Chapter 8

The Role of Echocardiography in the Management of Patients Undergoing a Ventricular Assist Device Implantation and/or Transplantation

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Abstract

Heart transplantation (HTx) is a curative treatment for patients with advanced heart failure (HF); however, since transplant opportunities are severely limited due to donor shortage, the left ventricular assist device (LVAD) has become a standard therapy for patients awaiting HTx. The role of echocardiography as a primary imaging modality to monitor the allograft function in transplant recipients as well as to optimize LVAD settings in LVAD recipients has been expanding. The purpose of this review is to highlight the clinical role of echocardiography in the management of patients undergoing LVAD implantation and/or HTx. In particular, we overview (1) how to detect LVAD malfunction and device-associated complication in LVAD recipients and (2) echocardiographic assessments of cardiac allograft rejection in transplant recipients.

Keywords: heart failure, transplant, rejection, ventricular assist device, echocardiography

1. Introduction

Heart transplantation (HTx) provides considerable survival benefits for patients with end-stage heart failure, but it is available for only a small fraction of such patients all over the world due to donor shortage [1]. Therefore, many heart transplant candidates require long-term support by a left ventricular assist device (LVAD) while they await transplantation [1, 2]. More recently, mechanical circulatory support has evolved into a standard therapy for patients with advanced heart failure, not only as a bridge to cardiac transplantation but also as a destination therapy or a bridge to myocardial recovery [3].

Echocardiography is a primary imaging modality in the assessment of cardiac structure and function in patients with advanced HF. In addition, echocardiography can be performed at the patient's bedside, and results are immediately available. In this review, we highlight the effectiveness of echocardiography in the management of patients undergoing LVAD implantation and/or HTx.

2. Echocardiography in LVAD recipients

A growing number of heart transplant candidates require long-term support by an LVAD while they await cardiac transplantation. Further, LVAD therapy has become a standard therapy for patients with advanced HF, not only as a bridge to cardiac transplantation but also as a destination therapy or a bridge to myocardial recovery. Here, we focused on the usefulness of echocardiography in patients undergoing LVAD implantation.

2.1. Preoperative assessment

It is important to assess the LVAD eligibility and rule out any contraindications against LVAD surgery prior to an operation. Several structural issues that can be surgically corrected at the time of LVAD implantation should be carefully evaluated prior to the LVAD surgery. The presence of clots, especially at the apex, should be carefully assessed because it will increase the risk of inflow cannula obstructions and/or perioperative stroke. Intracardiac shunts, including patent foramen ovale, should also be carefully assessed before and during surgery. Intracardiac shunts must be closed at the time of LVAD surgery. Further, coexisting valvular heart disease should be assessed prior to the LVAD procedure. Concomitant valvular surgery can be performed at the time of LVAD implantation; however, although such an additional approach can provide possible benefits, data regarding its long-term effect are limited, and the indications are still controversial. Another important issue to be carefully evaluated preoperatively includes right ventricular (RV) function because right ventricular failure (RVF) after LVAD placement is associated with increased morbidity and mortality.

2.1.1. Preoperative valvular assessment

Regarding tricuspid regurgitation (TR), several previous papers have revealed that tricuspid annular dilatation is highly associated with post-LVAD right ventricular failure [4]. Kukucka M et al. reviewed 122 patients without significant TR at the time of VAD implant and found that a tricuspid annulus diameter >43 mm was an independent predictor of survival after LVAD (**Figure 1**). On the other hand, whether the TR should be surgically managed at the time of LVAD surgery is controversial. Dunlay et al. performed a literature search of randomized controlled trials and observational studies (including 3249 patients) that compared the outcome of concomitant tricuspid valve surgery at the time of LVAD with that of LVAD alone [5]. They found that the addition of valvular surgery at the time of the LVAD procedure

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prolonged cardiopulmonary bypass times by an average of 31 minutes, but no differences were found between the groups for acute renal failure, early mortality, or the need for a right ventricular assist device. Having said that, a recent paper from Columbia University suggested that concomitant tricuspid valve procedures at the time of LVAD surgery can be performed safely and protect against worsening tricuspid regurgitation during the first two years of support [6]. In either case, the severity of TR and annular size need to be assessed preoperatively. Surgeons should also bear in mind that preexisting severe TR, especially with annular size >43 mm, is at higher risk of adverse events after surgery.

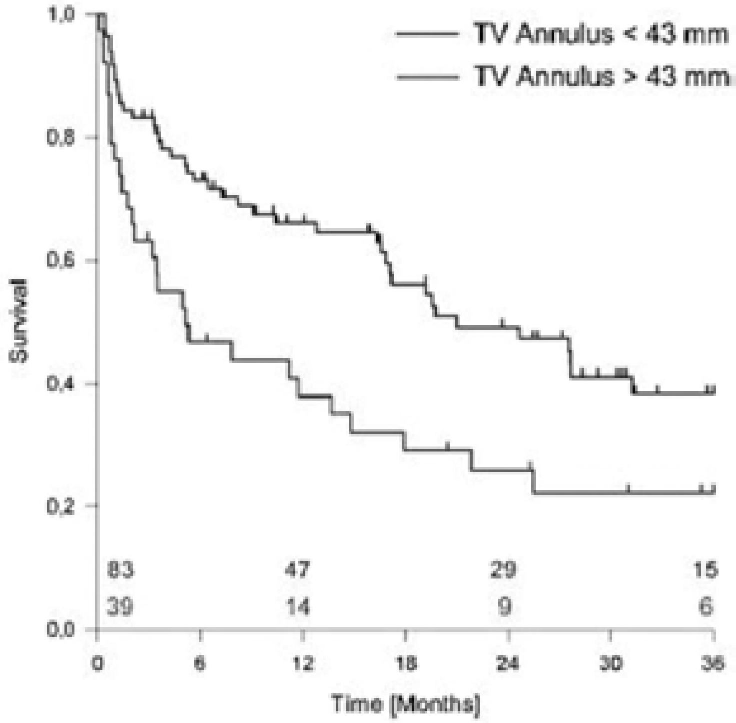

Figure 1. The impact on tricuspid valve annulus dilation on post-LVAD survival (quoted from Ref. [4]). Kaplan-Meier survival curves of patients with tricuspid valve (TV) annulus diameter <43 mm (blue) and >43 mm (red). Censored patients are represented by vertical marks. Numbers of patients at risk at 0, 12, 24, and 36 months of follow-up are presented above the x-axis (log-rank test, $p = 0.007$).

Aortic insufficiency (AI) occurs in up to 50% of patients within 1 year after continuous flow LVAD implantation. Although de novo AI can be commonly seen postoperatively, the presence of more than mild AI as well as any structural abnormality, as detected by transthoracic echocardiography (TTE), should be reported to the LVAD surgery team. In cases with poor TTE images, the results derived from intraoperative transesophageal echocardiography (TEE) should be carefully discussed. The valvular morphology, valvular calcification, possible fusion, and myxomatous changes should also be reported to the surgeons. The recently published comprehensive review of AI post-LVAD by Cowger et al. suggested the importance of intraoperative TEE to detect unmasked AI [7]. During the initiation of continuous flow LVAD support, as LV filling pressures drop with early unloading, the gradient between the aortic root and the LV increases, potentially exposing significant AI that was previously unrecognized. Because AI severity can be associated with an increase in pump speeds, we can quantitatively assess AI severity at different pump speeds to consider the necessity of concomitant aortic valve surgery in an operating room. This review summarized the risk and benefits of aortic valve surgery at the time of LVAD (**Table 1**).

