Predictors of Sudden Cardiac Death in Sarcomeric Hypertrophic Cardiomyopathy: Utilization of Advanced Imaging Techniques Before and After Interventional Treatment

Predictors of Sudden Cardiac Death in Sarcomeric Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a genetic disorder inherited in an autosomal dominant manner, characterized by abnormal and asymmetric hypertrophy of the myocardium in the left ventricle.[217] Its prevalence is estimated to be between 1 in 500 and 1 in 200 in the general population.[189] Pathogenic single gene variants have been found in approximately 40–60% of individuals diagnosed with HCM through genetic testing. These variants are mostly situated in sarcomeric protein genes, with β-cardiac myosin (*MYH7*) and cardiac myosin-binding protein C (*MYBPC3*) being the most commonly affected.[218] However, mutations in other genes like cardiac troponin T (*TNNT2*), cardiac troponin I (*TNNI3*), α-tropomyosin (*TPM1*), cardiac α-actin (*ACTC1*), myosin light chain 2 (*MYL2*), and myosin light chain 3 (*MYL3*) may also be observed, though less frequently.[219]

HCM stands as a prominent cause of sudden cardiac death (SCD) in young individuals and athletes. The annual incidence of SCD among adults with HCM is roughly 1%. Consequently, it is crucial to identify both the risk factors for SCD and individuals at high risk.[220,221]

In 2011, the American Heart Association (AHA) devised an SCD risk calculator tool to evaluate the appropriateness of implanting an implantable cardioverter defibrillator (ICD) in HCM patients. This model factored in various elements, including a family history of SCD, recent instances of unexplained syncope, non-sustained ventricular tachycardia (NSVT), abnormal blood pressure responses during exercise, and maximal left ventricular wall thickness. Subsequently, in 2014, the European Society of Cardiology (ESC) introduced a similar risk calculator, which augmented the model with additional parameters such as age, left atrium diameter, and left ventricular outflow obstruction.[222,223]

Lastly, the AHA guideline of 2020 identified left ventricular systolic dysfunction, the presence of a left ventricular apical aneurysm, and diffuse late gadolinium uptake (LGE) on cardiac magnetic resonance imaging (MRI) as high-risk indicators for SCD in HCM patients.[183]

Left Ventricular Systolic Dysfunction

Typically, left ventricular systolic function in HCM presents as hyperdynamic. However, a decrease in left ventricular systolic function may occur due to diffuse myocardial fibrosis in patients with end-stage disease. Left ventricular systolic dysfunction is defined as an ejection fraction (EF) below 50%, as determined by transthoracic echocardiography (TTE). Its incidence is estimated to be approximately 9%.[224] Patients with HCM who experience left ventricular systolic dysfunction during the disease course. face a poor prognosis. They are at heightened risk for SCD and malignant ventricular arrhythmias. The current AHA guideline recommends implantation of an implantable cardioverter defibrillator (ICD) with a class 2a indication in this patient cohort.[183]

In some cases, there may be a subtle impairment of longitudinal contractile function despite a preserved EF. This can be assessed by evaluating systolic annular velocities, strain, and strain rate using tissue Doppler imaging (TDI). In 2024, a study by Lee et al.[225] showed that integrating the left ventricular

global longitudinal strain (LV-GLS) value into conventional SCD risk models, as endorsed by guidelines, enhanced the prognostic effectiveness of the models. Additionally, LV-GLS emerged as an independent indicator of increased risk for SCD.

Left Ventricular Apical Aneurysm

A left ventricular apical aneurysm is found in approximately 2-5% of HCM patients.[226] It is theorized to develop due to myocardial damage resulting from elevated systolic intra-cavitary pressure caused by mid-ventricular obstruction and impaired diastolic perfusion due to low stroke volume, both common occurrences in HCM. While echocardiography is typically the initial diagnostic tool, TTE may not always reliably diagnose small aneurysms. The gold standard imaging modality is cardiac MRI. However, the use of contrast agents can enhance the sensitivity of TTE.

