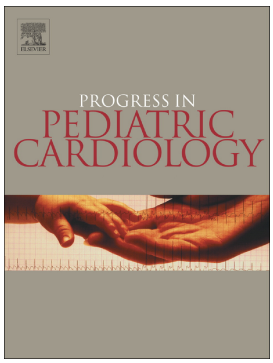

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Progress in Pediatric Cardiology

Echocardiographic Assessment of Mechanical Circulatory Support and Heart Transplant

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Abstract

Echocardiography plays a pivotal role in the pre-operative assessment, post-operative management and long-term follow-up of pediatric heart failure and heart transplant patients. Echocardiography may be a particularly useful modality for evaluating ventricular function and for providing noninvasive rejection surveillance. Mechanical circulatory support has an ever increasing role in heart failure management among pediatric patients. Echocardiography provides a non-invasive tool for assessment of cannula placement, ventricular function, optimization of the device, and routine surveillance for valve regurgitation, estimated pulmonary pressures, pericardial effusion, and thrombus formation while on mechanical support. Heart transplant is the ultimate management option, for those that qualify with end stage heart failure. Heart transplant recipients require frequent echocardiograms for the routine evaluation of the intracardiac structure, ventricular function, surveillance for rejection, as well as direct visualization of the myocardium during endomyocardial biopsy. Below we provide a review for clinicians and sonographers about the importance of echocardiography in the evaluation and management of mechanical circulatory support and heart transplant in children.

Introduction

Cardiovascular disease is a leading cause of morbidity and mortality world-wide. [1] End stage heart failure is a common final pathway that may be caused by congenital heart disease, genetic or acquired cardiomyopathies, myocarditis, valvular disease, coronary artery disease, or abnormalities of the heart's electrical system. Heart transplant has traditionally been considered as the best option for pediatric patients with end stage heart failure, however heart transplantation has significant limitations including prolonged waiting time, availability of appropriate donors and excess resource utilization. [2] Patients with irreversible pulmonary hypertension and cancer with a likelihood of recurrence are considered contraindicated for transplant and are left with minimal options. Technological advancements in mechanical circulatory support, have created a larger role for the use of extracorporeal membrane oxygenation and ventricular assist devices in the management of the pediatric heart failure patient as a bridge to transplant, bridge to recovery or as destination therapy. Below we will review the specific role that echocardiography has in the evaluation and management of pediatric heart failure patients on mechanical circulatory support and in the heart transplant recipients.

Mechanical Circulatory Support

1. Extra Corporeal Membrane Oxygenation

Extra corporeal membrane oxygenation (ECMO) is a form of cardiopulmonary life support for pediatric patients with cardiac, respiratory or cardio-pulmonary failure. This can be used as a form of cardiopulmonary resuscitation for short term recovery from an acute event, bridge to recovery in the case of myocarditis, bridge to ventricular assist device or bridge to heart

transplant. [3] From a very basic standpoint, an ECMO circuit drains venous (un-oxygenated) blood from the vascular system, circulates this blood outside the body via a mechanical pump, oxygenates and eliminates carbon dioxide from the blood and then returns the oxygenated blood back to the vascular system. The International Extracorporeal Life Support Organization (ELSO) registry report from January 2020 had over 129,000 ECMO cases with 33% in neonates, 22% in children/adolescents and 45% in adults [4]. In this report, 52% were on ECMO for respiratory support, 36% for cardiac support and 12% for extracorporeal cardiopulmonary resuscitation. [4] In order for a clinician or sonographer to perform an echocardiogram on an ECMO patient - they must first recognize the type of ECMO support being used: veno-venous or veno-arterial. Veno-venous ECMO is utilized in patients unable to oxygenate but who otherwise have stable hemodynamics to maintain cardiac output. A single cannula system can be used (cannula within a cannula) in which the outer cannula extracts venous blood from the inferior and superior vena cava, oxygenates this blood and returns it to the body via the interior cannula that delivers oxygenated blood back into the right atrium. **(Figure 1)** Veno-venous ECMO can also be performed using a two-cannula system: femoral vein for drainage and right internal jugular vein for infusion or right femoral vein for drainage and left femoral vein for infusion. Veno-arterial ECMO is utilized for those patients with unstable hemodynamics that can no longer support their metabolic demands. Common options for veno-arterial ECMO cannulation include: internal jugular vein (drainage) - carotid artery (infusion); femoral vein (drainage) – femoral artery (infusion) or central cannulation with right atrium (drainage) - ascending aorta (infusion). **(Figure 2).** Echocardiography is important for proper cannula placement, surveillance for effusion, thrombus, and function as well as determining when the

patient is ready to be weaned off of ECMO support (e.g., pulmonary pressures, heart size and ventricular function). [3, 4]

All echocardiograms performed on ECMO support should include the following features:

a. Define the cannula locations within the cardiovascular system
b. Assess for aortic regurgitation in veno-arterial cannulation with a carotid artery cannula - if this is positioned into the ascending aorta the infusion jet may injure the aortic valve and create regurgitation
c. Assess the right ventricular size, function and estimated right ventricular pressure
d. Assess the left atrial size
e. Assess direction of flow at any residual intracardiac shunts (e.g., atrial septal or ventricular septal defects)
f. Assess left ventricular function
g. Assess for pericardial effusion
h. Assess for thrombus formation on the cannula tips or within the heart

2. Left Ventricular Assist Devices

Although the definitive treatment for end stage heart failure unresponsive to traditional medical therapy is heart transplant, this therapy has limitations as listed above. Left ventricular assist devices (LVAD) have therefore emerged as a therapeutic option for those with chronic heart failure who require long-term circulatory support (days to years). Chronic heart failure in children whether from congenital heart disease, inherited cardiomyopathy, or acquired myocardial damage can manifest as systolic or diastolic dysfunction or a combination of both. Over time, the affected ventricle(s) may dilate, wall tension increase, and end diastolic pressure

rise, leading to pulmonary venous and/ or systemic venous hypertension. This cascade can cause additional myocardial damage and perpetuate heart failure such that medical therapy becomes ineffective. At this point, mechanical circulatory support is the next immediate treatment available. The primary goal of mechanical circulatory support is to maintain the cardiac output and preserve or recover end organ function. By relieving the cardiac output burden from a failing heart, ventricular assist devices unload the myocardium to reduce wall tension, allow for remodeling and, in some cases, recovery. Ventricular assist devices decrease pulmonary venous hypertension to limit pulmonary vascular damage and decrease systemic venous hypertension and its deleterious effects on function of the liver, kidneys and intestine. An LVAD's basic design consists of a drainage catheter placed in left ventricular apex that draws blood through a tube into a pump that that then delivers the blood back via a tube that has an outflow valve and delivers the blood into the ascending aorta. (**Figure 3)** demonstrates the drainage and infusion catheter sites by echocardiography.

In 2018, Hetzer et al. reviewed 78 pediatric patients with Berlin Heart LVADs used as a bridge to transplant. They reported one-year survival at 84.6% and common complications included: mediastinal bleeding, thrombus formation in the pump valves, thromboembolic events, cerebral hemorrhage, and skin infections. The mean duration of ventricular assist device support was 59 days (range 1-945 days). [5] An LVAD may be utilized as a bridge to heart transplant, but can also be utilized as a bridge to a decision (patients with chronic heart failure and additional end-organ dysfunction that temporarily prohibits them from heart transplant but may improve with time), bridge to recovery (circulatory support allows the myocardium to rest, remodel and recover from an acute injury), or destination therapy (permanent circulatory support for those who are ineligible for a heart transplant and unable to recover myocardial function). [5,

6] Some patients will also experience right ventricular failure over time that necessitates the need for conversion to a biventricular assist device. A complete overview of the different types of ventricular assist devices is beyond the scope of this review, however clinicians and sonographers that perform and/or interpret echocardiograms in ventricular assist device recipients require a thorough knowledge of the device and cannula position used at their institution.

A comprehensive echocardiogram is crucial for survival with a ventricular assist device. The American Society of Echocardiography (ASE) put forth its recommendations for the use of echocardiography in the management of patients with LVAD. [7] Heart failure treatment with a ventricular assist device is a dynamic process. As such, ASE recommends three categories for echocardiographic evaluation in the management of patients with LVADs.

1. LVAD surveillance echocardiogram with or without LVAD optimization echocardiogram. Echocardiographers perform the initial study typically within 2 weeks after LVAD implantation or just prior to discharge if the clinical course is uncomplicated, at monthly intervals for the first six months postoperatively, and semi-annually or annually thereafter.

2. LVAD problem-focused echocardiogram with or without LVAD speed change protocol. Worsening heart failure symptoms, history of LVAD controller alarms, or laboratory evidence of hemolysis may be indications for this type of echocardiogram.

3. LVAD recovery echocardiogram is important to assess for cardiac functional improvement during reduced LVAD settings for patients in whom the device may be explanted.

