT, findings in pediatric heart transplant patients indicate that it is highly specific but not sufficiently sensitive to serve as a standalone rejection marker [20].

Elevated troponin levels correlate with microvascular fibrin deposits, endothelial activation, macrophage infiltration, and depletion of vascular fibrinolytic and anticoagulant components—all factors contributing to CAV in transplant recipients. Interestingly, while recent studies suggest that high troponin levels in the donor heart at the time of transplantation predict worse outcomes, others report that modest elevations may be protective against long-term CAV development [19]. The extent to which the cTn fluctuations in machine perfusion allow us to make a critical decision on the graft calls for extensive future research.

3.2 Lactate dehydrogenase

Lactate dehydrogenase (LDH) is a cytoplasmic enzyme present in all tissues, where it plays a crucial role in cellular metabolism by catalyzing the conversion of pyruvate to lactate. This process is particularly significant under anaerobic conditions, such as ischemia or intense muscle activity, where it supports energy production despite oxygen limitations. In cardiac tissue, lactate serves as a primary metabolic substrate, contributing up to 60% of the heart's energy supply [21]. However, when myocardial cells are damaged due to ischemic stress, necrosis, or metabolic dysfunction, LDH is released into the surrounding fluid, making it a valuable indicator of cellular injury.

In heart transplantation, monitoring LDH levels provides critical insights into myocardial viability. During ex-vivo machine perfusion, the enzyme can be measured in the circulating perfusate to assess the extent of myocardial damage. A significant elevation in LDH suggests ongoing injury, which may result from prolonged ischemia, suboptimal preservation, or reperfusion-induced stress. A stable or moderate increase in LDH levels generally indicates good graft integrity, whereas a sharp rise may signal irreversible myocardial dysfunction, warranting further assessment before proceeding with transplantation.

The ability to monitor LDH in real-time during machine perfusion also allows for the optimization of preservation strategies. Adjustments in perfusion conditions, such as oxygenation levels, temperature regulation, and nutrient supply, can be made to minimize metabolic stress and improve graft outcomes [2]. This enzymatic marker thus serves not only as a diagnostic tool for assessing donor heart viability but also as a guide for refining ex-vivo perfusion protocols to enhance prolonged organ preservation during viability assessment and transportation.

3.3 Creatine kinase

Creatine kinase (CK) is another well-established marker for assessing cardiac injury and has been extensively used in both experimental and clinical settings. CK plays a crucial role in energy metabolism by catalyzing the conversion of creatine into phosphocreatine, which serves as an energy reservoir for cells. When myocardial tissue experiences damage due to ischemia, surgical intervention, or transplantation, CK, particularly its isoenzyme present in the myocardial tissue (CK-MB), is released into the bloodstream, making it a valuable indicator of myocardial stress. Its rapid and reproducible activity evaluation, requiring only small sample volumes, makes it a convenient tool for monitoring cardiac injury ex-vivo.

In clinical practice, some studies suggest that CK-MB elevation may be useful in detecting moderate-grade rejection, potentially aiding in the early assessment of graft function and response to immunosuppressive therapy [22]. However, its reliability as a standalone rejection marker is uncertain, as CK-MB can also rise due to other factors such as IR injury, surgical interventions, or underlying heart disease. Beyond its role in myocardial injury, CK has also been implicated in vascular contractility and sodium retention, suggesting a possible link to hypertension and cardiovascular complications. This raises the possibility that CK activity could influence post-transplant hemodynamics and long-term vascular health. Hence, further research is needed to establish its role in predicting transplant outcomes.

3.4 Heart-type fatty acid-binding protein

Heart-type fatty acid-binding protein (H-FABP) is a cytoplasmic protein primarily involved in the transport of long-chain fatty acids within cells. It is particularly abundant in cardiac myocytes, where it plays a crucial role in lipid metabolism and energy homeostasis. H-FABP represents a promising biomarker that could complement existing markers like cTn and CK-MB, enhancing early detection and risk stratification in cardiac grafts. Unlike cTn, which is bound to contractile elements within the cardiomyocyte, H-FABP exists in a freely soluble form, making it highly responsive to myocardial injury. Upon cardiac damage, such as ischemia or infarction, H-FABP is rapidly released into the bloodstream due to its small molecular size and cytoplasmic localization. This results in a steep rise in plasma concentrations within 1 hour of injury, peaking at 4–6 hours and returning to baseline within 24 hours, much faster than cTn and CK-MB [23].

Although H-FABP has been extensively studied as a biomarker for acute myocardial infarction (AMI), its potential role in cardiac transplantation remains largely unexplored. Given its rapid release kinetics, it may offer an advantage in detecting early graft injury, IR damage, or subtle myocardial stress that might not immediately elevate cTn levels. This suggests that in transplant settings, monitoring H-FABP levels in the perfusate during ex-vivo heart preservation or in early post-transplantation phases may help assess myocardial viability and detect subtle ischemic injury before irreversible damage occurs [2].

Despite its promise in the machine perfusion setting, the myocardial specificity of H-FABP is not absolute in in-vivo settings, as it is also present in skeletal muscle, kidneys, lungs, and other organs. This could lead to confounding elevations in conditions unrelated to cardiac injury, such as renal dysfunction, which may be particularly relevant in transplant recipients, making H-FABP a questionable marker for early graft monitoring in post-transplant patients.

4. Inflammatory markers

Inflammation plays a central role in the immune response following heart transplantation, influencing both short-term graft function and long-term survival. Various immunological and non-immunological factors contribute to inflammatory processes that can affect the transplanted graft, particularly in conditions such as PGD, CAV, and systemic infections [24]. These factors drive a cascade of immune responses, including cytokine release, T-cell activation, and subsequent tissue infiltration, ultimately leading to vascular remodeling and graft dysfunction. Inflammatory markers, including cytokines, chemokines, and their receptors, provide critical insights into the state of immune activation within the graft. However, distinguishing between alloimmune responses and inflammation caused by infections remains a major challenge when using these markers in clinical practice. However, ex-vivo perfusion systems offer a controlled setting to monitor these biomarkers, enhancing graft assessment and recovery.

4.1 Damage-associated molecular patterns

Damage-associated molecular patterns (DAMPs) are endogenous molecules released when cells experience significant stress, IR injury, or necrosis. Functioning similarly to pathogen-associated molecular patterns (PAMPs), DAMPs are recognized by pattern recognition receptors (PRRs) on innate immune cells, leading to immune activation and inflammation within the transplanted organ. This process plays a key role in PGD and rejection. Since DAMPs are widely present in various tissues, their systemic levels may not provide organ-specific insights in-vivo. However, assessing DAMP release during machine perfusion of donor hearts may offer a more targeted approach for evaluating graft viability in real-time.

During the course of heart transplantation, DAMPs can be released at multiple stages, including from the donor organ prior to retrieval, during reperfusion, and post-transplantation due to immune-mediated injury. Common DAMPs involved in cardiac transplantation include high-mobility group box 1 (HMGB1), heat shock proteins (HSPs), S100 proteins, nucleic acids, fibrinogen, tenascin C, and extracellular histones [25]. These molecules serve as danger signals, alerting the immune system to cellular distress and leading to the activation of inflammatory pathways that can compromise graft function [25].

In addition to nuclear and cytosolic DAMPs, mitochondria contribute to immune activation through mitochondrial DAMPs (mtDAMPs), which include mitochondrial DNA (mtDNA), cytochrome c, adenosine triphosphate (ATP), mitochondrial transcription factor A, N-formyl peptides, succinate, and cardiolipin [26]. Mitochondria-derived signals play a significant role in transplant outcomes, as increased circulating levels of mtDAMPs in organ donors have been linked to early allograft dysfunction. In experimental heart transplantation models, the release of cytochrome c and succinate during early reperfusion negatively correlates with cardiac functional recovery, highlighting their potential as prognostic markers [2, 26].

4.2 Cytokines

Cytokines play a crucial role in modulating inflammatory responses and have emerged as significant biomarkers in cardiac transplantation. These signaling

molecules can be broadly categorized into pro-inflammatory cytokines, such as tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), IL-6, IL-8, and IL-12, and anti-inflammatory cytokines, including IL-4, IL-6, IL-10, IL-11, IL-13, IL-1 receptor antagonist (IL-1RA), and transforming growth factor- β (TGF- β). While pro-inflammatory cytokines initiate immune activation and inflammation, anti-inflammatory cytokines serve to counterbalance these effects and regulate immune homeostasis [27]. Since cytokine measurements from cardiac biopsies strongly correlate with serum levels, non-destructive approaches such as analyzing donor blood or machine perfusion perfusate could offer valuable insights into graft viability, suggesting that cytokine profiling may aid in early diagnosis and management of transplant-related complications.

During heart transplantation, cytokine levels fluctuate in response to graft injury, immune activation, and rejection episodes. Elevated levels of TNF- α and IL-6 have been linked to post-transplant cardiac dysfunction. TNF- α is known to increase rapidly in cardiac myocytes following brain death, leading to detrimental effects such as the activation of inducible nitric oxide synthase, impaired excitation-contraction coupling, myocardial inflammation, and apoptosis. Studies indicate that elevated TNF- α levels in donor serum and cardiac tissue correlate with poor myocardial function and early right heart failure in transplant recipients. Similarly, increased IL-6 levels, secreted by immune cells, endothelial cells, fibroblasts, and mesenchymal cells, have been associated with poor graft quality and adverse patient outcomes [27, 28]. Suppressed IL-2 expression has also been linked to acute rejection, emphasizing its potential as a predictive biomarker [28].

4.3 Endothelial activation

The endothelium lining of blood vessels mediates tissue injury through cytokine production and leukocyte trafficking. Following brain death, the donor heart experiences early endothelial activation, leading to increased inflammatory load [29]. This response is further amplified by IR injury during transplantation, resulting in endothelial dysfunction and potential microvascular damage. Studies have indicated that the endothelium is particularly vulnerable post-transplant, often showing greater susceptibility to injury than the myocardium itself. While pre-clinical studies strongly suggest that endothelial activation contributes to allograft injury and rejection, clinical studies validating its predictive value are still limited [2, 30].

One of the key indicators of endothelial activation is the presence of endothelial microparticles (EMPs), submicroscopic vesicles shed from endothelial cells during activation, injury, or apoptosis. EMPs carry endothelial markers such as CD31 (constitutive markers) and CD62E (inducible marker), and their phenotypic analysis can provide insight into the functional status of the endothelium (cellular activation or apoptosis). Elevated levels of EMPs have been observed in conditions of vascular stress, including acute coronary syndromes and uncontrolled hypertension, suggesting their potential as biomarkers for endothelial injury [30]. Assessment of circulating EMPs in ex-vivo perfusion may offer a promising approach to monitoring endothelial health in transplant grafts. As such, monitoring and modulating endothelial responses in the peri-transplant period could lead to improved graft survival and long-term patient prognosis.

5. Omics markers

The advent of omics technologies has revolutionized biomedical research and clinical diagnosis, providing a comprehensive and high-resolution view of molecular interactions within biological systems. Unlike traditional methods that focus on individual biomarkers, omics approaches offer a holistic perspective by analyzing entire sets of genes (genomics), RNA transcripts (transcriptomics), proteins (proteomics), and metabolites (metabolomics) and hold significant promise for enhancing the evaluation of cardiac grafts during machine perfusion (**Figure 2**) [31]. By analyzing dynamic molecular profiles, such as metabolic shifts, protein expression patterns, or gene activation linked to IR injury, omics data could provide real-time insight into graft viability beyond traditional metrics like electrolyte levels or contractility [31]. Integrating multi-omics methods during machine perfusion could enable graft-specific interventions, such as targeted drug delivery or metabolic support, to resuscitate marginal grafts prior to transplantation [32]. This approach has the potential to refine

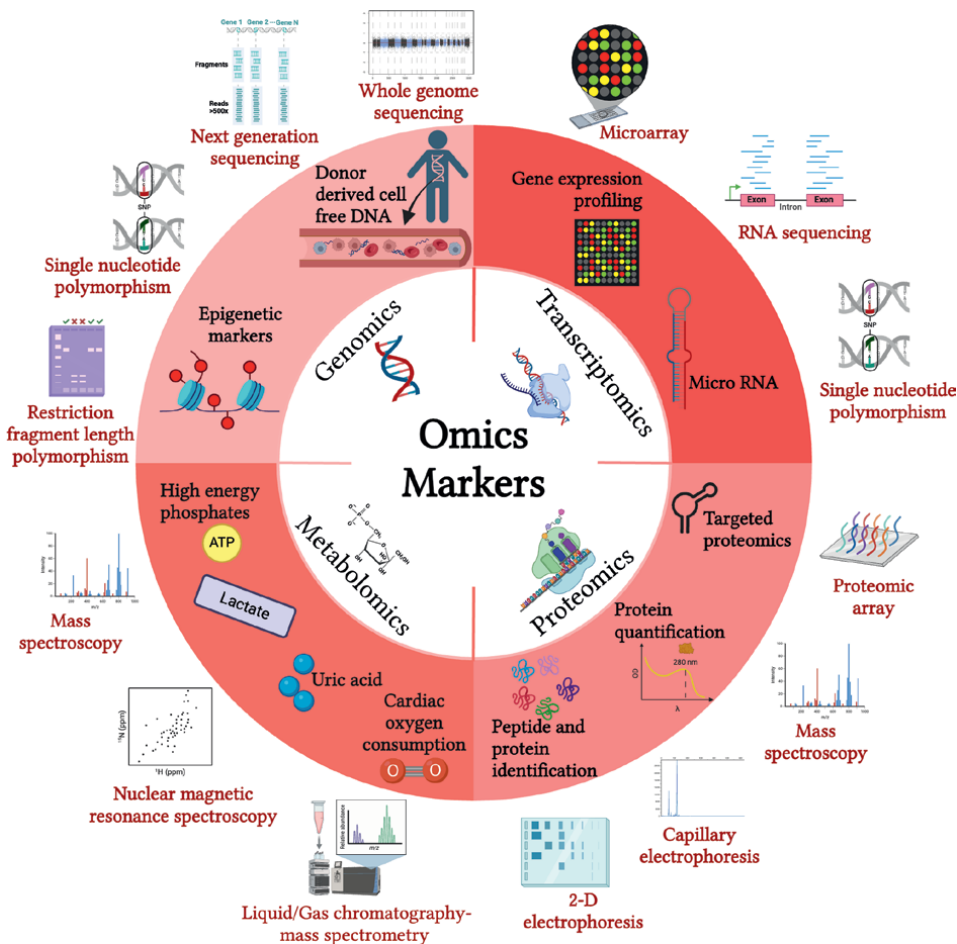


Figure 2. Classification of omics-based biomarkers and their corresponding evaluation methodologies for assessing cardiac graft viability during ex-vivo machine perfusion.

donor heart selection, reduce post-transplant complications and extend the pool of viable organs by objectively quantifying molecular health during machine perfusion.

5.1 Genomic markers

5.1.1 Donor-derived cell-free DNA

Cell-free DNA (cfDNA) refers to fragments of DNA circulating in the bloodstream, originating from dying cells. This DNA can originate from nuclear, mitochondrial, or even non-human sources, such as bacterial or viral DNA. In solid organ transplant recipients, cfDNA is released into the bloodstream due to cell death resulting from disease processes, such as chronic allograft rejection (CAR), or from normal cellular turnover, including apoptosis. In transplant recipients, cfDNA can come from both the donor organ and the recipient, with the portion derived from the graft known as donor-derived cell-free DNA (dd-cfDNA) [33]. This biomarker has gained significant attention for its potential in detecting allograft rejection, as increased levels of dd-cfDNA indicate heightened donor cell death, often due to immune-mediated injury. Recent advancements have led to the development of highly sensitive dd-cfDNA assays, including digital droplet PCR and targeted next-generation sequencing (NGS) methods with potential use cases in ex-vivo machine perfusion. The non-invasive nature of dd-cfDNA testing offers a compelling alternative to traditional surveillance methods such as EMB, reducing the need for repeated invasive procedures while providing real-time insights into graft health.

In heart transplant recipients, dd-cfDNA levels typically remain below 1% under stable conditions but can rise to 3–5% during acute rejection [34]. Studies reported that dd-cfDNA elevation has been detected months before histopathological evidence of rejection, making it a promising early-warning biomarker [33, 34]. Several techniques have been developed to differentiate donor and recipient cfDNA. One approach involves analyzing single nucleotide polymorphisms (SNPs) through genome-wide genotyping, comparing pre-transplant recipient DNA with post-transplant samples. Another method computationally estimates the recipient's genotype and then distinguishes donor DNA from recipient DNA based on SNP variations. Additionally, researchers have used the Y chromosome as a marker to detect donor DNA in female recipients of male donor hearts, though this method has limited applicability [34]. High-throughput sequencing assays, such as the Genome Transplant Dynamics (GTD) assay, have further improved the detection of dd-cfDNA, demonstrating its correlation with acute cellular rejection (ACR) and antibody-mediated rejection (AMR) [33].

5.1.2 Epigenetic markers

Epigenetic modifications alter gene expression without changing the DNA sequence, primarily through DNA methylation and histone modifications, which govern immune cell function, inflammation, and vascular integrity [35]. Understanding epigenetic markers in ex-vivo machine perfusion offers valuable insights into the mechanisms underlying graft rejection and transplant tolerance for more precise monitoring and therapeutic interventions.

DNA methylation, catalyzed by DNA methyltransferases, plays a crucial role in regulating immune cell differentiation and function. Aberrant methylation patterns

in recipient T cells can lead to excessive immune activation, increasing the risk of acute and chronic rejection [36]. Similarly, changes in DNA methylation within the donor heart can affect endothelial function, vascular remodeling, and inflammatory signaling, all of which are critical for long-term graft survival. Identifying methylation signatures associated with rejection or tolerance may help stratify transplant grafts based on their risk profile, allowing for individual graft-targeted immunosuppressive strategies [36].

Histone modifications, another key epigenetic mechanism, dynamically regulate chromatin structure and gene accessibility [35]. Acetylation, deacetylation, and methylation of histones influence the transcriptional activity of genes involved in inflammation, immune cell recruitment, and tissue remodeling. Histone acetyltransferases and histone deacetylases regulate these modifications, determining whether genes promoting inflammation and rejection are activated or suppressed [36]. Increased histone acetylation is associated with elevated immune responses, whereas histone deacetylation can suppress pro-inflammatory pathways. This balance has led to the exploration of histone deacetylase inhibitors (HDACi) as potential anti-rejection therapies. Studies suggest that HDACi, such as valproic acid and trichostatin A, can prolong graft survival by reducing inflammatory cytokine production, inhibiting B-cell antibody generation, and modulating immune cell differentiation without impairing normal immune function [36].

By combining epigenetic data with traditional biomarkers and clinical parameters, machine perfusion procedures could move toward a more organ-specific approach, enhancing long-term graft function while minimizing adverse effects associated with immunosuppressive therapy.

5.2 Transcriptomics markers

5.2.1 Gene expression profiling

Gene expression profiling (GEP) is a technique used to measure the expression levels of specific genes in different cell types. In transplantation, GEP has emerged as a minimally invasive tool for monitoring allograft health and detecting rejection. It involves analyzing messenger RNA (mRNA) levels through methods such as real-time PCR (rt-PCR) and NGS. Since mRNA serves as a template for protein synthesis, its expression reflects cellular activity and response to various physiological conditions, including organ rejection [37].

The Cardiac Allograft Rejection Gene Expression Observational (CARGO) study played a pivotal role in this advancement by identifying 11 genes linked to moderate-to-severe acute cellular rejection (ACR). The commercial test derived from this study, AlloMap®, assesses gene expression in peripheral blood mononuclear cells (PBMCs) to stratify rejection risk. Subsequent studies, such as the HEARTBiT trial, further validated the effectiveness of GEP-based testing in patients with a low pre-test probability of rejection and provided additional evidence supporting the use of AlloMap as an alternative to invasive EMB [37]. Recent research has explored the role of mitochondrial gene expression in PBMCs as a potential biomarker for rejection [34]. Studies suggest that mitochondrial RNA sequences may not only serve as indicators of rejection but also contribute to immune activation, underscoring their dual role as both mediators and markers of graft injury [34]. Additionally, transcriptomic analyses have extended to tissue-based assessments. Recent works demonstrated that profiling transcripts associated with natural killer cell burden,

endothelial activation, macrophage infiltration, and interferon-related pathways could provide insights into antibody-mediated rejection (AMR) and correlate with the severity of allograft injury [34].

While GEP has proven valuable in post-transplant monitoring, some limitations remain, as its interpretation can be affected by immunosuppressive therapy, infections, hematopoiesis-stimulating agents, and blood transfusions [33]. In clinical practice, GEP is often used alongside dd-cfDNA testing, which has shown higher specificity for detecting allograft injury. Studies have suggested that using these tests together can significantly reduce unnecessary biopsies, with some reports indicating that up to 84% of surveillance biopsies could be avoided when both tests yield negative results [33].

5.2.2 *MicroRNA*

MicroRNAs (miRNAs) are small, non-coding RNA molecules (20–25 nucleotides) that regulate gene expression by binding to mRNA or proteins, influencing cellular processes such as immune responses and tissue remodeling. miRNA levels were found to rise before clinical rejection and decrease after therapy, making them a potential tool for early detection and treatment monitoring. Beyond rejection, miRNAs have also been implicated in CAV and diastolic dysfunction. Their stability in circulation, due to their encapsulation within exosomes or association with lipoproteins, makes them promising biomarkers for monitoring PGD [33]. While further validation is required, miRNA profiling holds great promise in improving heart transplant outcomes in machine perfusion.

Different types of miRNAs are released by cells undergoing rejection, and specific miRNA signatures have been associated with ACR and AMR [19]. Researchers identified miR-139-5p, miR-151a-5p, and miR-186-5p as being elevated in heart transplant rejection, with miR-29c-3p linked to AMR and miR-486-5p to ACR. However, since miR-486-5p is also highly expressed in red blood cells, its levels may be affected by hemolysis, making careful interpretation necessary [19, 34]. The Genomic Research Alliance for Transplantation (GRAFT) study further demonstrated the potential of miRNA-based diagnostics by using NGS to identify ACR- and AMR-associated miRNAs [33]. In practice, integration of miRNA with other molecular approaches, such as dd-cfDNA and GEP, could potentially enhance post-transplant monitoring and reduce the need for frequent/extensive invasive procedures.

