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Rejection Surveillance: Integrating Cell-Free DNA and Gene Expression Panels to Decrease Invasiveness in Routine Monitoring of Heart Transplant Recipients

REVIEW

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ABSTRACT

Post-transplant rejection surveillance remains a cornerstone of heart transplant care. Although endomyocardial biopsy has long been the gold standard for monitoring rejection, its invasiveness and limitations have driven innovations in noninvasive techniques. Molecular diagnostics, including gene expression profiling (GEP) and donor-derived cell-free DNA (dd-cfDNA), have emerged as promising alternatives with demonstrated utility. GEP excels in identifying immune activation with high negative predictive value, while dd-cfDNA provides insights into allograft injury, with sensitivity up to 81% and specificity of 85%. Complementary cardiac imaging such as echocardiography and cardiac magnetic resonance enhance graft assessment by providing structural and functional data. Together, these investigations offer a multimodal approach to rejection surveillance, reducing the frequency of endomyocardial biopsy and improving overall care for transplant recipients.

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INTRODUCTION

Heart transplantation is a life-saving intervention for patients with end-stage heart failure, but post-transplant rejection remains a critical challenge. Acute rejection occurs in approximately 12% of heart transplant recipients within the first year despite advancements in immunosuppressive therapies, and rejection episodes, if undetected or inadequately treated, can result in allograft dysfunction and compromise patient survival.[1-3] Endomyocardial biopsy (EMB) has long been the gold standard for rejection monitoring, offering direct histopathological insights into graft health.[4] However, EMB is an invasive procedure with inherent limitations related to interobserver variability in the grading of rejection and distinguishing between acute cellular rejection (ACR) and antibody-mediated rejection (AMR).[5,6] The advent of noninvasive diagnostic tools, such as gene expression profiling (GEP) and donor-derived cell-free DNA (dd-cfDNA), offers a promising alternative, reducing reliance on EMB while maintaining diagnostic accuracy. This review discusses the current state of post-transplant rejection surveillance, with a focus on integrating EMB with emerging molecular diagnostics and advanced imaging techniques to optimize patient outcomes.

ENDOMYOCARDIAL BIOPSY: THE TRADITIONAL GOLD STANDARD

EMB has been the cornerstone of rejection surveillance since the 1970s, and allows for the identification of cellular infiltration, an indicator of immune-mediated rejection.[4] In the postoperative period after heart transplantation, the procedure is performed frequently to ensure prompt detection and management of rejection episodes, and multiple samples should be collected to improve diagnostic accuracy.[7] The International Society for Heart and Lung Transplantation (ISHLT) histological grading criteria categorizes rejection into different grades in ACR based on the histological findings of inflammatory cellular infiltration and myocyte necrosis, whereas a defining feature of AMR is the activation of the complement system with C4d deposition in capillaries with microvascular inflammation and macrophages infiltration.[8]

However, the diagnostic accuracy for EMB remains limited due to sampling errors, interobserver diagnostic variability, and low sensitivity to detect ACR, as distinguishing between grade 1R from ≥2R rejection showed the greatest discrepancy, with only 28% concordance among pathologists.[5] The incidence of complications related to the invasiveness of EMB ranges between 1% to 10% of cases and may include ventricular perforation, cardiac tamponade, arrhythmias, and tricuspid valve injury.[6] The ISHLT guidelines emphasize EMB's continued role in monitoring symptomatic or high-risk patients for graft rejection in the first 5 years, but they acknowledge the growing utility of noninvasive modalities in stable low-risk recipients to reduce the frequency of performing EMB.[9]

TRANSPLANT SURVEILLANCE WITH NONINVASIVE TESTING

Emerging protocols utilizing GEP and dd-cfDNA have demonstrated efficacy in reducing reliance on EMB to detect graft rejection as soon as 14 days post-transplant and transition to exclusive noninvasive monitoring by 4 to 12 weeks post-transplant.[10,11] Conversely, other biomarkers, such as troponin, C-reactive protein, and brain nautreic-peptide, offer supplementary assessment of graft function but with low specificity and sensitivity.[12] Donor-specific antibodies are associated with an increased risk of AMR and graft dysfunction, and routine periodic monitoring is endorsed by the ISHLT guidelines.[9] However, it is not recommended to rely on donor-specific antibodies results alone to monitor rejection status due to their low specificity.[13]

Determining the suitability of noninvasive cardiac transplant surveillance relies on a careful assessment of individual patient characteristics. Patients with favorable donor-recipient matching, low pretransplant sensitization, and consistent immunosuppressant adherence are ideal candidates for noninvasive protocols. High-risk patients, including those with preformed donor-specific antibodies or adherence issues, still require periodic EMB for comprehensive evaluation. Therefore, the decision to employ a noninvasive protocol should be a collaborative one, involving the transplant team, and tailored to each patient's specific clinical circumstances, balancing the advantages of noninvasive monitoring with the need for effective and timely detection of complications. Table 1 summarizes advantages and disadvantages of the noninvasive tests.