All echocardiograms should utilize a structured approach as outlined by the American Society of Echocardiography. [7] A quick checklist for a clinician or sonographer to remember include the following:

1. Blood pressure
2. Pump type and speed
3. Right heart
    a. Right atrium
    b. Residual atrial level shunts
    c. Estimate pulmonary artery pressure (tricuspid regurgitation jet, pulmonary regurgitation jet, or interventricular septal position)
    d. Right ventricular function assessment
4. Left heart
    a. Size of the atrium
    b. Mitral valve regurgitation
    c. Left ventricular size and function
    d. Degree of aortic valve opening / regurgitation
5. Device
    a. Left ventricular inflow cannula
    b. Inflow valve regurgitation
    c. Outflow valve regurgitation
    d. Outflow cannula to the aorta
    e. Cardiac output assessment
    f. Assess aorta for dissection

6. Pericardium
    a. Effusion
    b. Hematoma
7. Thrombus surveillance

The echo physician and sonographers may be tasked with specific roles at certain points during the care of an LVAD patient such as assessing the degree of ventricular decompression, assessing right ventricular function in order to determine the need for upgrading to biventricular support or adding pulmonary vasodilator therapy for pulmonary hypertension. Echocardiography may be used to optimize the hemodynamics of the pump, to ensure adequate cardiac output to avoid worsening clinical symptoms or progressive deterioration of the heart and lungs, and surveillance for thrombus or pericardial effusion that will dictate changes to the anticoagulation regime. Below we will review some of the specific details of these roles in LVAD patients.

3. Assessment of ventricular decompression

Left ventricular dilation is a common end point in a failing heart. Echocardiography is an essential tool to aid in evaluation of ventricular decompression after initiation of a LVAD. Left ventricular dilation may lead to progressive mitral regurgitation and left atrial dilation that can predispose to pulmonary hypertension. Sachdeva and colleagues reported their retrospective experience with echocardiographic assessments of 32 patients who received Berlin Heart Excor devices as LVAD or biventricular assist devices. [6] Left atrial and ventricular dimensions decreased significantly as measured by transesophageal echocardiogram immediately after device implantation compared to the preimplantation studies. Additionally, in the group who received only LVAD support, the right ventricular diastolic area significantly decreased suggesting biventricular benefit in unloading the heart acutely. In their checklist for regular

follow up echocardiograms after ventricular assist device implantation, these authors suggest the following:

1. Continued measurement of biventricular size and function plus septal position relative to the ventricles

2. Assessment of valve function, particularly the aortic valve to document its competence

3. Inflow cannula position and flow pattern to assess for obstruction

4. Surveillance for ascending aortic dissection.

4. Right ventricular dysfunction

Right ventricular dysfunction after placement of a left ventricular assist device is a challenging complication in the management of advanced heart failure but its significance is often neglected. This complication is found in both the adult and pediatric populations, though the incidence is higher in the pediatric population. [8, 9] Fortunately, right ventricular dysfunction after LVAD placement can often be medically managed in the pediatric population, resulting in excellent survival. [10] However, if a right ventricular assist device is required to manage the postoperative right ventricular dysfunction, mortality risk increases. [8] Therefore, adequate prediction of patients who will suffer right ventricular dysfunction after LVAD implantation could lead to better stratification of resources and optimization of post-operative management to reduce morbidity and mortality. Although echocardiography has been an accepted tool to qualitatively assess right ventricular function in patients with LVADs, this modality is known to be operator dependent and therefore of limited reproducibility. [8] The right ventricle function is complex and depends on longitudinal forces (the major component),

radial forces, movement of the right ventricular free wall inward, movement of the interventricular septum into the right ventricle, and dependency on left ventricular filling pressures in order to create forward cardiac output. In the adult literature, more novel and reproducible echocardiographic data have been identified as predictors of right ventricular dysfunction after LVAD placement, such as tricuspid annular plane systolic excursion (TAPSE). [10, 13] TAPSE is a measure of the displacement of the lateral tricuspid annulus toward the apex during systole. Using an M-mode from a four-chamber view along the right ventricular free wall, a sonographer can measure the excursion between end-diastole and peak systole of the tricuspid annulus. Modin et al. demonstrated that TAPSE <24mm was a predictor of cardiovascular disease in the general public. [11] Recently, Redlin et al. was able to identify TAPSE, normalized to the right ventricular end-diastolic long axis diameter, served as a significant predictor of right ventricular dysfunction after LVAD placement in a study of forty-eight consecutive pediatric patients undergoing LVAD implantation. Using a receiver operator curve determined cutoff of 17.1%, this pre-operatively normalized TAPSE measurement was able to positively identify 78% of patients who developed post-operative right ventricular dysfunction. [10] Further studies investigating the use of TAPSE for assessment of right ventricular function will provide critical predictive markers in the postoperative management of patients with ventricular assist devices.

5. Left ventricular assist device optimization

Echocardiography continues to play a vital role in the management of LVAD patients after device implantation. As described above, clinicians and sonographers should start with defining the cannula positions as well as full assessment of the intracardiac anatomy including

assessment for valve regurgitation and / or thrombus formation. Then, attention should be focused on optimization of LVAD speed in centrifugal and axial continuous-flow devices. LVAD optimization can be performed by echocardiography by performing a "ramp test", in which the LVAD's rotations per minute (RPM) are increased while echocardiography assesses cardiac decompression and function using four chamber and short axis views. [14] Additional hemodynamic factors can also be monitored simultaneously (blood pressure and heart rate). Echocardiographic speed optimization has been shown to improve ventricular septal geometry and position, allowing for adequate right ventricular output and LVAD preload. [13, 14] Moreover, optimization minimizes mitral valve regurgitation, tricuspid valve regurgitation and can help to establish periodic aortic valve opening, potentially minimizing progression to aortic insufficiency and attenuating the development of von Willebrand factor deficiency. [13, 14] Optimization may also illicit device malfunctioning, such as inappropriate wattage changes with minimal rpm changes consistent with thrombosis. [13, 14] Thus, post-implant patient management by a multidisciplinary team, including cardiologists and talented echocardiography technicians, has been shown to substantially improve outcomes in LVAD patients. [15]

Speed optimization may also play a role in diminishing the exercise intolerance frequently reported in LVAD patients. A recent study by Muthiah et al attempted to clarify this point. The authors demonstrated that while exercise induced a similar increase in LVAD flow as a ramp study alone, it did not adequately increase the cardiac output sufficiently to improve right ventricular off-loading, as evidenced by elevated pulmonary capillary wedge pressures and mean pulmonary artery pressures. They subsequently attempted to perform a ramp study during exercise, to improve left ventricular decompression and right ventricular off-loading. However even at significantly elevated ramp speeds during exercise, the investigators were unable to

achieve the “max” speeds achieved at rest or improve these parameters. The authors theorized that this was due to the afterload dependency of the centrifugal devices, as well as impaired central and peripheral perfusion associated with LVAD patients. However, further testing remains to determine if increased LVAD speeds (above the maximum speeds achieved in this study) might better off-load the right heart and improve the functional characteristics of exercise intolerance. [16]

In addition to assisting operators with optimal ventricular assist device speed settings and septal alignment in real time, recent studies have shown that echocardiography can also directly assess pulsatile ventricular assist device function. [16, 17] Using multiple echocardiographic modalities (2-dimensional, Doppler, color Doppler, M-mode and M-mode color Doppler), Di Molfetta et al assessed the Berlin Heart EXCOR ventricular assist device. They investigated the function of the inflow and outflow valves, as well as synchrony between the ventricular assist device and the native heart. Of the forty devices, 22 had some degree of inflow valve regurgitation and 24 presented with some degree of outflow valve regurgitation. While most of the regurgitation was mild (14/22 inflow, 21/24 outflow), 3 of the 22 inflow valves had severe regurgitation requiring either device replacement, cannula replacement or other surgical intervention. They concluded that the addition of echocardiographic examination of the ventricular assist device itself could contribute to the formulation of appropriate diagnoses for ventricular assist device dysfunction such as tamponade, cannula compression, arrhythmia or manufacturer’s defect. [16]

6. Assessing for thrombus formation

Thromboembolism in children with a ventricular assist device is a complex problem with multiple contributing factors including those specific to patients, varied clinical management strategies, and different device types. The manifestations of thromboembolism and their reported incidences include neurologic events 10-29%, intracardiac thrombus 2%, arterial thrombus in visceral organs or the peripheral circulation 2-9%, and device thrombus necessitating pump exchange 14-56%. [18-29] In a study by Huang and colleagues reviewing their overall center experience with pediatric ventricular assist devices, the Berlin Heart (BH) Excor pulsatile device had a much higher rate (38 events/100 patient months) of thromboembolic complications compared to the continuous flow HeartWare HVAD device (5.3 events/100 patients). [20] This same study showed a time element to thromboembolism where freedom from an event decreased over the first 100 days following the ventricular assist device implant and leveled off thereafter. [20] Despite multi-agent anticoagulation at levels considered therapeutic based on extrapolation from existing literature to guide systemic clot prevention, thromboembolism persists. Therefore, surveillance to detect thrombus or fibrin deposits within the cardiovascular system or the ventricular assist device is crucial to minimize morbidity and mortality from mechanical circulatory support.