5.3 **Proteomics markers**

Recent advancements in proteomics have led to the identification of differentially expressed biomarkers associated with allograft rejection. These biomarkers play key roles in cellular and antibody-mediated responses, acute-phase inflammation, and metabolic pathways, offering a potentially minimally invasive approach to diagnosing PGD [38]. Proteomic profiling of ex-vivo perfusate can be a novel approach for real-time graft monitoring, as it contains a wide array of proteins, including leakage markers from injured tissues, immunoglobulins, cytokines, peptide hormones, and disease-specific proteins. Analysis of these proteins yields signs of early rejection or IR injury during the graft transportation. This technique has the potential to refine organ selection criteria and optimize preservation strategies, ultimately improving the transplant success rate.

Early proteomic studies in cardiac transplantation using gel-based proteomic techniques identified 11 proteins that exhibited two- to five-fold changes in expression during acute rejection [39]. These proteins included cardiac-specific markers and stress-related proteins. More recent high-throughput proteomic analyses have identified and validated a panel of plasma proteins that can classify rejecting grafts with high accuracy, further demonstrating the clinical relevance of proteomic markers [39].

Standardizing proteomic assays, ensuring reproducibility across different patient populations, and integrating proteomic data with existing clinical workflows are critical steps toward broader adoption. A major advantage of proteomics is its unbiased, large-scale detection of proteins, enabling computational analysis to pinpoint those significantly upregulated during acute rejection. Unlike traditional hypothesis-driven research, which focuses on known molecules, proteomics can reveal unexpected relationships between proteins and transplant rejection, potentially leading to the discovery of novel biomarkers. As research in this field progresses, integrating proteomic markers into machine perfusion and post-transplantation workflows may revolutionize cardiac transplant monitoring, improving early rejection detection and long-term graft survival. However, large-scale multicenter studies are needed to validate identified biomarkers and establish robust diagnostic thresholds.

5.4 Metabolomics markers

5.4.1 High-energy phosphates

Phosphoester bonds commonly link low-energy phosphates, releasing approximately 2 to 3 kcal/mol of energy during hydrolysis. High-energy phosphates (HEPs), on the other hand, consist of various phosphate compounds that release more than 7 kcal/mol of energy [40]. Adenosine triphosphate (ATP) and creatine phosphate (CrP) are the primary HEPs found in the human body. HEPs are essential for maintaining cellular energy homeostasis, as these molecules serve as immediate energy reservoirs, fueling critical biochemical processes across various cell types. Unlike the distinct metabolic pathways of glucose, fatty acids, or amino acids, HEP biosynthesis and degradation are interconnected with multiple metabolic substrates, requiring specialized transporters and enzymatic systems for efficient transmembrane movement. The balance between ATP production and consumption is crucial for sustaining cellular function, particularly in energy-intensive tissues such as the myocardium. Non-invasive phosphorus-31 magnetic resonance spectroscopy (^{31}P -MRS) allows for the measurement of myocardial CrP/ATP ratios, providing valuable insights into cardiac energy metabolism and overall graft viability [40].

During ischemia, oxygen depletion forces a metabolic shift from oxidative phosphorylation to anaerobic glycolysis, favoring glucose over fatty acids for ATP production. However, glycolysis yields less energy, increasing reliance on endogenous CrP stores [2]. Hence, during organ transplantation, the preservation of HEPs during graft storage has been strongly associated with improved post-transplant outcomes. Studies in both donation after brain death (DBD) and DCD models suggest that higher HEP levels correlate with better graft function and survival. Preclinical investigations have demonstrated that replacing conventional static cold storage with continuous perfusion more effectively preserves HEPs, thereby enhancing contractile function and post-transplant recovery [41]. While human studies remain limited, available evidence suggests that maintaining metabolic homeostasis, rather than

simply minimizing metabolic activity, may be a superior strategy for optimizing graft preservation and function [2]. These findings underscore the critical role of energy metabolism in transplantation success and highlight the potential benefits of ex-vivo perfusion-based preservation techniques in improving graft viability.

5.4.2 Lactate

Lactic acidosis (LA) is a metabolic condition characterized by an imbalance between lactate production and clearance, often resulting in elevated lactate levels and metabolic acidosis. Under normal physiological conditions, lactate is continuously produced by tissues such as muscle, skin, and red blood cells and is efficiently metabolized by the liver and kidneys to maintain homeostasis. However, when the oxygen supply becomes insufficient to meet energy demands, lactate accumulation increases due to the shift from aerobic metabolism to anaerobic glycolysis. Several studies reported that elevated lactate levels observed post-heart transplantation, linked to longer ischemic times, indicate an increased need for inotropic support and higher glucose levels [42]. While most cases of severe LA after cardiac transplantation do not lead to adverse outcomes, persistently high lactate levels have been associated with longer hospital stays and increased mortality risk [42].

During ex-vivo machine perfusion, lactate metabolism has been explored as a potential indicator of graft viability. In DBD heart grafts, declining or stable lactate levels, along with a net lactate extraction rate, have been proposed as markers of graft quality and predictors of short-term graft survival. However, this approach appears to have limited sensitivity in evaluating DCD grafts, as some hearts with high lactate concentrations at the end of machine perfusion were still successfully transplanted without adverse consequences [2, 43]. This variability suggests that multiple factors, including donor physiology, perfusate composition, and erythrocyte metabolism, influence lactate dynamics in machine perfusion. Further research is needed to refine lactate-based assessment strategies and enhance their predictive value in cardiac transplantation.

5.4.3 Cardiac oxygen consumption

Monitoring oxygen consumption during machine perfusion provides valuable insights into graft metabolism and function in cardiac transplantation. Preclinical studies, particularly in DCD models, demonstrated that oxygen consumption correlates with post-transplant cardiac function under both loaded and unloaded perfusion conditions [44]. This measurement is relatively straightforward, as it can be obtained from arterial and venous perfusate samples using a standard blood gas analyzer. However, several factors, including myocardial contractility, coronary flow, and metabolic activity, can influence oxygen consumption, making it a dynamic and complex parameter. Oxygen extraction ratio and mitochondrial respiration rates are critical cardiac oxygen consumption indicators of metabolic efficiency and graft viability during ex-vivo machine perfusion. By measuring real-time oxygen utilization, ex-vivo systems can assess whether the heart maintains aerobic metabolism or shifts to anaerobic pathways—a sign of ischemia or mitochondrial dysfunction. Therefore, integrating continuous monitoring of cardiac oxygen consumption markers into machine perfusion protocols enables dynamic, data-driven viability assessments, helping to distinguish salvageable grafts from those at risk of failure and guiding strategies to optimize organ quality before transplantation.

5.5 Uric acid

Uric acid has emerged as a significant biomarker in cardiac transplantation, providing insights into inflammation, oxidative stress, and long-term graft outcomes. In heart transplant recipients, post-transplant hyperuricemia has been correlated with adverse outcomes, particularly an increased risk of developing CAV and PGD. Elevated serum uric acid levels are widely recognized as markers of systemic inflammation, and this association is believed to stem from heightened xanthine oxidase (XO) activity, which generates reactive oxygen species, contributing to endothelial dysfunction, cytokine release, and cell apoptosis [45]. Higher uric acid levels 1 year after transplantation have also been associated with higher mortality rates, suggesting its potential as a long-term prognostic marker [46]. However, it remains unclear whether these elevated levels primarily reflect donor-related factors or are more influenced by the recipient's pre-existing metabolic profile. Studies indicate that recipients with hyperuricemia before transplantation experience more severe rejection episodes post-transplant compared to those with lower baseline levels [2, 46].

Being a byproduct of purine metabolism, uric acid may serve as a biomarker for ischemic injury and oxidative stress during machine perfusion. Elevated uric acid levels in the perfusate could reflect cellular ATP degradation and XO activity, signaling hypoxia or reperfusion-related damage. Its dual role as both a pro-oxidant (via reactive oxygen species generation) and an antioxidant (as free radical scavengers) complicates real-time interpretation; however, ex-vivo dynamic monitoring might help balance these effects. A multimodal approach, wherein integrating uric acid levels with other markers (such as lactate and oxygen consumption), could refine the assessment of metabolic recovery and guide ex-vivo interventions to mitigate graft injury.

6. Hormone/pro-hormone markers

6.1 Natriuretic peptides

Natriuretic peptides (NPs) are a family of structurally related but genetically distinct hormones that play a crucial role in cardiovascular homeostasis by regulating blood pressure, fluid balance, and cardiac remodeling. This group includes atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP) [47]. While ANP and BNP are primarily secreted by cardiac myocytes, CNP is predominantly produced by endothelial cells. ANP is synthesized and stored in atrial myocytes and is rapidly released into circulation in response to atrial wall stretch caused by increased blood volume or pressure. It promotes vasodilation, enhances renal sodium excretion (natriuresis), and reduces fluid retention by suppressing the renin-angiotensin-aldosterone system (RAAS) [47]. BNP, which is secreted by both atrial and ventricular myocytes, particularly in response to ventricular overload, exerts similar physiological effects but has a longer half-life, making it a more stable biomarker for cardiac stress. In healthy individuals, BNP levels are generally lower than ANP; however, in pathological conditions such as heart failure, BNP exhibits a more pronounced elevation, making it a preferred biomarker for disease severity and prognosis [27, 47].

BNP, in particular, is synthesized as a pro-hormone and cleaved into its active form and N-terminal pro-BNP (NT-proBNP). BNP and NT-proBNP levels tend to increase during episodes of acute rejection, but their diagnostic accuracy remains uncertain, as

other post-transplant factors can also influence their levels [27]. While some studies have linked elevated BNP levels to treatable rejection episodes, no definitive cutoff value has been established to reliably differentiate rejection from other transplant-related complications [2, 47]. Despite these limitations, the utility of BNP as an ex-vivo marker for graft viability in machine perfusion is promising.

6.2 Copeptin

Arginine vasopressin (AVP) is a critical hormone involved in fluid balance, vascular tone, and the endocrine stress response. However, due to its short half-life, instability in circulation, and platelet association, direct measurement of AVP is challenging in clinical practice. Instead, copeptin, the C-terminal fragment of the AVP precursor, is co-released with AVP in equimolar amounts and serves as a more stable and easily measurable surrogate biomarker [48]. Elevated copeptin levels in donor blood can indicate cardiac cellular injury; however, its specificity for heart-related pathology is limited in *ex-vivo* conditions, as the primary site of copeptin synthesis is the hypothalamus, and the heart produces a very small amount of AVP during decreased cardiac function [49]. The utility of copeptin measurement is facilitated by commercially available assays, including the Brahms sandwich immunoluminometric assay and the immunofluorescent assay on the KRYPTOR platform. Further studies are necessary to determine whether copeptin can play a definitive role in predicting long-term graft function during machine perfusion [48].

6.3 Procalcitonin

Procalcitonin (PCT) is a 116-amino-acid polypeptide and the precursor of the hormone calcitonin. It is primarily produced in the liver and peripheral mononuclear cells in response to inflammatory stimuli, particularly bacterial and fungal infections [50]. Following heart transplantation, PCT serves as a critical marker for distinguishing between post-transplant complications such as bacterial and fungal infections, acute rejection, and systemic inflammatory responses [2].

In organ donation, elevated PCT levels in DBD patients have been linked to poor cardiac graft function both before and after transplantation. Measurements taken immediately before pericardial opening have been identified as independent predictors of early graft failure [2]. Studies on heart and lung transplant recipients have demonstrated that patients with bacterial or fungal infections exhibit significantly elevated PCT levels, while those experiencing acute graft rejection or viral infections show little to no increase [51]. Several commercially available tests facilitate rapid PCT measurement, including the LUMI-Test, the Q-Test, and the Kryptor Test. In comparison with LUMI-Test and Q-Test, the Kryptor Test offers the fastest turnaround with a high sensitivity [52]. The role of PCT in infection diagnosis and early graft function assessment highlights its value as a potential biomarker in graft survival and viability assessment.

7. Challenges in biomarker implementation

Several technical, logistical, and regulatory challenges hinder the clinical implementation of biomarkers in cardiac graft transplantation. One of the primary difficulties lies in standardization—biomarker assays often vary across laboratories due

to differences in sample handling, detection methods, and reference ranges, leading to inconsistent results. Additionally, biomarkers must undergo rigorous validation to demonstrate clinical utility, which requires extensive multicenter studies and regulatory approvals that can take years to complete. Another major obstacle is integrating biomarker testing into routine clinical workflows without delaying critical decision-making. While some biomarkers provide rapid results, others require complex laboratory processes, limiting their real-time applicability in transplant settings.

Furthermore, many promising biomarkers lack specificity, as multiple physiological and pathological factors beyond graft rejection may influence their levels. The economic feasibility of biomarker-based diagnostics also remains challenging, particularly in resource-limited settings where access to high-cost assays and specialized equipment is restricted. Beyond technical and financial considerations, there are also ethical and regulatory barriers, including data privacy concerns and the need for standardized guidelines on biomarker interpretation. Despite these challenges, the potential of biomarkers in improving graft assessment and patient outcomes remains significant. To provide a comparative overview of biomarker utility, we have summarized and scored these markers based on four critical parameters: predictive power, detection speed, cost, and mechanistic insights, as illustrated in **Figure 3**.

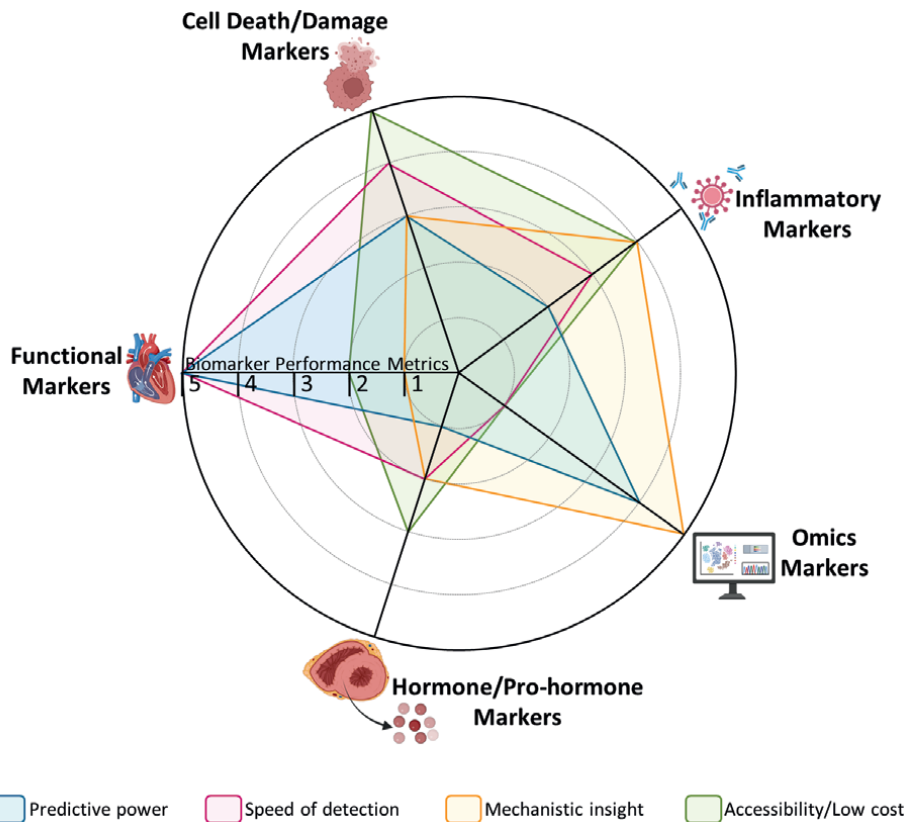


Figure 3. Radar chart comparing cardiac graft viability markers across predictive power, speed of detection, mechanistic insight, and accessibility/low cost. Each criterion is plotted as a radial axis, scaled from 1 (lowest) to 5 (highest).

Addressing the aforementioned challenges and limitations through improved assay standardization, cost-effective testing strategies, and enhanced regulatory frameworks will be crucial for advancing biomarker-driven ex-vivo machine perfusion in organ transplantation.

8. Integration of biomarkers into clinical protocols

The integration of biomarker data into clinical workflows is crucial for optimizing machine perfusion in cardiac graft assessment. This requires a structured approach linking biomarker validation, real-time analysis, and clinical decision-making. A proposed framework (**Figure 4**) outlines key phases: (1) pre-perfusion baseline assessment, (2) dynamic monitoring of the graft during transportation, and (3) post-assessment risk stratification to guide transplant eligibility. Advancements in machine perfusion have spurred the development of decision-support algorithms that integrate heterogeneous biomarker data with clinical variables. These algorithms employ weighted scoring systems or machine learning models to predict post-transplant outcomes, prioritizing biomarkers with high sensitivity for irreversible injury or strong prognostic value. However, algorithm training requires large, multicenter datasets to mitigate bias and ensure generalizability. Collaborative registries, such as an “International Machine Perfusion Consortium,” are critical for refining these tools and validating their predictive accuracy across diverse donor populations.

While biomarkers enhance objectivity in graft assessment, overreliance on isolated parameters carries significant risks. Biomarker levels may be confounded by ex-vivo machine perfusion conditions—for instance, hemodilution from perfusate can artificially lower inflammatory cytokine concentrations, while mechanical unloading during perfusion may mask systolic dysfunction. Additionally, temporal variability in biomarker release (e.g., delayed rise in cardiac-specific microRNAs post-ischemia) necessitates repeated sampling to capture dynamic trends. Notably, no single biomarker universally predicts graft viability; thus, clinical protocols must integrate multimodal approaches to contextualize biomarker findings. Institutions should also guard against “threshold fixation,” where rigid adherence to cutoffs leads to inappropriate discard of salvageable grafts or acceptance of high-risk organs.

Successful integration of biomarker-driven protocols demands institutional investment in infrastructure, interdisciplinary collaboration, and staff competency. Key adoption strategies include 1. standardized perfusion protocols: aligning machine perfusion with biomarker measurement requirements to ensure reproducibility; 2. cross-disciplinary teams: establishing “graft viability boards” comprising transplant surgeons, perfusionists, and bioengineers to interpret biomarker data and guide decisions; and 3. quality assurance programs: implementing regular audits of biomarker accuracy, instrument calibration, and clinical outcomes to refine institutional thresholds. Training programs must equip healthcare professionals with expertise in biomarker interpretation, perfusion system operation, and crisis management. Simulation-based modules and certification courses can standardize competencies. Furthermore, fostering partnerships between academic centers and industry stakeholders accelerates the translation of novel biomarkers into clinical workflows.

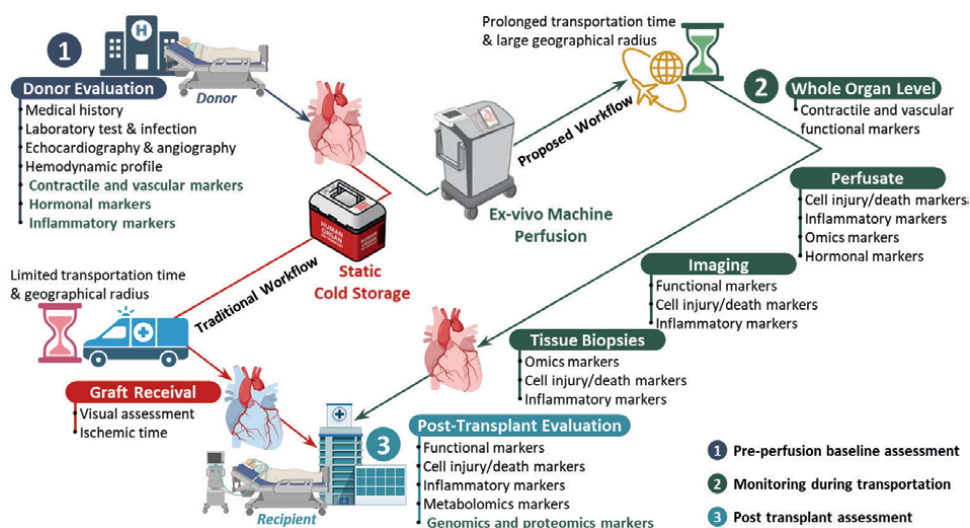


Figure 4. The conventional workflow for graft assessment during static cold storage and a proposed framework for incorporating biomarkers to evaluate cardiac grafts throughout key phases of transplantation. This framework encompasses modifications in pre-perfusion baseline assessment, real-time dynamic monitoring of the graft during transportation in ex-vivo machine perfusion, and post-assessment risk stratification to inform transplant eligibility decisions.

9. Future directions and research opportunities

The evolution of machine perfusion systems is poised to revolutionize cardiac graft assessment through innovations in real-time biomarker monitoring. Next-generation perfusion platforms are integrating biosensor arrays and microfluidic technologies capable of tracking dynamic biomarker shifts, such as redox state fluctuations, mitochondrial respiration rates, and microvascular permeability, with high temporal resolution. These systems may soon enable closed-loop perfusion, where biomarker data autonomously adjust perfusate composition, temperature, or pressure to optimize graft resuscitation. For example, impedance-based sensors monitoring edema may modulate oncotic gradients. Such innovations demand interdisciplinary collaboration between biomedical engineers, data scientists, and clinicians to ensure clinical translatability and scalability.

Artificial intelligence (AI) and machine learning (ML) are emerging as transformative tools for interpreting complex biomarker datasets and enhancing decision-making in graft viability assessment. Deep learning algorithms trained on multimodal data—including high-dimensional omics, contractile function metrics, and thermal/ultrasound images—can identify latent patterns predictive of post-transplant outcomes. For instance, neural networks analyzing temporal trends in troponin release and coronary flow resistance may forecast graft recovery potential more accurately than static thresholds. However, AI models require rigorous validation across diverse samples to address biases related to donor demographics or perfusion protocols. Federated learning frameworks, which pool anonymized data from global transplant centers without compromising privacy, offer a solution to dataset limitations. Additionally, explainable AI methodologies are critical to demystifying “black-box” predictions, fostering clinician trust, and meeting regulatory standards for transparency.

Bridging the bench-to-bedside gap necessitates prioritizing translational research that validates novel biomarkers in prospective clinical trials while addressing ethical and logistical barriers. Key priorities include standardizing biomarker panels for marginal grafts and developing portable, cost-effective perfusion systems for resource-limited settings. Concurrently, ethical frameworks must evolve to govern data ownership, algorithmic bias, and equitable access to advanced perfusion technologies. Regulatory agencies face the challenge of creating adaptive approval pathways for AI-driven perfusion devices and biomarker combinations, balancing innovation with patient safety. Logistically, institutional adoption requires addressing cost constraints, training gaps in bioinformatics, and interoperability between perfusion systems and electronic health records. A global collaborative “transplant research consortia,” for instance, can accelerate progress by harmonizing research agendas and sharing best practices. By addressing these multidimensional challenges, the machine perfusion field can unlock the full potential of biomarkers to transform cardiac transplantation into a precision-guided discipline.