The presence of a left ventricular apical aneurysm is associated with an increased risk of SCD and malignant ventricular arrhythmias in HCM individuals. According to the current AHA guideline, the presence of a left ventricular apical aneurysm, regardless of its size, is considered a major risk factor for SCD.[183]

Left Atrium Size

The primary causes of left atrial dilatation in HCM include elevated left ventricular filling pressure, mitral regurgitation, and intrinsic atrial myopathy, believed to be instigated by sarcomeric gene mutations.[227,228] Left atrial dilatation in HCM correlates with an elevated risk of mortality (Figure 45). In a study involving 1,491 HCM patients, a left atrial anteroposterior diameter exceeding 48 mm was identified as an independent predictor of heightened cardiovascular mortality. Similarly, left atrial volume emerged as an independent predictor of adverse cardiovascular events.[229] Both left atrial dilatation and impaired left atrial reservoir function are associated with an increased risk of SCD and malignant ventricular arrhythmias in HCM.[230]

Compared to MRI, left atrial volume measured by TTE may be underestimated. Therefore, cardiac MRI stands as the gold standard for left atrial volume measurement.[231]

Myocardial Fibrosis

Late gadolinium enhancement (LGE) detected on cardiac MRI serves as an indicator of myocardial fibrosis. LGE is observed in hypertrophic segments in over 50% of HCM patients. There exists a strong correlation between the extent of LGE and SCD in HCM. When LGE encompasses ≥15% of the left ventricular mass, it is associated with a twofold increase in the risk of SCD. The assessment of myocardial fibrosis plays a crucial role, particularly in the reclassification of patients initially categorized as low-to-intermediate risk for SCD based on conventional risk models.[232]

Left Ventricular Outflow Obstruction

Left Ventricular Outflow Obstruction (LVOTO) is present in approximately two-thirds of HCM patients, either at rest or when provoked.[13] It is a dynamic parameter influenced by preload, afterload, and left ventricular contractility. Diagnosis of LVOTO can be made by examining apical 3-chamber or apical 5-chamber views on TTE, utilizing M-mode, color Doppler, pulsed wave (PW) Doppler, and continuous wave (CW) Doppler modalities (Figure 46). The presence of LVOTO in adults with HCM is associated with

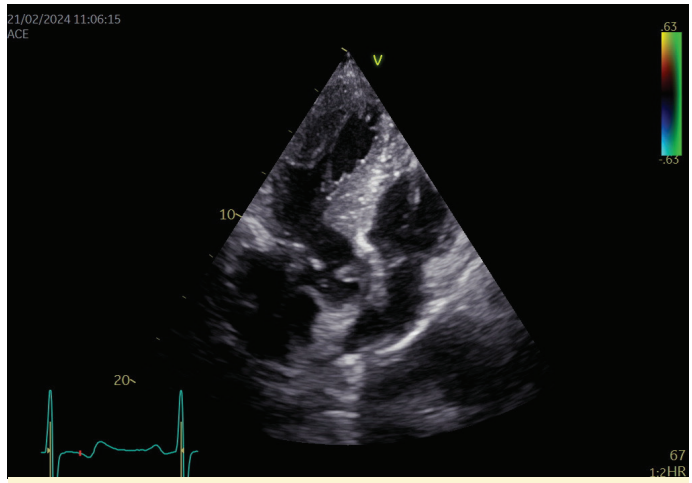

Figure 45. Left atrial dilatation.

