The cohort of long-term survivors of heart transplant is expanding, and the assessment of these patients requires specific knowledge of the surgical techniques employed to implant the donor heart, the physiology of the transplanted heart, complications of invasive tests routinely performed to detect graft rejection (GR), and the specific pathologies that may affect the transplanted heart. A joint EACVI/Brazilian cardiovascular imaging writing group committee has prepared these recommendations to provide a practical guide to echocardiographers involved in the follow-up of heart transplant patients and a framework for standardized and efficient use of cardiovascular imaging after heart transplant. Since the transplanted heart is smaller than the recipient’s dilated heart, the former is usually located more medially in the mediastinum and tends to be rotated clockwise. Therefore, standard views with conventional two-dimensional (2D) echocardiography are often difficult to obtain generating a large variability from patient to patient. Therefore, in echocardiography laboratories equipped with three-dimensional echocardiography (3DE) scanners and specific expertise with the technique, 3DE may be a suitable alternative to conventional 2D echocardiography to assess the size and the function of cardiac chambers. 3DE measurement of left (LV) and right ventricular (RV) size and function are more accurate and reproducible than conventional 2D calculations. However, clinicians should be aware that cardiac chamber volumes obtained with 3DE cannot be compared with those obtained with 2D echocardiography. To assess cardiac chamber morphology and function during follow-up studies, it is recommended to obtain a comprehensive echocardiographic study at 6 months from the cardiac transplantation as a baseline and make a careful quantitation of cardiac chambers. 3DE measurement of left (LV) and right ventricular (RV) size and function are more accurate and reproducible than conventional 2D calculations. However, clinicians should be aware that cardiac chamber volumes obtained with 3DE cannot be compared with those obtained with 2D echocardiography. To assess cardiac chamber morphology and function during follow-up studies, it is recommended to obtain a comprehensive echocardiographic study at 6 months from the cardiac transplantation as a baseline and make a careful quantitation of cardiac chamber size, RV systolic function, both systolic and diastolic parameters of LV function, and pulmonary artery pressure. Subsequent echocardiographic studies should be interpreted in comparison with the data obtained from the 6-month study. An echocardiographic study, which shows no change from the baseline study, has a high negative predictive value for GR. There is no single systolic or diastolic parameter that can be reliably used to diagnose GR. However, in case several parameters are abnormal, the likelihood of GR increases. When an abnormality is detected, careful revision of images of the present and baseline study (side-by-side) is highly recommended. Global longitudinal strain (GLS) is a suitable parameter to diagnose subclinical allograft dysfunction, regardless of aetiology, by comparing the changes occurring during serial evaluations. Evaluation of GLS could be used in association with endomyocardial biopsy (EMB) to characterize and monitor an acute GR or global dysfunction episode. RV size and function at baseline should be assessed using several parameters, which do not exclusively evaluate longitudinal function. At follow-up echocardiogram, all these parameters should be compared with the baseline values. 3DE may provide a more accurate and comprehensive assessment of RV size and function. Moreover, due to the
unpredictable shape of the atria in transplanted patients, atrial volume should be measured using the discs’ summation algorithm (biplane algorithm for the left atrium) or 3DE. Tricuspid regurgitation should be looked for and properly assessed in all echocardiographic studies. In case of significant changes in severity of tricuspid regurgitation during follow-up, a 2D/3D and colour Doppler assessment of its severity and mechanisms should be performed. Aortic and mitral valves should be evaluated according to current recommendations. Pericardial effusion should be serially evaluated regarding extent, location, and haemodynamic impact. In case of newly detected pericardial effusion, GR should be considered taking into account the overall echocardiographic assessment and patient evaluation. Dobutamine stress echocardiography might be a suitable alternative to routine coronary angiography to assess cardiac allograft vasculopathy (CAV) at centres with adequate experience with the methodology. Coronary flow reserve and/or contrast infusion to assess myocardial perfusion might be combined with stress echocardiography to improve the accuracy of the test. In addition to its role in monitoring cardiac chamber function and in diagnosis the occurrence of GR and/or CAV, in experienced centres, echocardiography might be an alternative to fluoroscopy to guide EMB, particularly in children and young women, since echocardiography avoids repeated X-ray exposure, permits visualization of soft tissues and safer performance of biopsies of different RV regions. Finally, in addition to the indications about when and how to use echocardiography, the document also addresses the role of the other cardiovascular imaging modalities during follow-up of heart transplant patients. In patients with inadequate acoustic window and contraindication to contrast agents, pharmacological SPECT is an alternative imaging modality to detect CAV in heart transplant patients. However, in centres with adequate expertise, intravascular ultrasound (IVUS) in conjunction with coronary angiography with a baseline study at 4–6 weeks and at 1 year after heart transplant should be performed to exclude donor coronary artery disease, to detect rapidly progressive CAV, and to provide prognostic information. Despite the fact that coronary angiography is the current gold-standard method for the detection of CAV, the use of IVUS should also be considered when there is a discrepancy between non-invasive imaging tests and coronary angiography concerning the presence of CAV. In experienced centres, computerized tomography coronary angiography is a good alternative to coronary angiography to detect CAV. In patients with a persistently high heart rate, scanners that provide high temporal resolution, such as dual-source systems, provide better image quality. Finally, in patients with insufficient acoustic window, cardiac magnetic resonance is an alternative to echocardiography to assess cardiac chamber volumes and function and to exclude acute GR and CAV in a surveillance protocol.

**Keywords**

heart transplantation • echocardiography • three-dimensional echocardiography • Doppler echocardiography • tissue Doppler imaging • myocardial deformation imaging • cardiac allograft rejection • cardiac allograft vasculopathy • stress echocardiography • coronary flow reserve • endomyocardial biopsy

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Introduction

Heart transplantation (HT) represents the mainstream therapy of end-stage heart failure, providing a 90% 1-year survival after surgery.\(^1\) More than 4000 HT are performed each year in over 300 countries.\(^2\) However, despite advances in surgical techniques, diagnostic approaches, and immunosuppressive strategies, survival after HT continues to be limited by the development of acute/chronic graft rejection (GR) and cardiac allograft vasculopathy (CAV), which represent the leading causes of morbidity and mortality in these patients.\(^3\) Since GR is usually an asymptomatic, rapid onset condition bearing a poor prognosis, regular surveillance of HT patients is mandatory, particularly in the first year after HT. In contrast with the rather rapid course of acute GR, CAV is a progressive process that develops over the years, usually without symptoms. Currently, the reference modalities to detect acute GR and CAV are endomyocardial biopsy (EMB) and coronary angiography, respectively.\(^4\) However, both modalities are invasive and expensive, and are associated with non-negligible risk. Although uncommon, EMB complications, including myocardial perforation, pericardial tamponade, arrhythmias, access-site complications, and iatrogenic tricuspid valve injury leading to significant regurgitation, may occur at a rate of 0.5–1.5%.\(^5\) Moreover, EMB may not detect GR in up to 20% of patients, due to sampling errors (related to the patchy nature of GR), variability in the interpretation of histological findings, and lack of routine screening for antibody-mediated rejection.\(^6\) Routine coronary angiography used for detecting CAV carries a small, but not negligible risk of complications, such as stroke, heart perforation, coronary artery dissection, and allergic reactions to intravenous contrast.\(^7\) Furthermore, routine coronary angiography should preferably not be performed in patients with moderate to severe chronic kidney disease because of the risk of acute kidney injury (relative contraindication in patients with renal dysfunction).\(^8\)

During the last decade, many efforts have been made in an attempt to create a new non-invasive strategy to detect GR and CAV. Several non-invasive cardiovascular imaging modalities and bio-molecular medicine techniques have been tested, including echocardiography, radionuclide imaging, cardiac magnetic resonance (CMR), intramyocardial electrogram recording, immunologic monitoring, gene expression profile, and biohumoral factors. Nonetheless, current guidelines for the management of heart transplant patients\(^9\) state that no alternative strategy either based on imaging (e.g. echocardiography, CMR) or biomarkers (e.g. natriuretic peptides, cardiac troponins, and C-reactive protein) can be recommended as an alternative to EMB for GR monitoring (Class III; level of evidence: C).

Nevertheless, echocardiography remains the most useful imaging modality to assess and monitor HT patients, as it is widely available, cheap, can be easily and rapidly performed, is safe for both operators and patients, well tolerated, and not associated with the risks of the invasive procedures. Moreover, recent development of new echocardiographic techniques has increased the likelihood of detecting graft dysfunction at an early stage.

Accordingly, the European Association of Cardiovascular Imaging (EACVI) and the Brazilian Cardiovascular Imaging Department developed this document to review and summarize the most recent evidence about the non-invasive assessment of patients who underwent HT, the diagnosis of CAV and acute/chronic GR, with the intent to set up a framework for standardized and efficient use of cardiovascular imaging after HT.

Heart transplantation

Surgical techniques and outcome

Orthotopic heart transplantation

Currently, the bicaval technique (five anastomoses) is the most frequently used surgical technique to perform orthotopic heart transplant (OHT), followed by the standard technique and the total OHT technique. The three techniques were used in 62, 34.7, and <3% of the OHT performed in 2007, respectively.\(^10\)

The standard technique, also known as biatrial technique, was the first surgical approach used for OHT.\(^11\) It entailed simple anastomoses at the mid-level of the left and right atria in addition to the aortic and pulmonary artery anastomoses just above the semilunar valves.\(^12,13\) In addition, the atrial appendages are removed to decrease the risk of post-operative thrombus formation. However, since the right atrial incision is usually close to the donor sinoatrial node, the necrosis of the sinoatrial node with post-operative sinus node dysfunction is a frequent complication. Moreover, with the standard technique, atrial geometry is grossly distorted, resulting in enlarged atria with a ‘snowman’ shape due to redundant atrial tissue\(^14\) (Figure 2).

With the bicaval technique\(^17–19\) (Figure 1B), the surgeon performs separate superior and inferior vena cava anastomoses instead of the right atrial anastomosis. The left atrial incision is carried to the base of the left atrial appendage, which is removed leaving a small margin of the atrial cuff around the four pulmonary veins. The

Abbreviations

- **GR**: graft rejection
- **CAV**: cardiac allograft vasculopathy
- **CFR**: coronary flow reserve
- **CMR**: cardiac magnetic resonance
- **CT**: computed tomography
- **DTI**: Doppler tissue imaging
- **EACVI**: European Association of Cardiovascular Imaging
- **EF**: ejection fraction
- **EMB**: endomyocardial biopsy
- **FFR**: fractional flow reserve
- **GLS**: global longitudinal strain
- **HT**: heart transplantation
- **HHT**: heterotopic heart transplantation
- **ISHLT**: International Society for Heart and Lung Transplantation
- **IVRT**: isovolumetric relaxation time
- **IVUS**: intravascular ultrasound
- **LV**: left ventricle/ventricular
- **MPI**: myocardial performance index
- **OHT**: orthotopic heart transplantation
- **RV**: right ventricle/ventricular
- **SR**: strain rate
- **STE**: speckle tracking echocardiography
- **TAPSE**: tricuspid annular plane systolic excursion
main advantage of the bicaval technique is to retain normal shaped atria, which may preserve atrial and sinus node function.

The total OHT technique (Figure 1C) is a complete atrioventricular cardiac transplantation with separate caval and pulmonary vein anastomoses. This technique, while carrying similar advantages to the bicaval operation, presents many technical issues, as bleeding from the suture lines of pulmonary veins and reduced patency of pulmonary veins due to twisting or stenosis at the level of the anastomoses, that may prolong the procedure and increase operative complication rates. Therefore, it is seldom employed today.