10. Conclusions

The integration of biomarkers into machine perfusion systems represents a cornerstone in advancing cardiac transplantation, offering unprecedented precision in graft viability assessment and resuscitation. Biomarkers—spanning functional, cell injury/death, inflammatory, omics, and hormones/pro-hormone—provide critical insights into myocardial health, enabling clinicians to objectively differentiate salvageable grafts from those at risk of post-transplant failure. Machine perfusion technology amplifies this potential by creating a controlled ex-vivo environment for real-time biomarker monitoring, dynamic graft optimization, and therapeutic intervention.

While many of the discussed biomarkers show significant promise, their clinical applicability remains under investigation, and the scarcity of validation studies in ex-vivo systems poses challenges in establishing definitive superiority across categories. Future research should prioritize further clinical validation to fully ascertain their efficacy. The synergistic use of multimodal biomarkers enhances predictive accuracy beyond conventional (isolated) parameters. However, realizing the full promise of this paradigm demands sustained innovation in biosensor technology, AI-driven data integration, and multicenter validation of biomarker panels. Furthermore, success hinges on multidisciplinary collaboration among transplant clinicians, bioengineers, data scientists, and regulatory bodies to standardize protocols, address ethical challenges, and ensure equitable global access. As machine perfusion evolves from an experimental tool to a clinical mainstay, its convergence with biomarker science will redefine donor heart utilization, transforming transplantation into a precision medicine discipline while expanding the frontiers of lifesaving therapy.

Conflict of interest

The authors declare the absence of any potential conflict of interest.

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Section 3

Immunology, Rejection, and Precision Medicine

Humoral Rejection: The Pathologist's Point of View

Diana Stefania Tudose, Nicola Leone and Cristiana Bellan

Abstract

Heart failure (HF) is a highly lethal condition, and heart transplantation represents the main treatment for end-stage HF. In this context, the treatment of acute rejection remains a significant challenge. Acute allograft rejection includes Acute cellular rejection (ACR), mediated by cytotoxic T-cell response, and Antibody-mediated rejection (AMR), which causes activation of the complement cascade, resulting in myocardial injury and microvascular damage. Endomyocardial biopsy (EMB) remains the gold standard for diagnosing AMR, based on criteria from the International Society for Heart and Lung Transplantation (ISHLT). Even though included in the essential diagnosis criteria, immunohistochemical positivity for C4d may lack specificity, being correlated to other nonimmunologic conditions, and, on the other hand, AMR can occur without complement activation (C4d-negative AMR). Therefore, AMR continues to pose significant diagnostic challenges, highlighting the need for more specific, less invasive biomarkers to improve its diagnosis and treatment.

Keywords: humoral rejection, C4d, complement cascade, heart failure, International Society for Heart and Lung Transplantation

1. Introduction

Heart transplantation (HT) is a surgical procedure to treat end-stage heart failure by replacing a diseased heart with a healthy one from a donor. There are several causes that can lead to this surgical intervention; among the most frequent are dilated cardiomyopathy and ischemic heart disease (more than 90% of cases). In general, all patients with heart failure no longer responsive to medical therapies are eligible for HT.

Every year, according to the International Society for Heart and Lung Transplantation (ISHLT), around 3500–4000 heart transplants are performed globally. Developed countries like the United States, Europe, and Japan have higher transplant rates due to better healthcare resources and organ donation policies. The prevalence of people living with a transplanted heart exceeds 50,000 worldwide.

Organ rejection is one of the main complications of heart transplantation. Based on ISHLT guidelines, acute cellular rejection and antibody-mediated rejection occur with a prevalence of 7.8% in a large single study of adult heart transplant recipients, most frequently within the first year after transplant [1].

The follow-up for heart transplant patients is a crucial part of postoperative care and long-term management. It involves regular monitoring to assess the function of

the transplanted heart, prevent organ rejection, and manage potential complications. Initially, patients are seen for follow-up visits every 1–3 months during the first few years after the transplant, and these visits may become less frequent later on. During these visits, electrocardiograms (ECG) and echocardiograms are used to assess the electrical and mechanical function of the heart. Endomyocardial biopsy (EMB) may also be performed to check for any signs of rejection; these biopsies are typically performed weekly for the first 4 weeks, biweekly for the next 6 weeks, monthly for 3–4 months, and then every 3 months for the first year. After the first year, routine biopsies have not shown added benefits [2].

Heart transplant rejection occurs when the recipient's immune system attacks the transplanted organ and leads it to failure. Rejection can be acute or chronic, with acute rejection typically presenting within the first-year posttransplant and the chronic rejection developing over time. The acute allograft rejection takes place by cellular or humoral (antibody-mediated) mechanism.

EMB is a key diagnostic procedure used to assess the condition of a transplanted heart and detect signs of organ rejection, especially in the early stages after a heart transplant. It consists in taking small tissue samples from the heart to examine whether the immune system is attacking the transplanted organ.

Despite advances in noninvasive techniques, such as blood tests and imaging methods to monitor rejection, endomyocardial biopsy remains the gold standard for diagnosing acute rejection in heart transplant recipients.

2. Heart transplant rejection

Heart transplant rejection (HTR) occurs when the recipient's immune system recognizes the transplanted heart and activates an immune response against it. When signs of heart failure are noted in transplanted patients, a possible rejection must be considered.

Cardiac graft dysfunction can present with a range of signs and symptoms, and they may occur gradually or suddenly, depending on the severity and timing of the dysfunction.

One of the most common early signs of cardiac graft dysfunction is fatigue. This can lead to a feeling of being unusually tired, weak, or unable to perform normal daily activities. Shortness of breath is another frequent symptom; swelling, particularly in the lower extremities such as the legs, ankles, and feet, is common due to fluid retention caused by heart dysfunction. Chest pain may also be a symptom. Palpitations or an irregular heartbeat can occur as well, and this could indicate the presence of arrhythmias, which are abnormal heart rhythms. These may be caused by rejection, ischemia, or imbalances in electrolytes. Patients may report a sensation of the heart racing or skipping beats.

A decrease in exercise tolerance is also a common symptom. Patients may find that they are no longer able to engage in physical activities at the same level as before their transplant. Additionally, hypotension or low blood pressure can develop, leading to symptoms such as dizziness, lightheadedness, or fainting, particularly when standing up quickly.

In some cases, cyanosis may be present. A fever can occur if there is an infection or an acute rejection episode. This is often accompanied by chills, malaise, or general discomfort.

An increased heart rate (tachycardia) is another sign that the body may be compensating for reduced cardiac output. This can happen even at rest and is often an

indication of the heart's struggle to meet the body's circulatory demands. In some cases, dizziness or syncope (fainting) can occur if there is reduced blood flow and low blood pressure due to impaired cardiac function.

The evaluation of symptomatic patients follows several steps starting from laboratory tests, imaging studies, and histological findings in the endomyocardial biopsy.

Depending on the time elapsed since the transplant and the pathogenesis, rejection can be classified as hyperacute, acute-cellular, and acute antibody mediated.

Hyperacute rejection occurs when preformed antibodies are present in recipient's body; these antibodies attack the transplanted tissue shortly after reperfusion and lead to an immune reaction that can be lethal.

Early graft dysfunction occurs within 24 hours from the transplant and can be further classified in primary or secondary. Primary graft dysfunction lacks an identifiable cause and is characterized by a severe ventricular dysfunction leading to a cardiogenic shock. Several factors can contribute to this dysfunction: a reperfusion injury, a preexisting heart disease or an allograft injury. One of the main factors that can lead to a primary graft dysfunction is the "ischemia-time," considered as the time from the clamping of the donor heart to its implantation in the recipient. This critical time causes a catecholamine stress that may lead to a myocardial ischemia and a consequent storm of pro-inflammatory mediators. In secondary graft dysfunction instead, an identifiable cause is present and leads to the rejection.

Late graft dysfunction refers to the progressive deterioration of heart function that occurs long after a heart transplant, typically beyond the first year. This includes acute rejection, subclassified into cellular and humoral, and the cardiac allograft vasculopathy (CAV), the latter linked to the progressive thickening of the intima due to the accumulation of lipid material, proliferation of smooth muscle cells, and infiltration of inflammatory cells, which cause occlusion of the epicardial and intramyocardial vessels [3].

2.1 Pathogenesis of acute cellular rejection

Briefly, effector T cells play a key role in ACR by inducing tissue damage through cytokine or chemokine secretion (leading to necrosis) or by direct contact with target cells (such as epithelial or endothelial cells), triggering cytotoxicity. T cells can also activate other immune cells, such as B cells, macrophages, and neutrophils, to contribute to rejection.

Upon activation by dendritic cells (DCs), naïve alloreactive CD4⁺ T cells differentiate into various subtypes like Th1, Th17, Th2, or regulatory T cells (Tregs). In a proinflammatory environment, CD4⁺ T cells mostly become Th1 and Th17 cells. Th1 cells produce IFN- γ and IL-2, helping to activate cytotoxic T lymphocytes (CTLs), stimulate the humoral immune response, and activate NK cells. Th17 cells secrete IL-17, which drives inflammation and recruits neutrophils and macrophages to the graft. In the absence of Th1, Th17 or Th2 cells can still promote rejection. Th2 cells release anti-inflammatory cytokines like IL-10 and IL-4. While the roles of T follicular helper and Th9 cells are less understood, they are involved in B-cell maturation and mast cell recruitment, respectively.

In contrast, Tregs help prevent graft rejection by suppressing the activity of CD4⁺ and CD8⁺ T cells and reducing antigen presentation by antigen-presenting cells (APCs). CD8⁺ T cells can differentiate into cytotoxic T lymphocytes (CTLs) like Tc1, Tc2, or Tc17 cells. These cells, which require activation by DCs and help from CD4⁺ T cells (*via* IL-2/IFN- γ), recognize target cells through their MHC class I molecules

and induce cell death through perforin, granzyme B, or Fas/FasL pathways. In graft rejection models, CTLs accumulate around the graft and progressively cause tissue destruction.

Memory T cells, which provide a quicker and stronger immune response compared to naïve cells, are associated with higher risks of acute rejection in transplant patients. The presence of donor-specific memory T cells before transplant correlates with poorer graft survival. Furthermore, the presence of memory T cells can hinder the development of transplantation tolerance [4].

2.2 Pathogenesis of acute antibody-mediated rejection

Acute antibody-mediated rejection (AMR) in heart transplant recipients is associated with several reported risk factors. These include an elevated panel-reactive antibody (PRA), cytomegalovirus (CMV) seropositivity, and a history of mechanical circulatory support prior to the transplant. Additionally, prior treatment with muromonab-CD3, an immunosuppressive drug, and the subsequent development of antibodies against this mouse monoclonal antibody are significant risk factors. Other factors include a history of retransplantation, multiparity (having multiple pregnancies), and a positive T-cell flow cytometry crossmatch.

Women, in particular, have a higher incidence of AMR. Recent research has shown a clear link between the presence of circulating anti-HLA antibodies after transplantation and histological signs of AMR, underscoring the importance of monitoring these antibodies as a potential marker for rejection.

AMR occurs when the recipient's antibodies target donor HLA antigens present on the endothelial cells of the transplanted organ. These antibodies activate the complement cascade, leading to tissue injury. Complement activation plays a central role in the development of AMR by triggering both innate and adaptive immune responses.

Specifically, various types of antigens can be recognized during transplant rejection. These antigens include HLA antigens (both class I and class II), which are the primary antigens involved in the immune system's recognition of the transplant. It also includes MICA and MICB antigens, molecules related to the major histocompatibility complex (MHC) class I, which play a role in the immune response. Minor histocompatibility antigens, which are not directly linked to the HLA system but can still stimulate an immune response, are also involved. Additionally, non-HLA antigens are recognized, such as the angiotensin II type 1 receptor, vimentin, myosin, ABO blood group antigens, type IV and VI collagen, agrin, unknown endothelial antigens, and ICAM-1 [4].

The generated antibodies activate complement *via* the classical pathway. The complement system (CS) includes more than 30 proteins, both soluble and membrane, forming part of the innate immunity. The CS is activated through three distinct pathways: the classical pathway (CP), the lectin pathway (LP), and the alternative pathway (AP). These pathways can be triggered by various pathological processes in the allograft, such as donor brain death, ischemia/reperfusion injury, and antibody-mediated rejection. Although the mechanisms initiating each pathway differ, they all lead to the same downstream effectors. The CP is activated when antibodies bind to their target ligands. The LP is activated when lectins bind to sugars on the surface of bacteria or injured cells. Key lectins involved include mannose-binding lectin (MBL), collectins, and ficolins. These molecules are complexed with mannose-associated serine proteases (MASPs), which get activated upon binding to target ligands and

cleave C4 or, in some cases, activate the alternative pathway. LP can also be triggered by the recognition of sugars expressed on damaged cells. Cleavage of C4 leads to C4b binding to nearby surfaces and the release of C4a.

In contrast to the CP and LP, the alternative pathway (AP) is constantly and nonspecifically activated in plasma through a process called “tick-over.” Since it is a spontaneous process, complement regulatory proteins are crucial for controlling AP activation.

Activation of all three pathways results in the cleavage of C3, producing C3a and C3b fragments. C3b has a reactive thioester bond that can bind covalently to nearby surfaces, marking them for opsonization. Full complement activation also results in the cleavage of C5, generating C5a (a soluble fragment) and C5b, which initiates the formation of the membrane attack complex (MAC). The MAC forms a pore in the target cell membrane, which can lead to cell activation or lysis. It is also true that the major biological effects of the complement system are mediated by the interaction of the various fragments with their respective receptors.

Once complement is activated within a transplanted organ, it can have both direct and indirect pathological effects. The activation generates multiple biologically active complement fragments, such as C3a, C5a, and C3b, which directly affect resident organ cells. These fragments also serve as chemotactic factors and activators for neutrophils and macrophages and provide key signals for T- and B-cell activation. The location of complement activation determines which cells are affected by the membrane attack complex (MAC) or opsonization with C3b. Soluble fragments like C3a and C5a can have more distant effects, but their impact may be influenced by their access to the circulation and peripheral blood cells [5].

B cells play a multifaceted role in allograft rejection due to their ability to present antigens, produce antibodies, and secrete cytokines. These functions allow B cells to contribute to rejection through various mechanisms. First, B cells can promote T-cell activation and differentiation by engaging costimulatory pathways or through cytokine release. Additionally, B cells are involved in the differentiation of alloreactive T cells into memory T cells, which can enhance the long-term immune response and contribute to the rejection process [4].

Chemokines are chemoattractant cytokines that play a critical role in directing immune cell migration. In transplantation, they are involved in several key phases of the immune response. Initially, chemokines help recruit mononuclear cells to the site of inflammation, where they contribute to the early immune reaction. They also promote the migration of antigen-presenting cells (APCs) to the draining lymph nodes, where these cells process and present antigens to T cells. In the lymph nodes, chemokines facilitate the interaction between unprimed T cells and APCs, leading to T-cell activation and differentiation. Finally, chemokines guide the migration of primed alloreactive T cells to the graft, where they can participate in transplant rejection.

Although the adaptive immune response plays a central role in allograft rejection, early proinflammatory signals are also considered crucial factors in the process. These early inflammatory responses are driven by the innate immune system, which is activated independently of the adaptive immune response. In transplantation, innate immune responses are triggered by events such as ischemia-reperfusion injury and infections, which lead to the release of damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). These molecules are recognized by pattern-recognition receptors (PRRs) expressed on hematopoietic cells.

PRRs are genetically determined, and several subclasses are distinguished based on their structure. Immediately after transplantation, the activation of PRRs by

danger signals leads to the activation of dendritic cells (DCs). These activated DCs undergo maturation, upregulate costimulatory molecules, and secrete proinflammatory cytokines. Donor-derived antigen-presenting cells (APCs) then migrate to the T-cell areas of secondary lymphoid organs, where they induce the activation and differentiation of alloreactive naïve T cells into effector T-helper cells. These effector cells subsequently migrate to the graft, where they activate macrophages and granulocytes (such as neutrophils, eosinophils, and basophils) that have infiltrated the graft in response to inflammatory stimuli. These innate immune cells contribute to tissue damage either directly or by producing additional proinflammatory cytokines and chemokines. Moreover, they help amplify and sustain the adaptive response [4].

Macrophages are a key population of innate immune cells that contribute significantly to tissue damage in rejected organs: a substantial number of monocytes are detected in graft infiltrates. These monocytes are recruited to inflammatory sites by monocyte chemoattractant protein-1 (MCP-1).

Macrophages exhibit a high degree of functional diversity, with specialized tissue-resident subsets, such as Kupffer cells in the liver and osteoclasts in the bone. They can also display different functional phenotypes depending on their activation state. Macrophages are classified into two major activation states: classically activated macrophages (M1) and alternatively activated macrophages (M2), which are analogous to T-helper cell subsets.

M1 macrophages are activated primarily by IFN- γ and TNF, which are released by Th1 cells. These macrophages have the ability to present antigens to T cells and express high levels of costimulatory molecules such as CD86 and CD80. They also produce large amounts of the proinflammatory cytokine IL-12 and promote Th17 responses through the secretion of IL-1, IL-6, and IL-23. M1 macrophages play crucial roles in defense against infections and tumors, but they can also contribute to chronic inflammation and autoimmune diseases.

M2 macrophages, on the other hand, are generally associated with immune regulation and tissue repair. Their activation is influenced by factors like IL-10 or immune complexes. M2 macrophages produce anti-inflammatory cytokines such as IL-10 and TGF- β , promoting regulatory responses. Importantly, macrophages are not strictly confined to a single phenotype. They can shift their functional profile depending on the environmental cues they receive.

Macrophages not only infiltrate the graft rapidly after reperfusion but also produce large quantities of proinflammatory cytokines, such as IL-1, IL-12, IL-18, IL-6, IL-23, TNF- α , and IFN- γ . In addition to cytokines, infiltrating macrophages produce reactive oxygen species (ROS) and reactive nitrogen species (RNS), which combine to generate peroxynitrites that cause lipid peroxidation and further exacerbate tissue damage during acute rejection.

Beyond their direct tissue damage effects, macrophages also mediate transplant rejection by activating adaptive alloimmune responses. Both donor and recipient macrophages function as antigen-presenting cells (APCs) and have substantial impacts on alloimmune responses. Alloimmune T cells are activated when their T-cell receptors engage with allogeneic MHC molecules on donor cells or with donor peptides presented by recipient APCs. Macrophages also provide costimulatory signals, which amplify T-cell activation, due to the high expression of costimulatory molecules on their surface [6].

Other mediators are also involved, such as natural killer cells, polymorphonuclear cells (such as neutrophils, eosinophils, and basophils), endothelial cells, and platelets.

It is therefore a complex inflammatory process driven by different cellular and protein elements.

3. Endomyocardial biopsy

Endomyocardial biopsy (EMB) is a useful tool in diagnosis of myocardial disease, mainly in the setting of heart transplant rejection. The procedure is minimally invasive and considered a safe procedure. It generally takes 20 to 30 minutes, and the patient is under local anesthesia or lightly sedation. Some complications are possible, for example bleeding at the biopsy site, infection or, in rare cases, arrhythmias. It starts with the insertion of a catheter into a vein, usually in the neck or groin area. The catheter is carefully guided through the blood vessels to the heart, with real-time imaging provided by fluoroscopy or echocardiography. Once the catheter reaches the heart, several fragments of myocardial tissue are biopsied, to ensure an accurate evaluation.

A good endomyocardial biopsy is characterized by several key features that ensure it is effective in detecting organ rejection and evaluating the health of a transplanted heart. Tissue fragments should be fixed in 10% buffered formalin; according to the specific clinical question, additional samples can be snap-frozen for molecular or histochemical studies or fixed in 4% glutaraldehyde for transmission electron microscopy (TEM). First, the biopsy should provide high-quality tissue samples that are large enough to allow for thorough pathological analysis; at least four samples (measuring 2–3 mm each) should be received and sectioned at three levels; one sample should be frozen for immunofluorescence if needed. It is important that the biopsy captures tissue from multiple areas of the heart, as rejection may not be uniform throughout the organ. Collection of specimens from multiple cardiac sites is recommended in cases of localized diseases. Biopsy samples should be processed in a fully equipped pathology laboratory, with access to immunohistochemical analyses, molecular tests, and TEM. The pathologist in charge of the diagnosis should be specifically trained.

Each component of the biopsy specimen including endocardium, myocardium, interstitium, and vasculature must be evaluated to avoid missing diagnostic entities. The interpretation of cardiac biopsies should never be performed in the absence of appropriate and adequate clinical information that may help to allow definitive diagnoses.

Normal endocardium is composed of an endothelial cell layer, a subendothelial layer of loose collagen and fibroblasts, and an elastic layer, often associated with collagen and smooth muscle cells; they can have different thickness in relation to the position (atrial or ventricular, outflow or inflow surface) and various pathological conditions [7, 8].

The most important pathological alteration of the endocardium is thickening, in general as a result of a combination of fibrosis and elastosis; various cellular infiltrates can be seen in the endocardium. “Quilty lesions” are characterized by focal endocardial cellular infiltrate composed mainly of T lymphocytes with admixed B cells, scattered macrophages and plasma cells. Such lesions can be detected in patients undergoing heart transplantation. They can be classified in Quilty A if they are confined to the endocardium and Quilty B if they extend to the myocardial interstitium surrounding cardiomyocytes. Their clinical relevance is still debated: there is a correlation between Quilty lesions and cardiac allograft vasculopathy in the graft, and they can be considered as an indicator of previous acute cellular rejection [9].

Myocardium is made up of cardiomyocytes, interstitial cells, and vascular endothelium. Cardiac myocytes are striated involuntary muscle cells measuring approximately 10–20 μm in diameter. Their components are a thin cell membrane named sarcolemma, a small round basophilic nucleus, and a sarcoplasm containing longitudinal fibers composed of myofilaments (actin and myosin) arranged in a staggered pattern to form the sarcomere, the contractile unit of the myocyte. Interstitium is composed of fibroblasts, extracellular matrix, adipocytes, and scattered inflammatory cells. There are penetrating capillaries and arterioles originating from epicardial coronary arteries that supply blood and oxygen to the cardiac myocytes, in an epicardial to subendocardial direction. Ischemic myocardial injury can also occur after transplantation, and it presents histologically as coagulative myocyte necrosis with contraction band. The extent may be variable, from spotty individual or small clusters to areas of confluent necrosis. In cases of previous ischemic injury, residual macrophages and necrotic myocyte dropout can be observed [7].