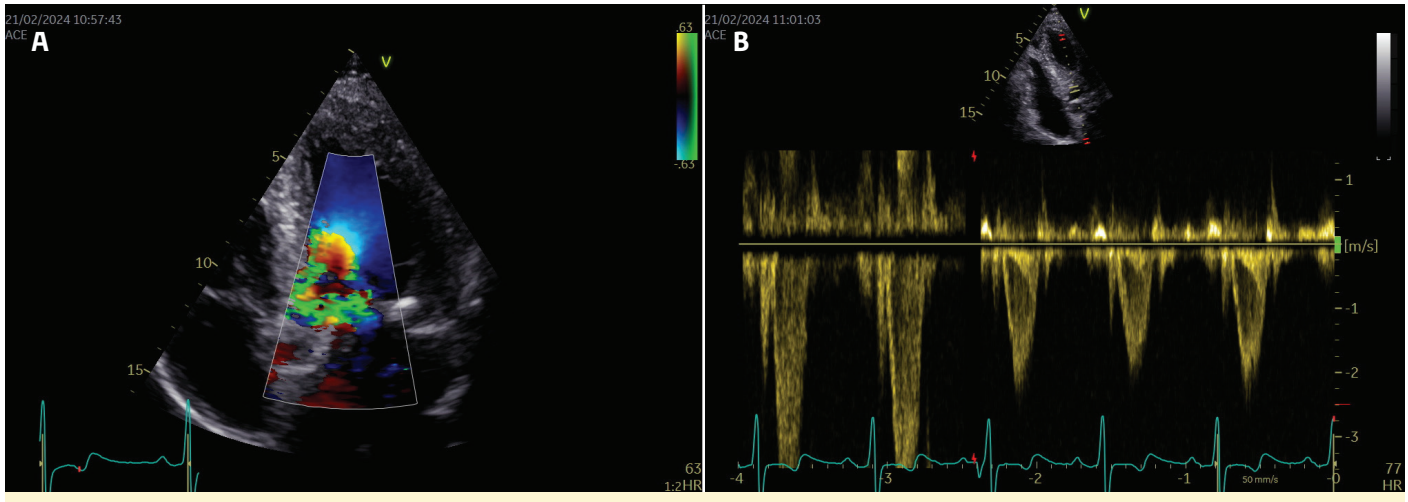

Figure 46. (A) Evaluation of left ventricular outflow obstruction with color Doppler. (B) Evaluation of left ventricular outflow obstruction with PW Doppler.

an increased risk of SCD. However, no further incremental risk is observed beyond values exceeding 30 mmHg.[193]

Use of Advanced Imaging Methods Before and After Interventional Treatment

In sarcomeric hypertrophic cardiomyopathy (HCM), left ventricular outflow tract obstruction plays a crucial prognostic role. Beta-blocker therapy is the primary recommendation for symptomatic patients with a gradient of 50 mmHg or greater at rest or upon provocation. If symptoms persist or if there's intolerance or contraindications to beta-blockers, Diltiazem or Verapamil can be prescribed. Disopyramide is also recommended for patients who remain symptomatic despite therapy with the aforementioned treatments. Mavacamten is listed as a class IIa treatment in the recent European Society of Cardiology Cardiomyopathy Guideline.[1]

Furthermore, septal reduction treatments are recommended with a class I indication for patients with left ventricular outflow tract gradients exceeding 50 mmHg, whose symptoms do not respond to medical treatment. Mildly symptomatic patients with an obstruction of the left ventricular outflow tract (LVOTO) of 50 mmHg or above (NYHA class II) should undergo septal reduction in experienced centers if they suffer from moderate-severe left atrial dilation, moderate-severe mitral regurgitation (MR) due to systolic anterior motion, atrial fibrillation, or pulmonary hypertension. Surgical septal myectomy or alcohol septal ablation are the two methods for reducing the septum.[183,233] Additionally, small case studies suggest that coils can be used instead of alcohol to close the septum, and that endocavitary/intramuscular ablation procedures can result in interventricular septum (IVS) scarring. However, due to the lack of comparative or safety studies of these methods,[1,234,235] the guidelines recommend only alcohol septal ablation and surgical myectomy.

Imaging techniques play a crucial role in selecting and evaluating these procedures. In the following sections, we discuss the multimodality imaging methods used in the preoperative period to determine the suitability of alcohol septal ablation or septal myectomy. Additionally, we discuss intraoperative guidance and postoperative assessment of the success and complications of the procedures using multimodality imaging.

Transthoracic Echocardiography

TTE is the most common method used to measure the LVOT) gradient for interventional procedures. Medical treatment is indicated for symptomatic (NYHA III-IV) patients with an LVOT gradient ≥ 50 mmHg measured at rest or during provocation (Valsalva maneuver, standing up). Interventional procedures are undertaken in patients who are refractory and/or intolerant to maximal medical treatment. TTE allows for the assessment of IVS thickness, midventricular or apical hypertrophy, and the presence of obstruction. It is recommended to measure myocardial thickness in end-diastole from a parasternal short axis view.[1] Contrast echocardiography can be useful when the image quality is suboptimal, particularly in assessing apical hypertrophy.[236]

TTE serves as the initial and primary imaging method, providing detailed information to guide decisions about surgical myectomy