GENE EXPRESSION PROFILING

GEP involves the collection of a peripheral blood sample from the transplant recipient, which is then analyzed for the expression levels of specific genes associated with immune activation. These gene sets are used to generate a gene expression score that reflects the likelihood of acute rejection. The AlloMap® test (CareDx), which was approved by the US Food and Drug Administration in 2008, became

one of the first validated GEP assays; it assesses the expression of a defined panel of 11 genes that have been associated with rejection and calculates a score that helps categorize patients into low, intermediate, or high risk for rejection. There are two randomized clinical trials that have demonstrated GEP non-inferiority to EMB for detecting ACR ≥ 2R, with a specificity of 73% and 89%.[14,15]

Different GEP thresholds are valid to exclude ACR based on timing post-transplant, since a score > 30 in the first 6 months post-transplant or a score of > 34 after 6 months post-transplant indicates a negative predictive value (NPV) of > 98%.[16] The ISHLT guidelines recommend GEP as a reliable alternative to routine EMB for ACR surveillance in low-risk, asymptomatic patients after 55 days post-transplant.[9] However, GEP utility is limited by confounders such as inflammation from non-transplant-related causes or presence of cytomegalo virus infection, receiving blood products, and the effects of immunosuppressive therapy when receiving prednisone doses more than 20 mg/day.[17,18]

DONOR DERIVED CELL-FREE DNA

Donor derived cell-free DNA, which are DNA fragments originating from the transplanted heart, are a valuable biomarker for detecting allograft injury as early as 14 days post-transplant.[20] Various methodologies exist for detecting and quantifying dd-cfDNA, with modern assays

FEATURE	DONOR-DERIVED CELL-FREE DNA (dd-cfDNA)	GENE EXPRESSION PROFILING (GEP)	DONOR-SPECIFIC ANTIBODIES (DSA)
Utility	Detects both ACR and AMR by measuring donor-derived DNA fragments in plasma	Evaluates immune activation by analyzing gene expression in PBMCs for ACR detection	Identifies AMR risk by detecting antibodies against donor HLA antigens
Sensitivity	Up to 81% for ACR and AMR detection	37.5-50% depend on study and threshold	Sensitivity varies widely for AMR detection
Specificity	85% specificity; NPV > 97% at thresholds > 0.15-0.2%	73-89% specificity; NPV > 98% for ACR ≥ 2R exclusion with score > 30	Low specificity; not reliable as a stand-alone test for rejection
Advantages	Noninvasive, sensitive, and specific, detects graft injury before clinical signs	Noninvasive, high NPV, widely available	Useful for AMR risk stratification; inexpensive and widely available
Disadvantages	Limited by cost, availability, and false positives due to ischemia or procedural trauma	Low sensitivity for AMR; influenced by infection, inflammation, and steroid use	Limited specificity, transient elevations may not indicate true rejection
Pitfalls in Results	False positives from ischemia, biopsy-induced injury, or infections; false negatives from chimerism	False positives due to infections, non-transplant-related inflammation, or high-dose steroids	False positives due to non-rejection immune responses; confounded by prior sensitization
Landmark Trials	GRAfT and D-OAR	CARGO, CARGO II, and IMAGE trials	
ISHLT 2023 guidelines recommendations	• GEP (ie, Allomap) of peripheral blood can be used in low-risk patients between 2 months and 5 years after HT to identify adult recipients who have low risk of current ACR to reduce the frequency of EMB (Class IIa, Level of Evidence: B) • After the first year, continued rejection surveillance (using a combination of noninvasive methods, GEP or EMB) is reasonable in patients at higher risk for late acute rejection (Class IIa, Level of Evidence: C) • Post-transplant monitoring for DSA should be performed at 1, 3, 6, and 12 months postoperatively and annually thereafter. Sensitized patients should be monitored more frequently (Class IIa, Level of Evidence: C)		