Outcome of OHT performed with the different techniques has been compared in several studies with conflicting results. Most data, however, indicate that the bicaval and the total OHT techniques are more physiological than the biatrial method. The first mentioned methods preserve sinoatrial node function and require less pacemaker implants. Tricuspid valve regurgitation is also significantly lower with these techniques, whereas no effect has been demonstrated on the incidence of mitral regurgitation. However, a true comparison between techniques is difficult, as the haemodynamic measurements were recorded at various intervals ranging from days to years post-operatively.

Specific complications for each technique have been documented. Standard technique may trigger arrhythmias and also promote atrial thrombi formation, whereas in patients who underwent bicaval or total OHT techniques, superior vena cava stenosis may occur with an overall incidence of 2.4%. There is a general consensus about the superiority of the bicaval technique due to the presence of normal right and left atrial sizes, lower right heart filling pressures, and almost normal flows in the caval veins post-operatively.

Heterotopic heart transplantation

Heterotopic heart transplant (HHT) refers to the placement of a donor heart without recipient cardiectomy. Anatomically, the allograft is placed to the right of the native heart in the right chest to avoid compression by the sternum and at an angle close to 90° to the native heart to allow for the widest possible connection between the native and donor atria. The donor’s superior vena cava is attached to the recipient’s right atrium so that blood from the body now flows to both hearts. A graft from one of the donor’s blood vessels connects the donor’s and recipient pulmonary arteries, allowing both hearts to send blood to the lungs. Donor’s and recipient’s left atria are connected so that blood from the lungs travels to both hearts. The donor heart is attached to the recipient’s aorta to transport blood from both hearts out to the body (Figure 3).

There are several recognized complications related to HHT. An early post-operative complication is compression of the right middle and right lower lobes of the lung by the allograft, leading to atelectasis, infection, and impaired ventilation. Premature deterioration of the recipient heart is often observed. Due to frequent dysrhythmias and different flow conditions, thromboembolic events may occur at an increased rate by leaving the often dilated native heart in place.

Compared with OHT, preservation of the ‘preconditioned’ native right ventricle (RV) seemed to offer better survival to recipients with severe pulmonary hypertension. Despite being rarely used today, the heterotopic approach remains a valuable option in recipients with high irreversible transpulmonary pressure gradients and expands the donor pool through use of undersized or

![Figure 1](image-url) Surgical techniques used in orthotopic cardiac transplantation. Ao, aorta; SVC, inferior vena cava; LAC, left atrial cuff; LPVC, left pulmonary veins cuff; PA, pulmonary artery; RA, right atrium; RPVC, right pulmonary veins cuff; SVC, superior vena cava.
Heart–lung transplantation

Heart–lung transplantation (cardiopulmonary transplantation) recipients receive an ‘en bloc’ harvested heart and lung allograft, performing tracheal, right atrial, and aortic anastomosis using cardiopulmonary bypass support during surgery. Care is taken to preserve the donor phrenic nerves and to address the bronchial artery circulation.

The follow-up of heart–lung transplant recipients is similar to that of double and single lung transplant patients. The majority of the post-operative complications, including acute and chronic GR, and infections are related to the lung allograft, not to the cardiac allograft. Isolated acute GR of the heart, however, is infrequent and much less common than after single HT. Therefore, most centres do not recommend EMB for routine heart–lung transplantation surveillance after 4–6 months follow-up. However, recommended non-invasive surveillance protocol for acute and chronic cardiac GR in heart–lung transplant is the same as for single HT. The 1-year survival rate after a heart–lung transplant is 65%; the otherwise compromised allografts. However, survival is poorer in HHT recipients, and with improving results in continuous flow ventricular assist devices, many patients can be bridged to normalization of pulmonary artery pressures, allowing OHT.

**Figure 2** Two- and three-dimensional echocardiography acquisitions in a patient who underwent heart transplant using the standard technique. Both the left and right atria are grossly enlarged and the atrial sutures (arrows) are visualized giving the left atrium the typical ‘snowman’ shape. Arrow, suture lines, Ao, aorta; LA, left atrium; LV, left ventricle; MV, mitral valve; RA, right atrium.

**Figure 3** Schematic drawing of the connections between the native and the donor heart in heterotopic heart transplantation. AO, aorta; LA, left atrial; LV, left ventricle; PA, pulmonary artery; RV, right ventricle; SVC, superior vena cava.
5-year survival rate is 40%.[41] Early mortality is secondary to surgical losses and acute allograft failure. The late attrition is due to obliterative bronchiolitis (the chronic GR process of the lung) and rejection.

**Physiology of the transplanted heart**

Despite the donor’s heart function is usually normal, the particular cardiovascular physiology of cardiac allograft (afferent and efferent allograft denervation) and surgical complications (myocardial injury and maladaptation that occur at the time of organ harvest, subsequent rejection injuries) determine the peculiar haemodynamic conditions observed in HT recipients. In addition, pre-existing, undetected, donor cardiac pathologies may also affect transplanted heart function.

Cardiac denervation is an inevitable consequence of HT, as the cardiac plexus is divided in the donor, resulting in a denervated donor heart.[42] With the standard technique, the atrial remnant of the recipient remains innervated, but no impulse will cross the suture line. As a result, the donor atrium is responsible for heart beat generation in the implanted hearts independent on the surgical technique, and it beats at a higher intrinsic rate (90–110 bpm) and shows reduced heart rate variability. Normal heart rate responses to postural changes and heart rate variations in response to stimuli such as the Valsalva manoeuvre and carotid sinus massage are reduced. Drugs or manoeuvres that act via autonomic nerve fibres are also ineffective. However, the heart retains its responsiveness to direct acting agents such as isoproterenol, epinephrine, norepinephrine, dopamine, and dobutamine.

Intrinsic cardiac functions such as impulse formation and conduction and Frank–Starling mechanism are preserved. Therefore, the initial response to Frank–Starling in a denervated heart is an increase in stroke volume, which is critically dependent on an adequate left ventricular (LV) end-diastolic volume. The increase in contractility secondary to increased heart rate is a secondary effect and is dependent on circulating catecholamines. The transplanted heart is, therefore, critically preload dependent, and higher filling pressures are needed to maintain a normal stroke volume.

In patients who underwent OHT using the standard technique, atrial mechanics is impaired, apparently due to the mid-atrial anastomoses between the donor and the recipient hearts. Assessment of LV diastolic function in the transplanted heart is challenging, because sinus tachycardia of the denervated heart often induces merging of E and A waves. In addition, after standard technique, the sinus nodes of the donor and recipient remain intact, with two P waves present on the electrocardiogram up to 3 weeks after surgery, and both donor and the remaining recipient atria may trigger mechanical activity provoking important variations in the transmural E and A velocities. Moreover, adequate transthoracic recording of pulmonary venous flow is technically demanding after HT, and pulmonary vein flow velocities are often altered by residual recipient atrial tissue contraction that usually occurs at early ventricular filling decreasing the systolic flow component. Finally, end-diastolic atrial contraction will increase pulmonary vein atrial reversal wave (Ar wave) velocity. As a result, the atrial contribution to net stroke volume is generally reduced compared with normal subjects. Bicaval and total HT techniques should provide better atrial mechanics and function, achieving greater left atrial emptying force and more physiological atrioventricular coupling.[26]

Usually, HT patients show restrictive physiology early after the transplant operation, which tends to improve during the follow-up.[43,44] However, early haemodynamic studies conducted in ‘healthy’ OHT patients reported normal intracardiac pressures at rest, but dramatic increase in LV end-diastolic pressure during exercise, suggesting an occult rather than absent restrictive pattern.[45] As a further confirmation, the first sign of the onset of acute GR is often overt restrictive physiology.[46]

**Early allograft failure**

Early allograft failure is the main cause of death in the first 30 days after HT and remains an important cause of death throughout the post-transplant period.[5] Main features of early allograft failure are LV or biventricular dysfunction with hypotension, low cardiac output, and high filling pressures. Graft failure is defined as primary in the absence of obvious anatomic or immunologic cause, or as secondary when it can be attributed to reperfusion injury, unresponsive pulmonary hypertension, immunologic cause, or hyperacute rejection.[5,47,48] Echocardiographic evaluation demonstrate reduced global myocardial function [LV ejection fraction (EF) < 45%], loss of contractile reserve, and increased RV volume with systolic dysfunction [tricuspid annulus plane systolic excursion (TAPSE) < 15 mm or a RV EF < 45%].

Reperfusion injury during surgery results from prolonged cold ischaemia time and/or reperfusion ischaemia. It may be transient (myocardial stunning), lasting 12–24 h after HT or may trigger early allograft failure after surgery.[49] Prolonged cold ischaemia time (longer than 5 h) has been associated with higher incidence of allograft dysfunction and is a significant cause of early allograft failure.[50,51] Hyperacute rejection is an extremely rare condition that occurs within the first 24 h after HT. The hyperacute rejection is the most ominous cause of perioperative LV dysfunction. It is initiated by preformed recipient antibodies (IgG or IgM) that cross-react with endothelial epitopes on the allograft, promoting widespread endothelial damage leading to global ischaemia and catastrophic allograft failure.[52] Hyperacute rejection is most often observed after implantation of an ABO-mismatched heart, or in highly sensitized patients, such as multiparous women or patients who underwent multiple blood transfusions.[52]

Isolated RV failure occurring in the operating room or detected by echocardiography performed during the first 48 h after surgery is defined by the presence of a TAPSE < 15 mm or a RV EF < 45% alongside normal or near-normal LV systolic performance, in the absence of other obvious causes of graft dysfunction triggering severe haemodynamic instability. RV failure accounts for 50% of all cardiac complications and 19% of death in the early period after HT.[53–55] Acute changes in haemodynamics after HT mainly affect RV function. Several factors may influence donor RV function after HT: (i) organ preservation, affecting donor RV contractility; (ii) pre-existing and underestimated pulmonary hypertension of the recipient; and (iii) cardiopulmonary bypass, which may increase pulmonary vascular resistances particularly in patients with abnormal pre-operative values.

**Acute graft rejection**

Acute graft rejection is the leading cause of mortality during the first year after HT. Its incidence is around 20–40% and is responsible for
Acute and chronic rejection.

Acute GR is well characterized by a fibro-proliferative process directed against donor major histocompatibility complex antigens, or peptides presented by dendritic cells. Acute GR is categorized into acute cellular or antibody-mediated rejection.56,57 Acute cellular rejection is well characterized and graded according to established histological criteria—International Society for Heart and Lung Transplantation (ISHLT) classification of body specimen, established in 1990 and then revised in 2004 (Table 1).58 Antibody-mediated rejection is less well characterized; the diagnosis is made on a number of histological and/or immunopathological features without standardized diagnostic criteria. Recently, the ISHLT has addressed this issue and a new grading system has been proposed.59 However, further work is required to test its consistency and reproducibility.

Most cases of acute cellular rejection are diagnosed by routine surveillance ‘protocol’ of frequent EMB, even if the patient is asymptomatic and LV EF remains in the normal range.5,54 Sampling error associated with the patchy nature of acute rejection, variability in the interpretation of histological findings, and non-routine screening for antibody-mediated rejection may result in underestimation of the severity or miss the diagnosis of acute cellular rejection. As a result, the absence of pathologic evidence for severe rejection in the presence of otherwise unexplained LV dysfunction, heart failure, or shock should not prevent treatment for rejection. Symptoms usually develop only when the heart damage is extensive.