3.1 Acute cellular rejection: Histo- and immunopathologic features

Acute cellular rejection (ACR) is defined as a lymphocyte predominant infiltration of perivascular and interstitial myocardial compartment resulting in a distorted myocardial architecture and dysfunction. The inflammatory infiltrate may vary, but it is generally composed of T lymphocytes (CD3+, CD4+, and CD8+), with variable macrophages and eosinophils. The presence of neutrophils is absent except in severe cases and should raise the question for an alternative process such as infection or ischemic injury; plasma cells are also not typically present. Furthermore, cardiac myocytes show an increase in intercellular adhesion molecules and MHC class II. The inflammatory infiltrate is proportionally greater than the degree of myocyte damage, which can present itself as mild in the form of myocytolysis (sarcolemmal and nuclear clearing, nuclear enlargement, and prominent nucleoli) and severe in the form of contraction band and coagulative necrosis. The presence of myocyte injury is frequently accompanied by encroachment of inflammatory cells at the periphery of myocytes resulting in irregular borders and distortion of its architecture [10].

ACR is classified according to the ISHLT guidelines in:

- 0R (no rejection)
- 1R (mild rejection), with interstitial or perivascular infiltrate with or without 1 focus of myocyte damage;
- 2R (moderate rejection), with >2 foci of infiltrate with associated myocyte damage;
- 3R (severe rejection), where there is a diffuse infiltrate with multifocal myocyte damage, vasculitis and interstitial hemorrhage.

3.2 Antibody mediated rejection: Histo- and immunopathologic features

The classic histopathologic features of antibody mediated rejection (AMR) include hemorrhage, interstitial edema, myocyte necrosis, capillary fragmentation, and endothelial cells pyknosis/karyorrhexis; all of these features are not specific to AMR, but in this perspective should trigger immunohistochemical and immunofluorescence staining, careful clinical assessment, and appropriate serological tests. It is important that only intact myocardium is evaluated, avoiding areas of ischemic injury, healing biopsy sites, and myocardial scars.

In identifying the histopathological changes in AMR, attention must be directed to the capillary beds because the changes appear almost exclusively at this level. The most common scenario of AMR on hematoxylin-eosin (H&E) stained section includes interstitial capillary injury with swollen endothelial cells, due to accumulation of intravascular macrophages, which appear to narrow or occlude the lumens. Endothelial cells may be seen in the interstitial spaces separating the myocytes, and in general, the myocardial interstitium is more cellular than normal. Interstitial lymphocytes and macrophages are typical of the diffuse acute cellular rejection; their localization outside the vascular lumen is an important diagnostic tool for the differential diagnosis (**Figure 1**).

Associated with the presence of activated mononuclear cells, interstitial edema can be reported. Edema is defined as the presence of proteinaceous strands between myocytes; its quantity and disposition vary according to the severity of the rejection. Edema can also be found in ischemic damage; however, unlike AMR, the pattern of edema is patchy in ischemia and associated with distinct myocardial change such as pyknotic nuclei, hypereosinophilic fibers, and the loss of cytoplasmic contractile elements.

Other findings, such as hemorrhage, neutrophilic infiltrate, intravascular thrombi, and myocyte necrosis, are rarely encountered in practice and, when present, are indicative of severe AMR.

The recommended protocol for the evaluation of the immunopathologic component of pathologic antibody-mediated rejection (pAMR) on the endomyocardial

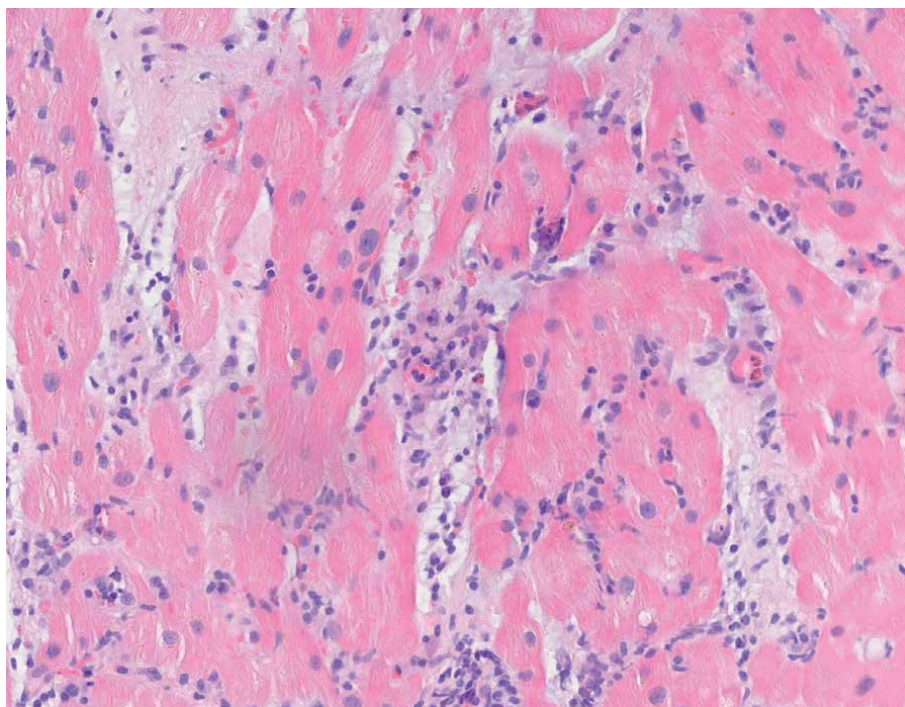


Figure 1.
Hematoxylin-eosin stained section that includes interstitial capillary injury with swollen endothelial cells and accumulation of intravascular macrophages; the myocardial interstitium is more cellular than normal.

biopsy included both frozen tissue for immunofluorescence (IF) and paraffin immunohistochemical (IHC) analysis. In diagnostic practice, the use of a variable panel of antibodies is essential for a correct diagnosis. Although there are numerous antibodies available, it would be advisable using a primary and a secondary (optional) panel.

The primary panel for paraffin IHC consists of C4d and an anti-macrophage marker CD68 **Figures 2 and 3**. Regarding the presence of macrophages, their poor specificity is well-known as they can be found in almost all forms of heart damage, so only macrophages within capillaries and small venules are to be considered. A positive interpretation is >50% multifocal/diffuse weak or strong C4d staining and >10% focal/multifocal/diffuse intravascular macrophages. Multifocal/diffuse weak or strong staining of >50% capillary C4d or C3d by IF is also considered a positive result. The combined use of these two markers is indicated considering the percentage of AMR cases that are C4d-/CD68+, C4d+/CD68-, or equivocal for both.

Based on the 2013 ISHLT consensus report, capillary complement deposition and infiltration of intravascular macrophages are the defining features of pAMR.

Beyond these, several other antibodies can be used: other anticomplement marker (C3d), vascular antibodies (CD31 and CD34) to assess microvascular integrity and distribution, or pan B/T cell markers (CD20 and CD3), respectively, to help localize mononuclear cells within the vessel lumen [11].

Based on histologic and immunopathologic findings, the 2013 ISHLT guidelines provide a five-tier classification to better stratify the severity of rejection.

pAMR 0 (absence of pathologic AMR), if both histologic and immunopathologic studies are negative;

pAMR 1 (H+), if only histologic studies are positive;

pAMR 1 (I+), if only immunopathologic studies are positive;

pAMR 2, if both histologic and immunopathologic studies are positive;

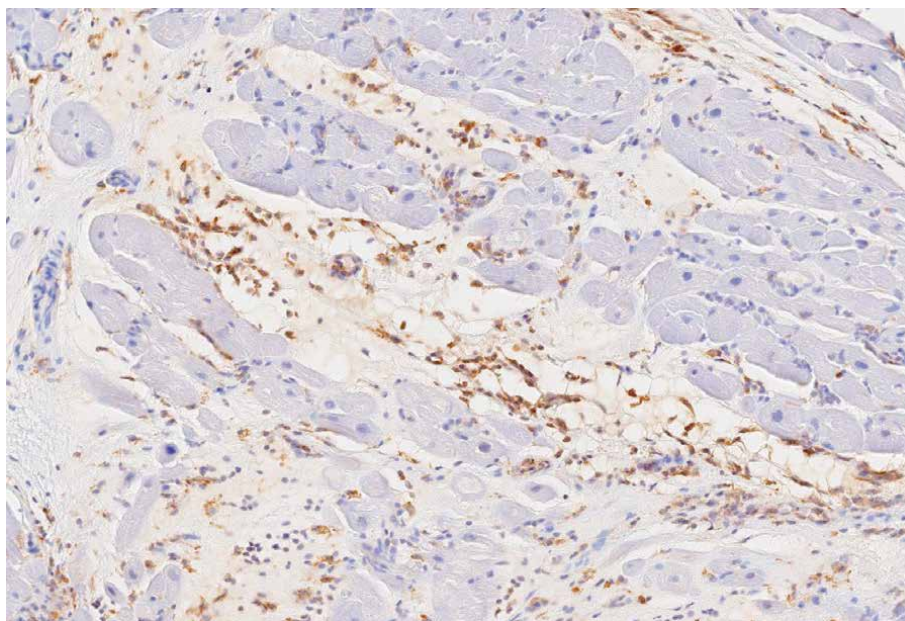


Figure 2.
Section stained with CD68 antibody showing both intravascular and interstitial macrophage infiltrate.

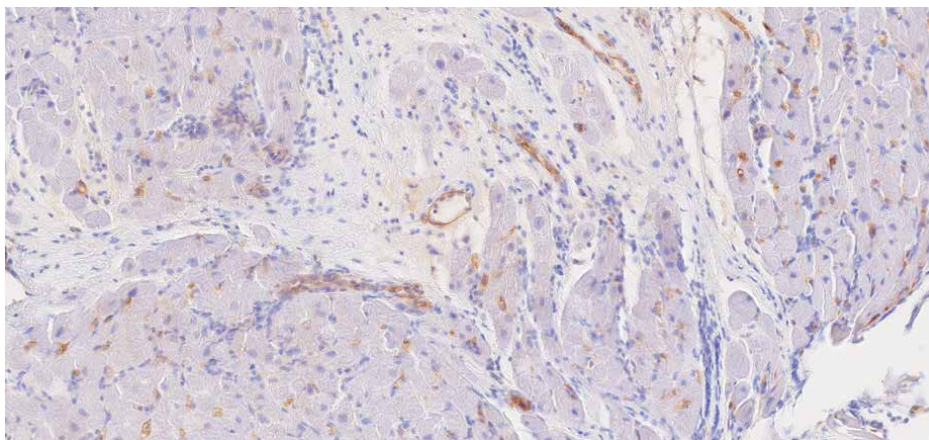


Figure 3.
Section stained with c4d antibody showing endothelial positivity indicating complement activation.

pAMR 3 (severe pathologic AMR), if histological characteristics such as interstitial hemorrhage, capillary fragmentation, mixed inflammatory infiltrate with endothelial cells pyknosis, and/or karyorrhexis or marked edema are present.

4. Therapy

Management of AMR is at the present nonstandardized; there are in fact no universally accepted guidelines. Furthermore, although it is widely accepted that AMR associated with allograft dysfunction should be aggressively treated, the management of asymptomatic AMR is less clear. Based on the 2011 ISHLT guidelines, in individuals with pathologic AMR, increased frequency of surveillance is recommended with assessment of allograft function every month and DSA monitoring every 3 months until two negative or unchanged results. It is important to remember that DSA may exist without causing allograft dysfunction and their detection without clinical and instrumental correlations may not require treatment.

Treatment strategies for AMR are directed at inhibiting the humoral response at various levels. In most cases, pulse steroids in combination with plasmapheresis are considered the first line of treatment. Although it is not free from such claims such as hypovolemia and infection and it is not standardized how often it should be done, with various line of treatment depending on the single center, plasmapheresis has been considered the cornerstone in treatment of AMR in combination with other immunosuppressive agents.

In case of recurrent AMR, exacerbation cyclophosphamide and intravenous immunoglobulins (IVIg) followed by plasmapheresis have been suggested. After 2002, Rituximab, a chimeric monoclonal antibody raised against the CD20 protein expressed on the surface of B lymphocytes, was added to the treatment regimen.

In recent years, several other molecules have been introduced, especially in cases resistant to first lines of therapy. Among these, there are drugs that act by blocking the complement cascade. Eculizumab, for example, binds the complement protein C5, preventing its breakdown and the consequent formation of membrane attack protein (MAC). Even the plasma-derived human C1 inhibitor have been validated in the treatment of resistant AMR cases. Anti-thymocyte globulins (ATGs), standardly

used in the setting of ACR, should be adapted for AMR treatment; there have been patients successfully treated with these drugs in combination with other immunosuppressive agents, although the latter is an experimental therapy, which requires randomized trials.

Emerging research is now focusing on advanced diagnostic methods and novel therapeutic strategies, among which gene editing technologies that offer the potential to modify immune response at genetic levels. Next-generation immunosuppressive agents, like JAK inhibitors and anti IL-6 agents, are being investigated for modulating immune response with greater sensibility; meanwhile, the use of nanotechnology and drug delivery system could reduce the side effects of immunosuppressive drugs addressing them directly to target cells and tissues or in response to specific antigenic stimuli, providing controlled and sustained drug release.

Finally, researchers are developing models that can predict individual response to different immunosuppressive drugs using machine learning algorithms and artificial intelligence (AI) [12, 13].

5. Conclusions

Antibodies primarily damage organ grafts by targeting the graft's microcirculation endothelium. Research by Sis et al., starting in 2007, has identified a form of antibody-mediated rejection (AMR) that is C4d-negative, particularly in chronic settings. This finding challenges the traditional reliance on C4d as a biomarker for AMR. Studies have shown that endothelial gene expression, when combined with donor-specific antibodies (DSAs), can offer high sensitivity for detecting chronic AMR, though with lower specificity than C4d. Further studies have highlighted the importance of mRNA levels of genes linked to endothelial activation and injury, where high expression of these genes, in combination with DSAs, often corresponds with histological signs of AMR. However, these cases would have been missed if relying solely on C4d positivity. Research by Loupy and Haas has confirmed that C4d-negative AMR can predict poor outcomes, particularly in sensitized patients.

A working group at the 2011 Banff Conference sought to refine diagnostic criteria for chronic AMR and consider whether C4d-negative AMR should be included in the Banff classification. If C4d-negative AMR exists, it likely results from a complement-independent mechanism, further highlighting the need for new diagnostic and therapeutic strategies to address these complex cases in the future. Recent *in vitro* studies by Reed and colleagues have shown that allo-antibodies can directly affect endothelial cells, causing them to express proinflammatory molecules, even without complement or other immune cells. This endothelial injury can be exacerbated when natural killer (NK) cells or macrophages interact with the antibodies [14].

In recent years, new methods including micro-RNA (mi-RNA), donor-specific antibodies (DSAs), donor-derived cell-free DNA (ddcfDNA), and gene expression profiling (GEP) have been introduced.

MicroRNAs (miRNAs) have gained attention in the context of organ rejection due to their ability to regulate a wide range of genes that are crucial for both innate and adaptive immune responses. These small, noncoding RNAs can modulate the expression of genes involved in inflammation, immune cell activation, and tissue injury, which are all key factors in the process of organ rejection. The interest in miRNAs is further heightened by their ability to be regulated by various inflammatory stimuli, which links them to the body's immune response during organ rejection. Some

miRNAs exhibit tissue-specific expression patterns and play roles in various biological processes, including regulating inflammation, adhesion, and angiogenesis. These properties make them ideal candidates for monitoring microvascular inflammation, especially in conditions such as humoral rejection. In fact, the expression profiles of certain miRNAs could identify which miRNAs are differentially expressed in rejecting allografts in both the tissue of the transplanted organ and in peripheral blood. This could provide valuable biomarkers for diagnosing organ rejection early, guiding treatment strategies, and improving transplant outcomes. Furthermore, understanding how miRNAs are involved in the rejection process could lead to the development of new therapeutic approaches that target specific miRNAs to modulate the immune response and prevent rejection. In summary, the potential of miRNAs as biomarkers in organ transplantation, especially heart transplantation, lies in their ability to reflect the underlying immune and inflammatory processes that drive rejection, making them promising candidates for improving monitoring and treatment strategies in the field [15].

DSAs are detected using solid-phase assays with beads coated with HLA antigens. They are associated with acute rejection (AMR and ACR), cardiac allograft vasculopathy (CAV), and graft dysfunction and are recommended for monitoring at specific intervals after transplantation. A study found that the presence of *de novo* DSAs in heart transplant patients was predictive of poor survival. However, only persistent DSAs are linked to worse survival outcomes; a serial evaluation of DSAs levels is therefore required, taking also into account the variability in techniques and reporting across laboratories [16].

As in other heart diseases such as cardiac ischemia and myocardial infarction, there have been recent investigations into proteomic (expression assays of multiple protein biomarkers) evaluation of rejection and graft dysfunction. While abnormal troponin and natriuretic peptides can signal allograft dysfunction related to rejection, their lack of significant evidence in diagnosing rejection limits their use in surveillance [16].

As included in ISHLT guidelines, gene expression profiling (GEP) is useful for detecting cellular rejection. Studies like IMAGE suggest that gene expression profiling of peripheral blood samples could be a viable alternative to routine biopsies for monitoring cardiac transplant recipients for rejection, particularly if at least 6 months have passed since the transplant and the patient is at low risk for rejection. However, the study's limited power prevents a definitive conclusion about gene-expression profiling as a substitute for biopsies. The AlloMap® test, which was used to carry out this study and evaluates 20 genes (11 of which are related to rejection), is an example of innovative methods of recognizing acute rejection: results are represented by a score between 0 and 40, indicating the probability of ACR. However, it cannot identify antibody-mediated rejection (AMR) and lack of reliability when patients are on higher doses of corticosteroids, receive blood transfusions, or have a cytomegalovirus infection. Combining ddcfDNA and GEP could offer superior diagnostic accuracy compared to using either method alone [17, 18].

Donor-derived cell-free DNA (ddcfDNA) is released from the allograft during cell destruction and can be measured in the recipient's blood. It consists of the evaluation of donor and recipient single-nucleotide polymorphisms (SNPs). Studies have shown that ddcfDNA levels correlate with acute rejection episodes and can serve as an alternative to EMB showing a higher positive predictive value compared to GEP and in distinguishing ACR and AMR. However, high ddcfDNA levels can also appear in non-rejection situations, such as myocardial ischemia, trauma, pregnancy, or multi-organ transplants, which complicates its interpretation [16, 17].

There are multiple ongoing trials assessing the effectiveness of these noninvasive rejection surveillance strategies, but despite the latter, endomyocardial biopsy (EMB) remains the gold standard method for diagnosing heart transplant rejection.

Acronyms and abbreviations

ACR	acute cellular rejection
AP	alternative pathway
AMR	antibody-mediated rejection
APCs	antigen-presenting cells
ATGs	anti-thymocyte globulins
CAV	cardiac allograft vasculopathy
CS	complement system
CP	classical pathway
CMV	cytomegalovirus
CTLs	cytotoxic T lymphocytes
DCs	dendritic cells
DSAs	donor specific antibodies
ddcfDNA	donor-derived cell-free DNA
ECG	electrocardiograms
EMB	endomyocardial biopsy
GEP	gene expression profiling
HF	heart failure
HT	heart transplantation
HTR	heart transplant rejection
H-E	hematoxylin-eosin
HLA	human leukocyte antigen
IF	immunofluorescence
IHC	immunohistochemistry
ISHLT	International Society for Heart and Lung Transplantation
LP	lectin pathway
MHC	major histocompatibility complex
MAC	membrane attack complex
mi-RNA	micro-RNA
NK	natural killer
PRA	panel-reactive antibody
Tregs	regulatory T cells
SNPs	single-nucleotide polymorphisms
TEM	transmission electron microscopy

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Palliative Medicine in Cardiac Transplant Patients

Piotr Jakubow

Abstract

The development of palliative medicine in recent years has been impressive. Knowledge of palliative medicine techniques facilitates the work of doctors, nurses, and all medical staff. The enormous development of palliative medicine is caused by the progress and development of medicine and the resulting social needs. The real physical and psychological needs of patients in the electronic post-industrial era are not met. Medical personnel, including doctors and nurses, who play an important instrumental technical and administrative role in the modes of operation of the health care system, focused on therapeutic and economic success, do not meet the needs of patients. That is why it is so important to disseminate knowledge in the field of palliative medicine, the content of which is the quality of life and well-being of patients. Cardiac surgery and intensive care, especially in the case of terminal conditions of patients after transplantation or disqualified from surgery, require the application of the principles of palliative medicine. This chapter discusses the basics of palliative medicine, its potential applications, explanations, and contraindications to palliative therapy, and a step-by-step discussion of problems that may arise during palliative treatment related to heart transplantation.

Keywords: palliative medicine, heart transplantation, heart failure, end-of-life pharmacotherapy, spiritual care

1. Introduction

Palliative medicine is an essential part of modern medicine, which plays a key role in the care of patients in the terminal phase of life. When the disease process cannot be reversed or stopped, the co-occurring disabling physical and psychological symptoms can and should be treated, providing patients with relief from suffering [1]. Recent studies show that early application of palliative principles improves the condition of patients, prolonging their life, providing a better quality of life, and contributing to the acceptance of the disease in the terminal stage [2]. Palliative medicine has historically focused on cancer patients at the end of their lives. Today, modern palliative medicine treats patients with cancer and non-cancer diseases according to the severity of their life-threatening symptoms [3]. Palliative medicine focuses on the quality of life of patients, relieving them of suffering. These distressing symptoms, both physical and psychological, are indicators of the application of palliative principles and are often included in patient needs assessment scales [4]. Life-limiting, distressing

symptoms are widely presented by patients undergoing heart transplantation at various stages of end-stage heart disease [5]. The use of specialist palliative treatment that focuses on the quality of life of patients waiting for a transplant, undergoing transplantation and in patients who have an unfavorable prognosis after surgery reduces the suffering of patients, allows them to function in a hospital and family environment, and improves the comfort of both the patient and those caring for them [6].

2. The place of palliative medicine in heart transplantation

2.1 Palliative medicine regulations

One of the early definitions of the World Health Organization, widely accepted, states that “... Palliative care is an approach that improves the quality of life of patients (adults and children) and their families who are struggling with the problems associated with life-threatening illness. It prevents and alleviates suffering through early identification, appropriate assessment, and treatment of pain and other problems, whether physical, psychosocial, or spiritual...” [1].