Similar to the ASE guidelines for surveillance or problem-focused echocardiograms to evaluate heart function and ventricular assist device performance, these experts recommend scanning for thrombus within the heart, aorta, or outflow cannulas. [7] A clinician and sonographer's knowledge of the type of device is crucial due to differences in the systems. In the continuous flow HeartWare HVAD device, the spatial relationship of the inflow cannula to the impeller leads to Doppler artifact that may obscures interrogation of inflow velocities. Therefore, assessment of inflow obstruction potentially from thrombus is not reliable in this

situation. [6, 7] In contrast, inflow assessment of the Berlin Heart device with echocardiography and 2-dimensional imaging may provide evidence for a thrombus surrounding or impeding blood flow. [5, 6] One advantage of the extracorporeal location of the Berlin Heart pump apparatus is it lends itself to visual inspection of the pump chamber and detection of visible thrombus or fibrin aggregates. In addition, Beasley and colleagues reported direct echocardiography of the Berlin Heart inflow and outflow valves. In a small case series using color-Doppler imaging, the investigators identified progressive valvar insufficiency. They exchanged the pumps in all three patients when the device valvar insufficiency worsened and found thrombus on the malfunctioning valves in each case. Whether thrombus caused or was a consequence of the device valve malfunction is unclear. However, surveillance for Berlin Heart valve function may allow for early detection of thrombus and limit thromboembolic complications. [30]

7. Left ventricular assist devices in single ventricle

Although the outcomes of patients with single ventricle physiology have significantly improved over the last few decades, these patients exhibit a constant and slow attrition due to failure of the Fontan circulation or decline in the function of the single ventricle. While cardiac transplantation provides the most comprehensive solution to restore a normal circulation, the use of mechanical circulatory support has become increasingly utilized as a bridge to decision, bridge to transplantation and more recently destination therapy for those not considered suitable candidates for transplantation. Due to a variety of important physiologic and anatomic considerations unique to this patient population, the implantation of ventricular assist devices can be particularly challenging and echocardiography can provide important anatomic information

and allow physiologic inferences which inform the management of this special group of patients. [31, 32]

Single ventricle or univentricular congenital heart disease patients undergo staged surgical palliation. In hypoplastic left heart syndrome, the most common form of single ventricular physiology, surgical palliation consists of stage 1 (Norwood procedure and systemic to pulmonary shunt), stage II (superior cavopulmonary connection with a bidirectional Glenn procedure or hemi-Fontan procedure) and stage III (total cavopulmonary connection or Fontan procedure). Circulatory failure may occur at any time but most commonly occurs beyond the initial palliation. Death may be attributed to single ventricular dysfunction, pulmonary vascular dysfunction, thromboembolic events, or arrhythmias. The unique anatomic configurations present following each staged intervention presents a specific challenge and complicates decisions around cannulation and type of support. Patients with superior cavopulmonary connection and ventricular failure can receive support (and therefore appropriate oxygenation) if the connection is working well; however, if obstruction exists within the cavopulmonary connection patients will develop inadequate oxygenation despite mechanical circulatory support. In the first scenario, support can be provided with conventional atrial or ventricular as well as aortic cannulation. In the latter scenario, inadequate function of the cavopulmonary connection results in hypoxemia, therefore the need to provide support for oxygenation or take down the cavopulmonary connection with placement of a systemic to pulmonary artery shunt. If gas exchange is inadequate, then insertion of an oxygenator is indicated. Ventricular circulatory support with a superior cavopulmonary connection (Hemi-Fontan or bidirectional Glenn) is associated with a significant venous pressure gradient between the upper and the lower body compartment, leading to development of multiple veno-veno collaterals and progressive hypoxia.

While the mechanical support may work well, the echocardiographic evaluation for hypoxia may demonstrate the presence of large veno-venous collaterals. [31, 32]

Ventricular assist devices in univentricular hearts can be challenging; and the presence of heterotaxy syndrome or abnormal arrangements of the internal organs within the chest or abdomen create significant challenges for cannulation**. (Figure 4).** This is especially an issue, when paracorporeal device (systems with the pump located outside the body) are utilized. Echocardiographic surveillance should start with an evaluation for reversible causes of single ventricular failure such as: significant atrioventricular valve, semilunar valve regurgitation or rhythm issues. An echocardiogram is important for pre-operatively facilitating identification of potential disturbances to inflow during cannulation. The site of cannulation can vary based on the different types of univentricular congenital heart disease. The placement of the inflow cannula in the ventricle can be challenging and prone to obstruction from intracardiac structures. This can be a challenge in smaller patients, who have a short distance between the apex and the acute margin of the heart, which may predispose the atrioventricular valve apparatus to obstruct the inflow. Removal of the atrioventricular valve has been described in order to eliminate any obstruction to inflow while providing full support. [33] In biventricular hearts on LVADs, the sonographer typically ensures the interventricular septum is positioned in the midline in order to avoid development of tricuspid regurgitation or inflow interference in patients with two ventricles, this is rarely an issue in patients with single ventricle who commonly have a large ventricular cavity. As with any form of mechanical circulatory support (ECMO or LVAD), the arterial return from the pump through the outflow cannula is most commonly into the ascending aorta. Therefore, competency of the semilunar valve is paramount in order to deliver the pump output into the systemic circulation, while avoiding ventricular distention and the obligatory

circular shunt (pump-aorta-ventricle-pump). **(Figures 5, 6)** Moreover, the presence of any ventricular distention, can be associated with pulmonary venous hypertension, which when transmitted backwards may have a deleterious effect on the circulation across the Fontan circulation. [31, 32]

Imaging in Pediatric Heart Transplant

1. Protocols for acquisition and timing of echocardiographic assessment

Pediatric heart transplantation is the ultimate management option for children with end-stage heart failure. Based on the International Society for Heart and Lung Transplantation (ISHLT) data pediatric heart transplantation represents approximately 10% of the total number of heart transplantations performed and the number has continued to increase steadily. Recently estimates cite approximately 500-600 pediatric heart transplant cases every year. [34] Echocardiographic evaluation is one of the main non-invasive imaging tools to evaluate heart transplant recipients. The current ISHLT Guidelines for Heart Transplant Recipients do not specify protocols or timing for detailed echocardiographic assessment and do not recommend echocardiography as an alternative to serial endomyocardial biopsy for rejection surveillance [35], and therefore the timing and protocols are center dependent. In addition to traditional echocardiographic protocols, new techniques are promising to help identify early rejection such as tissue Doppler, strain and 3D echocardiography. The protocols may have a different goal based on timing.

In the immediate post-operative period, the main purpose of echocardiogram is to identify signs of primary graft failure and to evaluate for possible surgical complications, including right ventricular dysfunction, pulmonary arterial hypertension, tricuspid regurgitation and effusions. [36]A detailed echocardiogram is also an important tool in the routine and long-term follow-up to evaluate graft function, monitor for signs of rejection or coronary artery vasculopathy and screen for adverse effects from endomyocardial biopsy. The frequency and the acquisition protocols vary at each pediatric center. Pediatric data is limited, but there are clear differences noted in the echocardiographic parameter of stable heart transplant recipients compared with healthy normal controls [37], and therefore it is important to consider individual baseline studies that can be compared with serial follow up assessments and can be more valuable clinically that an absolute objective measurement. Echocardiography plays a vital role in the structural and functional assessment of the transplanted heart, especially in rejection surveillance and during endomyocardial biopsies.

2. Structural assessment

Any clinician performing an echocardiogram on a heart transplant recipient must have knowledge of the technique used to implant the donor organ. The bicaval technique harvests the inferior vena cava and superior vena cava at maximal lengths in order to preserve the donor right atrium in hopes of avoiding atrial dilation, need for pacing, arrhythmias and tricuspid regurgitation that were commonly associated the older biatrial approach. Once implanted, the new heart will have suture lines along the inferior vena cava, superior vena cava, pulmonary artery, left atrium and aorta. These may predispose to significant stenosis of the vessels including caval stenosis, pulmonary artery stenosis, aortic rupture, pseudoaneurysms, aneurysms,

or dissection; therefore echocardiographic evaluation for potential complications should be conducted. In addition to the anastomosis sites, the cardiac valves are also crucial in the routine assessment of transplant patients. The tricuspid valve is particularly vulnerable after heart transplant, as tricuspid regurgitation is commonly a sign of increased right ventricular pressure and right ventricular dysfunction soon after transplant. In this case, the degree of regurgitation and the tricuspid regurgitation jet velocity often reduce as pulmonary vascular pressures normalize. Worsening tricuspid regurgitation and estimated right ventricular pressures by echocardiography are also seen as signs of rejection. Evaluation of the tricuspid regurgitation is important after endomyocardial biopsies, since worsening regurgitation may also occur as a result of direct injury to the tricuspid valve apparatus as a result of direct injury with the bioptome or simply as a result from repeated endomyocardial biopsies. Persistent tricuspid regurgitation can lead to right ventricular failure as well, which is a known factor that increases mortality, therefore routine and comprehensive echocardiography assessment of the tricuspid valve is of particular importance in the transplanted heart. Progressive mitral regurgitation has been described as a result of multiple episodes of graft rejection. This tends to improve with successful treatment of graft rejection. Irregularities in the aortic and pulmonary valves are not commonly seen after heart transplant. [38, 44]

Atrial size is also an important structural finding. Simultaneous increase in filling pressure of both ventricles frequently occurs during early post-transplant phase, which is thought to be due to a myocardial restrictive process from chronic rejection and / or myocardial fibrosis. Increased left ventricular filling pressure leads to left atrial dilation, elevated pulmonary pressures, increased right atrial pressure and right atrial dilation. [41] Long term persistent biatrial size increase was noted until death after heart transplant in small adult patients. [42] Post-

transplant atrioventricular valve regurgitation, tricuspid more than mitral, also affects atrial size, which is less prevalent these days after a bicaval technique has become a predominant surgical method. [43, 44]

3. Functional assessment

Impairment of biventricular systolic and diastolic function occur early after heart transplant with gradual improvement during the first year (**Figure 7**). [44] Serial changes in right ventricle are expected to occur in healthy rejection-free heart transplant recipients. All right ventricular echocardiographic markers, tricuspid annular plane systolic excursion (TAPSE), tissue Doppler-derived annular systolic velocity (S'), fractional area change (FAC), and myocardial performance index (MPI), were abnormal early after heart transplant despite nearly half of them presented with normal qualitative echocardiographic assessment. [45, 46] Ingvarsson et al. presented normal reference ranges for post-transplant echocardiographic findings compared with normal controls, showing larger right ventricular size and atrial volumes with reduced right ventricular systolic function. [47] In the pediatric heart transplant, right ventricular systolic function assessed by pulsed tissue Doppler imaging (TDI) remains abnormal 1 year post transplant. [48] Assessment of right ventricular performance helps understand the hemodynamic and myocardial evolution after heart transplant.