Chronic graft rejection

Chronic rejection is mainly determined by CAV and is characterized by a fibro-proliferative process affecting cardiac blood vessels, resulting in concentric narrowing and obliteration of coronary vessels. CAV has been reported to occur in 20% of patients after 3 years, 30% at 5 years, and up to 50% after 10 years.5 Recurrent acute antibody-mediated GR increases the risk of CAV. Initially, CAV is a diffuse process affecting the large epicardial coronary arteries, the coronary veins, and the microcirculation; later, CAV may also cause focal luminal stenosis.60 Histologically, CAV is characterized by concentric fibrous intimal hyperplasia and smooth muscle cell proliferation. ISHLT has defined CAV based on visual coronary angiographic stenosis parameters along with LV EF plus LV diastolic function assessment (Table 2).61 Diagnosis of CAV is usually made by coronary angiography and echocardiographic assessment of allograft function. However, angiography may provide a gross underestimation of this diffuse and concentric vasculopathy. Because of these limitations, alternative imaging modalities, such as intravascular ultrasound (IVUS) and fractional flow reserve (FFR), have been proposed to improve the sensitivity for CAV detection. However, even if IVUS is considered the most sensitive technique for detecting the anatomic features of CAV, its application is limited by its costs and lack of widespread expertise with this imaging technique.

Cardiac interstitial fibrosis, which leads to ventricular stiffness and diastolic dysfunction of the graft, is typically monitored by repeated EMBs.62 However, this invasive procedure often fails to detect patchy cardiac interstitial fibrosis at an early stage of its evolution. Of note, in some patients, chronic GR may also be triggered by recurrent, chronic immune response against the transplanted heart, which gradually impairs myocardial function by replacing myocardial cells with fibrous tissue.

Graft dysfunction due to other aetiologies

Other causes of graft dysfunction, mimicking GR and CAV, have been reported. The most common of them are cytomegalovirus, Toxoplasma gondii and coxsackievirus infections, as well as Chagas disease (Trypanosoma cruzi) reactivation and/or myocarditis. No cardiac imaging finding has been found to be diagnostic of a specific aetiological cause. In case of a graft dysfunction, serological and
specific immunohistochemistry testing is necessary for accurate aetiological diagnosis.\textsuperscript{3,6,3,6,4}

**Infective endocarditis in heart transplant patients**

There are limited data about the incidence and prognosis of infective endocarditis after HT. Even in the ESC guidelines on prevention, diagnosis, and treatment of infective endocarditis,\textsuperscript{6,5} this condition is not mentioned. However, it has been reported that the incidence of infective endocarditis among HT recipients was 50/110-fold higher than in the general population.\textsuperscript{6,6,67} Possible explanations for this markedly increased incidence include catheter-related and other nosocomial blood stream infections, LV assist device-related mediastinitis, donor heart contamination, deep wound infections following transplant, EMB, and suppression of cell-mediated immunity. Forty to fifty per cent of patients had tricuspid valve infection. This rate of tricuspid involvement approaches that in intravenous drug users with endocarditis. Aziz et al.\textsuperscript{6,8} reported a 0% bacteremia rate just prior to EMB, but a 70% rate of coagulase-negative Staphylococcus bacteraemia in atrial blood immediately following the biopsies. Despite the fact that it seems that increased numbers of EMB were associated with tricuspid valve infection, the true role of EMB (as opposed to catheter-related and other blood stream infections) as a predisposition to infective endocarditis remains undefined. In the reported series, the most common pathogens were Staphylococcus aureus (40% of cases) and Aspergillus fumigatus (30% of post-transplant endocarditis). All patients who developed A. fumigatus endocarditis following HT had antecedent Cytomegalovirus viremia. This finding suggests that patients with A. fumigatus infection had heightened immunosuppression prior to infective endocarditis. In literature, mortality of HT patients with infective endocarditis ranges from 22 to 80%, with a peak rate of 100% endocarditis-related mortality in Aspergillus infective endocarditis following HT.\textsuperscript{6,6}

The prevalence of endocarditis is high in HT recipients, and it should be treated promptly because of a high mortality rate. Therefore, a high score of suspicion should be used in this specific population. Echocardiography should be performed rapidly to exclude the diagnosis and even repeated when initial echocardiographic study is negative, but the clinical suspicion remains moderate or high.

**Conventional echocardiographic evaluation**

Echocardiography is the first line imaging modality to assess HT patients, providing accurate information about graft anatomy and function, which is part of all serial evaluations during post-transplant follow-up.\textsuperscript{6} The ISHLT Guidelines for Heart Transplant Recipients do not specify the timing of echocardiographic evaluations and do not recommend echocardiography as an alternative to serial EMB in rejection monitoring.\textsuperscript{6} Nevertheless, echocardiography is commonly used when there is a high clinical suspicion of acute GR despite negative EMB findings and to monitor LV function during confirmed GR episodes.

In the immediate post-operative period, echocardiography enables identification of surgical complications and early allograft dysfunction, while in long-term follow-up, serial echocardiographic studies are useful to detect acute GR (Figure 4), CAV (Figure 5), and to monitor pulmonary artery systolic pressure. A main technical issue is that echocardiographic parameters are more variable in HT patients than in the general population. This fact makes it difficult to define ‘normal’ transplanted heart morphology and function and to identify appropriate cut-off values for the different echocardiographic parameters to detect allograft dysfunction.\textsuperscript{6,9}

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### Table 2 International Society of Heart and Lung Transplantation (ISHLT) nomenclature for cardiac allograft vasculopathy

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<td>ISHLT CAV0 (not significant)</td>
<td>No detectable angiographic lesion</td>
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<tr>
<td>ISHLT CAV1 (mild)</td>
<td>Angiographic left main stenosis of &lt;50%, or primary vessel with maximum lesion of &lt;70%, or any branch stenosis &lt;70% (including diffuse narrowing) without allograft dysfunction</td>
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<tr>
<td>ISHLT CAV2 (moderate)</td>
<td>Angiographic left main stenosis of ≥50%; a single primary vessel ≥70%, or isolated branch stenosis ≥70% in branches of two systems, without allograft dysfunction</td>
</tr>
<tr>
<td>ISHLT CAV3 (severe)</td>
<td>Angiographic left main stenosis of ≥50%, or two or more primary vessels ≥70% stenosis, or isolated branch stenosis ≥70% in all three systems; or ISHLT CAV1 or CAV2 with allograft dysfunction (defined as LVEF ≤ 45%, usually in the presence of regional wall motion abnormalities) or evidence of significant restrictive physiology (which is common but not specific)</td>
</tr>
</tbody>
</table>

Definitions:

1. A ‘primary vessel’ denotes the proximal and middle 33% of the left anterior descending artery, the left circumflex, the ramus, and the dominant or co-dominant right coronary artery with the posterior descending and posterior branches;
2. A ‘secondary branch vessel’ includes the distal 33% of the primary vessels or any segment within a large septal perforator, diagonals and obtuse marginal branches, or any portion of a non-dominant right coronary artery;
3. Restrictive cardiac allograft physiology is defined as symptomatic heart failure with echocardiographic E to A velocity ratio > 2 (>1.5 in children), shortened isovolumetric relaxation time (<60 ms), shortened deceleration time (<150 ms), or restrictive haemodynamic values (right atrial pressure >12 mmHg, pulmonary capillary wedge pressure >25 mmHg, cardiac index <2 l/min/m²).

Adapted from Mehra et al.\textsuperscript{6,1}
Therefore, in this special population, having a comprehensive individual baseline echocardiographic study available for comparison during the serial follow-up studies is more useful than the absolute value of each measurement. Thoughtful baseline echocardiographic assessment should be performed after at least 6 months from the HT procedure. Earlier after HT, the adaptation of the new heart to the thoracic space, its different positioning in the chest compared with the native heart, and the presence of confounders such as early allograft dysfunction, pericardial effusion, and other co-morbidities (e.g., sepsis, mechanical complications of EMB, and multiple organ dysfunction) may affect the recorded echocardiographic parameters and decrease the sensitivity of echocardiography to detect acute GR during follow-up.

**Timing of echocardiographic assessment and acquisition protocol**

Due to the lack of evidences about the optimal timing of echocardiographic studies in HT patients, this writing committee reached a consensus on recommending echocardiographic evaluations as described in Figures 4 and 5.
As the donor heart is normal in size, it is smaller than the original recipient dilated heart; therefore, it is located more medially in the mediastinum and tends to be rotated clockwise. Due to this rotation and medial displacement in some patients, standard transthoracic views are obtained from non-standard transducer positions, with variability from patient to patients.

Standard echocardiographic evaluation protocol should include two-dimensional (2D) as well as spectral and colour Doppler imaging (Tables 3 and 4). In case of abnormalities of graft geometry or function, additional views and acquisitions are often required. In all studies, it is necessary to measure the size of the four cardiac chambers and great vessels, assess LV and RV function, assess heart valve function, estimate pulmonary artery systolic pressure, and describe the pericardium (Table 5). To address specific clinical questions and to improve sensitivity in detecting morpho-functional changes in the transplanted hearts, laboratories that have the techniques and expertise in using them can employ advanced echocardiographic techniques (Table 6).

### Cardiac chamber morphology and function

**LV geometry and systolic function**

During the first month after HT, the LV morphology is characterized by an increase in LV mass and in wall thickness, that is likely to be caused by inflammatory cell infiltration and graft oedema. LV wall thickness usually tends to decrease after 3 months, probably due to liquid reabsorption.

During long-term follow-up, a secondary increase in LV mass and wall thickness may occur as a consequence of many factors such as repetitive rejection episodes, chronic tachycardia, and systemic hypertension, usually induced by immunosuppressive agents. The increase in LV mass and wall thickness has also been described during acute GR episodes probably secondarily to myocardial inflammation which induces cellular oedema. However, several reports demonstrate a low sensitivity of this parameter because of the fluctuation of wall thickness related to scattered acute rejection cellular oedema pattern combined with immunosuppressive therapy antiedemigen effect. The recommendation is to monitor wall thickness during follow-up. Sudden and evident changes in LV mass and/or wall thickness should raise suspicion of acute GR.

Usually, in patients with uncomplicated HT, LV dimensions remain within the normal range, as demonstrated in a 10- to 15-year follow-up study.

LV pump function is usually normal after HT. Despite being the strongest predictor of outcome in HT patients, LV EF is not an early indicator of graft dysfunction and usually does not correlate with the grade of rejection found at the EMB. Moreover, LV EF is an insensitive marker of acute GR. Late reduction of LV EF is often associated with progression of CAV and carries a poor prognosis.
### Table 3 Two-dimensional echocardiography views, acquisition techniques, and parameters to be routinely assessed in patients who underwent heart transplant