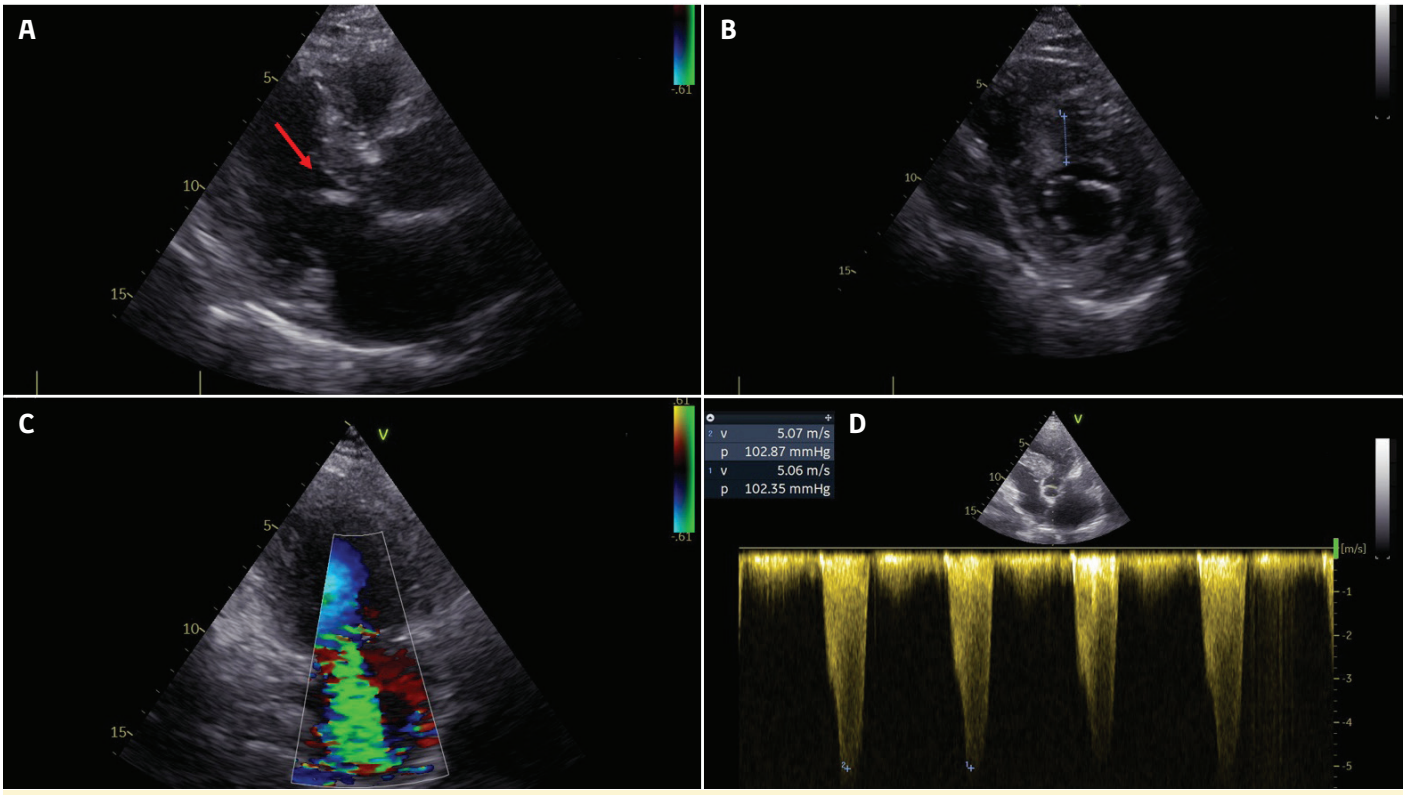

Figure 47. Transthoracic echocardiography images of the patient with a gradient of 102 mmHg in the left ventricular outflow tract. (A) The red arrow indicates anterior movement of the mitral anterior leaflet in systole. (B) Measurement of the IVS from a parasternal short-axis view of 2.1 cm. (C) Severe central mitral regurgitation.