Strategy	Pros	Cons
Partial closure with a single central stitch (Park's stitch)	• Simple and effective when the leaflet tissue has adequate tensile strength to hold sutures • Permit blood ejection through the aortic valve	• Questionable durability • Risk of progression to aortic stenosis • Need for AVR in the event of myocardial recovery leading to LVAD explant
Modified Park's stitch—additional pledgeted mattress suture between the central stitch and each commissure	• Relatively simple and can be effective, even if leaflets are thin • Permits blood ejection through the aortic valve but could be reduced compared to single central stitch	• Questionable durability • Risk of progression to aortic stenosis • Need for AVR in the event of myocardial recovery leading to LVAD explant
Complete closure of the ventriculo-aortic juncture with a circular patch	• Simple with relatively fast repair time • Long-term durability	• No blood ejection through the aortic valve • Risk of thrombus formation • Risk of death in the case of pump stoppage or failure
Replacement of incompetent aortic valve with bioprosthetic valve	• Maintenance of valve opening in the postoperative period • Testing for cardiac recovery • Tolerance to exercise	• Increase CPB and cross-clamp time • Risk of leaflet fusion • Risk of valvular and subvalvular thrombus formation due to fresh suture lines combined with decreased flow across the new valve

Table 1. Pros and cons of surgical management strategies of the native aortic valve (quoted from Ref. [7]).

Mitral valve insufficiency has fewer effects on postoperative outcome compared with aortic and tricuspid valve insufficiency. Indeed, a significant number of patients who had severe mitral regurgitation due to annulus dilatation and tethered pupillary muscle preoperatively showed a remarkable decrease in mitral regurgitation flow under LVAD support [8]. Although mitral valve surgery at the time of LVAD implant to correct severe mitral regurgitation does not affect postoperative mortality or cause other adverse events, the procedure can be considered in cases undergoing an LVAD procedure as a bridge to recovery. In addition, concomitant mitral valve repair can decrease pulmonary vascular resistance [9]. Kitada et al. investigated preoperative echocardiographic features associated with persistent mitral regurgitation after LVAD implantation (**Figure 2**) [10]. They found that the posterior displacement of the coapta-

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tion point of a mitral leaflet (30 vs. 24 mm), papillary muscle distance (49 vs. 43 mm), and tethering area (353 vs. 299 mm^2) before surgery were greater in patients who had persistent moderate to severe mitral regurgitation post-LVAD than those in patients who did not have significant MR postoperatively. A multivariate analysis showed that the posterior displacement was the only independent predictor for persistent MR.

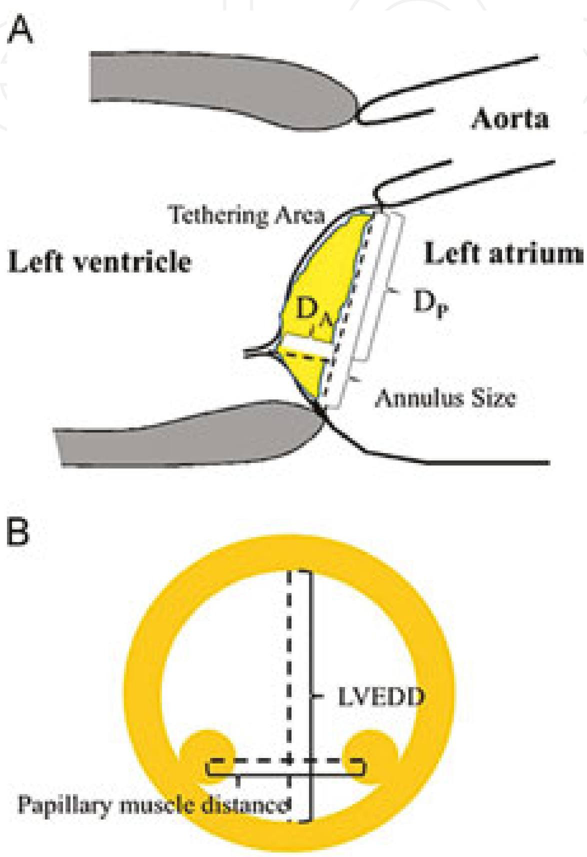

Figure 2. The measurements of echocardiographic parameters to quantify the mitral leaflet configurations in 2D echocardiography (quoted from Ref. [10]). DA, apical displacement; DP, posterior displacement; LVEDD, left ventricular end diastolic dimension.

2.1.2. Preoperative and perioperative right ventricular assessment

Right ventricular failure (RVF) remains a major cause of morbidity and mortality following LVAD surgery. The incidence of RVF post-LVAD is 10–30% despite the recent improvements in device technology and postoperative patient management. Under LVAD support, right ventricular (RV) preload increases as a result of increased circulatory volume, whereas RV afterload is expected to decrease, secondary to improvement in pulmonary vascular resistance [11]. A sepal wall shift induced by LVAD alters the RV structure, which may worsen RV contractile and relaxation abnormalities. Therefore, when considering RV systolic and diastolic reserve before and also after surgery, it is important to identify which patients may need RV-specific mechanical and medical support post-LVAD [12].

Study	Patients	RVF definition and rate	Multivariable predictors	Echocardiographic RV parameters considered
Michigan RV failure risk score (2008)[a]	197 LVADs 28 CF-LVAD 94% BTT	Need for RVAD/ inotropes RVF rate: 35%	Preoperative vasopressors (4 pts) AST ≥80 IU/L (2 pts) Bilirubin ≥2.0 mg/dL (2.5 pts) Creatinine ≥2.3 mg/dL (3 pts)	RV systolic function (visual semiquantitative) TR (visual semiquantitative)
Penn RVAD risk score[b] (2008)	266 LVADs 6 CF-LVAD BTT vs. DT not reported	Need for RVAD RVF rate: 37%	Cardiac index ≤2.2 L/min/m^2 RVSWI ≤0.25 mm Hg × L/m^2 Severe RV dysfunction Creatinine ≥1.9 mg/dL Prior cardiac surgery Systolic BP ≤96 mm Hg	RV systolic function (visual semiquantitative)
Utah RV risk score[c] (2010)	175 LVADs 25 CF-LVAD 58% BTT, 42% DT	Need for RVAD/ inotropes/ inhaled NO RVF rate: 44%	DT indication (3.5 pts) IABP (4 pts) PVR (1–4 pts) Inotrope dependency (2.5 pts) Obesity (2 pts) ACEI or ARB use (−2.5 pts) β-blocker use (2 pts)	Right atrial area
Kormos[d] (2010)	484 LVADs All CF-LVAD BTT 100%	Need for RVAD/ inotropes RVF rate: 20.2%	CVP/PCWP >0.63 (OR, 2.3) Need for preoperative ventilator support (OR, 5.5)BUN >39 mg/dL (OR, 2.1)	None
Pittsburgh Decision Tree[e] (2012)	183 LVADs 40 CF-LVAD BTT vs. DT not reported	Need for RVAD RVF rate: 15%	Age, heart rate, transpulmonary gradient; right atrial pressure; INR, white blood cell count, ALT, number of inotropic agents	None
CRITT[f] (2013)	167 LVADs, all CF-LVAD 51 BiVADsBTT vs. DT not reported	Need for BiVAD RVF rate: 23%	CVP >15 mm Hg (C) Severe RV dysfunction (R) Preoperative intubation (I) Severe TR (T) Heart rate >100 (tachycardia [T])	RV systolic function (visual semiquantitative) Severe TR (visual semiquantitative)