<table>
<thead>
<tr>
<th>View Description</th>
<th>Acquisition Techniques</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parasternal long-axis of LV</strong></td>
<td>2D loop + M-mode + color Doppler for MV and AV&lt;br&gt;Subject to assess and parameters to measure&lt;br&gt;- Left ventricle morphology, diameters, wall thickness, mass, function and motion abnormalities&lt;br&gt;- Left atrium morphology and anterior-posterior diameter&lt;br&gt;- Aortic and mitral valve morphology and function&lt;br&gt;- Pericardium</td>
</tr>
<tr>
<td><strong>Parasternal long-axis of RV inflow</strong></td>
<td>2D loop + color Doppler for TV + CW Doppler&lt;br&gt;Subject to assess and parameters to measure&lt;br&gt;- Tricuspid valve morphology and function&lt;br&gt;- Retrograde and anterograde flow pattern and velocities&lt;br&gt;- Right atrium morphology</td>
</tr>
<tr>
<td><strong>Parasternal short-axis of the PA</strong></td>
<td>2D loop + color Doppler for PV and PA + CW and PW Doppler for PV&lt;br&gt;Subject to assess and parameters to measure&lt;br&gt;- Pulmonary valve function and morphology, Anterograde and retrograde flow velocities&lt;br&gt;- Mean and diastolic pulmonary artery pressure&lt;br&gt;- Assessment of pulmonary stenosis at suture line</td>
</tr>
<tr>
<td><strong>Parasternal short-axis at papillary muscle level</strong></td>
<td>2D loop + M-mode&lt;br&gt;Subject to assess and parameters to measure&lt;br&gt;- LV wall thickness&lt;br&gt;- LV global and LV regional systolic function - mid-ventricular segments&lt;br&gt;- IVS morphology and movement&lt;br&gt;- Pericardium</td>
</tr>
<tr>
<td><strong>Apical 4-chamber</strong></td>
<td>2D loop + color Doppler for MV + CW and PW for MV&lt;br&gt;Subject to assess and parameters to measure&lt;br&gt;- Left atrium morphology and volume&lt;br&gt;- Mitral valve morphology and function, Anterograde and retrograde flow</td>
</tr>
<tr>
<td><strong>Apical 2-chamber</strong></td>
<td>2D loop + color Doppler for MV + CW and PW for MV&lt;br&gt;Subject to assess and parameters to measure&lt;br&gt;- Left atrium morphology and volume&lt;br&gt;- Mitral valve morphology and function, Anterograde and retrograde flow</td>
</tr>
<tr>
<td><strong>LV focused apical 4-chamber</strong></td>
<td>2D loop&lt;br&gt;Subject to assess and parameters to measure&lt;br&gt;- LV volumes and function&lt;br&gt;- LV regional systolic function&lt;br&gt;- IVS evaluation</td>
</tr>
<tr>
<td><strong>LV focused apical 2-chamber</strong></td>
<td>2D loop&lt;br&gt;Subject to assess and parameters to measure&lt;br&gt;- LV volumes and function&lt;br&gt;- LV regional systolic function</td>
</tr>
<tr>
<td><strong>RV focused apical 4-chamber</strong></td>
<td>2D loop + M-mode&lt;br&gt;Subject to assess and parameters to measure&lt;br&gt;- Right ventricle morphology, diameters and motion abnormalities</td>
</tr>
<tr>
<td><strong>Parasternal long-axis of aorta</strong></td>
<td>2D loop + color Doppler for AV&lt;br&gt;Subject to assess and parameters to measure&lt;br&gt;- Aorta diameters and morphology&lt;br&gt;- Aortic valve morphology and function&lt;br&gt;- Suture line&lt;br&gt;- LV outflow diameter</td>
</tr>
<tr>
<td><strong>Parasternal short-axis at aortic valve level</strong></td>
<td>2D loop + color Doppler for AV and TV + CW Doppler for TV&lt;br&gt;Subject to assess and parameters to measure&lt;br&gt;- Aortic valve morphology and function&lt;br&gt;- Tricuspid valve morphology and function, Anterograde and retrograde flow velocities&lt;br&gt;- RV outflow diameter</td>
</tr>
<tr>
<td><strong>Parasternal short-axis at mitral valve level</strong></td>
<td>2D loop + M-mode + color Doppler for MV&lt;br&gt;Subject to assess and parameters to measure&lt;br&gt;- Mitral valve morphology and function&lt;br&gt;- LV regional systolic function - basal segments&lt;br&gt;- Pericardium</td>
</tr>
<tr>
<td><strong>Apical 4-chamber</strong></td>
<td>2D loop + color Doppler for MV + CW and PW for MV&lt;br&gt;Subject to assess and parameters to measure&lt;br&gt;- Left atrium morphology and size&lt;br&gt;- Pulmonary vein flow pattern and velocities&lt;br&gt;- Mitral and tricuspid valve morphology and function, Anterograde and retrograde flow&lt;br&gt;- IAS evaluation</td>
</tr>
<tr>
<td><strong>Apical 3-chamber</strong></td>
<td>2D loop + color Doppler for MV and AV&lt;br&gt;Subject to assess and parameters to measure&lt;br&gt;- Left atrium morphology&lt;br&gt;- Mitral valve morphology and function, Anterograde and retrograde flow&lt;br&gt;- Aortic valve morphology and function, Anterograde and retrograde flow velocities</td>
</tr>
<tr>
<td><strong>LV focused apical 5-chamber</strong></td>
<td>2D loop&lt;br&gt;Subject to assess and parameters to measure&lt;br&gt;- LV regional systolic function&lt;br&gt;- IVS evaluation</td>
</tr>
<tr>
<td><strong>LV focused apical 3-chamber</strong></td>
<td>2D loop&lt;br&gt;Subject to assess and parameters to measure&lt;br&gt;- LV function&lt;br&gt;- LV regional systolic function</td>
</tr>
<tr>
<td><strong>LV focused apical 3-chamber</strong></td>
<td>2D loop&lt;br&gt;Subject to assess and parameters to measure&lt;br&gt;- LV function&lt;br&gt;- LV regional systolic function</td>
</tr>
<tr>
<td><strong>TAPSE</strong></td>
<td>M-mode&lt;br&gt;Parameters to measure&lt;br&gt;- Tricuspid annulus displacement</td>
</tr>
</tbody>
</table>

*Continued*
New wall motion abnormalities have been reported to be associated with the presence of CAV yielding a low sensitivity but a high specificity (69–100%). Detection of new wall motion abnormalities at rest should raise suspicion of progression of CAV, encouraging further tests to rule out this hypothesis. Side-by-side visualization of the current echocardiographic study with a previous one (or baseline one) will increase both sensitivity and specificity of new wall motion abnormality detection.

**LV diastolic function**
Changes in LV diastolic function are a more sensitive marker of acute GR than the reduction of LV EF. Early investigators found a clear relationship between severe impairment of diastolic function and development of graft failure. Evidence that has been collected so far suggest that rejection episodes may alter the diastolic dynamics of the heart earlier than the EF. This is probably caused by myocardial oedema or by initial fibrosis, which stiffens the LV myocardium. Impairment of diastolic function has been reported during episodes of acute GR with a subsequent improvement after effective treatment. A stiffer heart may also result from chronic GR. Moreover, diastolic dysfunction with a preserved LV EF has been associated with worse long-term prognosis, development of heart failure symptoms, higher number of rejection episodes and cumulative immune-mediated graft damage. Unfortunately, studies that attempted to correlate indexes of diastolic dysfunction (including pulmonary vein flow pattern, transmitral velocity of propagation) and myocardial performance index (MPI) with acute GR episodes have shown conflicting results. Table 7 summarizes the accuracy of different echocardiographic techniques to detect acute GR.

Doppler indices of mitral inflow have been the most widely investigated parameters. The filling pattern is usually more preserved in the bicaval technique surgery, because with this technique atrial contraction is kept more physiologic. Mena et al. performed a systematic review and found 19 good quality studies from 1985 to 2005 about the use of transmitral Doppler diastolic indexes (E wave, A wave, E/A ratio, deceleration time, isovolumic relaxation time) in predicting acute GR. They were unable to demonstrate any significant correlation between variations of LV filling parameters and proved acute GR. Other studies evaluated pulmonary vein flow parameters and mitral inflow propagation velocity, but again they were unable to demonstrate any clear correlation between these parameters and acute GR severity. Moreover, these parameters have been reported to be abnormal even in some 'healthy' HT patient. Unfortunately, the assessment of LV filling is affected by many variables, including pre-load conditions, atrial dynamics and morphology (dissociation of recipient and donor atrial contraction), LV compliance and contractility, end-systolic volume, and heart rate. Therefore, diastolic function may be impaired by different reasons and is therefore not specific to rejections. Finally, high heart rate, usually present in the denervated heart, makes the assessment of diastolic function more difficult due to the frequent fusion of E and A waves. Nevertheless, we recommend to continue evaluating diastolic parameters, because the occurrence of diastolic dysfunction carries significant prognostic value in any case and because the diagnosis of acute GR becomes increasingly accurate when additional echocardiographic parameters are impaired.

Based on the concept that GR affects both LV and RV diastolic and systolic function simultaneously, MPI has been proposed as an early marker of rejection in HT patients. At present, the accuracy of MPI to detect acute GR in HT patients is controversial. Tona et al. evaluated the role of MPI as a marker of long-term allograft dysfunction in 154 patients and found a progressive increase in MPI during long-term follow-up in HT patients with preserved LV systolic function. MPI resulted higher in patients with multiple rejection episodes but no correlation was found with the occurrence of CAV. Usually, DTI parameters are useful to improve the accuracy of the assessment of LV diastolic function. However, in HT patients the role of myocardial velocities should be interpreted with caution, because velocities may be affected by the exaggerated translation motion of the transplanted heart. Similarly to transmitral LV filling parameters, several studies have looked into the ability of DTI parameters to predict acute GR. In normal HT patients, LV e’ and s’ wave velocities tend to be low in the first weeks after transplantation and
then they increase gradually. After 1 year, DTI velocities in HT patients tend to be lower compared with the normal population. Dandel et al. and Puleo et al. found a strong association between the reduction of e′ wave velocity and episodes of acute GR and CAV, whereas Stengel et al. failed to confirm this finding. Due to high specificity of DTI parameters, severe rejection could be safely excluded in the presence of a mitral annular a′ wave velocity 9 cm/s, 10% reduction in diastolic mitral annular motion velocities. Similarly, Sun et al. described a large cohort of HT patients (264 patients with 400 echocardiographic studies performed) followed up to 3 years after HT. Based on EMB results, patients were divided into no rejection (ISHLT grade 0 and 1a) and rejection (ISHLT grade 1B or higher) groups. The authors found that several echocardiographic parameters were statistically different between the two groups. Patients in the rejection group showed more pericardial effusion (but with a high prevalence of pericardial effusion in both groups), shorter IVRT (<90 ms), and greater peak velocity and duration of Ar wave and a′ wave at both septal and lateral LV walls. However, the authors could not confirm the previous results on e′ wave reduction as a marker of acute GR, probably because of the different definition of the rejection group (in Dandel’s study, acute GR was defined as more than Grade 2 ISHLT rejection score). Notably, there was a significant correlation between the number of abnormal echocardiographic parameters and rejection grade. On the other hand, a completely normal echocardiographic examination provided a high negative predictive value for detecting acute GR at EMB. Mankad et al. combined peak systolic wave Doppler (s′ wave) together with peak diastolic e′ wave velocity (evaluated at lateral mitral annulus) in a new index, the peak-to-peak mitral annular velocity. They found that values equal or higher than 135 mm/s have a sensitivity of 93%, specificity of 71%, and a negative predictive value of 98% in excluding acute GR (defined as greater than grade 1B.