Summarizing palliative care improves the quality of life of patients and their families who are struggling with the challenges of life-threatening illness, whether physical, psychological, social, or spiritual. It also improves the quality of life of caregivers. It is a different approach to many areas of medicine where treatment is focused solely on the patient, and particularly in surgical specialties where treatment is directed at specific symptoms related to the disease [7]. Typically, these areas of medicine do not provide holistic care to the patient and their family, as palliative medicine does. Today, hospice and palliative care are essential components of health care systems around the world: in Europe, the United States, and low-income countries. However, there are significant differences in definition, practice, and availability across regions [8]. Hospice care in the United States and Canada is considered part of palliative care for patients who are in the final stage of life, usually from 6 to 12 months, due to an incurable disease. The World Health Organization and the European Society of Palliative Care, in turn, consider hospice and palliative care to be the same type of therapy and care that should be implemented as early as possible, in parallel with causal treatment. Both hospice care and palliative care are identical procedures and important aspects of medical support also for people with heart failure who are candidates for a heart transplant or have received a heart transplant and her rules are used in different stages of the disease in patients whose disease has been diagnosed in the final stage leading to death [9].

The aim of palliative care is to improve the quality of life of patients through a series of typically medical activities, understood as specialist activities and non-medical activities, consisting in improving the functioning in the health care system, including the family, among other close people in a difficult last period of life [10]. Palliative medicine offers many possibilities for both symptomatic and non-medical treatment in advanced disease. It has believed that the use of rules palliative medicine is particularly necessary in end-stage heart diseases.

3. Heart insufficiency and heart transplantation

Heart failure is a modern epidemic, about 40% of people hospitalized due to HF decompensation die or experience another exacerbation of requirements resulting in

hospitalization. Despite the undoubted progress in treatment, the prognosis for HF is still poor. Cardiovascular diseases, including heart failure, are the leading cause of death worldwide, far ahead of cancer. It is estimated that they cause over 1/3 of all deaths, while cancers cause only about 1/5 in Europe population [11, 12].

Heart transplant is a key medical procedure performed on patients with end-stage heart failure or other end-stage heart disease when other treatments have failed. Research and advancements in medical technology, such as artificial hearts and improved immunosuppressive therapies, potentially increase the number of successful transplants and improving patient outcomes [12]. This specialized procedure performed more and more often as the incidence of heart failure increases and medicine develops. In the United States alone, more than 4,000 heart transplants are performed annually. The average annual survival time is approximately 1 year, and the 5-year survival rate is approximately 70–80% and depends strictly on the medical center. Interventions such as mechanical circulatory support (MCS), extracorporeal membrane oxygenation, and ECMO as a bridge to transplantation or definitive targeted therapy are also increasing in frequency. This is related to many factors discussed in the previous chapters of this monograph. However, this raises important clinical implications for the treatment and care of these patients. Additionally, not all patients with end-stage heart disease are eligible for a heart transplant [13, 14].

The occurrence of acute rejection of a heart transplant, such as signs of heart failure: left or right ventricle (more on this topic indicated weakness, reduced physical capacity, dyspnea, edema, reduced diuresis), deterioration of left ventricular contractility, reduced diastolic compliance of the left ventricle, ventricular and supraventricular arrhythmias, increased body temperature without symptoms of infection [12, 15].

Therefore, it is necessary to indicate the needs of which patients require additional care at the end of life. It can be assumed that all patients waiting for a transplant, those ineligible for a transplant and patients undergoing heart transplantation can benefit from palliative care. Many observational studies have shown that palliative care for patients with heart failure leads to improved comfort for patients and their families and reduced readmissions Hospital Care for worsening heart failure [16, 17]. The benefits of adding multidisciplinary palliative care to the causal treatment of advanced heart failure were assessed in the randomized Palliative Care in Heart Failure (PAL-HF) trial [10]. It is proved that an interdisciplinary palliative care intervention in advanced HF patients showed consistently greater benefits in quality of life, anxiety, depression, and spiritual well-being compared with usual care alone [18, 19].

4. Patients qualified for palliative care in transplant departments

Heart transplantation (HTX) and mechanical circulatory support (MCS) are a method of treating end-stage heart failure, therefore all patients referred to palliative care have features of heart failure [20]. However, patients differ in terms of the severity of symptoms and comorbidities [21]. The primary indication for heart transplantation is the end-stage heart failure. Sometimes, acute heart failure also requires transplantation, for example during acute complicated myocarditis [22]. In addition, transplantation is necessary, by patients with end-stage cardiomyopathy, complex congenital cardiovascular defects, and other rare diseases that irreversibly impair the structure and function of the heart muscle.

Patients who may be recommended palliative care can be divided into different groups [23]. First, patients disqualified from transplantation for absolute reasons, such as pulmonary hypertension, ventilation disorders during lung diseases with forced vital capacity, FVC below 50%, liver failure, kidney failure with glomerular filtration rate, eGFR below 40 ml/min, treatment for malignancy in the last 5 years, mental illness, lack of patient cooperation, current alcohol or drug abuse [24, 25]. This group is the most difficult to palliative cure due to many comorbidities that cause troublesome symptoms that seriously limit the functioning and life of patients. A comprehensive interdisciplinary approach is necessary, in parallel with symptomatic cardiological treatment [26].

The next group are patients who could be conditionally qualified for transplantation, but for various reasons the transplant was not performed, most often due to the lack of a donor [17]. They include relative contraindications as patients in older age, over 70 years, patients with active infections, including viral liver infections, active peptic ulcer disease, renal failure, previous pulmonary embolism in the last 3 months, previous stroke, diabetes complications, advanced osteoporosis, obesity, and others. In this group, palliative treatment should place more emphasis on psychotherapy and spiritual therapy than on symptom control [27].

Another group of patients who have indications for palliative care are those whose surgical outcome is unfavorable. It can distinguish patients who have recently undergone surgery and patients in the distant postoperative period. In their case, the general procedure is also different, but palliative treatment will be characterized by a similar scheme of treatment of troublesome symptoms causing suffering and non-medical treatment, such as psychological therapy and, above all, therapy by a spiritual worker [28].

A specific group of patients are children qualified for heart surgery and those who undergone a heart transplant. Indications for heart transplantation in children include main groups of diseases: Cardiomyopathies of various etiologies. Complex, congenital defects of the cardiovascular system. Other, rare diseases that irreversibly impair the structure and function of the heart muscle. A small percentage of 2–3% of heart transplant procedures in children are retransplants. All these patients not only suffer from dyspnea and fatigue because of their disease process, but also have a high burden of somatic complaints, including pain, nausea, anxiety, and depression, leading to significant psychosocial distress for both patients and their caregivers. In this group of patients, as in the entire procedure in other groups, cooperation of the palliative team is necessary, including a pediatrician-cardiologist, psychologist, and a palliative medicine physician.

Patients from all groups, adults, and children will have features of progressive heart failure and other troublesome symptoms that cause suffering. In all of them, progressive heart failure with a series of terminal symptoms will gradually lead to death [29].

The palliative patient's death due to may occur in several expected scenarios [16]:

- Death of the patient due to a cause other than symptoms of progressive heart failure.
- End-stage HF develops, but symptomatic treatment and symptom control are possible.
- The patient dies from progressive heart failure HF.

It should be remembered that sudden death can interrupt any of the anticipated scenarios at any time.

5. The role of palliative medicine in heart transplantation

One of the factors that should be raised in the context of palliative care is the importance of a thorough assessment of the patient in order to determine the appropriateness of transplantation. There are many guidelines and scales for qualification for surgery. However, to avoid potential problems, it is worth planning palliative care as early as possible, in parallel with causal treatment. This is currently the desirable standard in oncological care planning, and palliative medicine is understood there as supportive care. Such a standard should be adopted in transplantology because the patient's contact with a palliative medicine physician contributes greatly to the understanding of the therapy and acceptance of the principles of treatment. In cases of high risk associated with surgery, it is good practice to have a palliative medicine specialist present during the patient qualification process. In some departments, this role is performed by anaesthesiologists and cardiologist who are vigilant to limit the possibility of using persistent therapy. It is crucial to select appropriate patients through a comprehensive medical and psychosocial assessment [18]. Palliative patients before and after transplantation with concomitant heart failure are characterized by specific psychosocial features that adversely affect their health. According to the available literature, in the final stage of heart failure they have impaired cognitive functions, causing non-adherence to the treatment regimen, psychopathological changes, and are at high risk of substance abuse. In terms of cognitive impairment caused by the disease and coexisting low cardiac output, accompanying depression, executive functions are most often impaired, followed by perception, memory, attention, and practical skills [25]. Non-adherence to medical recommendations is a serious health problem. It is estimated that the rate of non-adherence to medical recommendations after transplantation is as high as 30%. This contributes significantly to the development of symptoms of terminal heart failure and the intensification of troublesome somatic symptoms.

Psychopathological disorders are common among patients with advanced HF and have an impact on the course of treatment and disease. In patients with heart transplantation, both psychiatric disorders such as depression, anxiety, bipolar disorder, schizophrenia, and psychosis occur, as well as personality disorders that affect the patient's environment through maladaptive personality traits and difficulties in appropriate care for the patient [29].

Patients in both the stable and terminal stages have a high need for social support. Caregivers play a key role in helping with adherence to treatment, follow-up visits, patient hygiene, use of medical devices and providing emotional support, which is crucial for the patients' psychological well-being. Proper care reduces the risk of death and complications and improves the quality of life of patients [17].

6. Evaluation of somatic symptoms

A number of studies have investigated which symptoms occur in palliative patients and are characteristic of this group of patients. In palliative medicine, there are specialized scales that assess the severity of bothersome symptoms. Belongs to them: The

“Palliative Care Screening Tool for HF Patients” (PCST), Integrated Palliative care Outcome Scale (IPOS), Gold Standards Framework - Proactive Identification Guidance (GSF-PIG), Radboud Indicators for Palliative Care Needs (RADPAC), Supportive and Palliative Care Indicators Tool (SPICT), Needs Assessment Tool: Progressive Disease - Heart Failure (NAT:PD-HF), Necesidades Paliativas – Palliative Needs (NECPAL), Edmonton Symptom Assessment Scale (ESAS), The MIDOS survey (Minimal Documentation System For Palliative Care) [17, 22–29]. The scales include different items to identify patients with palliative care needs. It is assumed that the appropriate tools for qualifying for palliative care are the assessment of the severity of heart failure symptoms using the NAT:PD-HF, and IPOS scales. Additionally, it is believed that the SPICT scale measures the direction of palliative care needs correctly [14, 24].

The tools assessing the needs are selected locally and there are no national guidelines on which scale is most appropriate. In the case of oncology patients, individual centers and scientific societies publish lists of a number of scales for assessing the needs and troublesome symptoms in patients. Therefore, in cardiology, it is most appropriate to use a scale in the center that reflects the potential of the disease and is recognized and known in the center, so that there is ambiguity or doubt about its result obtained from the examination and the need for care. The scales are used to differentiate in patients with heart failure the severity of troublesome symptoms, such as: cardiac arrhythmias, peripheral vascular disorders, edema, ascites, hydrothorax, hypertension and hypotension, pain, nausea, vomiting, respiratory secretions, dyspnea, constipation, urinary retention and renal failure, weakness, loss of appetite, fatigue, insomnia, depression, anxiety [30].

7. Palliative care needs in HF patients

In summary, the following palliative care needs can be identified in patients with HF who are related to a prior or potential heart transplant (**Table 1**) [6–8, 18].

The treatment of symptoms should depend on the stage of the disease and the patient’s condition. It should always be individual. Basic principles should be followed, such as titration of pharmacotherapy, regular administration of medications without breaks for the occurrence of troublesome symptoms, anticipating potential symptoms by ordering the use of the appropriate drug, dealing with breakthrough symptoms by recommending rescue medications, and frequent monitoring of the drugs used, and the side effects caused by them. Revision of one’s own treatment is crucial [18, 31].

Serious complications of chronic heart failure (prognosis <12 months).
Serious comorbidities associated with poor prognosis.
Uncontrolled symptoms despite cardiology treatment.
Moderate to severe patient and/or family distress related to the diagnosis or therapy of chronic heart failure.
Patient and/or family concerns about disease course and decision-making.
Patient and/or family request palliative care consultation.
Cardiac team needs assistance with complex decision-making or goal setting.
To achieve a better quality of life, it is more important to relieve symptoms such as pain, shortness of breath, fatigue, and anxiety.

Table 1.
Palliative care needs in patients with heart failure associated with a prior or potential heart transplant.

8. Practical skills in palliative medicine

Among the many symptoms subject to palliative treatment in progressive end-stage heart failure, dyspnea and difficulty breathing predominate. Treatment is symptomatic, consisting of reducing the feeling of dyspnea and reducing anxiety. Oxygen therapy should be limited to patients with hypoxia at rest or with minor exertion. Respiratory training and respiratory physiotherapy, including the use of an air supply, may be helpful in reducing dyspnea. The pharmacotherapy of choice is the inclusion of fractionated doses of opioids, preferably morphine. Morphine in hospice conditions can be administered subcutaneously or orally because it has a stable level of the drug in the serum. In hospital conditions, however, intravenous use in slow infusion using an infusion pump with small doses is effective, so as not to cause respiratory depression and respiratory arrest, but to eliminate the feeling of dyspnea. In the case of administration using an infusion pump, administration together with a short-acting benzodiazepine and the use of the PCA system is effective in eliminating dyspnea.

Another symptom requiring palliative treatment is the symptoms of fluid accumulation: swelling of the legs, feet, and trunk. With long-term swelling, there is a risk of skin damage, bacterial and fungal infections, which contribute to the formation of ulcers that are difficult to heal. Swelling is usually accompanied by tissue distension, fluid seepage, a feeling of excessive heaviness in the limb, weakness, and paresthesia that may join over time. Swelling is the main problem that worsens comfort. Diuretics of various effects are used. In parallel, indications for pharmacotherapy and prevention of venous thromboembolism should be established, and continued treatment for congestive heart failure should be considered. The symptomatic therapeutic procedures of choice are physiotherapy and manual compression procedures, as well as compression therapy by bandaging the limbs and using dedicated compression products. During compression therapy, through regular careful compression bandaging with soft skin dressings, the size of the swelling, local and systemic infections, and general subjective symptoms such as quality of life and pain should be monitored. It is important to provide adequate analgesia to enable the initiation of appropriate manual therapy. Additionally, in severe periods of fluid accumulation in body cavities, possible paracentesis of tense ascites and possible thoracentesis with the assumption of permanent access to the pleura and its drainage should be considered. An important element that increases the swelling is the medication taken by the patient. The use of unnecessary pharmacotherapy should be limited; however, in palliative and hospice care for people who do not use steroids chronically, a single or several-day introduction of a steroid, for example, dexamethasone, should be considered, which has an anti-edematous effect in this situation. The treatment of choice also includes observation and implementation of local and systemic treatment of skin damage and possible infections.

In the discussed stages of end-of-life heart failure, cachexia occurs, accompanied by nausea and loss of appetite. It is characterized by permanent atrophy of skeletal muscles with or without loss of adipose tissue. The main cause of weight loss is sarcopenia, or progressive loss of muscle mass. In contrast to simple malnutrition, cachexia is the result of impaired intestinal circulation, edema of intestinal villi, metabolic disorders, and chronic inflammation, which lead to excessive catabolism. The treatment of choice is attempts at mobilization through physiotherapy and the supply of high-energy and protein products. The use of pharmacotherapy with anabolic drugs may be helpful, but this is controversial at this stage of the disease. It is believed that

cachexia cannot be reversed by increasing the caloric intake alone. Patients suffering from cachexia experience significant weakness, reduced physical capacity, and reduced immunity, which increases the risk of infection and postoperative complications. Paradoxically, in the last period of life, weight gain may occur associated with massive fluid retention, the balance of fluids must be maintained by nurse. Cachexia also affects the patient's psyche, leading to a sense of helplessness, depression, and a deterioration in the quality of life. There is difficulty in thinking clearly by patients.

In addition to the physical symptoms caused by end-stage heart failure, patients with often experience psychological symptoms, such as depression or anxiety about the future. Sleep problems, if not relieved by opioids, require short-acting sleep medications. Depression occurs in 50–70% of patients with advanced heart failure. Safe the effectiveness of selective serotonin reuptake inhibitors (SSRIs) in this group.

In addition to shortness of breath, cough, difficulty breathing, edema (accumulation of fluid and swelling) of the legs, feet and trunk, heart irregularities, syncope, and psychological symptoms, chest pain occurs in these patients. The workload of the heart muscle and ineffective pumping of blood can cause chest pain, as well as abdominal pain and pain in the distal parts of the limbs caused by blood stasis in the venous system. Paracetamol and weak opioids, such as tramadol, are acceptable for reacting with pain. Strong opioids are used rather to treat shortness of breath.

Patients with severe heart failure often complain of insomnia. The use of benzodiazepines to solve this problem is significantly less effective in their case than the administration of drugs such as zolpidem.

Implantable electronic devices, which include pacemakers, ICDs, and resynchronization pacemakers, are widely used in these patients. However, at the end of life, numerous, often painful ICD discharges may occur, which significantly worsens the quality of life of patients. In such a situation, high-energy therapies delivered by the ICD can be deactivated, maintaining its pacemaker function. This type of deactivation does not interrupt the patient's life and improves comfort in the event of fainting and cardiac arrest.

In palliative care, sudden cardiac death can be expected at any time: Sudden or gradual loss of consciousness and lack of contact with the patient are typical. Before losing consciousness, the patient may experience dizziness, chest pain, and a feeling of palpitations. Conscious patient does not take food or fluids. Pain treatment can be continued similarly to symptomatic care treatment with moistening with a slightly acidic fluid. The patient should be provided with a quiet place where the family can stay with the dying person. This stage of treatment should be preceded by talks with the patient and then after he expresses his consent with the family about the planned procedure in the event of death.

Another thread is the need for teamwork. Patient care should be coordinated by one person, but the management of symptoms and stress caused by care should be distributed to the palliative care team. The team should include a palliative medicine specialist, a cardiologist, palliative and cardiology nurses, a physiotherapist, a respiratory worker, a psychologist, volunteers, and the patient's family. In many cases, consultations with other specialists are also necessary. Such a large team requires coordination and good management. However, it has been noted in studies that multidisciplinary care helps to eliminate unfavorable symptoms and improves the patient's quality of life [25, 26].

It is important to respect the patient's autonomy and make a decision about how to proceed. Patient decision aids are interventions designed to support people in making decisions about their health. There is a large literature and a number of review studies

that address this issue. It is believed that the patient's views, following consultation and discussion with a trusted healthcare professional, clearly guide the decision, provide information about the options and associated benefits/harms, and help to clarify personal values about the features of the options. For more detailed information, see the 2024 Cochrane review [28, 31].

The palliative care process and decision-making should involve the patient's family or loved ones. It is good practice and a must to build relationships with the family and loved ones by doing the following [8, 17, 29]:

Palliative Care skills tree:

Gathering information: Understanding the problem.
Involving family members: Involving everyone in the discussion.
Discussing values and goals: Aligning the decision with the family's values and long-term goals.
Jointly evaluating options.
Considering everyone's needs.
Planning.
Reviewing and reflecting.
Be open to changes and suggestions.

The goal of palliative care is to help patients live better by relieving stress and symptoms to improve quality of life. Palliative care can provide relief from pain and heart failure symptoms. It can provide emotional and spiritual support and help with making complex treatment decisions. In addition, palliative medicine can help with practical issues such as advance directives or insurance issues [30].

An important aspect is that it can help organize and provide support services for caregivers, such as respite care and bereavement counseling.

In addition, palliative care is recommended for anticipatory care, which includes treatment planning: helping to make decisions about health and illness in the future. This is done by identifying the patient's personal goals and preferences and discussing end-of-life issues with family and healthcare providers.

9. Proactive plan in children and adult population

Palliative medicine also documents an advance directive plan, which can be updated if the patient wishes. Primary and specialist palliative care is considered the most advanced care for the pediatric population with end-stage heart disease, including heart transplant recipients. Advances in the care of patients with congenital and acquired heart disease in children have led to an overall decrease in mortality in a large population of infants, children, and young adults. It is believed that a significant number of patients and families live with advanced congenital and acquired heart disease. These patients experience long-term morbidity and uncertainty about the course of their disease and life expectancy after both curative and palliative therapies. Palliative and hospice care for these patients remains highly valued regardless of the circumstances [32].

In the treatment of adult patients before and after heart transplantation, palliative care depends on the transplant center. In most cases, cardiologists are responsible for the treatment, and the burden of care falls on cardiology nurses. Good clinical

management would mean the involvement of a multidisciplinary team and cooperation between cardiologists and cardiac surgeons and palliative medicine specialists to obtain the greatest possible benefit for the patient, by improving the quality of life during this difficult period.

10. Conclusions

Palliative care plays a key role in the care of heart transplant patients. It is necessary to develop specialist guidelines, published by national and international scientific societies. Guidelines for doctors and nurses caring for patients with heart failure should specify when and how to provide care to patients who are eligible or have had a transplant and always require palliative treatment in the late phase of the disease.

Conflict of interest

The authors declare no conflict of interest.

Acronyms and abbreviations

MUB:	Medical University of Bialystok
HTX:	heart transplantation
MCS:	mechanical circulatory support
ECMO:	extracorporeal membrane oxygenation

Appendices and nomenclature

PCST:	Palliative Care Screening Tool for HF Patients
IPOS:	Integrated Palliative care Outcome Scale
GSF-PIG:	Gold Standards Framework - Proactive Identification Guidance
RADPAC:	Radboud Indicators for Palliative Care Needs
SPICT:	Supportive and Palliative Care Indicators Tool
NAT: PD-HF:	Needs Assessment Tool: Progressive Disease - Heart Failure
NECPAL:	Necesidades Paliativas - Palliative Needs
ESAS:	Edmonton Symptom Assessment Scale
MIDOS:	Minimal Documentation System For Palliative Care

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Section 4

Emerging Topics in Transplant
Care and Regenerative
Strategies

Current Advancement in Stem Cell-Based Cardiac Regenerative Treatment in End-Stage Heart Failure

Esra Poyraz

Abstract

The prevalence of heart failure is increasing as human life expectancy increases. Currently, heart transplantation is the only available treatment for end-stage heart failure when drug and device therapies are insufficient. Cardiac regenerative therapies using human pluripotent stem cells (hPSCs), such as human embryonic stem cells (hESCs) and human induced pluripotent stem cells (hiPSCs), are expected to be an alternative to heart transplantation. Differentiation of hPSCs into cardiomyocytes mimics normal heart development. Pre-clinical studies demonstrating the transplantation of HPSC cardiomyocytes into animal hearts are available. However, several challenges remain after transplantation, such as arrhythmia, imaging, and immune rejection. Research in the field of cardiac regenerative therapy is still maintained. If we can also achieve this differentiation of hPSCs into cardiomyocytes in the human heart, we will break new ground in the treatment of end-stage heart failure.