Table 1 Comparison of donor-derived cell-free DNA, gene expression profiling, and donor-specific antibodies for cardiac graft rejection. ACR: acute cellular rejection; AMR: antibody mediated rejection; PBMC: peripheral blood mononuclear cells; EMB: endomyocardial biopsy; NPV: negative predictive value; HLA: human leukocyte antigen; GRAfT: genomic research alliance for transplantation study; D-OAR: donor-derived cell-free dna-outcomes allomap registry; CARGO: cardiac allograft rejection gene expression observational study; IMAGE: invasive monitoring attenuation through gene expression study; eIMAGE: early invasive monitoring attenuation through gene expression study; ISHLT: International Society for Heart and Lung Transplantation

GEP/dd-cfDNA COMBINATION	D-OAR STUDY RESULT INCIDENCE	RESULT INTERPRETATION	CLINICAL IMPLICATIONS
Low GEP/low dd-cfDNA	56%	High probability that the patient does not have acute rejection ACR > 99% NPV AMR 98% NPV	Reduce frequency of scheduled EMB
High GEP/low dd-cfDNA	26%	Early ACR Consider potential reasons for false positive GEP such as CMV infection or changes in immunosuppression regimen	Check steroid dose and adherence Evaluate for active CMV infection. Repeat testing earlier than protocol
Low GEP/high dd-cfDNA	11%	Early cellular rejection Antibody-mediated rejection (AMR) Consider potential reasons for false positive dd-cfDNA such as myocardial injury and CAV	Repeat EMB Review ancillary tests, eg, echocardiogram, DSA, troponin, nt-proBNP
High GEP/high dd-cfDNA	6%	High probability that rejection injury is present (~20% PPV)	Rejection workup, including EMB, DSA, echocardiogram and consider cardiac MRI

Table 2 Interpretation of gene expression profiling and donor-derived cell-free DNA (dd-cfDNA) results from the D-OAR Study Cohort. ACR: acute cellular rejection; AMR: antibody mediated rejection; EMB: endomyocardial biopsy; NPV: negative predictive value; PPV: positive predictive value; D-OAR: donor-derived cell-free dna-outcomes allomap registry; CMV: cytomegalo virus; CAV: cardiac allograft vasculopathy; DSA: donor-specific antibodies; NT-proBNP: N-terminal pro-brain natriuretic peptide

such as AlloSure® and Prospera® (Natura) using next-generation sequencing that provides high sensitivity and specificity.[21-23] There are no randomized trials comparing dd-dd-cfDNA to EMB, although large observational trials have consistently showed NPV > 97%, making it the ideal rule-out test.[19-21] Defining an abnormal dd-cfDNA result differs across laboratories and transplant programs, as previous trials have used different cut-offs to improve specificity and/or sensitivity to detect rejection. A median threshold of > 0.2% resulted in 44% sensitivity to detect rejection,[20] and alternative assays showed that a lower threshold of > 0.15% offers 78.5% sensitivity to detect rejection while maintaining an NPV > 97%.[21] Additionally, if dd-cfDNA and GEP yield discordant results with elevated GEP score and negative dd-cfDNA, it is more likely for EMB to show absent markers of rejection, suggesting higher specificity for dd-cfDNA.[23]

In the context of negative markers of rejection with EMB, elevated dd-cfDNA results may identify higher risk individuals with impending allograft dysfunction and warrant more aggressive surveillance and management.[20,21] Postoperative cardiac transplant recipients have elevated dd-cfDNA levels due to ischemia-reperfusion injury, therefore the test is recommended to be first performed at least 2 to 4 weeks post-transplant.[10,11] dd-cfDNA results may also be falsely elevated in the context of cardiac ischemia or injury due to EMB, and samples should be drawn prior to or 48 hours post EMB. Other situations such as donor-recipient chimerism, infections, malignancy, race, and pregnancy status affect the test accuracy.[23,24]

INTERPRETATION OF NONINVASIVE TESTS POST-CARDIAC TRANSPLANT SURVEILLANCE

The combined use of GEP and dd-cfDNA offers a more comprehensive picture than either test in isolation, and the integration of both tests strengthens the diagnostic capabilities and allows for a more nuanced interpretation. However, the optimal strategy for combining these data remains an area of ongoing research. Different weighting schemes and algorithms for combining the data might be necessary depending on the specific assays used and the characteristics of the patient population. Whereas a negative dual molecular testing may decrease the frequency of EMB, positive results in heart transplant recipients may trigger increased surveillance, including more adjuvant testing and potentially EMB.[25] Table 2 summarizes the clinical implications of noninvasive test results.