### Table 4  Doppler tracings and measurements to be routinely performed in patients who underwent heart transplant

<table>
<thead>
<tr>
<th>Septal Mitral Annulus</th>
<th>Acquisition techniques</th>
<th>PW Tissue Doppler Parameters to measure - Mitral annulus displacement velocities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral Anterograde Flow</td>
<td>Acquisition techniques</td>
<td>PW Doppler Parameters to measure - E and A wave velocities - E wave deceleration time</td>
</tr>
<tr>
<td>LVOT Flow</td>
<td>Acquisition techniques</td>
<td>PW Doppler Parameters to measure - LVOT anterograde flow velocities and VTI</td>
</tr>
<tr>
<td>Tricuspid Anterograde Flow</td>
<td>Acquisition techniques</td>
<td>PW Doppler Parameters to measure - E wave velocities</td>
</tr>
<tr>
<td>Pulmonary Regurgitant Flow</td>
<td>Acquisition techniques</td>
<td>CW Doppler Parameters to measure - Pulmonary regurgitant flow velocities - Pulmonary artery pressures</td>
</tr>
<tr>
<td>Lateral Mitral Annulus</td>
<td>Acquisition techniques</td>
<td>PW Tissue Doppler Parameters to measure - Mitral annulus displacement velocities</td>
</tr>
<tr>
<td>Pulmonary Vein Flow</td>
<td>Acquisition techniques</td>
<td>PW Doppler Parameters to measure - Ar wave peak velocity and duration</td>
</tr>
<tr>
<td>Aortic Anterograde Flow</td>
<td>Acquisition techniques</td>
<td>CW Doppler Parameters to measure - Aortic anterograde flow velocities and VT - Aortic gradients</td>
</tr>
<tr>
<td>Tricuspid Regurgitant Flow</td>
<td>Acquisition techniques</td>
<td>CW Doppler Parameters to measure - Maximum regurgitant flow velocity</td>
</tr>
<tr>
<td>Pulmonary Anterograde Flow</td>
<td>Acquisition techniques</td>
<td>PW Doppler Parameters to measure - Pulmonary anterograde flow acceleration time - Pulmonary artery pressure</td>
</tr>
</tbody>
</table>

CW, continuous wave; LVOT, left ventricular outflow tract; PW, pulsed wave; TVI, time-velocity integral.
ISHHLT rejection score at EMB). Palka et al. tested the hypothesis that during acute GR, there is an alteration of early diastolic untwist mechanisms of the LV and that this alteration may affect the RV too. Thus, they tested the differences in diastolic movements of LV and RV walls, by measuring timing differences between onset of early diastolic mitral inflow velocity ($E$) and onset of $e'$ velocity at lateral annulus, at septal annulus ($e'$ sep), and at tricuspid annulus ($e'$ tri). They found that increased time differences between the onset of $E$ and $e'$ septal annulus waves and between the onset of $e'$ of RV and LV lateral wall waves could help to discriminate patients. However, none of the evaluated parameters were significant enough to be used as a surveillance variable.

Finally, Bader et al. in a prospective study involving 54 HT patients did not find any echocardiographic parameters to be able to reliably predict acute GR assessed by EMB, and this result was confirmed by another smaller study. In conclusion, constant DTI velocities (e.g. $e'$ change <10% compared with baseline) and high DTI velocities (e.g. $e'$ >16 cm/s) seem to have good accuracy to exclude (more than detect) acute GR, with a negative predictive value of 92%. However, these parameters need further validation.

Echocardiographic evaluation of LV systolic and diastolic function is of great importance to detect GR. However, there is large discordance among the different studies. Alterations of diastolic and/or systolic function may be due to rejection, or other cardiac conditions like ischaemia, hypoxia, and sepsis. Therefore, the presence of alterations in LV function has an important role in the assessment of prognosis in HT patients, but it is not an accurate marker of GR or CAV. Some groups are proposing echocardiographic scores to rule out active rejection; however, there is a need for more extensive studies with larger sample sizes before these scores could be implemented in clinical practice.

### Recommendations

Obtain a comprehensive echocardiographic study at 6 months from the cardiac transplantation as a baseline and make a careful quantitation of cardiac chamber size, RV systolic function, both systolic and diastolic parameters of LV function, and pulmonary artery pressure. Subsequent echocardiographic studies should be interpreted in comparison with the data obtained from the 6-month study. An echocardiographic study, which shows no change from the baseline study, has a high negative predictive value for GR. There is no single systolic or diastolic parameter that can be reliably used to diagnose GR. However, in case several parameters are abnormal the likelihood of GR increases. When an abnormality is detected, careful revision of images of the present and baseline study (side-by-side) is highly recommended.
RV geometry and function
Right heart failure is a common and much feared complication after HT, being the single most important cause of death in the early post period, together with acute GR. Immediately after HT, the RV cavity size increases due to afterload mismatch with the relatively high pulmonary pressures of the recipient. Indeed, normalization in RV cavity size is expected the following weeks along with the progressive reduction of pulmonary resistances. Impaired RV longitudinal systolic function measured by TAPSE, DTI, and RV fractional area change is also present in all HT patients in the early weeks after HT, and two-thirds of HT patients show a partial recovery of RV longitudinal function during the first year, even if TAPSE remains significantly lower compared with normal. The incomplete recovery of RV systolic function after HT can be explained by pre-transplant pulmonary pressures, increased post-transplant pulmonary gradient, significant tricuspid regurgitation, and prolonged ischaemia time. However, it is well established that the RV longitudinal function is not a sensitive parameter of global RV function after cardiac surgery.

Atrial geometry and function
Atrial geometry and function of the transplanted heart are directly related to the surgical technique. In patients who underwent HT using the standard technique, a unique morphological shape is visualized by echocardiography (best seen in the apical four-chamber view) as an enlargement of the long-axis dimension of the atria with a ridge at the site of anastomosis (Figure 2A and B). In patients who underwent HT using the bicaval or total orthotopic HT techniques, the atrial geometry and function are better preserved.

Recommendations

**Assess RV size and function at baseline using several parameters, which do not exclusively evaluate longitudinal function. At follow-up echocardiogram, all these parameters should be compared with the baseline values.** 3D echocardiography may provide a more accurate and comprehensive assessment of RV size and function.

Cardiac valves

**Tricuspid valve**
Tricuspid valve regurgitation is the most common single valve disease after HT. It may result from multiple pathophysiological mechanisms. In the first weeks after HT, tricuspid regurgitation is usually secondary to pulmonary hypertension. Its severity often decreases spontaneously as pulmonary resistance decreases. Other frequent causes of tricuspid regurgitation are persistent high pulmonary pressures, tricuspid annulus enlargement secondary to RV dilation, lesion of valve apparatus during EMB, acute GR, papillary muscle dysfunction, and alterations in right atrial contraction with functional impairment of the valvular apparatus. The surgical technique used for HT seems to influence the occurrence of tricuspid regurgitation because of the alteration of right atrial morphology.

**Aortic and mitral valves**
Structural alterations of left-sided valves are uncommon after HT, and changes in morphology and dimension of these valve structures have not been associated with acute GR. Rates of mitral regurgitation are slightly higher than the aortic regurgitation (attributed to...
### Table 7  Accuracy of different echocardiography techniques to detect acute graft rejection

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (prevalence of acute GR)</th>
<th>Method (parameter cut-off value)</th>
<th>Gold standard (EMB score)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angermann et al.</td>
<td>52 (18%)</td>
<td>Integrated backscatter (PW 2D-IB increase &gt; 1.5 dB)</td>
<td>Grade ≥ 1B</td>
<td>88</td>
<td>89</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Septal 2D-IB increase &gt; 1.5 dB)</td>
<td></td>
<td>83</td>
<td>85</td>
<td>96</td>
</tr>
<tr>
<td>Puleo et al.</td>
<td>121 (13%)</td>
<td>PW-DTI (e’ of inferior wall &lt; 16 cm/s)</td>
<td>Grade ≥ 3A</td>
<td>76</td>
<td>88</td>
<td>96</td>
</tr>
<tr>
<td>Mankad et al.</td>
<td>78 (18%)</td>
<td>Colour-coded TDI (combined peak MV systolic and peak diastolic velocity &lt; 135 mm/s)</td>
<td>Grade ≥ 1B</td>
<td>93</td>
<td>71</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(posterior wall tissue Doppler diastolic time-gradient integral &lt; 0.26)</td>
<td></td>
<td>91</td>
<td>61</td>
<td>97</td>
</tr>
<tr>
<td>Moidl et al.</td>
<td>94 (20%)</td>
<td>Automated border detection (peak filling rate &lt; 4.0 EDV/s and &lt; 18% reduction)</td>
<td>Grade ≥ 2</td>
<td>100</td>
<td>70</td>
<td>100</td>
</tr>
<tr>
<td>Stengel et al.</td>
<td>41 (39%)</td>
<td>PW-DTI (As of lateral MV annulus &lt; 8.7 cm/s)</td>
<td>Grade ≥ 3A</td>
<td>82</td>
<td>53</td>
<td>82</td>
</tr>
<tr>
<td>Dandel et al.</td>
<td>408 (39.9%)</td>
<td>Sm reduction &gt; 10%</td>
<td>Clinically relevant</td>
<td>88.3</td>
<td>94</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TSm reduction &gt; 10%</td>
<td></td>
<td>82.3</td>
<td>94</td>
<td>90.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Em reduction &gt; 10%</td>
<td></td>
<td>86.6</td>
<td>96</td>
<td>92.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TEm reduction &gt; 10%</td>
<td></td>
<td>91.6</td>
<td>92</td>
<td>94.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sm/TSm reduction &gt; 10%</td>
<td></td>
<td>86.6</td>
<td>96</td>
<td>92.4</td>
</tr>
<tr>
<td>Vivekananthan et al.</td>
<td>40 (50%)</td>
<td>MPI increase ≥ 20% from baseline evaluation</td>
<td>Grade ≥ 3A</td>
<td>90</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Dandel et al.</td>
<td>190 (17%)</td>
<td>PW-DTI (Sm of basal posterior wall reduction &gt; 10%)</td>
<td>Clinically relevant</td>
<td>88</td>
<td>95</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Es of basal posterior wall reduction &gt; 10%)</td>
<td></td>
<td>89</td>
<td>97</td>
<td>98</td>
</tr>
<tr>
<td>Palka et al.</td>
<td>44 (27%)</td>
<td>PW and colour M-mode TDI (e’ of septal MV annulus &lt; 12 cm/s)</td>
<td>Grade ≥ 3A</td>
<td>69</td>
<td>46</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(peak late IVR MVG &gt; 0.1/s)</td>
<td></td>
<td>88</td>
<td>58</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(onset E wave – onset Em &gt; − 35 ms)</td>
<td></td>
<td>81</td>
<td>84</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(onset ETric – onset EMitr &gt; 15 ms)</td>
<td></td>
<td>81</td>
<td>84</td>
<td>92</td>
</tr>
<tr>
<td>Sun et al.</td>
<td>223 (37%)</td>
<td>2D and standard Doppler (≥ 2 among PE, IVRT &lt; 90 ms)</td>
<td>Grade ≥ 1B</td>
<td>57</td>
<td>54</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>183 (27%)</td>
<td>E/A &gt; 1.7)</td>
<td></td>
<td>60</td>
<td>93</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>264 (29%)</td>
<td>Post-OHT ≤ 6 months</td>
<td></td>
<td>67</td>
<td>49</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-OHT &gt; 6 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PW-DTI (Aa of septal/lateral MV annulus &lt; 0.9 cm/s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marciniak et al.</td>
<td>31 (32%)</td>
<td>Colour DTI (mild-LVPW radial peak systolic strain ≤ 30%)</td>
<td>Grade ≥ 1B</td>
<td>85</td>
<td>90</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(mild-LVPW radial peak systolic SR &lt; 3.0 s⁻¹)</td>
<td></td>
<td>80</td>
<td>86</td>
<td>90</td>
</tr>
</tbody>
</table>

Aa, peak late diastolic velocity; acute GR, acute graft rejection; dB, decibels; Ea, peak early diastolic velocity; EDV, end-diastolic volume; Em, peak early diastolic wall motion velocity; EMB, endomyocardial biopsy; OHT, orthotropic heart transplantation; IVRT, isovolumetric relaxation time; LVPW, left ventricle posterior wall; MPI, myocardial performance index; MV, mitral valve; NPV, negative predictive value; PE, pericardial effusion; PW 2D-IB, pulsed-wave 2-dimensional-integrated backscatter; Sm, peak radial systolic velocity; SR, strain rate; TDI, tissue Doppler imaging; TEm, early diastolic time—from onset of second heart sound to the peak of the early diastolic wave Em; TSm, systolic time—from onset of first heart sound to the peak of the systolic wave Sm.

*Prevalence of acute GR based on the percentage of biopsies with acute GR defined by the EMB score.

Clinically relevant acute GR defined as EMB grade > 2 plus Grades 1A and 1B when accompanied by clinical symptoms.

Peak late isovolumic relaxation myocardial velocity gradient of the LV posterior wall.