ACEI, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; BiVAD, biventricular assist device; BP, blood pressure; BTT, bridge to transplantation; BUN, blood urea nitrogen; CF, continuous flow; CRITT, central venous pressure-RV dysfunction-preoperative intubation-severe tricuspid regurgitation-tachycardia; CVP, central venous pressure; DT, destination therapy; IABP; intra-aortic balloon pump; INR, international normalized ratio; ITT, intention to treat; LVAD, left ventricular assist device; NO, nitric oxide; OR, odds ratio; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RV, right ventricle; RVAD, right ventricular assist device; RVF, right ventricular failure; RVSWI, right ventricular stroke work index; and TR, tricuspid regurgitation.
The data were obtained from the following papers: (a) Matthews JC, et al. J Am Coll Cardiol. 2008;51:2163–2172; (b) Fitzpatrick JR III, et al. J Heart Lung Transplant. 2008;27:1286–1292; (c) Drakos SG, et al. Am J Cardiol. 2010;105:1030–1035; (d) Kormos RL, et al; HeartMate II Clinical Investigators. J Thorac Cardiovasc Surg. 2010;139:1316–1324; (e) Wang Y, et al. J Heart Lung Transplant. 2012;31:140–149; (f) Atluri P, et al. Ann Thorac Surg. 2013;96:857–863.

Table 2. Clinical risk prediction scores for right ventricular failure in left ventricular assist device recipients (quoted from Ref. [13]).

Table 2 summarizes the clinical risk prediction scores that have been cited in the recently published review literature [13]. In addition to these risk scores, serial echocardiographic assessments are helpful in evaluating RV functional reserve prior to surgery. Previously reported echocardiographic parameters associated with the risk for developing RVF after LVAD implantation have included tricuspid annular dilation (>43 mm) [4], tricuspid annular motion (8 vs. 15 mm) [14], and RV-to-LV end-diastolic diameter ratio (>0.72) [15]. However, it is sometimes technically difficult to obtain ideal RV images that allow quantitative assessments of patients with advanced heart failure, particularly if the patients are severely congested, intubated, and/or have a markedly enlarged left ventricle (LV) that obscures the right ventricle (RV) [16]. Kato et al. focused only on left-sided 2D echo parameters that can predict RVF post-LVAD. They showed that patients with relatively small LV size, preserved LV contraction, and a dilated left atrium were at higher risk for RVF after LVAD surgery (**Figure 3**) [16]. In addition to the conventional echo parameters, Grant et al. reported that the incremental role of RV strain to predict RVF [17]. More recently, Kato et al. reported that serial echocardiograms using tissue Doppler imaging (TDI) and speckle tracking echocardiography (STE) before and soon after (within 72 hours) LVAD surgery may aid in identifying the need to initiate targeted RVF-specific therapy [12]. In this study, RV stiffness (as reflected by TDI-derived E/E′) and decreased RV contractility (as reflected by TDI-derived S′ and RV longitudinal strain) before and soon after LVAD surgery were found to be useful parameters to include in the perioperative management of LVAD patients (**Figure 4**).

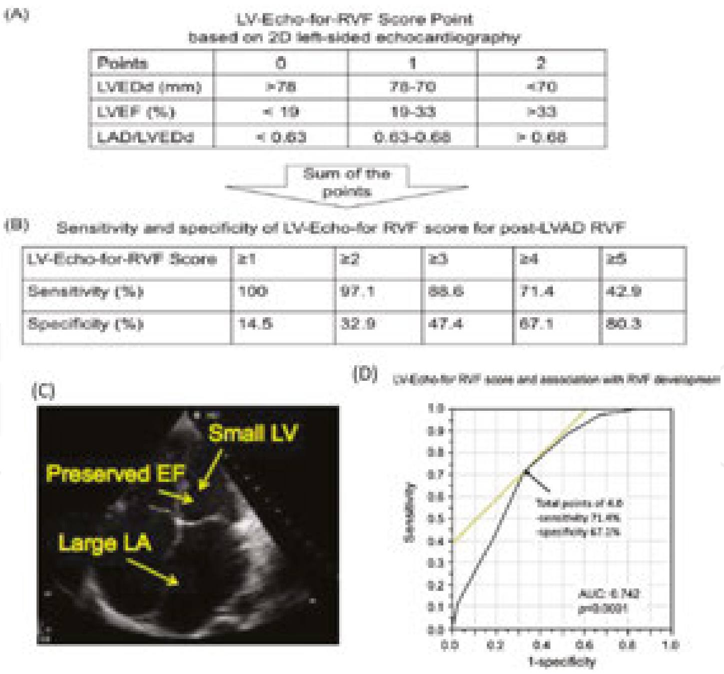

Figure 3. Left ventricular echocardiographic right ventricular failure score (LV-for-Echo-RVF) based on two-dimensional echocardiographic left-sided heart parameters (quoted from Ref. [16]). (A) Points associated with value of each variable. (B) Sensitivity and specificity of sum of points associated with right ventricular failure development after left ventricular assist device placement. (C) Representative 2D echo images in patients developing RVF post-LVAD. (D) Receiver operating characteristics curve for LV echocardiographic RVF score. AUC, area under the curve.

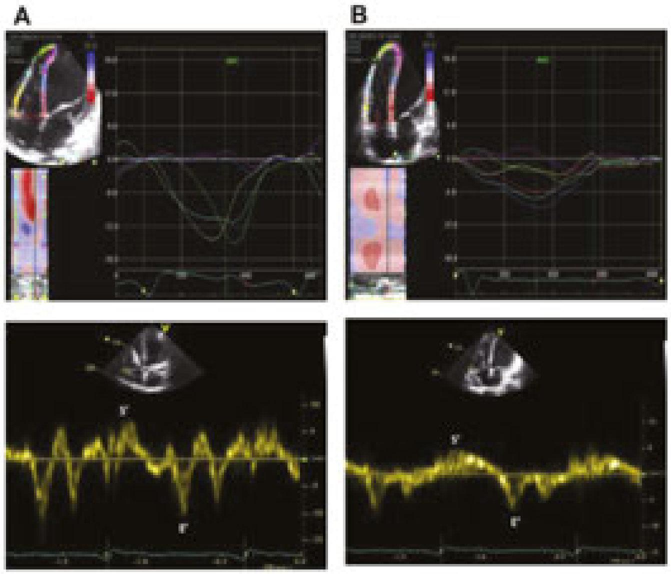

Figure 4. Representative global RV longitudinal strain and TDI obtained before surgery from a patient without RVF after LVAD and from a patient with RVF after LVAD (quoted from Ref. [18]). (A) The right ventricular (RV) global longitudinal strain; tissue Doppler image (TDI)-derived S′ and E′ for patient A was −14.3%, 7.8 cm/s and −10.8 cm/s, respectively. (B) These parameters were −6.2%, 4.6 cm/s and −5.3 cm/s, respectively. LVAD, left ventricular assist device; RVF, right ventricular failure.