Right ventricular function has great impact on the post-transplant clinical outcome, and can be associated with pulmonary hypertension, allograft dysfunction, and acute rejection. Residual pulmonary hypertension induces right ventricular dysfunction or failure, which worsen the prognosis of heart transplant recipients. [49] The right ventricular fractional area change was noted to be most closely correlated with right ventricular ejection fraction by cardiac magnetic

resonance imaging in adult heart transplant recipients. [50] Three dimensional right ventricular volume assessment correlated well with systolic pulmonary artery pressure by cardiac catheterization whereas TAPSE, tissue Doppler systolic motion of mitral annulus (S'), and right ventricular strain were not. [50] Primary diagnosis of restricted cardiomyopathy and congenital heart disease and pre-transplant elevated pulmonary vascular resistance are both linked to the evolution of acute right ventricular failure. [51, 52] Aggarwal et al. reported that deterioration of ratio of systolic to diastolic duration (S/D), myocardial performance index, and tricuspid regurgitant gradient to right ventricular outflow tract velocity (TRG/VTI) have high negative predictive values for acute rejection. [53] The newer modalities of echocardiographic such as Doppler imaging of tissue velocities, including strain and 3-dimensional echocardiography were developed to have a more objective evaluation of the regional myocardial function. [38]

Even though the right ventricular assessment is important; the left ventricular function drives the cardiac output and sustains life. The myocardium is at constant risk of rejection and ischemia from coronary allograft vasculopathy both of which can predispose to developing progressive fibrosis and a restrictive cardiomyopathy. Traditional methods of assessing left ventricular function such as ejection fraction and shortening fraction are commonly used to monitor graft function in the heart transplant population. These measures of left ventricular function are limited because they assess the global systolic function, which is usually a late finding during rejection episodes and not very helpful in the early stages. In recent years, the measurement of myocardial strain and strain rate have been demonstrated to be a useful tool for the evaluation of the allograft function in the short and long follow up of heart transplant patients, and are becoming an important tool to aid for rejection surveillance and detection of cardiac allograft vasculopathy. [54-61]

Diastolic dysfunction of the ventricle may be an early echocardiographic surrogate for the onset of rejection prior to the development of late systolic dysfunction. Typical diastolic filling of the ventricle consists of mitral inflow with an E-wave (passive filling of the ventricle) followed by an A-wave (filling due to atrial contraction). Tissue Doppler imaging can be used to assess mitral annular velocities (S'= systole, e' = early diastole, and a' = late diastole) at a single point. Tissue Doppler can also be used to measure strain, which is defined by the change in lengthening, shortening, or thickening, also known as regional deformation by describing the contraction/relaxation pattern of the myocardium. [55] The amount of deformation (positive or negative strain) is usually expressed in percentiles. Positive strain values describe thickening, negative values describe shortening, of a given myocardial segment related to its original length. The most recent literature has shown to have significant advantages compared with conventional techniques, since is not subject to limitations such as loading conditions variability in measurements, angle of image acquisition, regional wall motion abnormalities, and ventricular chamber geometry. [56] Normal references values have been stablished for normal children and adults. [57, 58] The pediatric literature is limited, however there is recent studies showing that strain appears to be a more sensitive method to evaluate the complexity of the left ventricular graft assessment of the transplanted heart. Budhhe et al. found that diastolic function measurements by strain correlate better with direct hemodynamic assessment of pulmonary capillary wedge pressures, which is an important finding given the invasive nature, costs, limitations and infrequent but possible complications of a cardiac catheterization in the pediatric population. [62] A study published in 2017 confirmed the feasibility and reproducibility of global longitudinal strain in pediatric heart transplant recipients compared with normal published values, but they also found a reduced baseline strain in the transplanted group compared with

healthy controls. [63] Kailin et al. also demonstrated that longitudinal strain and strain rate were reduced in transplant patients even without rejection when compared to age and gender matched normal controls. [64] Multiple studies in adults have shown that strain has the potential to diagnose acute rejection with better sensitivity and specificity than other echocardiographic indices. [65] In the pediatric population, Chanana et al. also demonstrated decrease in systolic strain associated with rejection and introduced the concept of a new ability to possibly distinguish between cellular and antibody rejection based on strain and strain rate. [66] Several studies are also looking into finding ways to predict coronary artery vasculopathy. Strain has the potential to assess regional wall abnormalities at rest and during stress that can potentially predict cardiac allograft vasculopathy. [56] Overall global longitudinal strain has become an important part of the surveillance echocardiographic protocol for heart transplant recipients, with the potential to aid in early diagnosis and treatment of acute rejection and cardiac allograft vasculopathy.

Three-dimensional echocardiography in real time allows assessment of the entire left ventricle in one single data set and therefore rapid quantification, it also has the advantaged to track the myocardium in motion in three dimensions and can be used to quantify left ventricular ejection fraction and global and regional strain in three dimensions **(Figure 8)**. [67] Adult guidelines, including a cardio-oncology article published in 2014 recommends using 3-dimensional to quantify left ventricular volume and ejection fraction when possible. [68] Dyskinetic septal motion, left ventricular regional wall motion abnormalities, and electrical conduction delays are frequently observed in transplanted hearts, and may predispose to left ventricular mechanical dyssynchrony (activation of the different parts of the heart are improperly synchronized), worsen heart failure symptoms and risk of ventricular tachycardia. Kutty et al.

demonstrated that the ejection fraction varied greatly in transplant patients and had a strong positive correlation with systolic dyssynchrony index (an echo parameter measured by three dimensional echo and defined as the time from onset of the cardiac cycle (R-wave) to the minimum systolic volume for each segment of the heart, then calculating the standard deviation and expressed as an index by the standard deviation as a percentage of the cardiac cycle. [69] The clinical significance for these novel roles of echo in transplanted hearts hold promise to reduce morbidity and mortality.

4. Rejection assessment

Although endomyocardial biopsy remains the "gold standard" for the diagnosis of rejection among heart transplant recipients, echocardiography provides opportunity for non-invasive routine surveillance in the inpatient or outpatient setting. Large, multi-center studies evaluating the sensitivity and specificity of non-invasive imaging for identifying cellular and antibody mediated rejection in children have not been performed. Studies evaluating the potential for non-invasive assessments of cardiac function, tissue Doppler imaging and strain to correlate with biopsy and histochemically diagnosed cellular and antibody mediated rejection, among pediatric heart transplantation recipients, have been largely based upon reports from single center, retrospective cohort studies. [70-78]

According to the International Society for Heart and Lung Transplantation, in the current era (2010-2018), cellular and antibody mediated rejection (treated) occurs in approximately 10-15% of pediatric heart transplantation recipients within the first 1 year following pediatric heart transplantation. [79] Acute cellular rejection is defined by as a mononuclear inflammatory response, mediated largely by lymphocytes.

International Society for Heart and Lung Transplantation acute cellular rejection grading [79]

- Grade 0 – No rejection
- Grade 1 R, mild – Interstitial and/or perivascular infiltrate with up to one focus of myocyte damage. (grade 1A, 1B and 2 in 1990 system)
- Grade 2 R, moderate – Two or more foci of infiltrates with associated myocyte damage. (Grade 3A in 1990 system).
- Grade 3 R, severe – Diffuse infiltrate with multifocal myocyte damage, with or without edema, hemorrhage, or vasculitis.

Antibody mediated rejection (AMR) is defined by the presence of graft dysfunction, histopathologic changes based upon biopsy stained findings of capillary endothelial changes, macrophages in the capillaries, immunologic evidence of antibody mediated injury (e.g., C4d and C3d staining), and serologic evidence of elevated donor specific antibody. Positive immunofluorescent staining for C4d, C3d, and Anti HLA-DR or immunoperoxidase staining for C4d and CD68 (or C3d) is also diagnostic of antibody mediated rejection.