Timing difference between onset of mitral early diastolic velocity (E wave) and early diastolic septal MV annulus velocity (Emed).

Timing difference between onset of early diastolic velocity, a lateral tricuspid (ETric) annulus, and an LV early diastolic lateral MV annulus velocity (Emitr).
Oedema of the papillary muscles) but tend to decrease over time and it is usually mild mitral regurgitation.73,113

**Recommendations**

Tricuspid regurgitation should be looked for and properly assessed in all echocardiographic studies. In case of significant changes in severity of tricuspid regurgitation during follow-up, a 2D/3D and colour Doppler assessment of its severity and mechanisms should be performed. Aortic and mitral valves should be evaluated according to current recommendations.

**Aorta and pulmonary artery**

The anastomoses of the donor heart to the aorta and pulmonary artery can be visualized (Figure 6, left panel). In the normal transplanted heart, Doppler flow velocities at the aortic and pulmonic level are usually normal. Occasionally, there is a mismatch between the diameter of the donor and recipient proximal pulmonary arteries and the suture line in the proximal pulmonary artery offers an aspect of ‘pseudo-narrowing’. However, no significant gradient is usually detected by Doppler. The aortic anastomosis may also be a site of potential surgical complications. An echocardiographic evaluation of the aorta assessing diameters and potential wall thinning or leaking are recommended. Few reports have described the occurrence of aortic rupture, pseudoaneurysms, aneurysms, or dissection related to compliance mismatch, flow turbulence, and systemic hypertension.114

**Superior and inferior vena cavae**

Special attention should be paid to the superior vena cava, particularly in patients operated with non-standard surgical technique, since stenosis at the level of the surgical anastomosis has been described in 2.4% of these cases.24

**Pericardium**

Documentation of new pericardial effusion has been reported to be associated with GR.115 However, the presence of pericardial effusion per se is not due to GR and its high prevalence in HT patients, as an early response to surgical ‘injury’ or as compensation for differences in volumes between the recipient and the donor heart size, results in low sensitivity and specificity to detect GR.71 It is seen in approximately two-thirds of patients at 3 months after HT, and in 25% of patients at 6 months, independent of GR status.71

A localized intrapericardial haematoma may occur early or late after open heart surgery and not uncommonly is localized anterior and lateral to the right atrium making the diagnosis with trans-thoracic echocardiography challenging. If the haematoma is large or if it is an expanding one, it may compress the right atrium and cause haemodynamic impairment (e.g. low output state) resembling acute GR.

**Recommendations**

Pericardial effusion should be serially evaluated regarding extent, location, and haemodynamic impact. In case of newly detected pericardial effusion, GR should be considered taking into account the overall echocardiographic assessment and patient evaluation.

**Advanced echocardiography**

**Deformation imaging (speckle tracking and Doppler TISSUE imaging)**

Strain and strain rate (SR) are parameters of myocardial deformation. First assessment of strain and SR was derived from DTI velocity data, and several studies evaluated diagnostic accuracy of these parameters in OHT patients.91,116,117 Overall, the majority of the studies found that, even if conventional echocardiographic examination (including DTI) and right heart catheterization did not reveal any significant changes compared with previous studies, global longitudinal peak systolic strain (GLS) was reduced in patients with histologically proven acute GR. Moreover, segmental longitudinal strain was reduced in LV segments, which showed inducible...
wall motion abnormalities during stress test, and strain values could predict CAV. This may be explained by the fact that the regional changes induced by patchy rejection may not be large enough to alter global LV function indices, as rejection can be a non-uniform process.91 This also explains the relative insensitivity in detecting < Grade IIB rejection using global LV function parameters. In the study by Marciniak et al.,91 the authors postulated that subclinical myocardial modifications secondary to early acute GR are best detected by techniques that do not rely on reference points external to the heart to be able to detect regional changes in systolic function. They found that radial peak systolic strain was significantly reduced in the group with EMB-proved rejection. However, only regional strain/SR from the LV lateral wall was predictive with acute GR, and not the strain/SR from the septum, probably due to paradoxical septal motion that is common after cardiac surgery.

2D-Speckle tracking echocardiography (STE) is an echocardiographic technique that overcomes several limitations of DTI derived strain/SR (Figures 7 and 8). This technique has been proved to be accurate for the quantification of myocardial deformation, and it has already been validated in special subset of patients as an early marker of myocardial dysfunction.118 The first studies of STE in HT have been conducted in rats in which both global strain and peak systolic or diastolic strain were significantly reduced in graft with alloimmune rejection, while LV EF and fractional shortening did not show any difference between hearts with and without rejection.117 The study by Eleid et al.120 was the first one to use STE to assess myocardial function in HT patients. During a 3-year follow-up of 51 HT patients, they were able to show that all patients showed a reduced GLS immediately after HT, but those who did not improve their GLS during follow-up experienced higher incidence of death and cardiac events. These results were independent from biopsy-detected acute GR, suggesting that STE is able to detect early and subtle alteration of LV systolic function, which may carry a poor prognosis even in the absence of detectable acute GR.

Many studies demonstrated that strain/SR measurements are abnormal in many clinical settings with preserved LV EF; thus, it is uncertain whether the lower GLS values found in transplanted heart recipients represent normal values of this population or are the first subtle alterations that consequently lead to myocardial dysfunction.121–123 Nevertheless, these studies confirm that longitudinal strain values remain stable (even if lower in absolute values compared with general population) over the years and therefore a reduction over time of such parameters must be interpreted as pathological. Accordingly, Lisi et al. described a case of biopsy-proven acute GR associated with marked reduction in longitudinal, radial, and circumferential strain, with no alteration of other echocardiographic parameters, and complete recovery of myocardial deformation parameters after appropriate immunosuppressive therapy and regression of acute GR at the biopsy.124 Table 8 summarizes the results of the different studies which tested the accuracy of STE in detecting acute GR.

In 167 patients studied with STE during the first weeks after transplantation, GLS has been reported to be an independent predictor of 1-year mortality. Using a cut-off value of –9%, the sensitivity was
73% and the specificity was 91%. However, because the causes of death in the cohort were various (from acute GR to CAV, HIT, and sepsis), no suggestion can be made on the relation between low GLS and the presence of acute GR and/or CAV at autopsy. Moreover, there were no differences in GLS, early after HT, among patient who experienced rejection within the first year and in those who did not. Therefore, from this study, GLS can be regarded as a predictor of poor clinical outcome but not as a sensitive marker of rejection.

Recently, an echocardiographic rejection score was proposed considering a multiparametric evaluation according to the formula: 

\[
\text{Score} = (\text{PWT} + \text{LVMI}) - (\text{Lat-e} + \text{Sep-TS})
\]

where PWT (posterior wall thickness measured in mm); LVMI (LV mass index in g/m²); Lat-e (lateral peak systolic strain); and Sep-TS (septal time to systole.

**Table 8** Accuracy of the different parameters obtained with speckle tracking echocardiography to detect acute graft rejection

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of biopsies (prevalence of acute GR)*</th>
<th>STE method (parameter cut-off value)</th>
<th>Gold standard (EMB score)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Predictive accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sato et al.</td>
<td>301 (8.9%)</td>
<td>25% reduction in LV torsion values compared with baseline values</td>
<td>Grade ≥ 2</td>
<td>73.7</td>
<td>95.1</td>
<td>92.9</td>
</tr>
<tr>
<td>Kato et al.</td>
<td>396 (11.3%)</td>
<td>Systolic e = −27.4% Diastolic SR = 2.8 s⁻¹</td>
<td>Grade ≥ 1b²</td>
<td>82.2</td>
<td>82.3</td>
<td>82.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>75.6</td>
<td>74.9</td>
<td>75</td>
</tr>
<tr>
<td>Marciniak et al.</td>
<td>106 (16.9%)</td>
<td>LV PW radial e ≤ 30% SR ≤ 3.0 s⁻¹</td>
<td>Grade ≥ 1b²</td>
<td>85</td>
<td>90</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>80</td>
<td>86</td>
<td>89</td>
</tr>
</tbody>
</table>

E, strain; GR, graft rejection; LV, left ventricle; PW, posterior wall; SR, strain rate; STE, speckle tracking echocardiography.
*Prevalence of acute GR based on the percentage of biopsies with acute GR defined by the EMB score.
*ISHLT 1990 classification criteria for acute GR.
in ms). This score has been proved to be useful to discard an acute GR episode (with 100% negative predictive value), when the result is 0. Further studies are needed to prove the utility of this score as a screening tool to rule out the presence of acute GR and avoid an EMB.

### Recommendations

GLS is a suitable parameter to diagnose subclinical allograft dysfunction, regardless of aetiology, by comparing the changes occurring during serial evaluations. Evaluation of GLS could be used in association with EMB to characterize and monitor an acute GR or a global dysfunction episode.

### Stress echocardiography

Stress echocardiography has been reported to increase the specificity in detecting CAV. Dobutamine has been the most frequently used pharmacological stressor and a sensitivity between 70 and 80% to detect significant CAV at coronary angiography has been reported (Table 9). Due to the diminished heart rate response to exercise, related to cardiac denervation state, exercise protocols have a limited sensitivity of 15–33%. When intimal thickening by IVUS is used as the gold standard, dobutamine stress echocardiography increases its specificity up to 88%. Even considering non-focal and non-significant stenotic disease, the sensitivity of dobutamine stress echocardiography remains high. Deterioration between serial stress echocardiography tests yields an increased risk of events, compared with no deterioration, with a relative risk of 7.3. A positive dobutamine test was found to be an independent predictor of cardiac events or death in a 4-year follow-up study by Bacal et al. On the other hand, a negative stress test indicates a low likelihood of a prognostically relevant CAV and low rate of occurrence of major adverse cardiac event at 1 year. Quantitative analysis of segmental LV function, considering a peak systolic longitudinal strain rate increase of >0.5/s at peak stress test as a pathological response, improves the sensitivity to 88% for detecting any angiographic abnormalities and with negative predictive value of 92%. A post-systolic strain index >34% at peak stress was reported to be the best parameter to detect CAV. Combination of myocardial contrast echocardiography with quantitative assessment of myocardial perfusion during dobutamine stress echocardiography has been reported to increase the sensitivity from