2.2. Perioperative assessment

Other than the speed adjustment to avoid RV failure due to excessive RV preload by LVAD support, several important points should be evaluated by intraoperative TEE. First, de-airing of the heart chamber should be confirmed. Careful observation of trapped air at the site of anastomosis sites and around the LVAD inflow/outflow cannula is required [18]. Second, adjusting LV speed to maintain appropriate LV unloading without a septal shift under TEE guidance is required. The positioning of the inflow cannula at the apex should be monitored by TEE as well. Third, as mentioned above, the existence of valvular diseases and intracardiac shunts, which can be corrected simultaneously at the time of LVAD implantation, should be communicated to the surgeons. Finally, pericardial effusion and its amount should also be carefully observed by TEE. Cardiac tamponade can occur relatively often because patients under LVAD support require sufficient anticoagulation soon after surgery to prevent clot formation at the cannula and inside the device.

2.3. Postoperative assessment

Table 3 illustrates the checklist that will help sonographers/echocardiologists to perform an LVAD echo. In general, we can simply summarize the purposes of echo in LVAD recipients as follows: (1) to carefully monitor device malfunction, (2) to adjust appropriate LVAD setting/speed (appropriate peripheral perfusion and RV preload), and (3) to evaluate myocardial recovery and to seek optimal timing for LVAD weaning.

The points to be evaluated by TEE on a periodic basis are as follows: the location and thrombus at the inflow cannula; LV cavity diameters; septal position; RV function; valvular regurgitation, especially about the aortic valve opening/intervals and regurgitation.

View	Points to be checked
Parasternal views	• LV dimensions (ensure they are taken on axis) • AV opening (long acquisitions, use long and short axis, and M-mode) • Mitral regurgitation (tethering is the hallmark of functional regurgitation, and the degree may change according to LVAD rpm) • Consider evaluating cardiac output through RV out flow
Apical views	• Evaluate LV and RV function • Evaluate inlet cannula flow (position and suctioning) • Rule out thrombus in LV, RV, LA, and RA (use contrast as needed) • Evaluate aortic regurgitation
Image the inlet cannula	• Use multiple views including nonstandard • Rule out thrombus or other cause of obstruction (use contrast as needed) • Positioning (against LV wall)

Table 3. Echo LVAD checklist.

2.3.1. General postoperative assessment in LVAD recipients

Recommendations for device speed adjustment include the target measures of mean arterial pressure above 65 mmHg, maintaining the position of interventricular septum and shape, and intermittent aortic valve opening, under the condition of no more than mild mitral regurgitation to ensure appropriate unloading of the LV. Optimization of speed settings is extremely important to prevent several of the key complications associated with chronic LVAD support. The importance of ensuring the middle septal position for optimal RV function has been well established [19, 20].

Serially monitoring the timing and its interval of aortic valve opening in all LVAD recipients are necessary. Also, adjusting the LVAD speed to maintain the aortic valve opening is important to prevent the development of aortic valve regurgitation. At least 10 cardiac cycles should be recorded to evaluate the aortic valve opening. Because the interval of aortic valve opening, LV diameter, and grade of MR entirely depend on the degree of LV unloading, the LVAD setting together with the echo report needs to be recorded (**Figure 5**). Aortic regurgitation is sometimes seen with atypical timing (**Figure 6**) or continuously, both during the diastolic and systolic phases [21].

Cardiac output using RV outflow-derived Doppler estimation can be calculated as follows: cardiac output = stroke volume × heart rate, stroke volume = $\pi \times (\text{RV outflow diameter}/2)^2 \times$

time velocity integral at RV outflow. In patients who have at least an intermittent aortic valve opening, RV cardiac output minus LV outflow-derived cardiac output is equivalent to the estimated pump flow.

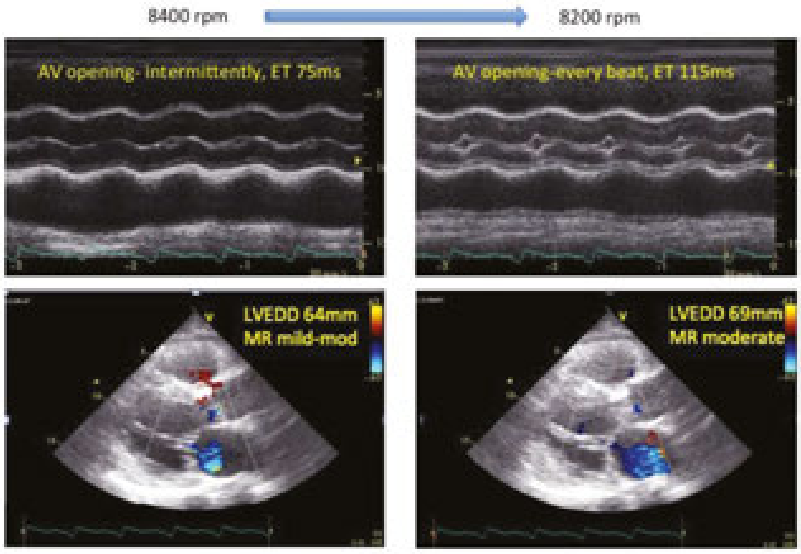

Figure 5. Representative images in a LVAD recipient with different LVAD speeds. This patient received HeartMate II (Thoratec Corp) implantation. Under 8400 rpm, the aortic valve opened intermittently, and the ejection time was only 75 ms. When we set the speed down to 8200, the aortic valve opened every beat, but due to less unloading, the LV diameter increased and the amount of mitral regurgitation also increased.

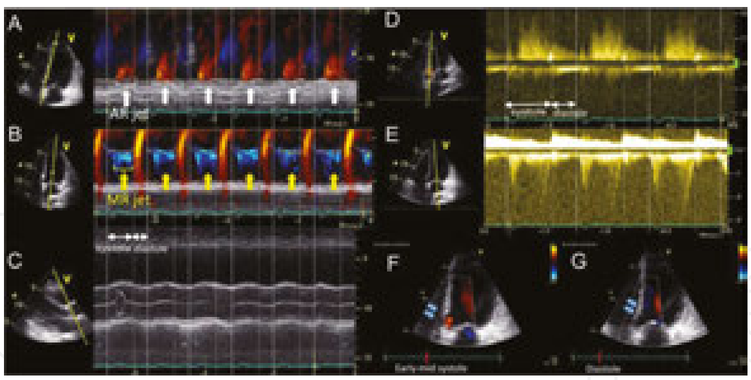

Figure 6. Aortic regurgitation during systolic phase accompanied by mitral regurgitation in patients with a continuous-flow left ventricular assist device (quoted from Ref. [22]). Echo images obtained from a patient undergoing LVAD implantation who showed systolic-phase aortic regurgitation (AR). The timing of the regurgitation jet started at the mid-systolic phase and ended at the early diastolic phase (A). The AR occurred slightly after the onset of mitral regurgitation (MR) (B), and both MR and AR timings were consistent with the systolic phase. No remarkable AR jet was documented during the diastolic phase. The AV was mostly closed throughout the cycles, which opens once every 8–10 beats (C). The mean pressure gradients of the trans-AV and trans-mitral valve based on the continuous wave Doppler measurements of AR (D) and MR flow (E) were 3.7 and 24.3 mmHg, respectively. The morphology of AV annulus changes through the cycles irrespective of the AV opening, with the AV annulus abnormally distorted and dilated during early mid-systole (F), whereas the septum wall as well as the AV annulus edge slightly pushed toward the LV during diastole (G).