Antibody mediated rejection grading

- Grade 0- Negative histologic and immunopathologic findings
- Grade 1- Presence of positive histologic or immunopathologic findings
- Grade 2- Presence of both histologic and immunopathologic findings
- Grade 3- Presence of severe histologic plus immunopathologic findings

Grade ≥ 2R cellular mediated rejection or antibody-mediated rejection has been associated with systolic and diastolic dysfunction within the left ventricle. Novel markers of diastolic and global function may have an advantage over traditional systolic markers of function (shortening fraction and ejection fraction). Tissue Doppler imaging (TDI) is useful for its negative predictive value for excluding rejection. Lunze et al. reviewed echocardiographic data for children without rejection at baseline and absence of rejection at second biopsy (non-rejection pair) to data from children without rejection at baseline and the presence of rejection at the time of a subsequent biopsy (rejection pair) and found the absence of decline in left ventricular S' (systole) by greater than or equal to 15% and the absence of a decrease in left ventricular A' (late diastole) by greater than or equal to 5% was associated with a high negative predictive value for rejection. [72] However, the positive predictive value for rejection was low for left ventricular ejection fraction and left ventricular E/E' ratio. [72] Thus tissue Doppler imaging values during systole and late diastole, may be helpful in ruling out rejection, but may miss subtle cases of rejection. [72] Tissue Doppler imaging can also be utilized to assess strain and strain rate during rejection surveillance. In one single center study, cellular mediated rejection, antibody-mediated rejection and mixed rejection were associated with a decline in global longitudinal strain (GLS) (GLS -18.2 versus -14.1 at baseline versus at time of rejection, $p<0.05$), longitudinal strain rate (-1 vs -0.8, $p<0.05$), peak longitudinal early diastolic strain rate (1.3 vs 1.0, $p< 0.05$), and ejection fraction (62.1 vs 58.4%, $p<0.05$). Changes in strain may be observed during the first year post transplant as the graft remodels. However, strain values remain stable unless rejection occurs. [70] In adults, systolic strain and strain rate have been used to evaluate both global and regional ventricular deformation. [66] Chanana et al. found that not only is myocardial deformation abnormal in children with evidence of rejection, but that more specifically, strain and strain rate

can be used to distinguish cellular mediated rejection from antibody-mediated rejection, potentially allowing for targeted therapy. [66] Average left ventricular longitudinal systolic strain and strain rate are significantly reduced in all rejection types (cellular, antibody-mediated and/or mixed), **(Figure 9)** while mean left ventricular radial systolic strain are reduced only in cellular rejection. [66]

Echocardiography to guide endomyocardial biopsy

Endomyocardial biopsy has traditionally been performed in the cardiac catheterization lab with fluoroscopic guidance, however several studies have demonstrated the efficacy of using echocardiography guidance during endomyocardial biopsy. [80, 81] A retrospective analysis of 200 patients who underwent 2,665 endomyocardial biopsies with echo guidance, demonstrated that endomyocardial biopsy guided by echocardiography is safe with a low rate of complications and it lowers the procedural fluoroscopy time **(Figure 10)**. [81] Complications occurred in only five patients (2 pneumothorax, 3 with transient alterations in the electrocardiogram and in 25 patient's vascular access could not be achieved). In this study, no patient developed cardiac tamponade or other serious adverse effects leading to death. Echocardiography during endomyocardial biopsy allows the cardiologist to directly visualize the bioptome during the procedure. [81] It is useful for determining the specific site of myocardial sampling, avoiding injury to the tricuspid valve apparatus and papillary muscles, and the rapid and reliable detection of a pericardial effusion after the biopsy. [80, 81] Endomyocardial biopsies with echocardiographic guidance can be performed at bedside and may avoid the need for transferring critically ill patients to the cardiac catheterization lab. Three-dimensional echocardiography has also successfully been used during endomyocardial biopsy with no complications. The use of echocardiography guidance versus fluoroscopy for endomyocardial biopsy may be used safely

and has the advantage of improved visualization of the bioptome within the right ventricle and may significantly minimize the cumulative effect of radiation exposure, especially in the pediatric population. [80, 81]

Conclusion

Echocardiography is a reliable non-invasive tool in the management of pediatric heart failure patients on mechanical circulatory support or status post heart transplant. Echocardiography is crucial for the pre-operative evaluation, device optimization prior to transplant, rejection surveillance after transplant and during endomyocardial biopsies. Its role in the appropriate selection of patients, cannula placement, device optimization, detection of thrombus, pericardial effusions and early detection of rejection following heart transplant can significantly reduce morbidity and mortality in this cohort. Emerging technologies such as tissue Doppler imaging, strain and three-dimensional imaging hold promise for increasing roles in pediatric patients who are supported with mechanical circulatory support or heart transplant.

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Figure legends:

Figure 1: VV-ECMO with double lumen, single cannula. Subcostal long axis (Bi-Caval) view of the ECMO catheter. Venous drainage ports in SVC/IVC and the return port (marked with *) in the RA.

Figure 2: VA-ECMO with peripheral cannulation. Venous cannula in RA (panel A), and Art cannula at the base of the innominate artery (panel B)

Figure 3: L-VAD drainage catheter in the left ventricle (Panel A- parasternal long axis view), and infusion catheter in the ascending aorta (Panel B- Suprasternal notch). Catheter tip marked with (*).

Figure 4: Showing the drainage catheter position of a ventricular assist device on echocardiography (apical 4-chamber view) and CXR (PA and Lateral) in the systemic right ventricle of a patient with Fontan circulation (left side panel) and the left ventricle of a patient with dilated cardiomyopathy (right side panel).

Figure 5: Neo-aortic regurgitation in a patient with Fontan circulation supported with ventricular assist device.

Figure 6: Transthoracic echocardiography of aortic insufficiency in a patient with dilated cardiomyopathy supported with LVAD.

Figure 7. Showing the relative normalization of the Global Longitudinal Strain in a patient during the first year Post Transplant. From left to right: First week post-op, one month and 3 months post-transplant.

Figure 8. Three-dimensional speckle-tracking echocardiography of left ventricle in a post-transplant patient.

Figure 9. Abnormal Strain in a patient with acute cellular rejection Post Transplant

Figure 10. Transthoracic echocardiography guidance of biopsy. Apical 4-chamber view. Note bioptome tip in the right ventricle's septal surface.

Highlights:

- Echocardiography is a non-invasive tool for management of heart failure and heart transplant patients.
- Echocardiography is critical in heart transplant patients for rejection surveillance and during endomyocardial biopsies.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests

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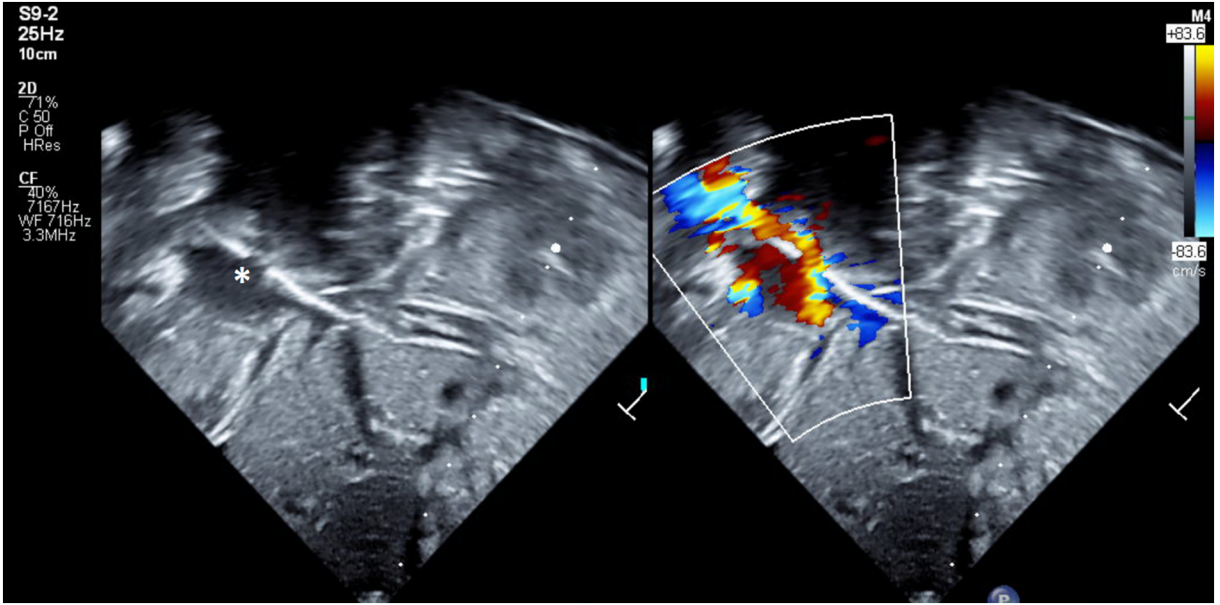
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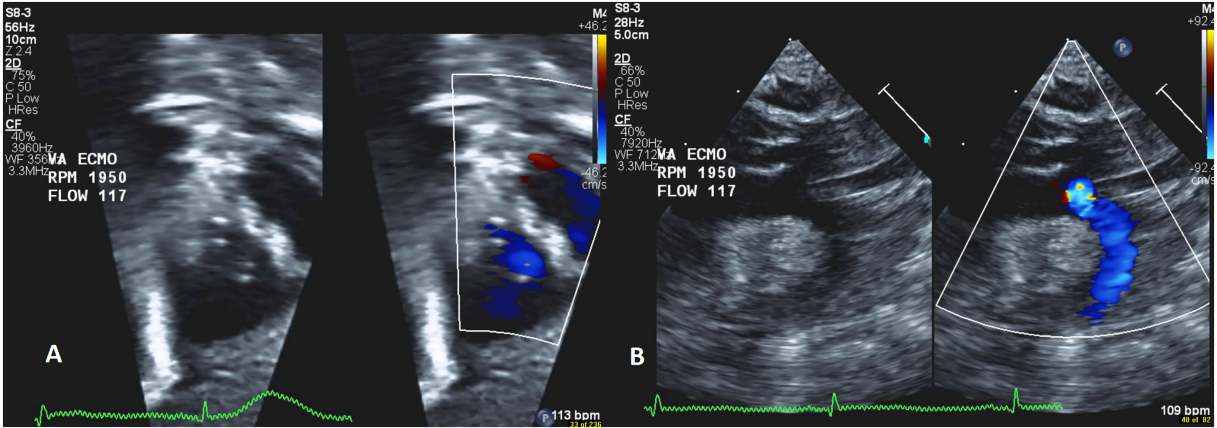
25Hz
10cm
2D
71%
C 50
P Off
HRes
CF
40%
7167Hz
WF 716Hz
3.3MHz
M4
+83.6
-83.6
cm/s