Keywords: end-stage heart failure, cardiac regenerative therapy, human pluripotent stem cell, human embryonic stem cell, human induced pluripotent stem cell

1. Introduction

Heart failure is becoming more common with the increase in the aging population. The regeneration of the human heart is progressively decreased as the proliferation of cardiomyocytes (CMs) is gradually reduced during cardiac development. It also becomes highly differentiated shortly after birth [1], so once damaged, CMs are rarely recovered [2]. When myocardial infarction (MI) occurs, the infarcted area is transformed into scar tissue with reduced contractility due to loss of CMs and fibrosis [3]. In addition to fibroblastic scar development, adverse remodeling leads to the emergence of heart failure [4–6]. Heart failure is a progressive disease because the compensatory mechanisms activated during heart failure will ultimately lead to myocardial cell death, further compromising myocardial function [7]. When end-stage heart failure occurs, individuals may not respond to new drugs and ventricular assist

devices [8]. In such a situation, heart transplantation is offered as an alternative to these treatment applications as a vital opportunity in end-stage heart failure [9, 10]. The previous trial announced that the average waiting period for heart transplantation in the United States between 2011 and 2017 was approximately 200 days, with a mortality rate of about 7.0% [11]. In countries like Japan, the situation is even worse. Even finding a donor in Japan is quite hard. The annual number of heart transplants is less than 100 and the average waiting time is approximately 5 years [12]. Besides all these difficulties, all individuals with end-stage heart failure may not be eligible for heart transplantation [13]. Otherwise, cardiac regenerative therapy consisting of human pluripotent stem cell (hPSC)-derived cardiomyocytes can provide myocardial regeneration. Therefore, in the future, regenerative therapies using human pluripotent stem cells (hPSCs), such as human embryonic stem cells (hESCs) [14] and human induced pluripotent stem cells (hiPSCs) [15], are hoped to be an alternative treatment to heart transplantation in end-stage heart disease (**Figure 1**).

Several studies have confirmed that hPSC cardiac derivatives improve myocardial performance [17]. hESCs are pluripotent stem cells derived from the embryo's days 4 to 7 blastocyst stage [18]. Due to their ability to proliferate indefinitely and differentiate into cells of all three germ layers [19, 20], hESCs are highly promising therapies for treating end-stage heart failure. Caspi et al. [21] showed that hESC-derived cardiomyocytes enhanced myocardial contraction in chronically infarcted rats. Growth factors or WNT signals are utilized during the differentiation of hPSCs into CMs [22]. CHIR99021 and XAV939 which are WNT signaling activators allow us to produce CMs with high efficiency. Mensah et al. rapidly and efficiently generated CMs from mouse ESCs using WNT signaling activators [23].

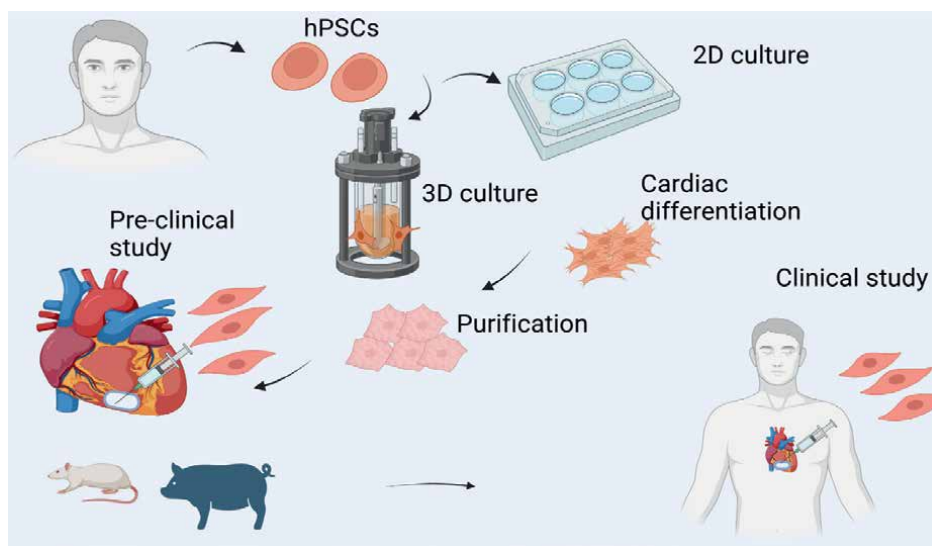


Figure 1. Development scheme of cardiac regenerative therapy from past to present. hPSCs were generated by the addition of various transcription factors to human somatic cells. 2D and 3D large-scale cultures were used to increase the number of hPSCs and to differentiate hPSC-CMs. With the purification method, undifferentiated hPSCs are eliminated in the culture medium. Thus, tumor formation is prevented. Then, these hPSC-CMs were injected into animals such as pigs and mice in pre-clinical studies. Clinical applications of hPSC-CMs have just started recently. It is still ongoing. If their efficacy and safety are confirmed by clinical trials in the future, they will be widely applied in humans with end-stage heart failure. Note: This image was created with biorender.com [16].

2. Culture of hPSC-CMs

Directed differentiation of hPSCs into CMs can be achieved by CM-specific factors added to appropriate culture media [24]. If hPSCs are not completely differentiated, tumors such as teratoma may develop [25]. Therefore, the safety of hPSCs has been questioned. According to recent studies, teratoma formation seems to be closely related to the engraftment site. Teratoma formation has been reported during hPSC transplantation into the testis [26], renal capsule [27], and liver [28]. Various methods have been developed to prevent teratoma formation, eliminating undifferentiated hPSCs and allowing only hPSC-CMs to survive. The addition of phosphor-D-peptide (D-3) [29], recombinant lectin-toxin fusion protein [30], cardiac glycosides [31], and surviving inhibitors [32] to cell cultures can eliminate undifferentiated hPSCs. Metabolic regulation is also essential in removing undifferentiated hPSCs and is a slightly cheaper method. For example, prolonged methionine depletion caused apoptosis of hPSCs [33]. Furthermore, in lactate-supplemented glucose- and glutamine-deficient media, non-CMs, including undifferentiated hPSCs, could not survive, whereas hPSC-CMs survived because they were able to take up lactate and use it as an energy source [34]. Inhibitors of stearoyl-CoA desaturase [35] and fatty acid synthase (Orlistat) [36] cause cell death in hPSCs because fatty acid synthesis is essential for their survival.

Several studies [37] suggest that 2D cultures are better for the production of hPSC-CMs, while others [38–40] suggest that 3D cultures are superior. 3D cultures involving a bioreactor or spinner flask are suspension cultures that, in contrast to traditional 2D cultures monolayers, enable the expansion of hPSCs. This feature increases the productivity of 3D cultures [17]. This has led to a growing preference for 3D culture. 3D culture is more advantageous than 2D culture for large-scale culture. Because 3D culture does not require coating proteins to adhere to the cell. So the cells float. This condition allows cells to be easily collected from the medium [39]. Otherwise, it was shown that 2D cultures might be a better choice to produce CMs at higher purity for cardiac infarct modeling. Because the differentiation efficiency of hPSCs into hPSC-CMs and expression of cardiac markers were better in 2D culture than in 3D culture, this was attributed to Matrigel in 2D culture. Because Matrigel was a supporting substrate that assisted cells in differentiating into CMs under adherent conditions. However, it was observed that hPSC-CMs in both 2D and 3D cultures were not fully mature. Because CASQ2, TCAP, and ion channels, genes indicating functionality in cardiac myocytes, were expressed less in both cultures compared to cardiomyocytes in normal individuals, ventricular-specific MLC2v was almost absent in these cultures. In contrast, TCAP was upregulated after 1 week and MLC2v-positive cells were observed in cultures after 2 weeks. Otherwise, hPSC-CMs in 3D culture were superior to those in 2D culture regarding the physiological maturation of hPSC-CMs. Cells in 3D had a higher proportion of ventricular/early ventricular-like cardiomyocytes and higher homogeneity in the action potential duration than those in 2D [37]. Another study demonstrated that the structural and functional maturation of hPSC-CMs in 3D culture was earlier than in 2D culture because of the lower oxygen level inside 3D culture. Hypoxia in 3D culture caused earlier differentiation of hPSCs to CMs compared to 2D culture [40]. Automated culture systems are currently being developed. The robotic technique established a system that automatically induces the differentiation of hPSCs into retinal pigment epithelial (RPE) cells, enabling the automatic production of large amounts of hPSC-CM [41]. Thus, thanks to new culture models, hPSC characteristics will be better understood and allow the production of large numbers of hPSC-CMs required for clinical applications.

3. Cardiac differentiation

hESCs have been known to be differentiated into functional cardiomyocytes using multiple differentiation methods. Moreover, it has been demonstrated that hiPSCs can develop into cardiomyocytes when cultured in a controlled environment, which is remarkable [42–44]. Although the differentiation of both hESCs and hiPSCs into adult CMs is similar, differences in gene expression between the two stem cell types may result in adult CMs with different phenotypes. According to research by Zhang et al., cardiomyocytes generated from hESCs have a higher proportion of cells that beat spontaneously and a faster beat frequency [42]. Human ESC-derived cardiomyocytes have Ca^{2+} handling that is substantially more similar to the adult phenotype than the more immature Ca^{2+} handling of human iPSC-derived cardiomyocytes, as demonstrated by Lee et al. [45].

Cell cultures based on robustly defined scaffolds containing biomaterials similar to *in vivo* conditions have been studied. Achieving cardiac differentiation requires a wide range of approaches such as; modulating signal pathways (TGF β , BM4), Glycogen Synthase Kinase 3 inhibitors (CHIR99021), Wnt inhibitors/ β catenin inhibitors (IWR1, Sfrp2), 3D culture technique, chemical factors, peptides, human recombinant proteins, and extracellular matrix (ECM) modulation (Matrigel, Vitronectin, and Synthetmax), coculture with non-parenchymal cells, antibodies (bovine serum albumin (BSA), AlexaFluor 488), electrical and mechanical stimulation. Through the production of cardiac structural proteins such as α -actinin, α -myosin heavy chain (α -MHC), or the cardiac isoform of Troponin-T (cTnT) from day 7 to day 10, maturing cardiomyocytes can be detected. By day 10, the cells are expected to exhibit cardiomyocyte features such as spontaneous contraction, expression of cardiac markers, and cardiac action potential as measured by immunofluorescence (IF) staining and other techniques to be deemed a successful differentiation. Sometimes, obtaining adult CMs takes longer (at least 2 months). In contrast, it takes less time to generate adult CMs from hESCs and can be more effective [46–48]. The differentiation efficiency is highly dependent on the hPSC density and the amount of time in culture prior to differentiation. For efficient differentiation, the beginning density should be greater than 80% confluence [48]. But it is not enough just to increase the efficiency of differentiation, we will produce a much larger number of CMs from cells that can be used for cardiac regenerative therapy. In addition to high differentiation efficiency, the reduction of fetal-like CMs will increase our clinical success by producing CMs that are more similar to adult CMs in terms of maturity. As maturity increases, the CMs produced will resemble human CMs both functionally and physiologically. Thus, the electrical conduction in the CMs produced, the duration of the action potential, and the synchronized contraction and relaxation of the CMs will be similar to the CMs in humans. Also, as maturity increases, teratoma formation will decrease. For this, cardiac differentiation cultures should contain bioproducts similar to those of *in vivo* architecture.

Although CRISPR-Cas9 somatic gene editing has the potential to impede research into cardiac gene function as a whole, it may prove useful in elucidating how CMs mature. After employing CRISPR-Cas9 to silence the putative enhancer for MYH7 in iPSC-CMs, the produced CMs contracted more quickly, and MYH6 increased in a dose-dependent manner [49]. Through *in vivo* CRISPR screening, Vandusen et al. showed that the transcriptional regulators RNF20 and RNF40, which form a complex that monoubiquitinises H2B on lysine 120, are the most important genes

in the regulation of CM maturation and that their depletion significantly negatively affects CM maturation. The H2Bub1 epigenetic mark is written by a ubiquitin ligase complex that Rnf20 and Rnf40 interact to create. By blocking critical transcriptional changes and eradicating H2Bub1 writing, Rnf20/40 depletion severely affected CM maturation [50].

The fibronectin receptor, integrin alpha-5 subunit, is abundantly expressed in a wide variety of cell types. In addition, there is prior evidence that mice lacking $\text{I}\alpha 5$ die during pregnancy as a result of heart abnormalities [51]. Integrin alpha-5 subunit, is critical for the early stages of human pluripotent stem cell cardiac differentiation. When the expression of the $\text{I}\alpha 5$ subunit was reduced in cells that serve as precursors to mesoderm by use of the CRISPRi system. GATA4, Islet-1, and NKX2-5 were significantly downregulated in terms of messenger RNA expression, which are hallmarks of cardiac progenitors. Crucially, cardiomyocytes produced from situations where $\text{I}\alpha 5$ was downregulated showed considerably decreased contraction and peak amplitudes. To summarize, lower levels of the $\text{I}\alpha 5$ subunit throughout the initial phases of heart development resulted in less differentiation of cardiomyocytes and worse contractility [52].

4. Transplantation of hPSC-CMs

In the injection method, hPSC-CMs are injected into the host heart using needles. Improvement in cardiac function has been observed following the injection of hPSC-CMs in myocardial infarction models of animals such as mice, rats, pigs, and monkeys [53–58]. Guan et al. evaluated the prognosis of intramyocardial transplantation of hPSC-CM by creating an infarcted rat heart model. hPSC-CMs were injected intramyocardially into the hPSC-CM group, while only albumin solution was injected into the control group. Mortality decreased and left ventricular (LV) performance improved in the hPSC-CMs group compared to the controls [59].

Epicardial patches are engineered cardiac tissues implanted on the heart's outer surface adjacent to the infarct site. Implantation of engineered cardiac tissues (EHTs/patches) onto the epicardium is a less invasive procedure than hPSC-CM injection into the host myocardium because this procedure does not involve an injection application that damages the host myocardium. Indeed, in the study of Pecha et al. implantation of EHTs/patches formed by hiPSC-CMs onto the host epicardium was similar in terms of arrhythmia to the control group in which cell-free constructs were implanted [60]. It is uncertain if EHTs are electrically coupled to the host myocardium. According to Gerbin et al., hPSC-CMs injected into rats' myocardium have the ability to fuse with host CMs. On the other hand, the epicardium serves as an insulator between the myocardium and hPSC-CMs; hPSC-CMs implanted onto it were unable to fuse [61]. In comparison, Higuchi et al. used host cardiomyocytes to implant hPSC-CM patches onto the epicardium of nude rats. The actin-myosin cross-bridge motion was seen with the use of the high-flux synchrotron X-ray diffraction technique. They contend that fusion depends on the epicardium's microenvironment. Kawamura et al. found that the number of engraftments was lower when the implantation of ECTs/patches onto the epicardium was compared with the intramyocardial insertion method [62]. On the contrary, Riegler et al. reported that EHT/patch transplantation was associated with a higher engraftment rate and longer survival. Also, improved maturation was observed with EHT/

patch. Because of the connection, 43 gene expression, an indicator of advanced maturation, was increased in their study [63]. Interestingly, one of the recent studies with EHTs/patches implied that the improvement in left ventricular (LV) performance caused by immature EHTs/patches obtained without preculturing was similar to the improvement in LV performance caused by mature EHTs/patches in earlier studies [64].

Transcatheter intracoronary and transcatheter trans-endocardial injection methods enable transplantation of hPSC-CMs into the host heart without needing thoracotomy. Results were unsatisfactory after intracoronary administration of hPSC-CMs or hPSC-derived cardiac spheroids (hPSC-CSs) into the host heart. This application method caused coronary ischemic injury and scar formation [65]. However, another study showed that the infarcted pig heart could be safely and successfully remuscularized by trans-catheter-based endocardial administration of hESC-CMs. Additionally the combined use of ivabradine and amiodarone for engraftment arrhythmias developed during this application was successful to stop arrhythmias. But this study did not focus on graft function [66].

5. Improvement of cardiac function by transplanted hPSC-CMs

First, transplanted hPSC-CM grafts begin remuscularization in the host heart and express the connexin 43 gene [55, 56, 67]. In general, hPSC-CM grafts move in tandem with the host heart [55]. Even yet, it is challenging to verify how the transplanted hPSC-CMs affect the host's mechanical function. The weight ratio of the graft to the host myocardium was shown by Stüdemann et al. to be usually linked with the contribution of transplanted hPSC-CMs to cardiac function [68].

In the Tachibana et al. study, transplanted hPSC-CMs into the host myocardium led to a decrease in scar size and acceleration of angiogenesis by secreting growth factors and cytokines such as (TNF- α , vascular endothelial growth factor (VEGF), and CXCR4). Thus, apoptotic cell ratio decreased, vascular endothelial cell number was higher and cell migration increased in the periinfarct region of the hPSC-CM transplantation group compared to controls [69]. Besides growth factors and cytokines, other components of the paracrine effect, microRNAs [70], noncoding RNA [71], and extracellular vehicles (EVs)/exosomes [71–73] increase in the periinfarct region of the hPSC-CM. In conclusion, endogenous repair mechanisms in the host myocardium are stimulated by paracrine effects.

A pro-survival cocktail involving a cell permeant peptide can decrease the apoptosis of transplanted hPSC-CMs, blocking mitochondrial death pathways. Also, a pro-survival cocktail involving cyclosporine A can reduce apoptosis of transplanted hPSC-CMs, blocking cyclophilin D-dependent mitochondrial pathways. Gelatin hydrogel [74], polyethylene glycol hydrogel [75], and laminin [76] have been used as scaffolding and cell carriers. Thus, the therapeutic effects of transplanted hPSC-CMs have increased. For example, Splenic-Gel, a decellularized extracellular matrix hydrogel, involves multiple fibrous proteins and proteoglycans [77, 78]. And it reduces oxidative stress. The transformation of hiPSCs into endothelial cells (ECs) and cardiomyocyte cells (CMs) was successfully boosted on Splenic-Gel in the Guan et al. study. Moreover, the combined use of EC/CM-laden Splenic-Gel benefited cardiac function and repair in infarcted heart mice by improving transplanted cell survival, revascularization, and remuscularization [79].

6. What can we do to increase the efficiency of Engraftment?

6.1 Co-transplantation and paracrine effect

Co-transplantation of hPSC-CMs can improve cardiac function after cardiac damage with different cells such as mesenchymal stromal cells (MSCs), hPSC-derived epicardial cells (hPSC-EPIs), hPSC-derived endothelial cells (hPSC-ECs). These cells ensure the survival of hPSC-CMs in ischemic conditions through paracrine secretion of cytoprotective chemicals. Research has shown that paracrine factors play an important role in promoting heart regeneration. These factors do this through several pathways, such as restricting inflammatory and pro-fibrotic processes, neovascularization, cytoprotection, and the differentiation of resident stem cells. Akt 1, a paracrine factor released from MSCs improved cardiac function and decreased infarct size in a rat model of myocardial infarction [80]. One of the paracrine factors, Sfrp2, is bound directly to Wnt3a and prevents Wnt3a-induced caspase activation in a dose-dependent manner [81]. Hypoxic induced Akt regulated stem cell factor (HASF), a novel paracrine factor produced by MSCs, inhibited caspase activation and mitochondrial pore opening and reduced the frequency of TUNEL positive nuclei, thereby preventing the loss of cardiac function during myocardial infarction [82]. Transplantation of hPSC-CMs together with MSCs into the myocardium reduces inflammation by suppressing the production of pro-inflammatory cytokines such as TNF- α , IL-1 β , IL-6, and MCP-1. MSCs achieve this by releasing paracrine factors [83]. MSCs even suppress T cell-mediated cytotoxicity by releasing paracrine factors such as TGF β , nitric oxide, and prostaglandin-E2 (PGE2) [84, 85]. Paracrine factors such as fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and neuregulin-1 (NRG1) released from MSCs help cardiomyocyte proliferation by activating PI3K [86–88]. Damage to the cardiac myocytes causes fibrosis, hypertrophy of cardiomyocytes, and alterations in the size and function of the ventricles as a result of changes in the extracellular matrix (ECM). Paracrine factors such as Sfrp2 released by MSCs can alter the ECM and prevent post-infarction remodeling. In a number of animal models, Sfrp2 decreases fibrosis in the heart by regulating ECM proteins such as metalloproteinases and serine proteases [89, 90].

Paracrine substances such as fibroblast growth factor (FGF), hepatocyte growth factor (HGF), and vascular endothelial growth factor (VEGF) are secreted by MSCs. MSC-induced paracrine actions promote angiogenesis in the heart and reduce the extent of fibrotic infarction. New et al. reported that LV performance was better in combined hPSC-CMs and MSCs than in the single-cell group. Moreover, when MSCs were transplanted either alone or in combination with hPSC-CMs, they boosted the capillarization in the myocardium. However, the reduction in infarct scars occurred when only transplanted with combined hPSC-CMs and MSCs [91]. Epicardial-derived cells are pivotal in cardiac proliferation and compaction [92]. Connexin 43 and contractile proteins, which are markers of maturity, were expressed more in the graft when hESC-EPI and hESC-CMs were co-cultured. Therefore, whether compared to primary MSCs, hESC-derived MSCs, or CMs alone, cardiac maturation was greatest in this group. Additionally, it was noted that this group had the best contractions and relaxations [93].

6.2 Genetic modification

In some studies, modulation of gene expression had positive effects on graft survival and function, while in other studies, it had negative effects [94, 95].

Nsp6, M, and Nsp8 were identified as SARS-CoV-2 genes that negatively affect both the survival and energy production of human CMs. These genes had a positive effect on the expression of genes responsible for apoptosis and inflammation in human CMs, while they had a negative effect on the expression of genes related to contraction. The Annexin V+ gene, which triggers apoptosis, was expressed more frequently by these genes. Furthermore, by interfering with the ATPase subunits of human CMs, these genes disrupted the ATP biosynthesis of CMs, which in turn reduced the energy output of CMs. By influencing the protein factors that lead to heart injury, these genes result in cardiac hypertrophy. They disrupted intracellular Ca handling and produced mitochondrial dysfunction, which led to arrhythmias in CMs in addition to increased apoptosis, poor intracellular ATP production, and cardiac hypertrophy [94]. However, another study found that elevated levels of alpha-actinin 2 (ACTN2) are a sign of CM development, and transcriptional enhancers can aid in cardiac maturation. By turning on the CRISPR enhancer, the ACTN2 enhancer was activated. Therefore, CM maturation was accomplished by using genetic manipulation to raise ACTN2 levels [95].