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Serial assessments of pulmonary artery pressure by Doppler-derived TR pressure gradients are also important. In general, LVAD support can successfully unload LV, which results in the correction of pulmonary hypertension due to left-sided heart failure. However, some patients have showed residual pulmonary vascular resistance post-LVAD; therefore, echo-guided optimal medical therapy, including the necessity of pulmonary dilators such as PDE5 inhibitors (sildenafil®, etc.), is required.

2.3.2. Detection of LVAD malfunction

The careful observation of the inflow cannula is critically important. By using multiple views, including nonstandard ones, the thrombus or other causes of obstruction should be ruled out. The direction of the inflow cannula should also be reported. The direction may sometimes change after the surgery and direct toward the lateral wall, which may cause suctioning or inadequate LVAD support. Contrast echocardiography can provide additional information. Detecting the outflow cannula obstruction by echocardiography is difficult, but practitioners should try to find a good echo window and investigate any abnormality, including kinking (**Figure 7**) [22, 23].

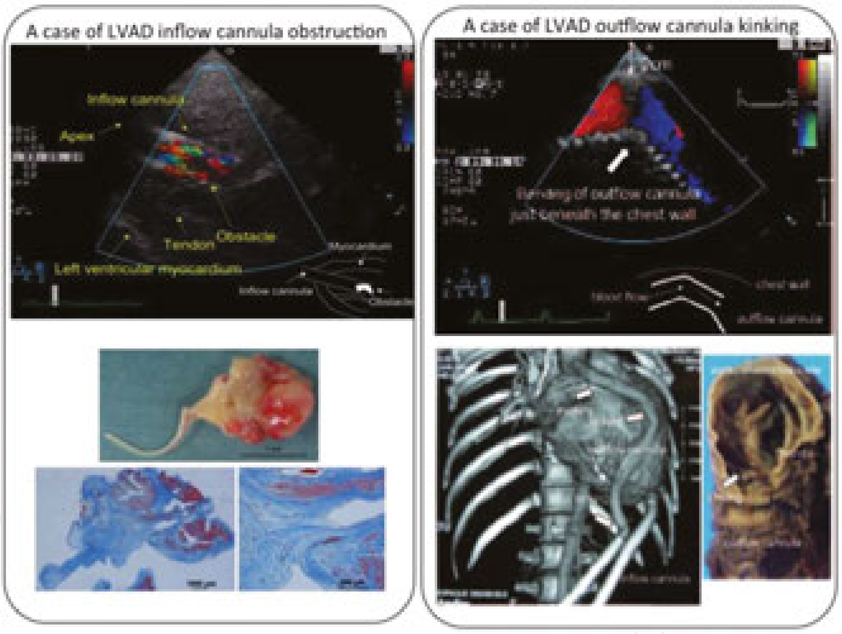

Figure 7. Cases of LVAD malfunction detected by echocardiography (quoted from Refs. [23, 24]). Left: A 29-year-old male developed low output syndrome 5 months after LVAD implantation. Echocardiography revealed pendulating obstacles at the inflow cannula of the LVAD. The obstacle was removed surgically, which histologically turned out to be myocardium with fibrous tissue and thrombi. Right: A 53-year-old man undergoing LVAD implantation developed low output syndrome. Echocardiography indicated distortion of the outflow cannula of the LVAD. A 3D CT also showed the kinking of the cannula. The autopsy revealed thrombus at the kinking site.

The protocol for a ramp study was established by Uriel N [20]. It is useful in optimizing LVAD settings and in diagnosing device malfunctions. Ramp test echocardiography can be performed at the time of discharge for speed optimization and/or if device malfunction is suspected (**Figure 8**) [24]. The patient's left ventricular size, the frequency of the aortic valve opening, valvular insufficiency, blood pressure, and continuous flow-LVAD parameters should be recorded according to the increments of the device speed. Serial assessments of ramp tests are also helpful to detect LVAD clots [24].

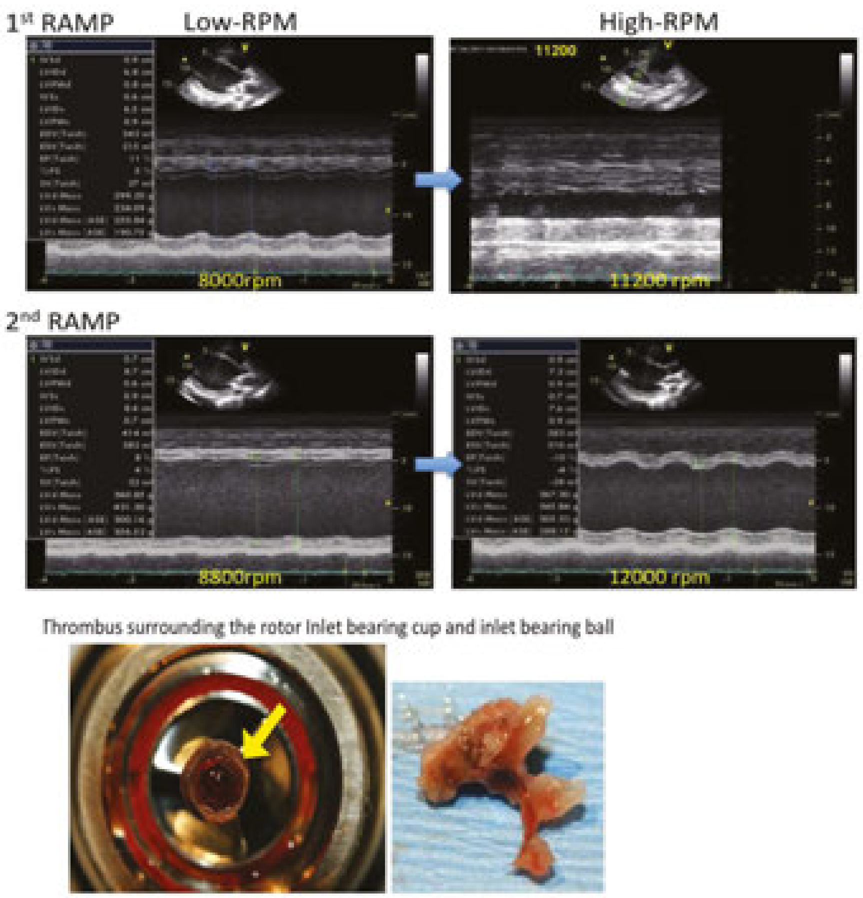

Figure 8. A representative case with device thrombosis was detected by a ramp echocardiography device (quoted from Ref. [24]). A case of a 29-year-old woman undergoing HeartMate II LVAD implantation; serial ramp studies were used to diagnose intradevice thrombus after device implantation. The first ramp study on postoperative day (POD) 26 revealed an adequate reduction in ventricular size according to the increase in LVAD. The patient was discharged home and received routine anticoagulation maintenance therapy. However, a second ramp test was performed on POD 56 due to increased lactase dehydrogenase and brain natriuretic peptide levels and showed a marked increase in the LV chamber size without an adequate response to the LVAD speed changes. Given the suspicion for partial pump thrombosis, the patient was immediately hospitalized and received intravenous heparin infusion. The patient eventually underwent cardiac transplant successfully, and the partial clot was found inside of the pump (lower panel).