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (prevalence of CAV)</th>
<th>Stress</th>
<th>Reference for CAV</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collings et al.</td>
<td>51 (27%)</td>
<td>Exercise</td>
<td>Angiography&lt;sup&gt;a&lt;/sup&gt;</td>
<td>29</td>
<td>82</td>
</tr>
<tr>
<td>Mairesse et al.</td>
<td>37 (11%)</td>
<td>Exercise</td>
<td>Angiography&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0</td>
<td>97</td>
</tr>
<tr>
<td>Cohn et al.</td>
<td>51 (51%)</td>
<td>Exercise</td>
<td>Angiography&lt;sup&gt;c&lt;/sup&gt;/IVUS&lt;sup&gt;d&lt;/sup&gt;</td>
<td>33/15</td>
<td>85</td>
</tr>
<tr>
<td>Ciliberto et al.</td>
<td>80 (31%)</td>
<td>Dipyridamole</td>
<td>Angiography&lt;sup&gt;a&lt;/sup&gt;</td>
<td>100</td>
<td>72</td>
</tr>
<tr>
<td>Ciliberto et al.</td>
<td>68 (37%)</td>
<td>Dipyridamole</td>
<td>Angiography&lt;sup&gt;a&lt;/sup&gt;</td>
<td>100</td>
<td>87</td>
</tr>
<tr>
<td>Akosah et al.</td>
<td>41 (51%)</td>
<td>Dobutamine</td>
<td>Angiography&lt;sup&gt;a&lt;/sup&gt;</td>
<td>100</td>
<td>41</td>
</tr>
<tr>
<td>Herregods et al.</td>
<td>28 (50%)</td>
<td>Dobutamine</td>
<td>Angiography&lt;sup&gt;a&lt;/sup&gt;</td>
<td>50</td>
<td>71</td>
</tr>
<tr>
<td>Akosah et al.</td>
<td>45 (53%)</td>
<td>Dobutamine</td>
<td>Angiography&lt;sup&gt;a&lt;/sup&gt;</td>
<td>96</td>
<td>52</td>
</tr>
<tr>
<td>Derumeaux et al.</td>
<td>41 (38%)</td>
<td>Dobutamine</td>
<td>Angiography&lt;sup&gt;a&lt;/sup&gt;</td>
<td>100</td>
<td>77</td>
</tr>
<tr>
<td>Derumeaux et al.</td>
<td>64 (47%)</td>
<td>Dobutamine</td>
<td>Angiography&lt;sup&gt;a&lt;/sup&gt;</td>
<td>100</td>
<td>NR</td>
</tr>
<tr>
<td>Spes et al.</td>
<td>46 (26%)</td>
<td>Dobutamine</td>
<td>Angiography&lt;sup&gt;a&lt;/sup&gt;/IVUS&lt;sup&gt;d&lt;/sup&gt;</td>
<td>83/79</td>
<td>56/83</td>
</tr>
<tr>
<td>Akosah et al.</td>
<td>22 (32%)</td>
<td>Dobutamine</td>
<td>Angiography&lt;sup&gt;a&lt;/sup&gt;</td>
<td>100</td>
<td>59</td>
</tr>
<tr>
<td>Derumeaux et al.</td>
<td>37 (46%)</td>
<td>Dobutamine</td>
<td>Angiography&lt;sup&gt;a&lt;/sup&gt;</td>
<td>65</td>
<td>95</td>
</tr>
<tr>
<td>Spes et al.</td>
<td>37 (70%)</td>
<td>Dobutamine</td>
<td>Angiography&lt;sup&gt;a&lt;/sup&gt;</td>
<td>92</td>
<td>73</td>
</tr>
<tr>
<td>Bacal et al.</td>
<td>109 (46%)</td>
<td>Dobutamine</td>
<td>Angiography&lt;sup&gt;a&lt;/sup&gt; and/or IVUS&lt;sup&gt;d&lt;/sup&gt;</td>
<td>72</td>
<td>88</td>
</tr>
<tr>
<td>Eroglu et al.</td>
<td>39 (38%)</td>
<td>Dobutamine</td>
<td>Angiography&lt;sup&gt;a&lt;/sup&gt;</td>
<td>64</td>
<td>91</td>
</tr>
<tr>
<td>Rodrigues et al.</td>
<td>42 (19)</td>
<td>Dobutamine</td>
<td>Angiography&lt;sup&gt;a&lt;/sup&gt;</td>
<td>63&lt;sup&gt;e&lt;/sup&gt;</td>
<td>88&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tona et al.</td>
<td>35 (29%)</td>
<td>Contrast-enhanced</td>
<td>Angiography&lt;sup&gt;a&lt;/sup&gt;</td>
<td>70</td>
<td>96</td>
</tr>
<tr>
<td>Rodrigues et al.</td>
<td>73 (47%)</td>
<td>Contrast-enhanced</td>
<td>Angiography&lt;sup&gt;a&lt;/sup&gt;</td>
<td>82</td>
<td>87</td>
</tr>
</tbody>
</table>

CAV, cardiac allograft vasculopathy; IVUS, intravascular ultrasound.
<sup>a</sup>Coronary stenosis >50% in at least 1 vessel.
<sup>b</sup>Any angiographic abnormalities including luminal irregularities.
<sup>c</sup>Stanford classification Grade III to IV.
<sup>d</sup>Approximating to Stanford classification Grade III–IV; angiographic luminal irregularities or intravascular ultrasound (IVUS) severity approximating to Stanford classification Grade III–IV.
<sup>e</sup>Conventional regional wall motion analysis.
<sup>f</sup>Regional peak systolic strain rate analysis.
Quantitative myocardial perfusion by contrast echocardiography

An advantage of quantitative contrast myocardial perfusion echocardiography is that it provides both structural (rBV—the vascular density relative to the surrounding tissue) and functional (B—microvascular conductance index) parameters, which actually constitute the microvasculature at the arteriolar and capillary level. An rBV value < 0.14 at rest can accurately detect severe CAV with a sensitivity of 90% and specificity of 75%. However, because quantitative analysis is a time-consuming procedure, requiring specialized trained personnel and because the software analysis is not widespread, myocardial perfusion imaging is currently assessed semiquantitatively by visual analysis.

Echocardiographic evaluation of coronary flow reserve

Direct measurement of coronary blood flow velocity at rest and during adenosine stress in the distal left anterior descending artery, using transthoracic Doppler echocardiography, could be applied and used to calculate the ratio between peak test velocity/baseline velocity which correlates with invasively measured coronary flow reserve (CFR). A CFR ≤ 2.7 by transthoracic echocardiography has demonstrated good accuracy (87% specific and 82% sensitive) for detecting CAV. In addition, echocardiographic CFR has been reported to have prognostic value for CAV-related major cardiac events (3.3 relative risk of death, myocardial infarction, congestive heart failure, or need for percutaneous intervention at a mean of 19 months). A CFR < 2.9 can detect a maximal intimal thickness of ≥ 0.5 mm by IVUS with 80% sensitivity, 100% specificity, and 89% negative predictive value.

Recommendations

Dobutamine stress echocardiography might be a suitable alternative to routine coronary angiography to assess CAV at centres with adequate expertise with the technique. CFR and/or contrast infusion to assess myocardial perfusion can be combined with stress echocardiography to improve the accuracy of the test.

Integrated backscatter

Integrated backscatter is an echocardiographic technique based on myocardial acoustic properties, which aims to characterize myocardial tissue. Initial studies reported higher values of end-diastolic integrated backscatter measured at the LV infero-lateral wall in Grade 1B, 2, or 3 acute GR, compared with Grade 0. Backscatter signal measurements in the LV infero-lateral wall were more discriminatory than those measured in the anterior septum, with a 88% sensitivity and 89% specificity for detecting ≥ 1B grade acute GR (1.5 dB increased backscatter signal), and 92% sensitivity and 90% specificity for detecting ≥ 3 grade (5.5 dB increased backscatter signal).

Recommendations

Integrated backscatter is highly dependent on acoustic window, it is technically demanding and with high inter- and intra-observer variability. Therefore, integrated backscatter is not recommended for clinical purposes.

Three-dimensional echocardiography

There are two studies evaluating the role of three-dimensional echocardiography (3DE) in HT patients. Assessment of LV mechanical dyssynchrony by 3DE (time to minimum systolic volume adjusted by R–R interval length in a 16-segment model of LV) showed a 95% sensitivity and 73% specificity for predicting acute GR. In another study, 3DE has been used to assess RV geometry and EF, suggesting that it is a more accurate methodology to perform a functional evaluation.

According to recent studies, 3DE should have an important role in assessing HT patients since it has been reported to be more accurate and reproducible than two-dimensional echocardiography in quantitating LV and RV volumes, LV mass, and atrial volumes. Moreover, during stress echocardiography, 3DE may improve the assessment of regional wall motion, possibly improving the accuracy of acute GR and CAV screening.

Recommendations

In echocardiography laboratories equipped with 3DE scanners and specific expertise with the technique, 3DE may be a suitable alternative to conventional 2D echocardiography to assess the size and the function of cardiac chambers. 3DE measurement of LV and RV size and function are more accurate and reproducible than conventional 2D calculations. Cardiac chamber volumes obtained with 3DE cannot be compared with those obtained with two-dimensional echocardiography.

Echocardiography to guide EMB

Traditionally, fluoroscopy has been used to guide EMB, but this imaging modality has a number of limitations, including cumulative radiation exposure, limited portability, and the limited area of access (interventricular septum) for biopsy. In contrast, echocardiography provides greater portability, eliminates radiation exposure, provides
important information about cardiac function, and safely allows biopsy of any area of the RV, including the free wall and apex.\textsuperscript{155} Several observational studies demonstrated the benefits of echocardiography over fluoroscopy in guiding EMB: (i) more adequate positioning of the biopsyte against the septum;\textsuperscript{155–157} (ii) higher percentage of adequate biopsy samples;\textsuperscript{158} (iii) less biopsy-related complications;\textsuperscript{158,159} and (iv) less radiation exposure.\textsuperscript{155–157,159} However, there is no randomized study to prove the superiority of echocardiography over fluoroscopy.

### Recommendations

In experienced centres, echocardiography might be an alternative to fluoroscopy to guide EMB, particularly in children and young women, since it avoids repeated X-ray exposure and permits visualization of soft tissues and safer performance of biopsies of different RV regions.

### Role of other imaging modalities

#### Invasive imaging

**Coronary angiography**

Coronary angiography remains the main screening tool for CAV in most centres, also being able to guide management, and to predict adverse events in HT recipients. The latest guidelines for management of HT recipients consider coronary angiography as the gold-standard method to detect CAV (Class I, evidence C). The Stanford classification system is used to describe the morphology of coronary lesions from a discrete atherosclerosis to concentric arterial obliteration.\textsuperscript{160,161} However, coronary angiography can underdiagnose both the prevalence and extent of CAV due to the vascular remodelling, involving the entire coronary tree, which in an early stage does not necessarily reduce the luminal diameter.\textsuperscript{162,163} Therefore, angiograms should be interpreted serially as new and concentric lesions may be missed on one-time angiograms.

**Invasive CFR**

Evaluation of invasive CFR may provide additional information about the presence and severity of CAV, and may identify early CAV in patients without angiographically evident narrowings.\textsuperscript{164,165} However, there is little evidence that invasive CFR is of any prognostic relevance.\textsuperscript{61} A possible explanation may be related to the uniformly high resting heart rate, which impairs the reliability of the CFR assessment in detecting microvascular impairment. Furthermore, the presence of LV hypertrophy and higher donor ages independently contribute to a reduced CFR in patients after HT.\textsuperscript{166} In HT patients, the reduction in CFR is due to elevated baseline flow velocities rather than to a change in hyperaemic flow velocities and should be taken into account for the test interpretation.

Recently, the instantaneous wave-free ratio has been proposed as an alternative invasive pressure-only index of coronary disease severity.\textsuperscript{167} Because instantaneous wave-free ratio is calculated under baseline coronary haemodynamics—precluding induction of hyperaemia\textsuperscript{168}—it emerges as a potential tool to investigate stenosis in transplanted patients. Instantaneous wave-free ratio could circumvent the limitations of FFR in such sub-population of patients with known microvascular disease and variable response to coronary vasodilators.\textsuperscript{169}

**Intravascular ultrasound**

IVUS has emerged as the gold standard for early detection of CAV due to high-resolution images of the cross-section of the vessel. It allows the accurate quantitative assessment of lumen size, intimal thickening, vessel wall morphology, and composition.\textsuperscript{162,170} Numerous studies have demonstrated that even in the presence of a normal coronary angiogram, IVUS findings are predictive of CAV and are reliable prognostic markers of subsequent mortality and non-fatal major adverse cardiac events at 1 and 5 years after HT.\textsuperscript{171–177} Indeed, an intimal thickness measured by IVUS correlated with microvascular impairment, even when FFR and angiograms were normal.\textsuperscript{178} Therefore, the guidelines for the management of heart transplant patients state that ‘IVUS in conjunction with coronary angiography with a baseline study at 4–6 weeks and at 1 year after HT is an option to exclude donor coronary artery disease, to detect rapidly progressive CAV, and provide prognostic information’, giving a class of recommendation IIa and level of evidence B (Table 10).