7. Complication of clinical application of hPSC-CMs

7.1 Post-transplant arrhythmia

Transient ventricular arrhythmias, termed engraftment arrhythmias (EA), are challenging in clinical applications of hPSC. Nakumora et al. demonstrated that focal mechanisms, not macro-reentry, are responsible for graft-associated tachyarrhythmias with the contribution of electroanatomical mapping and pacing investigations [66]. Furthermore, they discovered that in a porcine infarction model, amiodarone and ivabradine worked well to treat arrhythmias triggered by hPSC-CM intramyocardial engraftment. The findings of another study supported theirs. The lack of response of EA to overdrive pacing or direct current (DC) cardioversion favors that these arrhythmias are of focal origin rather than macro-reentry [96]. Conversely, Yu et al. suggested that conduction slowing or blocking in areas of transplanted cardiomyocytes and electrophysiological heterogeneity may encourage susceptible substrates for re-entry in the infarcted heart [97].

Marchiano et al. reported that EA was more intense in immature hPSC-CMs compared to mature CMs [98]. In their trial, immature hPSC-CMs had a more depolarized membrane potential and shorter AP duration. By eliminating the depolarization-inducing multiple ion channel genes HCN4, CACNA1H, and SLC8A1 and overexpressing hyperpolarization-associated KCNJ2, they generated hPSC-CMs that could contract only upon external stimulation. When transplanted in this final form of grafts, these cells were observed to establish an electromechanical connection with host cardiomyocytes without causing sustained EAs.

Cardiac fibroblasts are known to transform into myofibroblasts during cardiac injury [99]. Myofibroblasts can change the electrophysiology of cardiomyocytes, either through paracrine signaling or direct heterocellular coupling [100, 101]. In another experimental study, inhibition of IL6 signaling in cocultures containing both host cardiac myofibroblasts and hiPSC-CMs attenuated the negative effects of myofibroblasts on the electrophysiological and Ca^{2+} handling properties of hiPSC-CMs through paracrine-mediated mechanisms. However, the negative impact of myofibroblasts on hiPSC-CMs persists through direct heterocellular coupling mechanisms.

On the other hand, the knockdown of Cx43 and the blockade of IL 6 signaling in cocultures also inhibited the direct heterocellular attachment mechanisms of myofibroblasts on hiPSC-CMs. Thus, EA was reduced or even prevented [102].

7.2 Immune rejection of hPSC-CMs

Immune cells fight the graft by releasing cytokines, causing inflammation, using cytotoxic processes, and phagocytosing it. This is known as immunological rejection. The immunological rejection process has two phases. When the recipient's lymphocytes recognize antigens on the graft, they are activated and replicate during the sensitization stage. The graft must be eliminated in the second stage, the effector stage. T cells are the primary cells that start the rejection process during the reaction [103]. Furthermore, there are two types of rejection: acute and chronic rejection. The most common period of acute rejection is the first few weeks following transplantation. This type of rejection is associated with syngeneic grafts and occurs approximately 10 days after transplantation. Pathological sections of this rejection contain marked lymphocyte infiltration, and the tissue is destroyed by macrophages [104]. In contrast, in chronic rejection, the acute response is reduced by the use of immunosuppressants so that rejection occurs after a long time, even years.

Following tissue or organ transplantation, the immune rejection response is significantly influenced by human MHC, also called human leukocyte antigen. Recently, hypoimmunogenic hPSCs have been formed to prevent immune rejection. Lu et al. damaged beta 2-microglobulin, the HLA class I light chain, to produce HLA class I-deficient hESCs. They were thus spared an attack by T cells, but this time, they were attacked by NK cells due to HLA class I deficiency [105]. Deusse et al. generated hPSCs in which hPSCs with MHC class I and II were inactivated, and CD47 was overexpressed so that hPSCs could escape the attack of both T cells and NK cells [106].

Otsuka et al. constitutively expressed the mouse Foxn1 gene in hiPSCs and evaluated the differentiation of hiPSC into hiPSC-TEC in the presence of the Foxn1 gene. The Foxn1 gene positively affected the differentiation of hiPSC-TEC. Thus, the differentiation of hiPSC-TEC was increased. Immune tolerance was achieved in mouse iPSC-derived grafts when mouse iPSC-TECs were implanted into the renal subcapsular area of immune-competent mice [107].

8. Extracellular vesicles

Extracellular vesicles (EVs) are an exciting area of research because they offer a way to heal the heart without needing to transplant cells directly. EVs contain various bioactive molecules such as micro-ribonucleic acids (miRs) and proteins in a lipid bilayer. EVs provide protection of the cardiovascular system by regulating many different functions in target cells, while on the other hand, they can cause the development of CVDs by changing miR and protein compositions under pathological conditions [108]. In myocardial infarction (MI), hypoxia-induced MSC-derived EVs promote ischemic cardiac healing by preventing cardiomyocyte mortality and ameliorating cardiomyocyte apoptosis through miR-125b [109]. As a defense mechanism against hypoxia and inflammation, cardiomyocytes in MI release endothelial-related miRs (miRs) such as miR-143 and miR222 into extracellular vesicles (EVs) [110]. Implanting a specially designed hydrogel patch onto the hearts of rats following myocardial infarction improves ejection fraction recovery, decreases arrhythmic burden, prevents

cardiomyocyte apoptosis, decreases infarct size, and inhibits cell hypertrophy. The patch can release EVs secreted by induced pluripotent stem cell (iPSC) cardiomyocytes slowly and provides sustained delivery of these cells [73]. There is a great deal of promise for therapies that involve boosting or lowering miR-containing EVs because of the crucial role EVs play in the remodeling of cardiac muscle following MI.

9. Clinical applications of stem cells

In Menasché et al. study, hiPSC-CMs were embedded in a fibrin scaffold, followed by amplification of these cells and subsequent transplantation of the differentiated progeny into patients with end-stage heart failure by surgical pericardial patching. No adverse events were observed in recipient patients during this study [111, 112]. One patient died in the early postoperative period due to comorbidity. The follow-up of the remaining patients was uneventful. Neither tumors nor arrhythmias were observed during follow-up, and no arrhythmia was observed in any patient. However, three patients experienced alloimmunization that was clinically quiet. All patients had increased systolic motion at the cells transplanted sites and symptomatic improvement, although one patient died of heart failure after 22 months. Since immunosuppressant treatment was stopped after 1–2 months, the impacts of the transplant are thought to be primarily paracrine [113]. In another study, EHM composed of stromal cells obtained by suspending hiPSC-CMs in bovine collagen type I hydrogel were transplanted onto the beating heart through a left-lateral mini-thoracotomy. With these EHM grafts, angiogenesis was observed along with thickening of the muscle tissue in the transplanted area of the recipient human heart. It was also pleasing to observe improvement in both LVEF and symptoms of the recipient at the 12-month follow-up [114]. Catheters will be utilized for injecting hESC-CMs from the endocardial side into the myocardium in the US HECTOR trial, which is aimed at patients with persistent ischemic cardiomyopathy [115]. Phases 1–2 of the HEAL-CHF trial treat heart failure with hPSC-CMs. This study aims to evaluate the pros, cons, and practicality of delivering cardiomyocytes intramyocardially during coronary artery bypass grafting to patients suffering from chronic heart failure. Patients with $20\% \leq \text{LVEF} \leq 45\%$ and NYHA class III–IV cardiac function even after improved medication for advanced chronic heart failure treatment, will be included in the study. Cardiomyocytes produced from allogenic human pluripotent stem cells (hPSC-CMs) will be used to treat heart failure patients. Cardiomyocytes produced from allogenic human pluripotent stem cells (hPSC-CMs) injected into the heart during coronary artery bypass grafting (CABG) procedure. The myocardium will be injected with a suspension of 200 million hPSC-CMs in 2.5–5 mL of media. These cells will come from healthy donors. Myocardial infusion of the cells will occur during coronary artery bypass grafting. At 1, 3, 6, and 12 months post-transplant, patients will undergo safety, feasibility, and efficacy evaluations [116]. The study, Treatment of severe chronic ischaemic heart failure by epicardial injection of hiPSC-CMs, will evaluate the feasibility, safety and efficacy of injecting cardiomyocytes generated from hiPSCs (HiCM-188) into the heart of patients undergoing coronary artery bypass grafting (CABG) surgery for severe chronic ischaemic heart failure. Up to 36 patients with severe ischemic heart failure will participate in an open-label, single-center study, which will consist of a dose-escalation (phase I) and a dose-extension (phase IIa) component. About 18 individuals undergoing coronary

artery bypass grafting (CABG) surgery will reportedly receive an intramyocardial injection of HiCM-188. Dosage escalation and extension studies can only include a maximum of 12 patients per dosage group. Immunosuppressants must be taken by all participants following transplantation [117]. IPS Differentiated Cardiomyocytes Vein Transplantation for Chronic Heart Failure (IDCVTCHF) is a phases 2–3 trial. The results of animal experiments confirmed the safety and effectiveness of intravenous myocardial cell transplantation, and clarified its possible mechanism. And now the safety, and effectiveness of intravenous myocardial cell transplantation from hiPSCs into the heart of patients chronic heart failure [118]. In a phase 1 trial called ESCORT utilizing hESCs-CMs, the potential benefits and risks of transplanting cardiac-committed progenitor cells produced from human embryonic stem cells to individuals suffering from advanced heart failure would be examined [119].

10. Conclusion

Transplantation of hPSC-CMs into humans has only been performed very rarely. And clinical trials are still ongoing [115–119]. As the efficacy of engraftment increases, mortality after transplantation of hPSC-CMs into humans will decrease, and both left ventricular ejection fraction and NYHA class symptoms will improve. Thus, cardiac regeneration therapy with hPSC-CMs will be preferred as it is a less invasive treatment method than surgical transplantation in end-stage heart failure. Firstly, we need to increase engraftment efficacy before transplantation. For this, we need to produce more hPSC-CMs and ensure the structural, physical, and functional maturation of these hPSC-CMs. We need to provide the ideal culture medium during the production of hPSC-CMs. We can achieve this by adding supportive substances such as Wnt signals, BMP4, Matrigel, SpGels, SpGels, ascorbate transferrin/selenium, gel, or non-CMs such as MSCs, ECs, and EPIs to the culture medium. In addition, Micro RNA techniques can provide information about the efficiency of hPSC differentiation into CMs and the status of hPSC-CM maturation.

Post-transplantation arrhythmias are one of the post-transplantation complications that should be emphasized. More studies on gene expression are needed to prevent these arrhythmias. In addition, immune rejection after transplantation is a challenging condition. Studies on gene expression in immune rejection may also be useful. For example, Foxn 1 gene expression was found to cause immune tolerance in grafts, and these grafts also induced immune tolerance in the host [107]. Studies about imaging of hPSC-CM grafts are ongoing. In the future, thanks to advances in imaging techniques, we will have more information about the status of hPSC-CM grafts transplanted into the host heart.

For hPSC-CM grafts to become preferable to surgical transplantation today, clinical trials with a larger number of people and long-term follow-ups are needed. Hopefully, in the future, it will be a reliable treatment of first choice in patients with end-stage heart failure who do not respond to medical therapy.

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Oral Health in Heart Transplant Recipients: Implications and Strategies

Yasemin Sezgin and Jafar Alabdullah

Abstract

This chapter explores the crucial role of oral health in the management of heart transplant recipients. Heart transplantation offers significant improvements in survival and quality of life, but it also requires lifelong immunosuppressive therapy to prevent graft rejection, which increases the risk of infections, metabolic disorders, and cardiovascular complications. The oral cavity, as both a reservoir for pathogenic microorganisms and a potential gateway for systemic infections, plays a critical role in transplant success. Periodontal disease, a common chronic inflammatory condition, is shown to have a bidirectional relationship with systemic health, contributing to conditions like cardiovascular disease and diabetes. For heart transplant recipients, poor oral health may exacerbate systemic inflammation, heighten the risk of infections, and negatively impact transplant outcomes. Despite limited studies on oral health in heart transplant patients, existing evidence highlights the increased periodontal treatment needs and poor oral health behaviors in this population. This chapter emphasizes the importance of early dental assessments, pre- and post-transplant care protocols, and interdisciplinary collaboration between dental and transplant teams to reduce the risk of complications. Regular dental care, including periodontal management, is vital to mitigate systemic inflammation and improve overall health outcomes for heart transplant recipients.

Keywords: heart transplantation, oral health behavior, periodontal disease, systemic inflammation, transplant outcomes

1. Introduction

Heart transplantation is a crucial life-saving intervention for individuals with end-stage heart failure, offering significant improvements in both survival rates and quality of life. However, long-term post-transplant care necessitates continuous immunosuppressive therapy to prevent graft rejection, which, in turn, increases the risk of systemic complications such as infections, metabolic disorders, and malignancies [1–3]. Oral health is an important factor contributing to the overall well-being of heart transplant recipients. The oral cavity acts as both a reservoir for pathogenic microorganisms and a gateway for systemic infections, highlighting the importance

of dental care in post-transplant management [4]. Gaining a deeper understanding of the role of oral health in transplant outcomes is essential for minimizing complications and promoting long-term success. This chapter aims to explore the critical role of oral health in heart transplant recipients, emphasizing its influence on systemic health and transplant success. It highlights the need for periodontal care to minimize complications and improve long-term outcomes.

2. Bidirectional link between periodontal disease and systemic health

Periodontal disease is a chronic inflammatory condition widely associated with systemic diseases, including cardiovascular diseases (CVD). The bidirectional relationship between periodontal disease and systemic health suggests that periodontal inflammation can contribute to systemic disease progression, while systemic conditions may exacerbate periodontal deterioration [4–6].

For heart transplant recipients, who are immunocompromised due to lifelong immunosuppressive therapy, understanding this relationship is particularly important. Poor periodontal health may increase systemic inflammation and infection risks, potentially affecting transplant outcomes. Recognizing these associations highlights the need for periodontal assessment and management as an integral part of transplant care to minimize complications and promote long-term health.

Periodontal diseases are inflammatory conditions of the tooth-supporting structures initiated by bacterial biofilms. Gingivitis and periodontitis are the two most prevalent forms, with gingivitis causing localized inflammation confined to the gingiva, while periodontitis leads to the progressive destruction of the periodontium [6–8]. Bacterial biofilms accumulating at or below the gingival margin trigger dysbiosis within the oral biofilm, disrupting immune-inflammatory processes and leading to periodontal tissue destruction [5–7].

Clinical characteristics of periodontal disease include changes in gingival color, size, and texture, bleeding on probing (BOP), increased periodontal pocket depth (PPD), clinical attachment loss (CAL), gingival recession, alveolar bone loss, furcation problems, increased tooth mobility, and tooth drifting [8, 9]. Systemic conditions can influence the onset and progression of periodontal disease. Disorders affecting neutrophils, monocytes, macrophages, and lymphocytes may disrupt inflammatory mediator production or activity, leading to early periodontal destruction or an accelerated rate of tissue breakdown [10, 11].

Evidence has also highlighted the reverse relationship between systemic health and oral health: the impact of inflammatory periodontal diseases on systemic conditions. Over the past few decades, a significant body of evidence has supported independent associations between severe periodontitis and systemic diseases such as diabetes [12–14], cardiovascular disease [15–17], chronic obstructive pulmonary disease [6, 18–20], and chronic kidney disease (CKD) [21–23]. Proposed mechanisms include the systemic spread of bacteria from the inflamed periodontium and inflammatory mediators [16, 24, 25].

2.1 Systemic spread of bacteria from the inflamed periodontium

As periodontal disease progresses, persistent inflammation leads to gingival swelling and periodontal pocket formation. The anaerobic environment at the pocket's base fosters biofilm development. Ulceration of the pocket epithelium allows

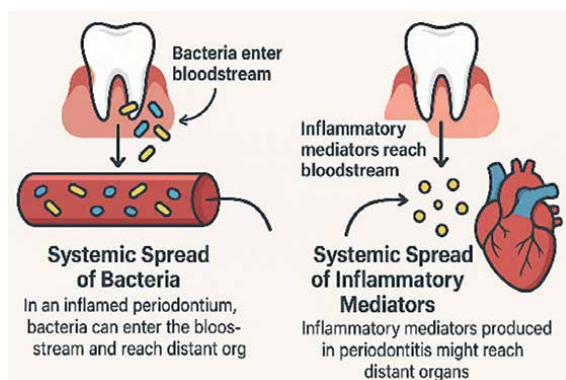


Figure 1.
 Systemic inflammation pathways.

periodontitis-associated bacteria to enter the systemic circulation, reach distant organs, and exert their effects (**Figure 1**) [16, 26, 27].

2.2 Systemic spread of inflammatory mediators

Periodontitis involves complex immune responses. Matrix metalloproteinases (MMPs) and reactive oxygen species drive tissue destruction, while proinflammatory mediators like IL-1, TGF- β , and prostaglandin E₂ enter circulation, increasing systemic inflammation and contributing to disease pathogenesis. Elevated C-reactive protein (CRP) levels in periodontitis patients confirm that periodontitis acts as a source of inflammatory mediators capable of circulating to distant organs and influencing systemic conditions (**Figure 1**) [16, 28–30].

3. The connection between periodontal disease and cardiovascular diseases (CVD)

Cardiovascular diseases (CVDs) encompass a wide range of pathological conditions, including ischemic heart disease, stroke, hypertension (which can lead to heart failure), rheumatic heart disease, cardiomyopathies, and atrial fibrillation [6]. In 2012, a joint workshop by the European Federation of Periodontology (EFP) and the American Academy of Periodontology reviewed links between periodontitis and systemic diseases, including cardiovascular disease (CVD) [15]. In 2019, the European Federation of Periodontology (EFP) and the World Heart Federation (WHF) jointly conducted a workshop to explore epidemiological connections, biological mechanisms, outcomes of intervention studies, and the risks and complications of periodontal therapy in patients on antithrombotic treatment. The consensus reports of both workshops concluded that strong epidemiological evidence links periodontitis to an increased risk of future atherosclerotic cardiovascular disease (CVD). The workshop concluded that periodontitis could plausibly influence CVD through the translocation of oral bacteria into the bloodstream. These bacteria may directly or indirectly trigger systemic inflammation, contributing to the development of atherothrombogenesis. While epidemiological and mechanistic links are well-documented, intervention studies on periodontal treatment's impact on CVD outcomes remain inconclusive [15, 16].

4. Relevance to heart transplant recipients

Heart transplant recipients are particularly prone to the systemic effects of periodontal disease due to their immunosuppressed state, which is essential to prevent graft rejection. This immunosuppression can impair the host's ability to control oral bacterial colonization and inflammation, increasing the risk of developing periodontitis. Furthermore, the systemic inflammatory burden associated with periodontitis may exacerbate cardiovascular complications, which are already a leading cause of morbidity and mortality in transplant patients.

Periodontitis can act as a source of circulating bacteria and inflammatory mediators, such as C-reactive protein (CRP), IL-6, and tumor necrosis factor-alpha (TNF- α), contributing to vascular inflammation [15, 17]. For heart transplant recipients, these mechanisms could potentially compromise graft function or increase the likelihood of adverse cardiovascular events. The detection of periodontal pathogens in atheromatous plaques highlights the systemic impact of oral health, further highlighting the importance of periodontal care in this population.

5. Oral behavior in heart transplant recipients

Over the past decades, advancements in organ transplantation have revolutionized medicine, offering life-saving treatments to patients with end-stage organ failure. The long-term success of transplantation is intricately linked to continuous immunosuppressive therapy, which plays a pivotal role in preventing chronic graft rejection. However, the necessity for lifelong immunosuppressive therapy to prevent chronic transplant rejection places all transplant recipients at a higher risk of developing systemic complications including renal failure, infectious complications, and malignancy [1, 31–34].

As the oral cavity acts as both a key habitat for bacteria and a major entry point for these microorganisms into the systemic circulation, routine dental care is crucial, as it helps transplant recipients maintain proper oral care behaviors and protect their oral health, both of which are essential for minimizing infection risks during their immunosuppressed state [4]. While maintaining good oral health is crucial, there is a limited number of studies in literature addressing this topic. When examining the literature on the oral behaviors of transplant recipients, it becomes evident that most studies have focused on liver, lung, and kidney recipients [31, 35–40]. Although the number of studies on this topic is limited, research comparing the oral health status of heart transplant recipients to systemically healthy, age-matched controls has shown that heart transplant recipients have higher periodontal treatment needs (measured by the CPITN index) and worse periodontal clinical parameters, including plaque index, probing depth, gingival recession, and clinical attachment loss. However, the prevalence of dental caries was found to be similar between the two groups [41, 42].

Interestingly, despite the increased plaque levels observed in the transplant group, bleeding on probing was comparable to that of the control group. This outcome is likely influenced by the immunosuppressive medications used by transplant recipients, which may modulate the inflammatory response in periodontal tissues [41]. An analysis of oral health-related behaviors revealed that the number of transplant recipients who visit the dentist once or twice a year was significantly lower compared to the control group. Additionally, the frequency of tooth brushing and the number of participants using dental floss or interdental brushes were also lower in the transplant group [41, 42].

When examining the systemic effects of periodontitis in heart transplant patients, a study evaluating serum high-sensitivity C-reactive protein (hs-CRP) levels was conducted. The results demonstrated that transplant recipients with periodontitis had significantly higher serum hs-CRP levels compared to those in the periodontal health and gingivitis groups. This finding suggests a potential link between periodontal inflammation and systemic inflammatory burden in heart transplant patients and reinforce the need for the inclusion of regular periodontal visits as part of post-transplant care to monitor and manage periodontal inflammation, thereby potentially reducing the systemic inflammatory burden in heart transplant recipients [43].

When evaluating the oral health behaviors of heart transplant recipients and heart insufficiency patients, both groups were reported to have a high periodontal treatment need (79.5% for transplant recipients and 87.6% for heart insufficiency patients). Additionally, inadequate oral health behaviors were observed in both groups. However, when assessing participants' dental visits, it was found that the heart transplant group had a higher rate of allocation to a dentist and received more information regarding oral procedures compared to the heart insufficiency group. Considering these findings, the implementation of special care programs for both heart transplant candidates and recipients has been recommended to address their specific oral health needs [44].

Given the high periodontal treatment needs and the established relationship between periodontal disease and systemic inflammation in heart transplant recipients, regular dental follow-up both before and after transplantation is essential. Implementing structured oral health care programs and integrating routine periodontal assessments into transplant care protocols may help mitigate potential complications and improve overall health outcomes in this vulnerable patient population. It should be noted that there are few studies in literature addressing this topic. Future studies should focus on longitudinal evaluations to better understand the long-term effects of periodontal disease on systemic health in heart transplant recipients.

6. Complications of immunosuppressive therapies on oral health

Immunosuppressive therapies, commonly employed in the management of autoimmune diseases, organ transplantation, and certain malignancies, can significantly affect oral health. These treatments, which function by attenuating immune system activity to prevent organ rejection or control disease progression, are associated with a range of oral health complications. Immunosuppressive medications like cyclosporine are commonly used to treat autoimmune diseases and prevent organ transplant rejection.