2.3.3. Assessment of native cardiac function

It is important to assess native LV function, especially in patients receiving LVAD as a bridge to recovery. We cannot assess LV function without turning off the LVAD because it drastically affects preload and afterload; therefore, we need to reduce the LVAD speed under adequate anticoagulation during weaning test echocardiography. Strain assessment has been reported to be more sensitive in evaluating the myocardial systolic and diastolic reserve, and 2D speckle tracing echocardiography for the assessment of myocardial recovery in LVAD recipients may be useful [25].

3. Echocardiography in transplant recipients

3.1. Donor heart evaluation

Evaluating a donor heart as accurately as possible at the time of procurement provides essential information to a recipient team leading the delicate posttransplant management of the heart [26]. If an organ procurement team has a cardiologist or sonographer who knows which patient is going to receive the heart, the team can gather detailed information by bedside echocardiography on the donor in light of the potential recipient's conditions at the organ procurement.

Measuring the heart size of the donor from bedside echocardiography at the time of organ procurement can provide useful information for judging the appropriateness of proceeding with the heart transplant in the case of a donor-recipient size mismatch. The wall thickness of the donor heart may also be useful information for optimizing the medical therapy after transplantation, as well as for deciding whether or not to use the organ. Information regarding the presence or absence of a septal defect would be of help to surgeons planning the additional procedure of septal closure at the time of transplantation. Information about the coronary flow in the left anterior descending artery of the donor heart, especially in cases with coronary risk factors, is useful for judging the availability of the heart, as well as for considering issues related to posttransplant medical management. Finally, information about preexisting localized wall motion abnormalities from bedside echocardiography is useful for speculating on the possibility of rejection or other reasons for wall motion abnormality after transplant surgery.

According to such information, the team can make a final decision whether or not to harvest the heart. For example, the donor heart may be relatively small for the potential recipient. If a donor heart with a lower limit of normal systolic function shows decreased coronary flow and localized right heart wall motion abnormality, the heart should be declined in cases where the potential recipients have moderately high pulmonary vascular resistance. Such recipients need to receive a donor heart with good right ventricular function.

3.2. A noninvasive rejection diagnosis

Advances in immunosuppressive therapy have resulted in a marked decrease in the incidence of acute allograft rejection in heart transplant recipients; however, acute rejection still remains an important determinant factor for long-term morbidity and mortality. Acute rejection can result in not only the immediate risk of graft loss or heart failure but also of subsequent allograft vasculopathy [27]. Therefore, early diagnosis of rejection and consequent timely treatment are crucial for the early and long-term care in heart transplant recipients. Detection of allograft rejection based on the findings derived from endomyocardial biopsy (EMB) is still a gold standard; however, EMB is invasive, cost and time consuming, and may have a possibility of sampling error and interobserver variability. Although many noninvasive modalities, including radionuclide imaging, MRI, and gene expression profiling, have been investigated for their potential to detect rejection, none of them have been found to be sufficient for replacing EMB. Echocardiography has been routinely used in the management of cardiac transplant recipients. Indeed, it is an easily applicable, repeatable, and powerful noninvasive tool in the management of posttransplant recipients [28].

Variables	Characteristics and pitfalls
LVEF ↓ LV %FS ↓	• Occurs in the late phase of the rejection process • Mild/moderate rejection cannot be detected
LV wall thickness ↑ LV mass ↑	• May be related to inflammatory cell infiltration • Myocardial edema/preoperative ischemia also cause increase in LV wall thickness; so difficult to interpret during early postoperative periods
Mitral E/A ratio ↑ Mitral DcT ↓ IVRT ↓	• Abnormal filling pattern/restrictive physiology is associated with rejection • Relatively pre/after-load dependent • Doppler angle dependent • Heart rate dependent (not appropriate for patients with tachycardia)
TEI Index* (MPI) ↑	• Can evaluate global ventricular performance (both systolic and diastolic) • Derived from Doppler-derived time intervals • HR independent
Pericardial effusion↑	• May be related to the inflammatory process of rejection, but can have many causes, especially during the early postoperative phase

A, late diastolic mitral inflow velocity; DcT, deceleration time; E, early diastolic mitral inflow velocity; EF, ejection fraction; FS, fractional shortening; LV, left ventricle, left ventricular; IVRT, isovolumic relaxation time; IMP, myocardial performance index. *MPI = (isovolumic contraction time – IVRT)/ejection time.

Table 4. Conventional echocardiographic variables associated with rejections (quoted from Ref. [29]).

3.2.1. Conventional echocardiography

Table 4 summarizes the conventional echocardiographic parameters associated with acute cellular rejection [28]. Conventional echocardiography soon after the surgery can provide information about global systolic and diastolic functions, wall motion abnormality, and the hemodynamics of the transplanted hearts. Any apparent abnormal findings such as remarkable systolic and/or diastolic impairment may acute or hyperacute rejection, including antibody-mediated rejection, although primary graft failure, donor-related graft dysfunction, and any perioperative accidents should also be considered. The ability of conventional echo parameters to detect rejection is still limited to severe clinically detectable rejection. However, the findings are still useful for assessing responsiveness to treatment. In general, patients with rejection develop restrictive physiology accompanied by various degrees of systolic dysfunction. Valantine HA et al. reported that a 15% decrease in mitral deceleration time or isovolumic relaxation time (IVRT) is associated with biopsy proven rejection [29]. More recently, Sun et al. reported that a combination of IVRT less than 90 ms, a mitral E/A ratio more than 1.7, and other clinical parameters is independently associated with rejection [30]. However, because transplant recipients usually have higher resting heart rates than the nontransplant population due to denervation, their mitral E and A waves can be fused. Indeed, it is difficult to obtain clear Doppler waves from transplant recipients. They frequently have extended adhesion of the transplanted heart to the chest cavity, which hinders the acquisition of an appropriate Doppler angle. The TEI index or myocardial performance index (MPI), which is a parameter of a Doppler-derived combination of systolic and diastolic time intervals, is a useful parameter in patients with E-A fusion and high heart rate; therefore, the MPI has the potential to detect rejection more accurately than traditional Doppler indices [31]. Representative conventional 2D echo images associated with and without rejection are shown in **Figure 9**.