Figure 1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56Hz
10cm
Z 2.4
2D
75%
C 50
P Low
HRes
CF
40%
3960Hz
WF 356
3.3MHz
VA ECMO
RPM 1950
FLOW 117
A
113 bpm
S8-3
28Hz
5.0cm
2D
66%
C 50
P Low
HRes
CF
40%
7920Hz
WF 712
3.3MHz
VA ECMO
RPM 1950
FLOW 117
B
109 bpm

Figure 2

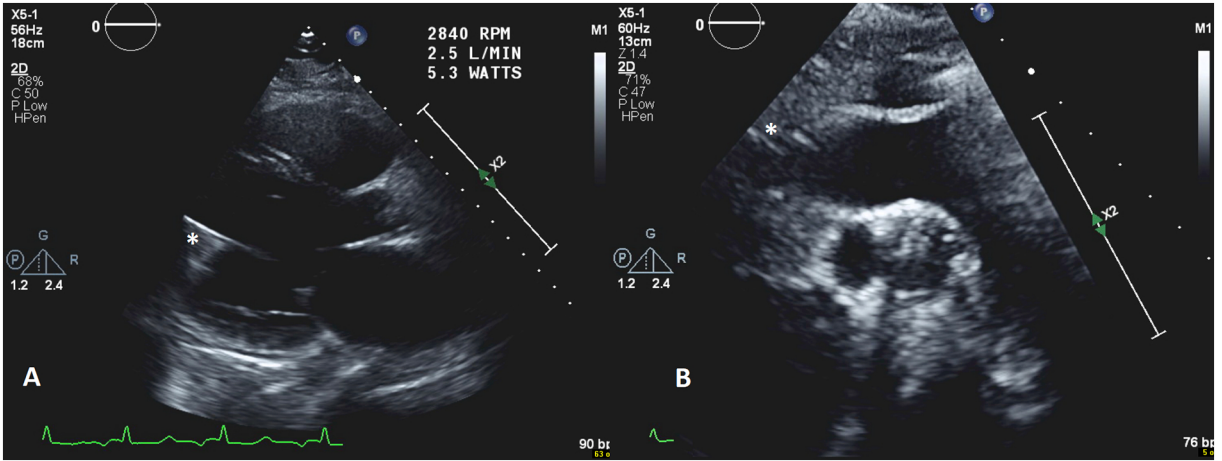
X5-1
56Hz
18cm
2D
68%
C 50
P Low
HPen
2840 RPM
2.5 L/MIN
5.3 WATTS
M1
X2
G
1.2 2.4
A
90 bp
X5-1
60Hz
13cm
Z 1.4
2D
71%
C 47
P Low
HPen
M1
X2
G
1.2 2.4
B
76 bp

Figure 3

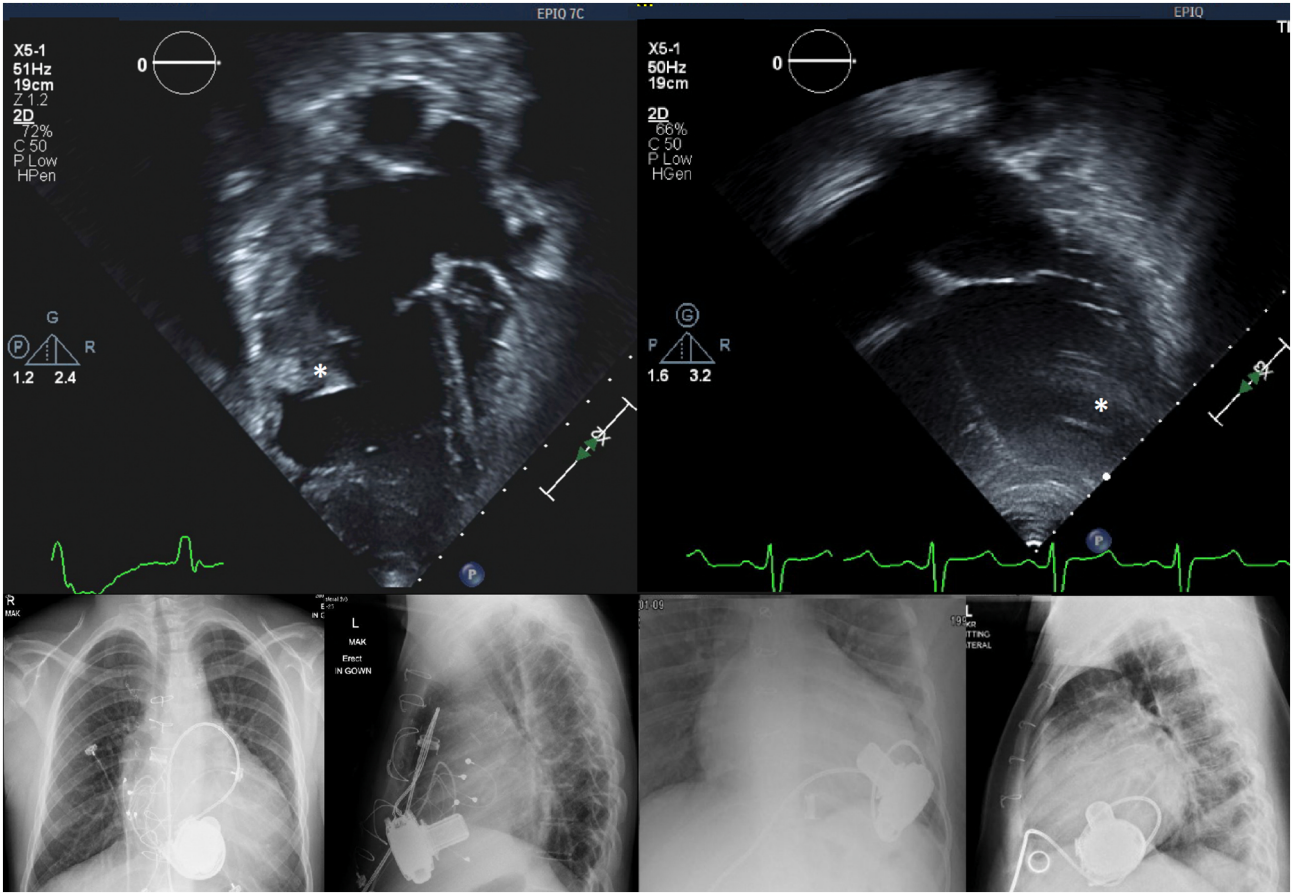
EPIQ 7C
X5-1
51Hz
19cm
Z 1.2
2D
72%
C 50
P Low
HPen
G
P
R
1.2 2.4
EPIQ
X5-1
50Hz
19cm
2D
66%
C 50
P Low
HGen
G
P
R
1.6 3.2
L
MAK
Erect
IN GOWN