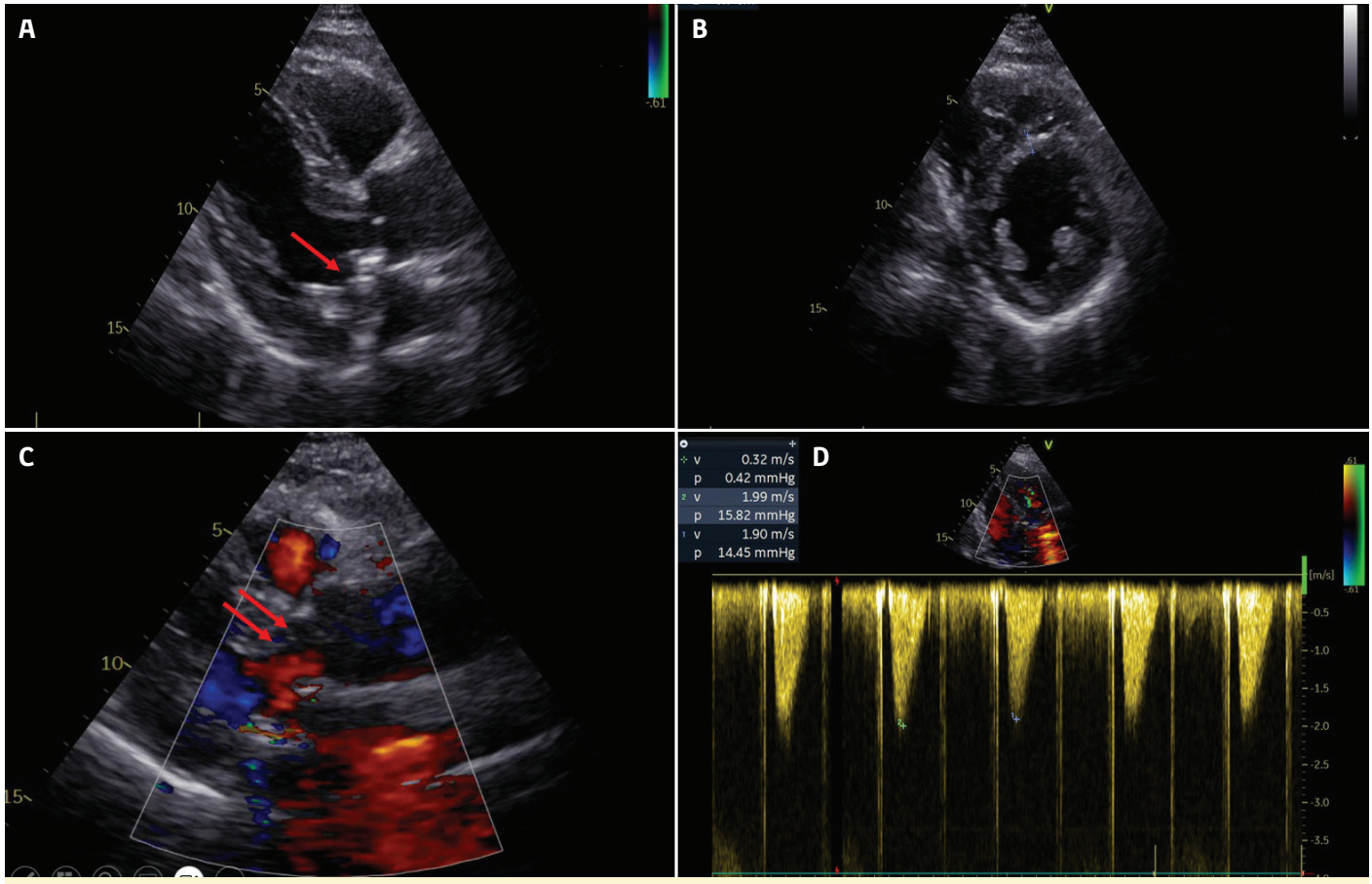

Figure 48. Transthoracic echocardiography images of a patient with HCM and severe mitral regurgitation after septal myectomy and mitral valve replacement. (A) A red arrow indicates mitral valve replacement (MVR). (B) Measurement of the IVS from a parasternal short-axis view of 0.7 cm. (C) Two red arrows indicate the disappearance of turbulence in the left ventricular outflow tract. (D) There is no gradient in the left ventricular outflow tract.

or alcohol septal ablation in the preoperative period. Surgical septal myectomy is preferred when hypertrophy is detected in the mid and apical regions of the heart, apart from the IVS base, and when papillary muscle involvement is causing obstruction in the midventricular region.