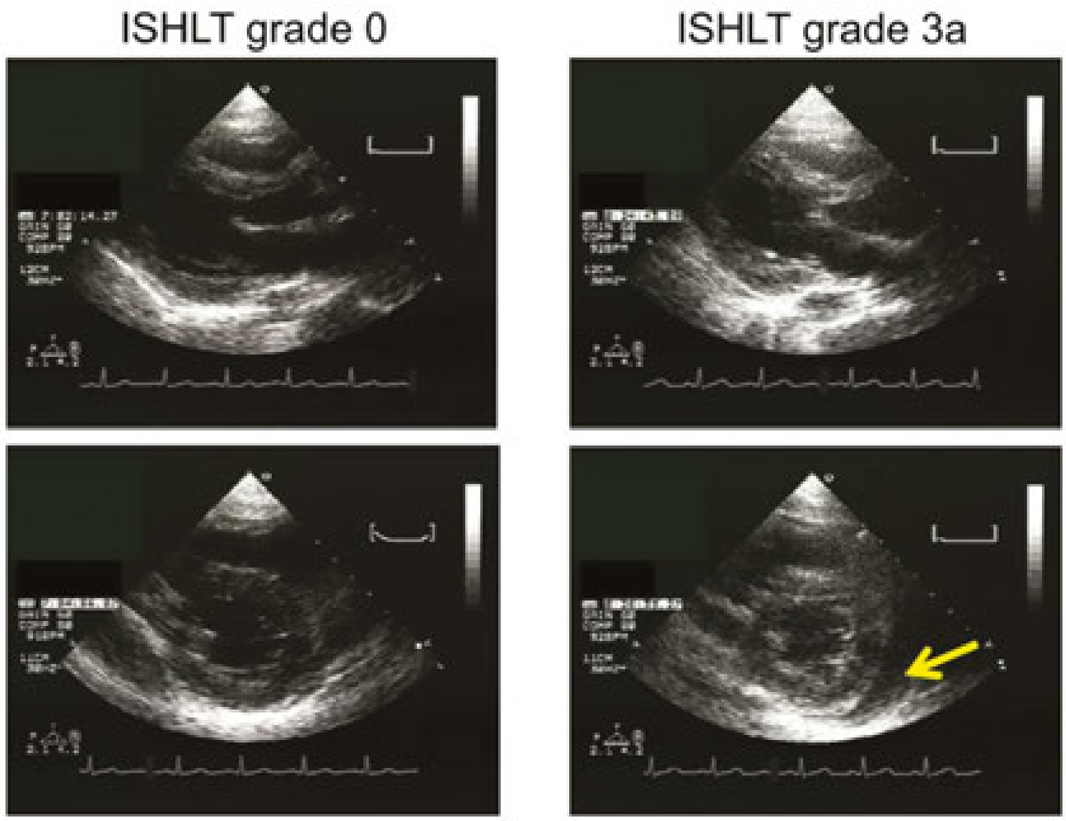

Figure 9. Representative 2D echocardiography in a patient with and without cellular rejection. Representative conventional 2D echocardiograms obtained from a 26-year-old female transplant recipient at the time when her EMB showed conventional ISHLT grade 0 (left) and ISHLT grade 3a rejection (right). The posterior wall thickness of LV and the LV mass index without rejection (left) were 9 mm and 88 g/m^2, respectively. The same parameters associated with rejection (right) were 13 mm and 112 g/m^2. The arrow in the right lower panel indicates a pericardial effusion. EMB, endomyocardial biopsies; ISHLT, International Society for Heart and Lung Transplantation; LV, left ventricular and left ventricle.

Variables	Characteristics and pitfalls
TDI derived E′ ↓ A′ ↓ E/E′ ↑	• Reflecting increased LV filling pressure/relaxation abnormalities • Angle dependent
TDI-derived longitudinal systolic strain ↓ TDI-derived radial systolic strain ↓	• Reflecting both systolic and diastolic abnormalities • Possibility of reflecting heterogeneous myocardial abnormalities • Ability to detect subclinical rejection • Angle dependent • Frame rate limitations
TDI-derived diastolic strain rate ↓	• Reflecting relaxation abnormalities • Ability to detect subclinical rejection • Angle dependent • Frame rate limitations
2D-STE-derived LV torsion ↓	• Reflecting relaxation abnormalities • Ability to detect subclinical rejection • Angle independent • Values can be calculated offline using stored 2D images
2D-STE-derived global radial systolic strain ↓	• Reflecting both systolic and diastolic abnormalities • Possibility of reflecting heterogeneous myocardial abnormalities • Ability to detect subclinical rejection • Angle independent • Values can be calculated offline using stored 2D images
2D-STE-derived systolic and diastolic global strain rate ↓	• May be more sensitive for the early detection of rejection than systolic and early diastolic global strains • Angle independent • Values can be calculated offline using stored 2D images

A′, late diastolic mitral annular velocity, E′, early diastolic mitral annular tissue velocity. * LV torsion = (apical end-systolic rotation) – (basal end-systolic rotation).

Table 5. Tissue-Doppler imaging and 2D-speckle-tracking echocardiography-derived variables associated with rejections (quoted from Ref. [29]).

3.2.2. Tissue Doppler imaging and speckle tracking echocardiography

Tissue Doppler imaging (TDI) enables the measurements of systolic and diastolic velocities within the myocardium. Several studies have evaluated the usefulness of TDI-derived mitral annular velocities to detect allograft rejection, which are summarized in **Table 5** [28]. Strain rate analysis has a potential to detect even mild rejection. Kato TS et al. reported that the attenuation of LV longitudinal strain and the diastolic strain rate derived from TDI were associated with conventional ISHLT (International Society for Heart and Lung Transplantation) grade 1b or higher rejection without hemodynamic alterations (**Figure 10**) [32]. Marciniak et al. found significantly lower LV longitudinal and radial peak systolic strain and strain rate

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values in patients with conventional ISHLT grade 1b or higher rejection. TDI-derived strain and strain rate potentially reflect abnormalities [33].