Figure 4

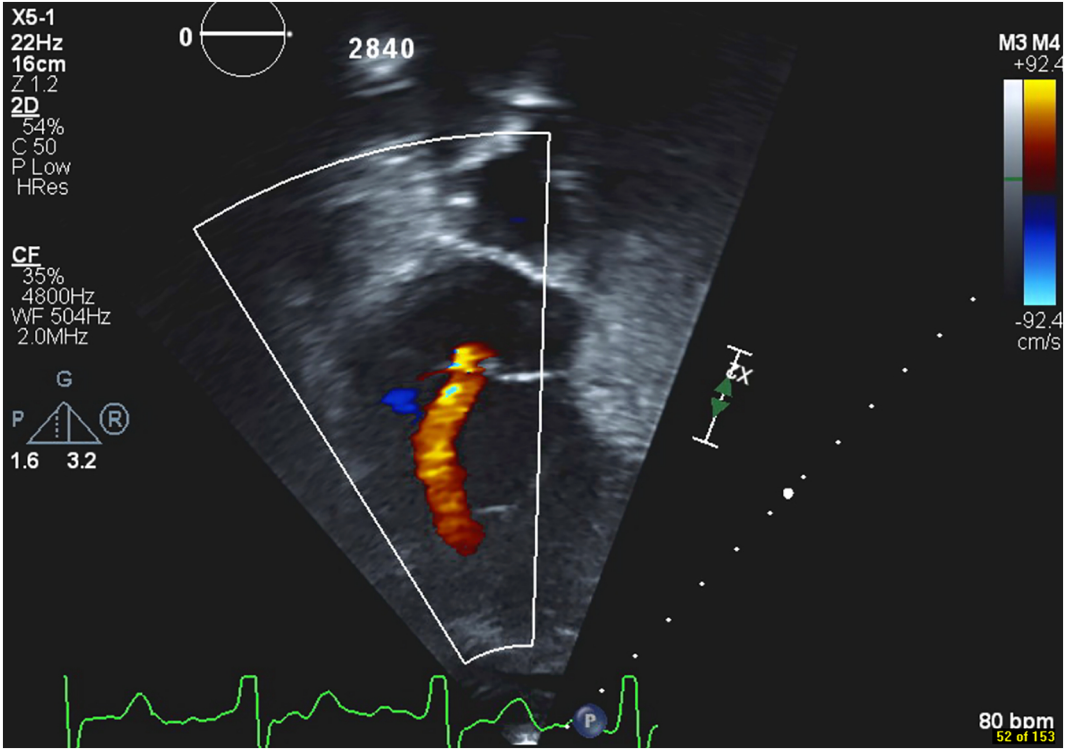
X5-1
22Hz
16cm
Z 1.2
2D
54%
C 50
P Low
HRes
CF
35%
4800Hz
WF 504Hz
2.0MHz
G
P
R
1.6
3.2
0
2840
M3 M4
+92.4
-92.4
cm/s
80 bpm
52 of 153

Figure 5

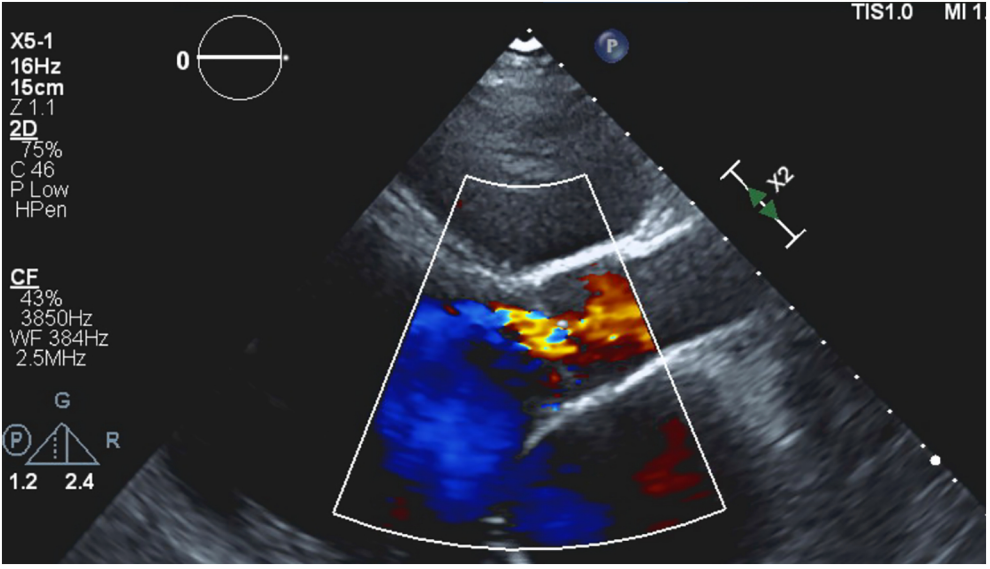
TIS1.0
MI 1.
X5-1
16Hz
15cm
Z 1.1
2D
75%
C 46
P Low
HPen
0
P
X2
CF
43%
3850Hz
WF 384Hz
2.5MHz
G
P
R
1.2
2.4

Figure 6

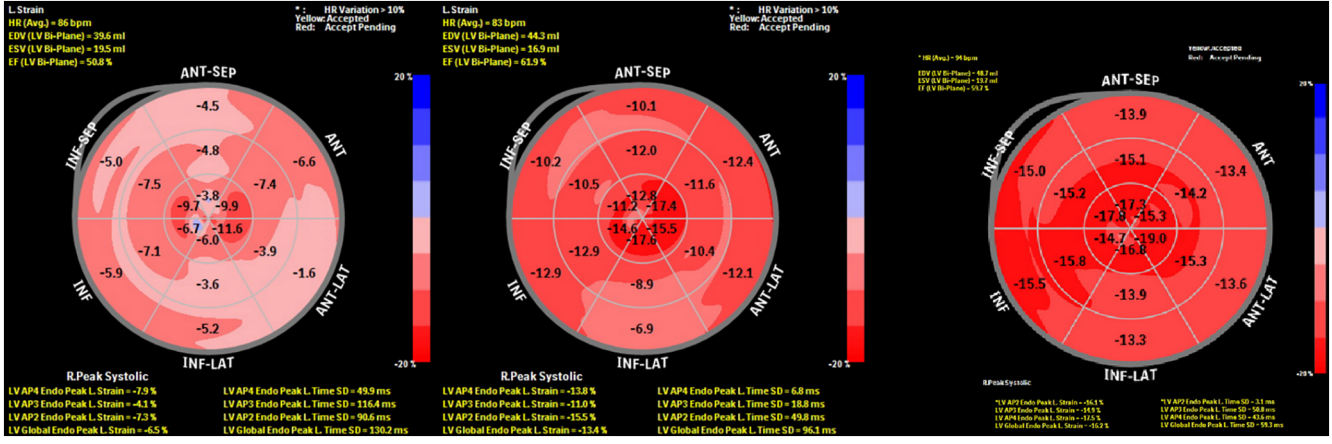
L. Strain
HR (Avg.) = 86 bpm
EDV (LV Bi-Plane) = 39.6 ml
ESV (LV Bi-Plane) = 19.5 ml
EF (LV Bi-Plane) = 50.8 %
* : HR Variation > 10%
Yellow: Accepted
Red: Accept Pending
ANT-SEP
ANT
ANT-LAT
INF-LAT
INF
INF-SEP
-4.5
-4.8
-5.0
-6.6
-7.5
-7.4
-3.8
-9.7
-9.9
-6.7
-11.6
-6.0
-7.1
-3.9
-5.9
-1.6
-3.6
-5.2
20 %
-20 %
R.Peak Systolic
LV AP4 Endo Peak L. Strain = -7.9 %
LV AP3 Endo Peak L. Strain = -4.1 %
LV AP2 Endo Peak L. Strain = -7.3 %
LV Global Endo Peak L. Strain = -6.5 %
LV AP4 Endo Peak L. Time SD = 49.9 ms
LV AP3 Endo Peak L. Time SD = 116.4 ms
LV AP2 Endo Peak L. Time SD = 90.6 ms
LV Global Endo Peak L. Time SD = 130.2 ms
L. Strain
HR (Avg.) = 83 bpm
EDV (LV Bi-Plane) = 44.3 ml
ESV (LV Bi-Plane) = 16.9 ml
EF (LV Bi-Plane) = 61.9 %
* : HR Variation > 10%
Yellow: Accepted
Red: Accept Pending
ANT-SEP
ANT
ANT-LAT
INF-LAT
INF
INF-SEP
-10.1
-12.0
-10.2
-12.4
-10.5
-11.6
-12.8
-11.2
-17.4
-14.6
-15.5
-17.6
-12.9
-10.4
-12.9
-12.1
-8.9
-6.9
20 %
-20 %
R.Peak Systolic
LV AP4 Endo Peak L. Strain = -13.8 %
LV AP3 Endo Peak L. Strain = -11.0 %
LV AP2 Endo Peak L. Strain = -15.5 %
LV Global Endo Peak L. Strain = -13.4 %
LV AP4 Endo Peak L. Time SD = 6.8 ms
LV AP3 Endo Peak L. Time SD = 18.8 ms
LV AP2 Endo Peak L. Time SD = 49.8 ms
LV Global Endo Peak L. Time SD = 96.1 ms
ANT-SEP
ANT
ANT-LAT
INF-LAT
INF
INF-SEP
-13.9
-15.1
-15.0
-13.4
-15.2
-14.2
-17.3
-17.8
-15.3
-14.7
-19.0
-16.8
-15.8
-15.3
-15.5
-13.6
-13.9
-13.3