LVOTO may lead to the anterior mitral valve leaflet moving anteriorly and contacting the interventricular septum (known as SAM) during systole. While this phenomenon was previously attributed to the Venturi effect, the primary mechanism involves the sweeping of the mitral valve apparatus by the flow in the LVOT, pushing it towards the IVS.[237] MR occurs due to the anterior motion of the anterior leaflet during systole. MR resulting from SAM typically manifests in mid to late systole and is oriented posteriorly or laterally. Both myectomy and alcohol septal ablation are effective in treating MR in this scenario.[195]

Patients with HCM often present anomalies associated with the mitral valve and subvalvular apparatus. These anomalies may include an abnormally located papillary muscle, elongated leaflets, anterior displacement of the papillary muscle, mitral valve prolapse, and chordal rupture. It is crucial to thoroughly evaluate these abnormalities, particularly in the presence of centrally and anteriorly oriented MR.[1,238]

Transesophageal echocardiography (TOE) or cardiac magnetic resonance imaging (CMR) is recommended for evaluating the mitral valve and its apparatus in patients suspected of primary valve disease when assessment by TTE is insufficiently clear.[197,239] Dyspnea may solely result from primary valve disease. In patients with LVOTO ≥ 50 mmHg and moderate-to-severe MR resulting from anomalies of the mitral valve apparatus, advanced imaging methods should be employed if the mitral valve cannot be adequately evaluated by TTE (Figure 47). This is particularly important as septal reduction procedures will necessitate surgical myectomy along with potential mitral valve repair or replacement.

Furthermore, left atrial dilation detected by TTE serves as a prognostic indicator. The primary cause of left atrial dilation is an elevation in left ventricular filling pressure and MR due to SAM.

TTE serves as the initial imaging method for evaluating and monitoring left ventricular outflow tract obstruction (LVOTO) following septal reduction interventions. Additionally, TTE can detect potential complications such as ventricular septal defect and aortic insufficiency following septal myectomy. After septal reduction procedures, TTE plays a crucial role in assessing left ventricular systolic and diastolic function to determine the success of the intervention and prognosis (Figure 48).

Transesophageal Echocardiography

TOE is an essential imaging method in determining the course of septal reduction treatment. TOE should be conducted to identify and rule out conditions that may mimic HCM, such as a subvalvular membrane. Additionally, a TOE is necessary if primary mitral valve disease is suspected. During the intraoperative period, TOE is crucial for detecting and managing complications that may arise during septal myectomy, such as aortic regurgitation or ventricular septal defects. It also guides the surgeon throughout the procedure. Similarly, when identifying the appropriate septal branch for alcohol septal ablation, TOE must be employed to visualize the contrast or agitated saline administered and to guide the operator. A study by La Canna et al.[240] demonstrated that three-dimensional TOE enhances the identification of the target artery for alcohol septal ablation, resulting in high long-term success rates. Consequently, TOE should be a standard component of all septal reduction procedures.

During the procedure, TOE can assess the reduction in LVOTO and determine the degree of MR. It is also valuable in evaluating the valve during repair or replacement in patients with primary mitral valve anomalies. Moreover, it enhances the success rate during septal ablation and ensures that the infarct area is minimized, thereby reducing complications like heart block. While LVOTO reduction is typically observed during the procedure, septal scar resolution may take time (usually within three months). Thus, follow-up TTE should be performed to assess LVOTO reduction. Monitoring the LVOT gradient by TTE is also recommended to detect recurrence of obstruction.[183]

In patients with severe MR who are not suitable candidates for surgery, TOE can be utilized as part of a percutaneous procedure, such as Mitraclip insertion.[241]

Cardiac Magnetic Resonance Imaging

Cardiac MRI serves as an imaging method that can be employed before septal reduction procedures, particularly in cases where the acoustic windows of echocardiography are suboptimal. Moreover, it can detect abnormally located papillary muscles. If a hypertrophied anterolateral muscle without chordae is directly attached to the mitral valve, this may significantly contribute to mid-cavitary hypertrophy, which warrants assessment by cardiac MRI if there is any uncertainty with TTE. Additionally, cardiac MRI is useful for evaluating mitral valve anomalies, complementing the information obtained from TOE. To ensure the success of the septal reduction procedure, it is recommended to identify hypertrophic segments before the procedure and to utilize MRI to determine the degree of fibrosis.

Cardiac Computed Tomography and Nuclear Imaging

Cardiac computed tomography can be utilized to assess left ventricular functions in situations where TTE is suboptimal and CMRis not feasible. It is primarily advised for identifying the target septal perforator before alcohol septal ablation.[242] After septal reduction procedures, nuclear imaging can be employed to evaluate the procedure's success. A positive change in the perfusion pattern typically indicates a successful intervention.[243,244]