One of the most common oral manifestations of immunosuppressive agent use is *gingival hyperplasia*, characterized by excessive proliferation of gingival tissue (**Figure 2**). This condition is particularly prevalent in patients receiving calcineurin inhibitors such as cyclosporine, commonly prescribed to organ transplant recipients. Cyclosporine appears to suppress helper T cells, which play a vital role in the immune system's response. When the daily dosage of cyclosporine A (Sandimmune) exceeds 500 mg, it can lead to gingival overgrowth [11, 45]. The gingival overgrowth occurrence varies from 25 to 70% of patients who using Cyclosporine. Gingival hyperplasia can exacerbate the risk of periodontal disease and hinder effective oral hygiene practices, contributing to an elevated risk of oral infections and further periodontal complications [11, 46].



Figure 2.
Drug-induced gingival overgrowth in a patient on immunosuppressive therapy.

The primary intervention to manage gingival overgrowth in transplant patients involves rigorous plaque control through mechanical (brushing, scaling, and root planning) and chemical (chlorhexidine and mouthwash) methods [47]. In drug-induced cases, discontinuation or substitution is advised, though therapeutic alternatives are limited. Tacrolimus demonstrates a lower risk profile for gingival overgrowth.¹¹ Adjunctive azithromycin has been reported to attenuate CsA-induced gingival enlargement, while chlorhexidine exhibits a mitigating effect [48, 49]. A latency period of 6–12 months post-drug cessation is recommended before considering surgical intervention [50]. Surgery is warranted when gingival overgrowth compromises function or esthetics [51]. Gingivectomy, typically performed via scalpel or CO₂ laser, reduces pocket depth and contours gingival architecture [48, 52]. Recurrence occurs in 34% of cases within 18 months, though outcomes generally persist for at least a year. Laser gingivectomy offers superior hemostasis and reduced recurrence rates compared to conventional techniques [52, 53].

Another adverse effect of immunosuppressive therapy is *xerostomia* or dry mouth, which results from reduced salivary flow. Medications such as calcineurin inhibitors and corticosteroids are commonly implicated in the development of xerostomia. Xerostomia significantly increases the risk of oral infections, dental caries, and complications related to speech and swallowing, due to the lack of protective saliva in the oral cavity [11, 54].

Furthermore, *oral infections*, particularly fungal infections like *oral candidiasis*, are more prevalent in individuals undergoing immunosuppressive therapy. The suppression of immune function diminishes the body's ability to combat pathogens, thereby increasing susceptibility to infections within the oral cavity. Oral candidiasis, for instance, is commonly observed in patients receiving prolonged immunosuppressive treatment [11, 55].

7. Pre-transplant Oral health assessment and care

A comprehensive dental evaluation is essential before heart transplant surgery to address oral health conditions that may increase the risk of transplant rejection. Given the high-dose immunosuppressive therapy required post-transplant, these patients face an elevated risk of severe infections, including life-threatening sepsis from oral sources. Poor oral health and untreated bacterial infections, such as periodontal disease, can contribute to systemic inflammation, posing serious risks for transplant

recipients who are already immunosuppressed. To determine if a transplant recipient has infections, dental caries, and periodontal diseases that might contribute to bacterial translocation and raise the risk of systemic infection, a comprehensive dental exam should be conducted [54, 56–59].

7.1 Timing and objectives

The European Society of Cardiology emphasizes the need to address all potential sources of dental infection at least two weeks before transplantation to minimize the risk of bacterial translocation and systemic infection. The American Heart Association (AHA) similarly underscores the importance of a thorough preoperative dental evaluation to mitigate post-transplant complications such as infective endocarditis. However, sudden donor availability or logistical constraints may shorten this window, necessitating close collaboration between dental and transplant teams [57, 60].

7.2 The primary objectives of pre-transplant dental assessment include

- Identifying and managing active or potential dental infections
- Reducing microbial load through preventive and therapeutic measures
- Minimizing post-transplant complications by optimizing oral health
- Ensuring adequate healing time to reduce infection risks.
- Assessing medical stability and suitability for dental procedures
- Assessment components [42, 54, 56, 57, 61].

7.3 Comprehensive dental examination

A thorough evaluation should assess:

- *Dental infections*: Identification of abscesses, periodontal disease, and pulpal involved teeth
- *Advanced caries and non-restorable teeth*: Extraction of compromised teeth to prevent future infections.
- *Mucosal conditions*: Screening for opportunistic infections such as oral candidiasis
- *Periodontal status*: Chronic periodontitis is linked to systemic inflammation, which can affect transplant outcomes. Reducing microbial load and inflammatory mediators in the gingival tissues through scaling and root planning is critical.
- *Radiographs and microbiological testing*: These helps detect hidden infections that could contribute to bacterial translocation and systemic infection. Panoramic radiographs and intraoral periapical X-rays help identify hidden infections, periapical pathology, and alveolar bone loss.

Pre-transplant dental care should ideally be completed at least 2–3 weeks before transplantation to allow adequate healing and reduce infection risks. Routine antibiotic prophylaxis is not always necessary but may be indicated for patients with a history of infective endocarditis. Decisions should be made in collaboration with the transplant team, with clear documentation of indications. Local Anesthesia: Adrenaline-containing anesthetics should be used cautiously, limiting doses to 0.04 mg in severe heart failure patients (**Table 1**) [60].

Category	Pre-transplant care	Post-transplant care
Objectives	• Identify and manage active or potential dental infections	• Prevent infections and manage immunosuppression-related complications
	• Reduce microbial load through preventive and therapeutic measures	• Monitor for opportunistic infections, malignancies, and wound healing issues
	• Optimize oral health to minimize post-transplant complications	• Promote oral hygiene and prevent gingival hyperplasia
	• Allow adequate healing time before transplantation	• Ensure long-term maintenance and surveillance
Timing of Dental Care	• At least 2 weeks before transplantation	• Avoid elective dental care for the first 6 months post-transplant
	• Emergency dental care in collaboration with transplant team	• After 6 months, elective dental care may resume based on stability
Assessment Components	• Comprehensive dental examination	• Routine monitoring and management of oral complications
	• Identification of dental infections (abscesses, periodontal disease, and caries)	• Screening for opportunistic infections (e.g., candidiasis)
	• Radiographs and microbiological testing for hidden infections	• Regular periodontal care to prevent gingival overgrowth
Infection Prevention & Management	• Address all dental infections to reduce bacterial translocation risk	• High vigilance for infections due to immunosuppression
	• Minimize systemic inflammation to prevent transplant rejection	• Prophylactic antibiotics for patients with severe neutropenia ($<1.0/\mu\text{l}$)
Medication Considerations	• Assess patient stability for dental procedures	• Be aware of immunosuppressant-related oral side effects
	• Caution with adrenaline-containing anesthetics (limit to 0.04 mg in severe heart failure)	• Monitor for drug-induced conditions such as gingival hyperplasia (common with cyclosporine)
	• Collaboration with transplant team for antibiotic prophylaxis decisions	• Consider alternative immunosuppressants (e.g., tacrolimus) to reduce gingival overgrowth
Bleeding Risks	• Evaluate anticoagulation status before extractions	• Avoid inferior alveolar nerve blocks if platelet count $<30 \times 10^9/\text{L}$
	• - Use local hemostatic measures	• Avoid extractions if platelet count $<50 \times 10^9/\text{L}$
Anesthesia Considerations	• Limit adrenaline use in severe heart failure cases	• Use prilocaine with felypressin instead of adrenaline-containing anesthetics

Category	Pre-transplant care	Post-transplant care
Coordination with Cardiac Team	• Ensure clearance from transplant team before dental procedures • Document all oral health findings for transplant team	• Monitor drug interactions and immunosuppressant levels • Manage systemic effects such as myelosuppression and infections
Follow-up and Maintenance	• Pre-transplant oral health education • Ensure healing before transplantation • Implement structured preventive strategies	• Regular dental reviews every 6–12 months • Routine oral cancer screening (every 3 months for first 2 years, then every 6 months) • Reinforce oral hygiene education for long-term maintenance

This table provides a clear and structured overview of the key considerations for managing oral health in heart transplant recipients before and after the procedure.

Table 1.
Pre- and post-transplant oral health care for heart transplant recipients.

8. Post-transplant dental care protocols for preventing infections and oral diseases

Post-cardiac transplant patients require specialized dental care protocols to mitigate infection risks, manage immunosuppression-related complications, and promote optimal oral health. Immunosuppressive regimens used to prevent organ rejection, including calcineurin inhibitors (e.g., cyclosporine and tacrolimus) and corticosteroids, significantly elevate the risk of opportunistic infections, oral malignancies, and delayed wound healing. The balance between sufficient immunosuppression to prevent rejection and minimizing adverse effects such as infection and malignancy is crucial in post-transplant care [54, 61].

8.1 Immunosuppressive regimens and their impact on dental care

Following heart transplantation, patients undergo induction regimens that provide intense early post-operative immunosuppression, generally lasting 2–3 weeks. Maintenance regimens, which may include a combination of calcineurin inhibitors (cyclosporine A, tacrolimus, and sirolimus), antimetabolites (e.g., mycophenolate mofetil), and steroids, are then initiated [62]. Immunosuppressive therapy, particularly in the initial 3 months post-transplant, is associated with the highest risk for infections and complications. The risk of infection diminishes as the patient stabilizes and the immunosuppressive doses are reduced, usually over a period of 6–12 months [62].

8.2 Timing of dental care and protocols for management

During the first 6 months post-transplant, elective dental care should be avoided due to the heightened infection risk. If dental emergencies arise, these should be managed in a hospital setting, in close coordination with the patient's cardiac team. Dental professionals must be informed of the patient's medical status, including the frequency of cardiac team visits, the stability of immunosuppressant doses, and any recent rejection episodes. After the first 6 months, elective dental care may be considered, with the interval between visits increasing as the patient stabilizes [63].

8.3 Infection prevention and management

The post-transplant patient is particularly susceptible to opportunistic infections due to immunosuppressive treatment. Oral complications, including gingival hyperplasia, periodontal conditions, and infections such as candidiasis, are commonly observed. Early detection and treatment of infections are critical, as immunosuppressed patients may not present with typical symptoms. Dental professionals should maintain a high index of suspicion for infections and collaborate with the medical team to assess the need for prophylactic antibiotics, particularly if the patient is undergoing high-dose immunosuppressive therapy. For patients with severe neutropenia (neutrophil count $<1.0/\mu\text{l}$), antibiotic prophylaxis may be necessary [42, 64].

8.4 Management of oral conditions

Gingival hyperplasia is a common oral complication, especially in patients taking cyclosporine A (CsA), affecting up to 67% of transplant recipients. To manage this, dental professionals should work closely with the patient's cardiac team to consider alternative immunosuppressants, such as tacrolimus, which have a lower incidence of gingival hyperplasia. In addition to medication adjustments, regular periodontal care and reinforced oral hygiene are essential to minimize gingival complications and maintain oral health. Routine oral cancer screenings should begin 3 months post-transplant and continue every 3 months for the first two years, transitioning to 6-month intervals thereafter [61, 65].

Xerostomia management includes hydration, humidification, and salivary stimulation with sugar-free gum or lozenges [66]. Systemic sialagogues like pilocarpine (5 mg TID) and cevimeline (30 mg TID) stimulate muscarinic receptors, though side effects such as diaphoresis and cardiovascular risks necessitate caution [67, 68].

Topical therapies, including saliva substitutes and stimulants, offer adjunctive relief, with formulations like malic acid (1%) and mucin-based sprays improving lubrication [69]. Mucoadhesive tablets, lipid-based gels, and maltose lozenges may enhance minor salivary gland function [70, 71]. Medication adjustments, such as dose modification or substitution with less xerogenic alternatives, remain viable under physician supervision. Emerging approaches like intraoral electrostimulation (e.g., Saliwell Crown) and acupuncture show promise. Personalized treatment remains key to optimizing outcomes [71–73].

Management of oral candidiasis begins with a thorough clinical examination to confirm diagnosis and identify predisposing factors. First-line treatment involves topical antifungals such as nystatin (oral rinse, suspension, or pastilles) or clotrimazole troches, administered for two weeks while maintaining strict oral hygiene. Systemic antifungals, including fluconazole and itraconazole, are recommended for refractory cases, immunocompromised patients, or those at risk of systemic infection. Prophylactic antifungal therapy, particularly with fluconazole, reduces incidence in patients and those with recurrent infections. Maintaining proper oral hygiene, adjusting risk factors, and selecting appropriate antifungal therapy are crucial for effective management and prevention of recurrence [74–78].

8.5 Bleeding risks and anesthesia considerations

Patients on anticoagulants or antiplatelet agents, or those with myelosuppressive effects from immunosuppressants, may be at increased risk of bleeding. The dental

team should be familiar with the guidance, which recommends avoiding inferior alveolar nerve blocks when platelet counts are less than $30 \times 10^9/\text{L}$ and avoiding extractions with platelet counts below $50 \times 10^9/\text{L}$. Local hemostatic measures should be employed, and staged treatments may be necessary for higher-risk patients [56, 64]. Local anesthetics containing adrenaline should be used with caution due to the transplanted heart's hypersensitivity to catecholamines. It is recommended to use anesthetics such as prilocaine with felypressin to avoid exacerbating heart rate and cardiac output [79].

8.6 Coordination with cardiac teams

Given the complexity of post-transplant care, coordination with the cardiac team is paramount to ensure safe dental treatment. Monitoring immunosuppressant drug levels, managing medication interactions, and addressing potential side effects such as myelosuppression and increased infection risk are all critical components of post-transplant dental management. A collaborative approach allows for individualized care, reducing the likelihood of complications and ensuring patient safety [61].

8.7 Follow-up and maintenance

Regular dental reviews, ideally every 6–12 months, help detect new diseases and allow timely intervention. Pre- and post-transplant oral health education is essential to reducing long-term complications and maintaining systemic health. By implementing structured dental assessments and preventive strategies, the risk of severe post-transplant infections can be significantly minimized, ultimately improving patient outcomes [80] (Table 1).

9. Interdisciplinary collaboration in transplant care

Interdisciplinary collaboration is fundamental in the comprehensive care of heart transplant recipients. Coordinated efforts between dental professionals, cardiologists, transplant specialists, and other healthcare providers ensure early identification and management of oral health issues that may impact overall transplant success. The integration of dental care within transplant protocols not only mitigates the risk of post-transplant complications but also enhances patient outcomes through proactive prevention strategies. Heart transplant recipients face unique challenges due to lifelong immunosuppressive therapy, which increases susceptibility to infections, oral diseases, and systemic complications. The oral cavity serves as a significant entry point for infections, with poor oral health linked to bacteremia, endocarditis, and systemic inflammation, all of which can jeopardize transplant success. Consequently, interdisciplinary collaboration is essential to ensure the following: [81].

Pre-transplant planning: Early dental evaluations help identify and manage oral infections, reducing bacterial translocation risks before transplantation [61].

Post-transplant monitoring: Continuous oral health surveillance prevents opportunistic infections, gingival overgrowth, and oral malignancies due to immunosuppressive medications [82].

Personalized treatment approaches: Coordination among providers ensures tailored treatment plans based on the patient's cardiac status, medication regimen, and immune function [80].

9.1 Strategies for effective interdisciplinary collaboration

1. Establishing communication protocols: Regular case discussions between dental professionals and transplant teams help ensure timely interventions and shared decision-making.
2. Standardized oral health assessments: Implementing standardized pre- and post-transplant dental screenings ensures early detection of risk factors.
3. Education and training: Cross-disciplinary education programs enhance awareness among healthcare providers about the oral-systemic link in transplant patients.
4. Integrating dental care in transplant protocols: Including dental evaluations as a mandatory step in pre-transplant assessments ensures comprehensive patient care [61, 80, 82].

Case Studies and Clinical Insights (Collaborations among healthcare providers)

Case Study 1: Managing Gingival Overgrowth in a Transplant Recipient

A heart transplant recipient on cyclosporine therapy presented with severe gingival hyperplasia, leading to difficulty in maintaining oral hygiene. Collaboration between the transplant team and dental specialists resulted in a modification of the immunosuppressive regimen to tacrolimus, known for a lower incidence of gingival overgrowth. In conjunction with professional periodontal therapy, significant improvement was noted, reducing the risk of secondary infections.

Case Study 2: Preventing Bacteremia in a High-Risk Patient

A patient with a recent heart transplant required emergency dental treatment for an infected tooth. Given the high risk of bacteremia and systemic infection, the dental team consulted with the transplant specialist to implement prophylactic antibiotic coverage and perform the procedure in a hospital setting. The patient successfully underwent treatment without complications, underscoring the importance of interdisciplinary communication.

Case Study 3: Long-Term Oral Health Surveillance

A transplant recipient was referred for routine dental follow-up and exhibited early signs of oral candidiasis, a common complication in immunosuppressed patients. Immediate antifungal therapy was initiated, and adjustments to the patient's immunosuppressive regimen were made in collaboration with the transplant team. This early intervention prevented further complications and demonstrated the value of integrated care.

10. Future directions: Emerging technologies in oral health management

Advancements in dental technologies offer promising future directions for improving oral health outcomes in heart transplant recipients. Salivary diagnostics—non-invasive, rapid tests based on biomarker detection—can aid in early detection of systemic inflammation, infection, or even transplant rejection. Biomarkers like IL-6, CRP, and TNF- α in saliva may reflect systemic immune activity, allowing real-time monitoring without invasive procedures. These innovations not only hold promise for enhancing early detection and individualized care but also enable safer and more efficient monitoring—critical in this immunocompromised population.

10.1 Salivary diagnostics: A window into systemic health

Saliva has emerged as a powerful diagnostic fluid, capable of reflecting both oral and systemic conditions through non-invasive sampling. In heart transplant recipients, where immunosuppressive therapy increases vulnerability to infections, systemic inflammation, and graft complications, salivary diagnostics offer a convenient and cost-effective means of surveillance. Recent advances in salivary biomarker detection allow clinicians to monitor key inflammatory mediators such as interleukin-6 (IL-6), C-reactive protein (CRP), tumor necrosis factor-alpha (TNF- α), and matrix metalloproteinases (MMPs)—all of which are implicated in both periodontal disease and transplant-related inflammatory responses. Elevated levels of these markers in saliva have been linked to systemic inflammation and could serve as early indicators of complications such as infection, transplant rejection, or the onset of cardiovascular events.

10.2 Teledentistry: Expanding access and ensuring continuity of care

The COVID-19 pandemic has accelerated the adoption of teledentistry, highlighting its potential to deliver safe, accessible oral healthcare—particularly for immunocompromised individuals. Heart transplant recipients often face challenges attending in-person dental appointments due to travel restrictions, physical vulnerability, or fear of exposure. Teledentistry provides a viable alternative, enabling clinicians to conduct visual assessments, monitor healing, deliver oral hygiene instructions, and triage urgent issues. These technologies can enhance preventive care, reduce infection risks, and promote multidisciplinary coordination in transplant medicine.

10.3 Applications of teledentistry include

- Post-transplant monitoring of gingival hyperplasia, oral lesions, and healing of extraction sites
- Remote consultations with interdisciplinary teams to coordinate medication adjustments for oral side effects.
- Oral health education and behavioral coaching to improve compliance with preventive regimens.

Future research should investigate the integration of these technologies into transplant care pathways, exploring their impact on systemic inflammation, graft survival, and patient quality of life. More studies are also needed to examine how periodontal disease treatment could reduce heart transplant failures by decreasing systemic inflammation. Research should focus on the validation of salivary biomarkers in predicting transplant-related complications. Randomized controlled trials (RCTs) are needed to evaluate the effectiveness of personalized dental care protocols in reducing systemic inflammation and improving transplant survival outcomes.

11. Conclusion

In conclusion, the relationship between oral health and the overall health of heart transplant recipients is critical for optimizing transplant outcomes. Periodontal disease, as a chronic inflammatory condition, can exacerbate systemic inflammation, which is of particular concern for heart transplant patients who are immunosuppressed. This heightened risk underscores the need for regular dental assessments and the management of oral health to prevent complications such as infections, gingival hyperplasia, and systemic diseases like cardiovascular issues. While the literature on the oral health of heart transplant recipients is limited, existing studies suggest that these patients face unique challenges that necessitate tailored dental care protocols. Collaboration between dental professionals and the transplant team is essential to ensure early identification of oral health issues and reduce the risk of post-transplant complications. By integrating oral health care into the transplant process, both pre- and post-operatively, patients can benefit from improved systemic health and long-term transplant success. Given the high periodontal treatment needs and the established relationship between periodontal disease and systemic inflammation in heart transplant recipients, future research should focus on investigating the direct impact of oral health interventions on graft survival and overall transplant outcomes. Prospective longitudinal studies are needed to assess how periodontal therapy, preventive dental care, and improved oral hygiene practices influence systemic inflammation, cardiovascular health, and transplant success. Additionally, randomized controlled trials (RCTs) could provide valuable insights into the effectiveness of structured oral health programs in reducing post-transplant complications, particularly infections and cardiovascular events. Expanding research in this area will help develop evidence-based guidelines and reinforce the integration of dental care into routine transplant management, ultimately improving the long-term health of heart transplant recipients.

Conflict of interest

The authors declare no conflict of interest.

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*Edited by Chawannuch Ruaengsri,
Yasuhiro Shudo and Marc Leon*

Heart Transplant – Current Status and Recent Updates provides a comprehensive and up-to-date overview of one of the most complex and evolving fields in cardiovascular medicine. This volume examines the latest advancements in donor and recipient selection, surgical techniques, immunosuppressive therapies, and innovations in mechanical circulatory support, which are revolutionizing patient outcomes. Readers will gain insights into cutting-edge strategies for managing end-stage heart failure, optimizing transplantation success, and expanding the donor pool through novel preservation and utilization methods. The book highlights emerging trends, including personalized immunosuppression protocols, advances in artificial hearts, and innovative approaches to long-term care, providing clinicians, researchers, and healthcare providers with a valuable resource for enhancing patient care. Designed for professionals involved in cardiac transplantation and heart failure management, this volume emphasizes practical applications, evidence-based practices, and future directions that are shaping the future of heart transplantation. Whether you are seeking to refine your clinical approach, stay current with technological innovations, or deepen your understanding of the current landscape, this book provides a well-rounded and insightful guide to the most recent developments in the field. Unlock essential knowledge and discover how cutting-edge research and clinical practice are transforming the prognosis and quality of life for patients worldwide, making this an indispensable resource for anyone dedicated to advancing heart transplant care.

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