Figure 7

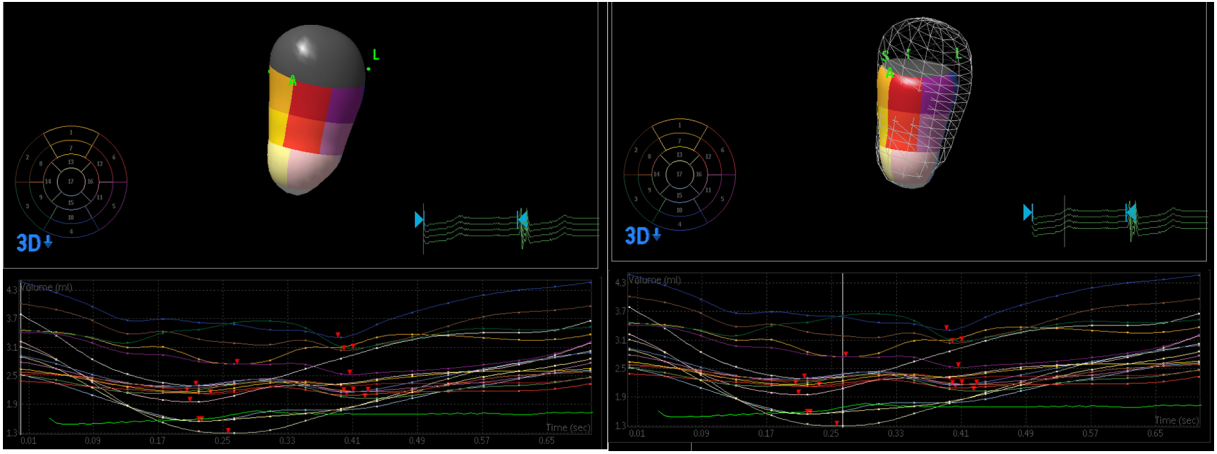
L
3D
Volume (ml)
Time (sec)
0.01
0.09
0.17
0.25
0.33
0.41
0.49
0.57
0.65
3D
Volume (ml)
Time (sec)

Figure 8

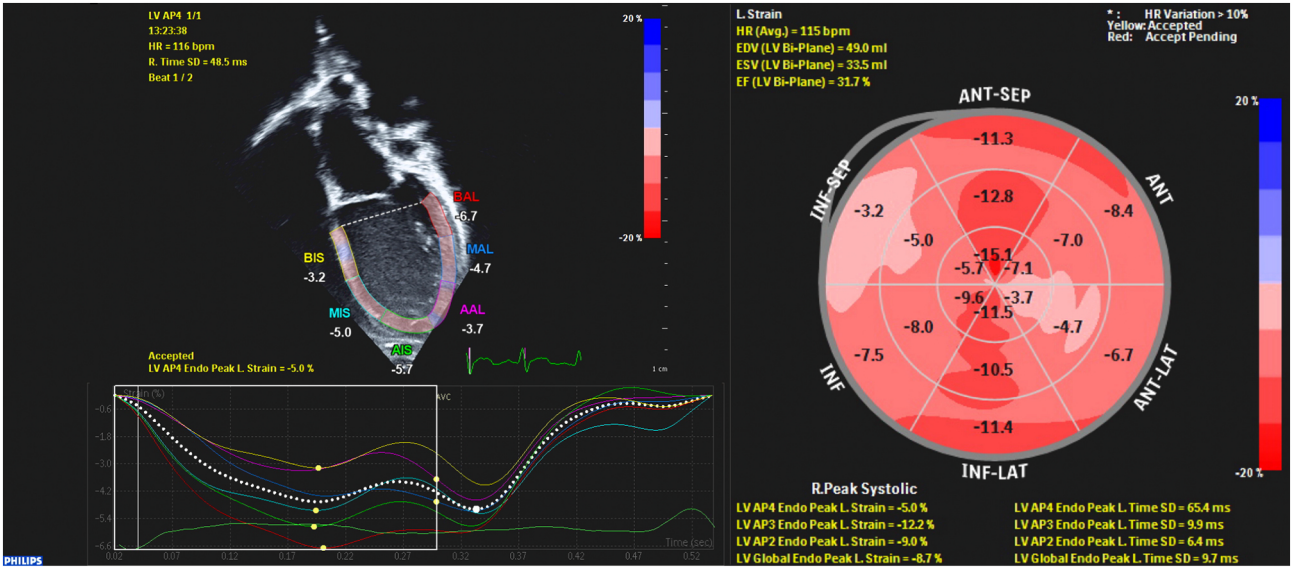
LV AP4 1/1
13:23:38
HR = 116 bpm
R. Time SD = 48.5 ms
Beat 1 / 2
20 %
-20 %
BAL
-6.7
MAL
-4.7
AAL
-3.7
AIS
-5.7
MIS
-5.0
BIS
-3.2
Accepted
LV AP4 Endo Peak L. Strain = -5.0 %
1 cm
Strain (%)
-0.6
-1.8
-3.0
-4.2
-5.4
-6.6
AVC
Time (sec)
0.02
0.07
0.12
0.17
0.22
0.27
0.32
0.37
0.42
0.47
0.52
PHILIPS
L. Strain
HR (Avg.) = 115 bpm
EDV (LV Bi-Plane) = 49.0 ml
ESV (LV Bi-Plane) = 33.5 ml
EF (LV Bi-Plane) = 31.7 %
* : HR Variation > 10%
Yellow: Accepted
Red: Accept Pending
ANT-SEP
ANT
ANT-LAT
INF-LAT
INF
INF-SEP
-11.3
-12.8
-15.1
-5.7
-7.1
-9.6
-3.7
-11.5
-10.5
-11.4
-3.2
-5.0
-8.4
-7.0
-8.0
-4.7
-7.5
-6.7
20 %
-20 %
R.Peak Systolic
LV AP4 Endo Peak L. Strain = -5.0 %
LV AP3 Endo Peak L. Strain = -12.2 %
LV AP2 Endo Peak L. Strain = -9.0 %
LV Global Endo Peak L. Strain = -8.7 %
LV AP4 Endo Peak L. Time SD = 65.4 ms
LV AP3 Endo Peak L. Time SD = 9.9 ms
LV AP2 Endo Peak L. Time SD = 6.4 ms
LV Global Endo Peak L. Time SD = 9.7 ms

Figure 9

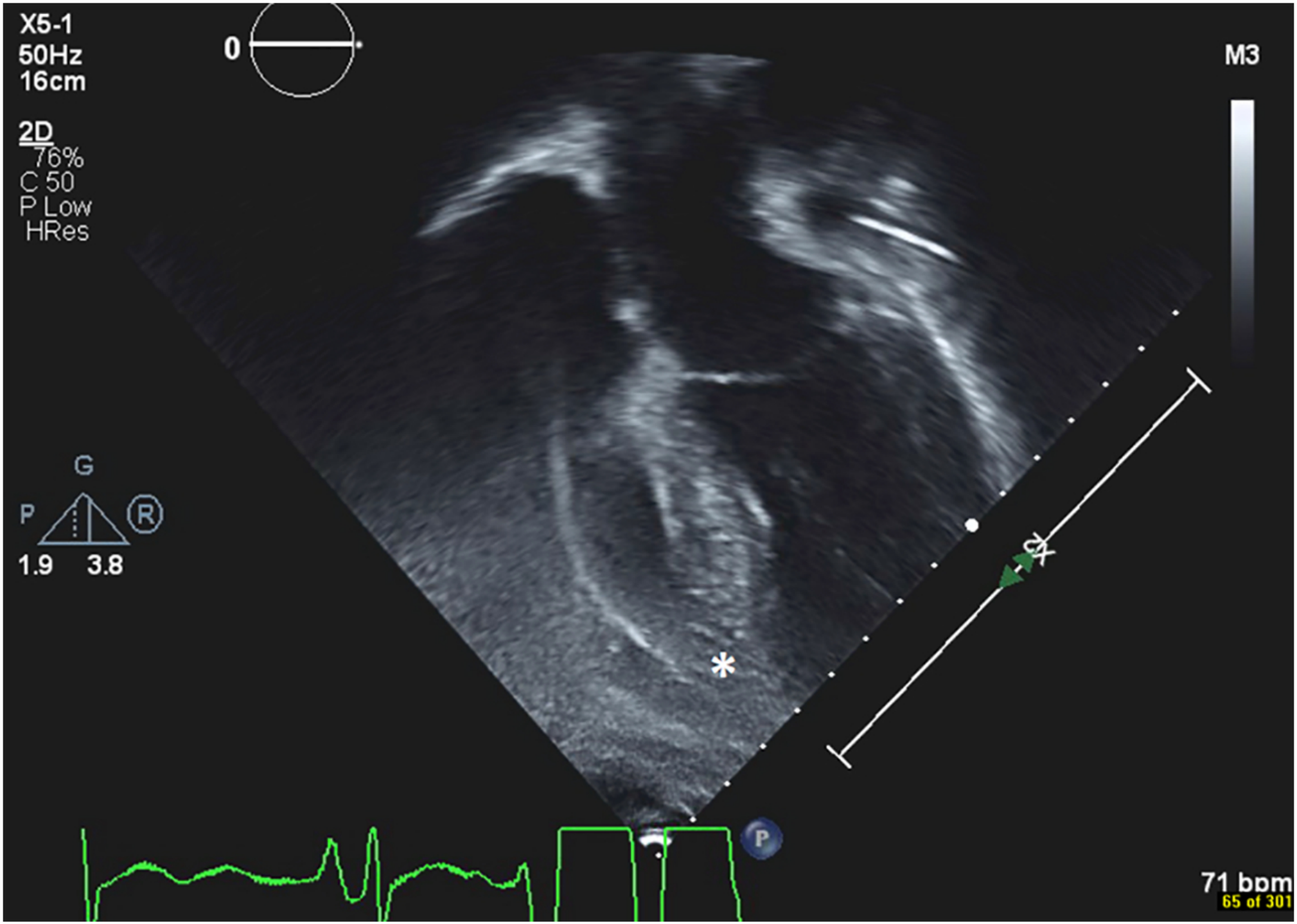

Figure 10