It is also crucial to emphasize that positive results do not automatically equate to rejection due to multiple confounders, which may affect false positive results. However, it is unknown if a positive dual molecular testing result would warrant adjustments to immunosuppression therapies without EMB, as the presence of circulating dd-cfDNA may represent a form of sub-clinical graft injury, and further research is still needed. The adoption of routine use of dd-cfDNA in Europe and the rest of the world outside of the United States remains a challenge, limited by regulatory, financial, and logistical challenges. Ongoing studies enrolling patients in these regions may improve global availability.[26]

UTILIZATION OF CARDIAC IMAGING FOR CARDIAC TRANSPLANT SURVEILLANCE

Cardiac imaging is crucial for assessing post-transplant graft function and outcomes. Echocardiography serves as a foundational tool in the immediate postoperative period for evaluation of left and right ventricular systolic function, any mechanical complications, or pericardial disease.[27] Periodic transthoracic echocardiography surveillance for graft dysfunction is recommended by the ISHLT in low-risk cases where EMB is not possible, and presence of worsening left ventricular ejection fraction (LVEF) warrants further evaluation with EMB.[9] However, the severity of histopathological rejection stage on EMB does not correlate with change or drop in LVEF.[28] Other echocardiographic signs may detect graft dysfunction preceding changes in LVEF, such as impaired tissue relaxation and worsening diastolic function.[29]

Echocardiographic strain imaging offers higher specificity to evaluate segmental graft function, where a global longitudinal strain value of less than -15.5% and right ventricle free wall strain value more negative than -17% can exclude the presence of ACR degree ≥ 2R with 98.8% negative predictive value.[30] Additionally, dobutamine stress echo is recommended in the ISHLT guidelines to evaluate for cardiac allograft vasculopathy to alternate with coronary angiography in low-risk patients.[9]

Cardiac magnetic resonance (CMR) imaging, considered the gold standard for tissue characterization, identifies inflammation, edema, and fibrosis using T1/T2 mapping and late gadolinium enhancement.[31] T2 mapping with a cut off value exceeding 55 milliseconds is more sensitive than other CMR tissue characterization techniques for detection of acute graft rejection, with 86% sensitivity and specificity.[32] In a randomized noninferiority trial involving 40 heart transplant recipients, CMR demonstrated high diagnostic accuracy (93% sensitivity, 92% specificity, and 99% NPV) for detecting ACR, and the CMR group had fewer hospitalizations and infections compared with the EMB control group.[33] The ISHLT guidelines suggest performing CMR for graft rejection evaluation in the context of absent or low histopathological EMB findings with abnormal graft function.[9]

The role of other imaging modalities such as computed tomography angiography and nuclear imaging have limited use in detecting rejection and could be used for screening and detection of cardiac allograft vasculopathy.[34] Positron emission tomography measures myocardial flow reserve, which is a strong prognostic indicator of cardiac allograft vasculopathy, and can detect microvascular dysfunction before the development of significant epicardial coronary artery disease.[35,36]

CONCLUSION

The integration of molecular diagnostics and imaging into post-transplant rejection surveillance offers a less invasive, more patient-centered approach. While EMB remains crucial for high-risk patients, tools such as GEP and dd-cfDNA enhance diagnostic accuracy and reduce procedural risks. Multimodal strategies combining these tools with advanced imaging techniques will continue to improve outcomes for heart transplant recipients.

KEY POINTS

- Endomyocardial biopsy (EMB) is indispensable for cases where rejection is suspected due to clinical instability or graft dysfunction.
- In low-risk stable patients, a tailored approach to pursue noninvasive testing can reduce the frequency of performing EMB and its associated complications.
- Gene expression profiling is ideal for ruling out acute cellular rejection (ACR) in asymptomatic low-risk patients. However, it is not validated for antibody-mediated rejection (AMR).
- Donor-derived cell-free DNA can be used as an adjunct to EMB in low-risk settings with high sensitivity and specificity for detecting both ACR and AMR.

COMPETING INTERESTS

The authors have no competing interests to declare.

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