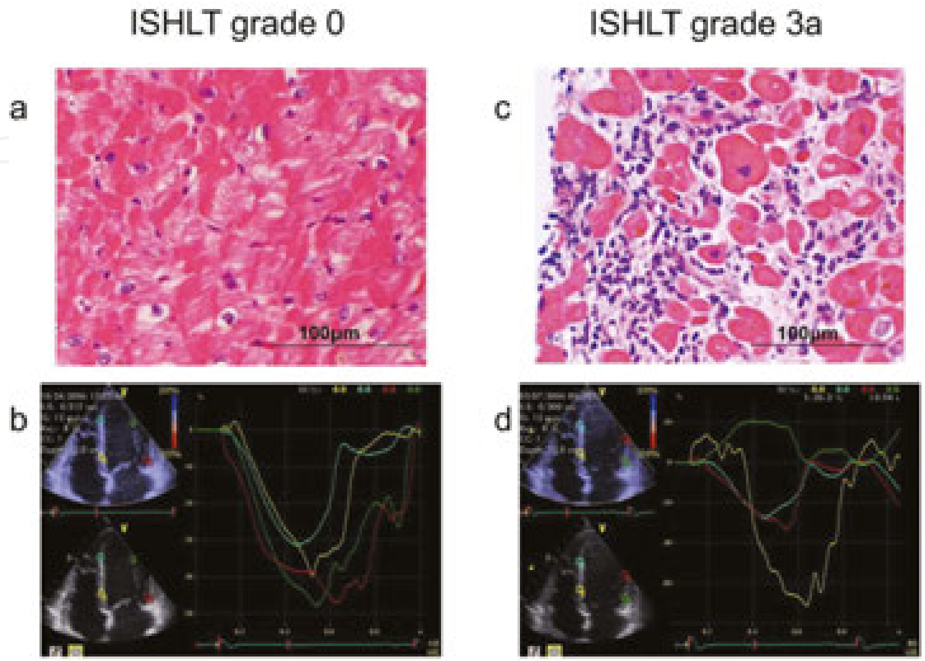

Figure 10. Representative TDI-derived strain analysis in a patient with and without rejection (quoted from Ref. [33]). Representative pathological findings for EMB specimens (a, b) and strain analysis (c, d) of HTx with ISHLT grade 0 (a, c) or 3a (b, d) rejection. Sections in (a) and (b) were stained with hematoxylin-eosin; scale bars, 100 mm. EMB, endomyocardial biopsies; HTx, heart transplant recipients; ISHLT, International Society for Heart and Lung Transplantation.

Two-dimensional speckle-tracking echocardiography (2D-STE) was developed as an angle-independent echocardiographic modality to evaluate cardiac mechanical function. The 2D-STE-derived parameters associated with rejection are also shown in **Table 5** [28]. The association between LV torsional deformation and rejection in transplant recipients has been reported since the 1980s. Sato et al. reported that 2D-STE-derived LV torsion values are decreased in patients with rejection, and the serial assessments of an intra-patients comparison showed that a cut-off value of a 25% reduction of LV torsion from the baseline is associated with ISHLT grade 2 or higher rejection, which returns to the baseline after adequate rejection treatment (**Figure 11**) [34]. LV global strains are also calculated using 2D-STE in an angle-independent manner. Sera F et al. reported that 2D-STE-derived LV global longitudinal strain was associated with treatment-requiring rejection [35] (**Figure 12**). In addition to its major advantage of angle independency, 2D-STE has other advantages over TDI, such as spatial resolution, translational artifacts, the sensitivity to signal noise, the time needed for data acquisition, and the necessity of employing expert readers. Three-dimensional (3D) STEs are useful echocardiographic modalities to assess various strain and rotation parameters more accurately than 2D-STE by tracking the same speckle throughout the cardiac cycle. However, it will take several years for the validation studies of 3D-STE to be performed to verify the value of rejection-detecting tools in heart transplant recipients.

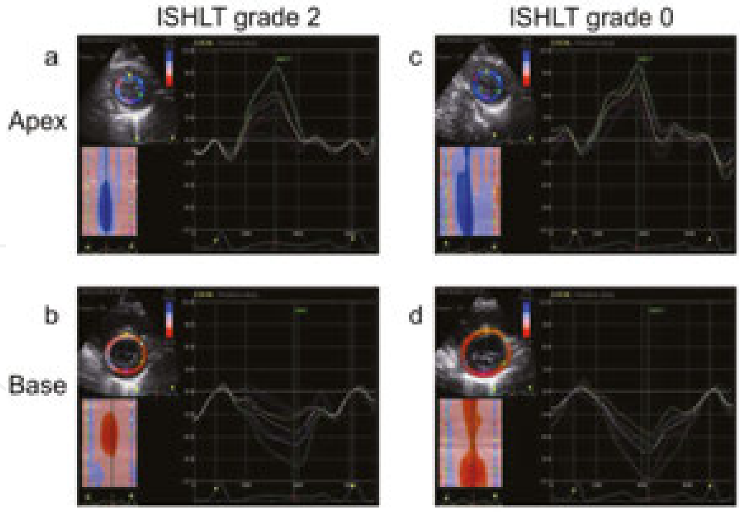

Figure 11. Representative 2D speckle-tracking echocardiogram and analysis of torsion in a patient with and without rejection. (quoted from Ref. [35]). Representative 2D-STE imaging with rotation curves obtained from the same recipient (a 32-year-old man) at LV short-axis views of the apex (a, c) and the base (b, d). Each color of the deformational curve represents one segment of the LV, and the dashed white curve depicts the mean rotation of six segments. The LVtor, defined as the difference between apical basal end-systolic rotation when the patient had ISHLT grade 2 rejection, was 10.9 degrees (a, b). The LV torsion accompanied with ISHLT grade 0 after rejection treatment was 15.6 degrees (c, d). The % change of LV torsion in this patient at the time of rejection was approximately 30% decreased from his baseline. ISHLT, International Society for Heart and Lung Transplantation; LV, left ventricular; 2D-STE, 2D speckle-tracking echocardiography; EMB, endomyocardial biopsies; HTx, heart transplant recipients.

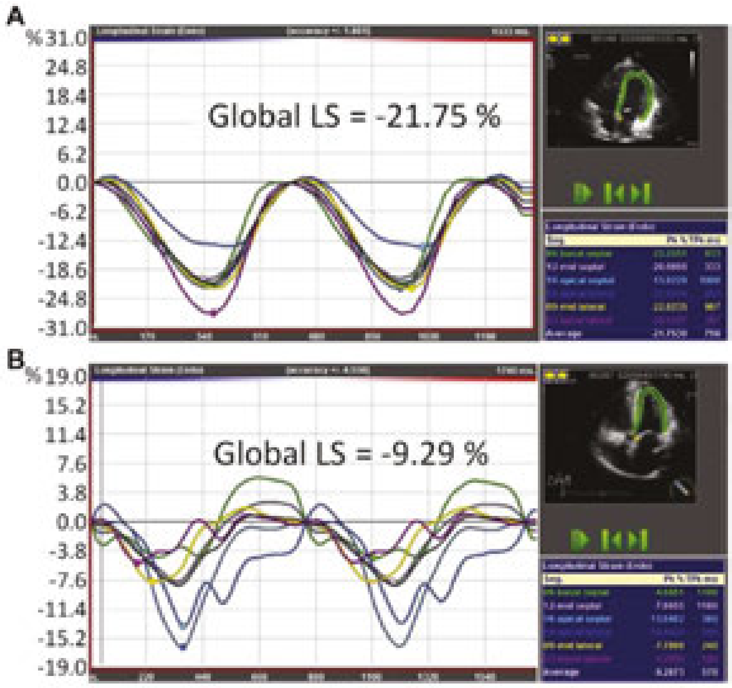

Figure 12. Representative 2D speckle tracking echocardiogram and analysis of global longitudinal strain in a patient with and without rejection (quoted from Ref. [36]). LS curves obtained from a patient without rejection (grade 0) (A) and another patient with grade 3a rejection (B). LS, longitudinal strain.

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3.2.3. Transplant vasculopathy and echocardiography

Echocardiography is a helpful and an ideal noninvasive tool to detect transplant vasculopathy or chronic rejection as well. Dobutamine or/and exercise stress echocardiography has been used to detect allograft vasculopathy, especially for pediatric patients or those with renal insufficiency [36]. Decreases in strain and strain rates at rest and with dobutamine stress are also useful to detect significant transplant vasculopathy. Contrast echocardiography is another useful method.

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