**Optical coherence tomography**

Optical coherence tomography is an optical signal acquisition and processing method, typically employing near-infrared light, which captures micrometer-resolution, 3D images from within optical scattering media (e.g. biological tissue). The use of relatively long wavelength light allows it to penetrate into the scattering coronary wall providing an even higher spatial resolution than IVUS and, in theory, an earlier detection of morphological changes in the coronary wall. Good correlation with IVUS for measurement of maximal intimal thickness and luminal area has been demonstrated, with a lower inter-observer variability.\textsuperscript{176}

### Recommendations

Currently, coronary angiography is the gold-standard method for the detection of CAV.

<table>
<thead>
<tr>
<th>Severity</th>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
<th>Class IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intimal thickness</td>
<td>Minimal</td>
<td>Mild</td>
<td>Moderated</td>
<td>Severe</td>
</tr>
<tr>
<td>Extent of plaque</td>
<td>&lt;180</td>
<td>&gt;180</td>
<td>&gt;0.5 mm,</td>
<td>&gt;1.0 mm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;180</td>
<td></td>
</tr>
</tbody>
</table>

CAV, cardiac allograft vasculopathy; IVUS, intravascular ultrasound. Reproduced from St Goar FG et al.\textsuperscript{175}
Nuclear cardiac imaging
Considerable variations in study methodologies (different stressors protocols and tracer agents, time of the evaluation, and variable criteria to diagnose CAV) and results have been found when trying to evaluate the accuracy of nuclear cardiac imaging in detecting CAV.177 – 184 Despite dobutamine has been reported to be advantageous as a stressor, recent studies demonstrated comparable accuracy to stress protocols using dipyridamole.183 – 186 A large study evaluating dipyridamole-stress Sestamibi SPECT to assess CAV, demonstrated 92% sensitivity and 86% specificity to detect significant vascular disease (luminal narrow ≥ 50%), and only 56% sensitivity to detect angiographic abnormalities of any grade.186 Prognostic information is also provided from both dobutamine-stress and dipyridamole-stress SPECT protocols, where dobutamine protocol demonstrated higher sensitivity and negative predictive value for major adverse cardiac events.184,186,187 A range of molecular components of acute GR has been targeted with radionuclide scintigraphy; however, based on the lack of availability of large multicenter trial results, the conflicting results in published studies and the high burden of radiation related to this imaging technique, it can be recommended in clinical practice only in patients unsuitable for stress echocardiography.188

Recommendations
In patients with inadequate acoustic window and contraindication to contrast agents, pharmacological SPECT is an alternative imaging modality to detect CAV in HT patients. However, in centres with adequate expertise, IVUS in conjunction with coronary angiography with a baseline study at 4–6 weeks and at 1 year after HT should be performed to exclude donor coronary artery disease, to detect rapidly progressive CAV, and to provide prognostic information. IVUS should also be performed when there is discrepancy between non-invasive imaging tests and coronary angiography concerning the presence of CAV.

Computed tomographic coronary angiography
Computer tomographic (CT) coronary angiography can be employed to exclude relevant CAV. One possible limitation of this method is the difficulty to reach the appropriate heart rate necessary to obtain good quality images in OHT patients, since transplanted hearts are denervated and beat at high heart rate. Scanners that provide high temporal resolution, such as dual-source systems, provide

Figure 9 Cardiac magnetic resonance acquisitions using different protocols for quantitating changes in myocardial structure and detect myocardial tissue inflammatory and perfusion alterations.
more guarantee for sufficient image quality in patients with a persistently high heart rate. The use of CT in the evaluation of CAV has been reported in the guidelines for the management of HT patients as a Class IIb recommendation (Level of Evidence: C). This imaging modality offers the possibility of evaluating the coronary lumen, as well as the wall thickness and intimal hyperplasia, with a potential for early CAV detection. CT coronary angiography can detect up to 50% more coronary segments with increased wall thickness than conventional coronary angiography.\(^{189,190}\) Although relatively high sensitivities (70–100%) and specificities (81–100%) have been reported in the detection of significant coronary stenosis, comparative studies with IVUS or optical coherence tomography to assess its true sensitivity are scarce.\(^{61,189–191}\) Its high negative predictive value to exclude coronary stenosis makes this technique a possible screening test before undergoing coronary angiography.\(^{190,192–194}\) Although concerns regarding the exposure to ionizing radiation and nephrotoxic contrast remain, exposure generally does not exceed nuclear imaging or invasive coronary angiography, and contemporary scanner technology allows coronary imaging at ever decreasing radiation doses.

In addition, using CT, calcium is detected more frequently than would be suggested by studies using intravascular ultrasound. It is associated with the presence of angiographic disease and with some conventional risk factors for coronary disease. At follow-up, the presence of coronary calcium was associated with an adverse clinical outcome.\(^{195}\)

CT is a powerful imaging technique for undisturbed interrogation of the cardiovascular morphology, which is particularly effective in various acute conditions, and when echocardiography cannot be performed adequately. In more exceptional situations, cardiac CT can be employed to quantify global LV and RV function. Dynamic myocardial perfusion imaging during pharmacological vasodilation allows quantification of myocardial perfusion and may provide a non-invasive alternative to PET imaging for the detection of microvascular disease in the future.\(^{196–198}\)

### Table 11

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Technique</th>
<th>Class</th>
<th>Annotations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiography</td>
<td>Conventional TEE</td>
<td>Recommended</td>
<td>In centres with specific expertise, to assess LV and RV geometry and function in patients with good acoustic window</td>
</tr>
<tr>
<td></td>
<td>3D</td>
<td>Reasonable</td>
<td>In patients with specific expertise, in patients with good acoustic window</td>
</tr>
<tr>
<td></td>
<td>Speckle tracking</td>
<td>Reasonable</td>
<td>In patients with insufficient acoustic window</td>
</tr>
<tr>
<td></td>
<td>Contrast LVO</td>
<td>Recommended</td>
<td>In centres with specific expertise, to detect CAV</td>
</tr>
<tr>
<td></td>
<td>TOE</td>
<td>Not recommended</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dobutamine stress echo</td>
<td>Reasonable</td>
<td>In centres with specific expertise, to detect CAV</td>
</tr>
<tr>
<td></td>
<td>Coronary flow reserve</td>
<td>Not recommended</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Contrast MCE</td>
<td>Not recommended</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Integrated backscatter</td>
<td>Reasonable</td>
<td>In patients with inadequate acoustic window despite contrast</td>
</tr>
<tr>
<td>Cardiac magnetic resonance</td>
<td></td>
<td>Reasonable</td>
<td>In patients with contraindication to CMR</td>
</tr>
<tr>
<td>CT</td>
<td></td>
<td>Reasonable</td>
<td>To detect CAV</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td></td>
<td>Recommended</td>
<td>When there is discrepancy between coronary angiography and non-invasive tests about the presence of CAV</td>
</tr>
<tr>
<td>IVUS</td>
<td></td>
<td>Reasonable</td>
<td>To detect CAV with non-invasive tests about the presence of CAV</td>
</tr>
<tr>
<td>Invasive coronary flow</td>
<td></td>
<td>Questionable</td>
<td></td>
</tr>
<tr>
<td>reserve</td>
<td></td>
<td>Reasonable</td>
<td>In centres with specific experience</td>
</tr>
<tr>
<td>Optical coherence</td>
<td></td>
<td>Reasonable</td>
<td></td>
</tr>
<tr>
<td>tomography</td>
<td></td>
<td>Reasonable</td>
<td></td>
</tr>
<tr>
<td>Pharmacological SPECT</td>
<td>Either dobutamine or dipyridamole</td>
<td>Reasonable</td>
<td>In patients with inadequate acoustic window and contraindications to contrast agents</td>
</tr>
<tr>
<td>CT coronary angiography</td>
<td></td>
<td>Not recommended</td>
<td>For routine clinical use</td>
</tr>
</tbody>
</table>

3DE, three-dimensional echocardiography; CAV, cardiac allograft vasculopathy; CT, computed tomography; IVUS, intravascular ultrasound; LVO, left ventricular opacification; MCE, myocardial perfusion contrast echocardiography; SPECT, single-photon emission computed tomography; TTE, transthoracic echocardiography.

### Recommendations

In experienced centres, CT coronary angiography is a good alternative to coronary angiography to detect CAV. In patients with a persistently high heart rate, scanners that provide high temporal resolution, such as dual-source systems, provide better image quality.

### Cardiac magnetic resonance

CMR provides accurate measurements of LV and RV diastolic and systolic volumes and hence LV and RV EF in addition to its unique ability to quanitate changes in myocardial structure and detect myocardial tissue alterations (oedema and fibrosis) secondary to acute GR and
CAV (Figure 9A and B). T2 relaxation time is the most widely investigated parameter for acute GR screening, showing a significant positive correlation with rejection severity by histology and ex vivo myocardial water content.199–203 A longer T2 relaxation time (≥56 ms) had a 97% negative predictive value for detecting significant acute GR (≥ ISHLT grade 2), but only 35% positive predictive value.201,202 Shortening of T2 relaxation time during immunosuppressive therapy has also been reported.200 Data about myocardial signal intensity analysis with T2-weighted imaging to assess acute GR are inconsistent. Most of the studies have been performed using technology which were inferior to current standards in scanner hardware and sequence design; this may explain why some studies failed to demonstrate significant difference relative myocardial signal intensity.203

Myocardial inflammatory changes can be detected with the use of gadolinium (Figure 9C). An increase in relative myocardial contrast uptake has been identified in patients with myocardial necrosis on EMB.204 Estep et al.205 reported that areas of hyper enhancement are detected in acute GR, and these areas appear to be reduced in extent after immunosuppressive treatment. However, the presence and extent of hyper enhancement was not related to EMB ISHLT grade.202,206 A multi-sequential CMR protocol, combining ‘short tau inversion recovery’ sequence for calculation of oedema assessment of these patients requires specific knowledge of the role of CMR and CT coronary angiography, in diagnosing GR and non-GR.195,196 Standard versus non-invasive myocardial deformation imaging, 3D echocardiography, non-invasive imaging writing group committee has prepared these recommendations to provide a practical guide to echocardiographers involved in the follow-up of HT patients and a framework for standardized and efficient use of cardiovascular imaging after HT (Table 11).

Conflict of interest: None declared.

References

Conclusions
The cohort of long-term survivors of HT is expanding, and the assessment of these patients requires specific knowledge of the surgical techniques employed to implant the donor heart, the physiology of the transplanted heart, complications of invasive tests routinely performed to detect GR, and the specific pathologies that may affect the transplanted heart. A joint EACVI/Brazilian cardiovascular imaging writing group committee has prepared these recommendations to provide a practical guide to echocardiographers involved in the follow-up of HT patients and a framework for standardized and efficient use of cardiovascular imaging after HT (Table 11).

Recommendations
In patients with insufficient acoustic window, CMR is an alternative to echocardiography to assess cardiac chamber volumes and function and to exclude acute GR and CAV in a surveillance protocol.

Future directions in research
Single-centre studies have shown the potentialities of different imaging modalities to diagnose GR and CAV and to predict outcome in HT patients. However, these results need to be confirmed by multicenter outcome studies involving large numbers of patients from and different institutions. The role of new echo technologies (e.g. speckle tracking myocardial deformation imaging, 3D echocardiography, non-invasive CFR, and myocardial perfusion echocardiography), as well as the role of CMR and CT coronary angiography, in diagnosing GR and CAV seems to be particularly promising and should be tested in a specifically designed multicentre trial. This type of trial should not only test the accuracy of different multimodality protocols to assess HT patients, but also their safety and cost-effectiveness.


Echo in heart transplant patients


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