Diagnosis and Risk Stratification in Acute Pulmonary Embolism: The Role of Echocardiography

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Pulmonary embolism (PE) is a frequently encountered clinical condition with a high mortality rate that is affected by various factors such as age, hemodynamics, and other comorbidities. Early diagnosis and risk stratification are crucial to achieving a favorable clinical outcome. New risk stratification algorithms have been proposed in order to identify high-risk patients who will benefit from early thrombolytic treatment. Among the various validated diagnostic methods, the role of echocardiography is increasingly accepted. Recent advances in studying right ventricular function have made echocardiography an attractive tool for establishing or excluding the diagnosis of acute PE in the emergency setting and initiating optimal therapy.

Pulmonary embolism (PE) is a common clinical entity with high mortality rates, occurring in ∼ 0.4% of hospitalized patients.[1] PE commonly presents with nonspecific symptoms and signs, and the true incidence may be underestimated. The disease is fatal in ∼ 10% of patients within the first hour of occurrence and is diagnosed promptly in only ∼ 30% of cases.[2]

Bedside echocardiography, in addition to electrocardiography and chest radiography, is a powerful tool for the differential diagnosis between acute PE and other serious disorders with a similar clinical

presentation such as aortic dissection, acute myocardial infarction, or pericardial tamponade. It is useful for evaluating the morphology and function of right-sided chambers and less frequently for direct visualization of thrombi within the inferior vena cava (IVC), right atrium, right ventricle (RV), and the pulmonary artery (PA). However, almost half of the patients diagnosed with PE demonstrate normal echocardiographic manifestations[3]; therefore, findings should always be interpreted in concordance with the clinical signs, history, and the results of more sensitive diagnostic imaging methods, such as contrast-enhanced CT pulmonary angiogram (CTPA) or ventilation/ perfusion lung scan (V/Q scan).

The value of echocardiography in the diagnosis of PE has been evident since the late 1970s[4,5] and has been extensively investigated during the past two decades. Earlier studies mainly emphasized the significance of direct visualization of right cardiac thrombi,[6] whereas later studies focused on the correlation of echocardiographic manifestations to the area of the affected pulmonary vasculature.[7,8] More recent studies evaluated the presence of RV dysfunction as a predictor of mortality,[9-11] the persistence of echocardiographic findings in relation to treatment outcomes,[12] and the value of various echocardiographic signs.[13]

Pathophysiology of RV Dysfunction

Dysfunction of the RV following acute PE is the result of a sudden rise in PA pressure. A further increase in PA pressure and pulmonary vascular resistance (PVR) is due to the presence of hypoxia and reflex vasoconstriction, as well as the release of vasoconstricting hormones, such as serotonin. This abrupt increase in the afterload leads to increased RV wall tension and subendocardial ischemia, followed by dilation and shifting of the interventricular septum (IVS) toward the LV. The above results in decreased LV filling and cardiac output, systemic hypotension, coronary hypoperfusion, and myocardial ischemia, which further compromise RV and LV function.

LV dysfunction secondary to RV failure has long intrigued physiologists. More than pressure overload, recent studies have demonstrated that the immediate mechanisms for RV damage include subendocardial ischemia and shear-mediated ultrastructural damage to myocytes. Watts and colleagues[14] showed a large increase in expression of the chemokine monocyte chemoattractant protein in the RV (but not the LV) of rats with experimental PE. Iwadate and associates[15] observed large numbers of CD68-staining cells on histologic examination of RV tissue from humans with fatal PE. These findings suggest that PE initially causes ischemic and structural injury to the myocardium followed by an inflammatory response of the RV.[3]

Echocardiography in Relation to the Size of PE

The severity of hemodynamic compromise is directly related to the thrombotic burden, the extent of the affected pulmonary vasculature, the time period in which the embolization of the pulmonary vessels occurred, and the coexistence of other cardiovascular and respiratory comorbidities. Large or multiple emboli might abruptly increase PVR to a level of afterload, which cannot be matched by the RV. This causes RV dilatation and impairment with subsequent reduction of LV preload and cardiac output. Several studies have assessed the correlation between RV dysfunction and the size of the affected pulmonary arterial tree. Wolfe and colleagues[16] reported that hemodynamically stable patients with acute PE and RV dysfunction on echocardiography had a defect of 54% on lung perfusion scan. In the same study, RV

Figure 1. Transesophageal study of a patient with acute PE demonstrating a large, mobile thrombus (*arrowhead*) within the right atrium. RA, right atrium; RV, right ventricle.

hypokinesia on echocardiography was seven times more likely to be found in patients with large defects ($\geq$ 30%). Ribeiro and associates[8] showed that defects > 20% on lung scintigraphy correlated more often with RV hypokinesis, RV dilation, and pulmonary hypertension (PH) on echocardiography, compared with defects < 20% of the affected lung area. However, a large variability was observed among the two patient groups. In a study by Chung and colleagues,[17] tricuspid annular motion and RV basal late-diastolic velocity independently predicted the extent of PE on lung scintigraphy. In addition, RV apical to RV basal systolic velocity ratio was strongly correlated to the size of PE. Tricuspid annular motion and RV basal systolic velocity were the only echocardiographic parameters to correlate with small residual scintigraphic perfusion defects on 42-day follow-up. The same team showed that elderly patients with large PE, defined as > 30% obstruction on lung scan, demonstrated RV dysfunction on echocardiography.[18] RV systolic impairment, RV end-systolic dilatation, right:left atrial end-systolic area ratio, and RV:LV end-diastolic area ratio consistently correlated to the extent of PE. In a more recent study, Kjaergaard and colleagues[19] proved that significant RV dysfunction is only found in patients with perfusion defects > 25%. RV diameter, RV systolic pressure, and RV systolic function correlated to the size of PE; however, no correlation was found with RV myocardial performance index (RV-MPI) or peak tricuspid annular systolic velocity. PA acceleration time was shortened even in patients with small emboli and < 25% perfusion defects on V/Q scan.

In contrast, a study that included hemodynamically stable patients with acute PE and no history of
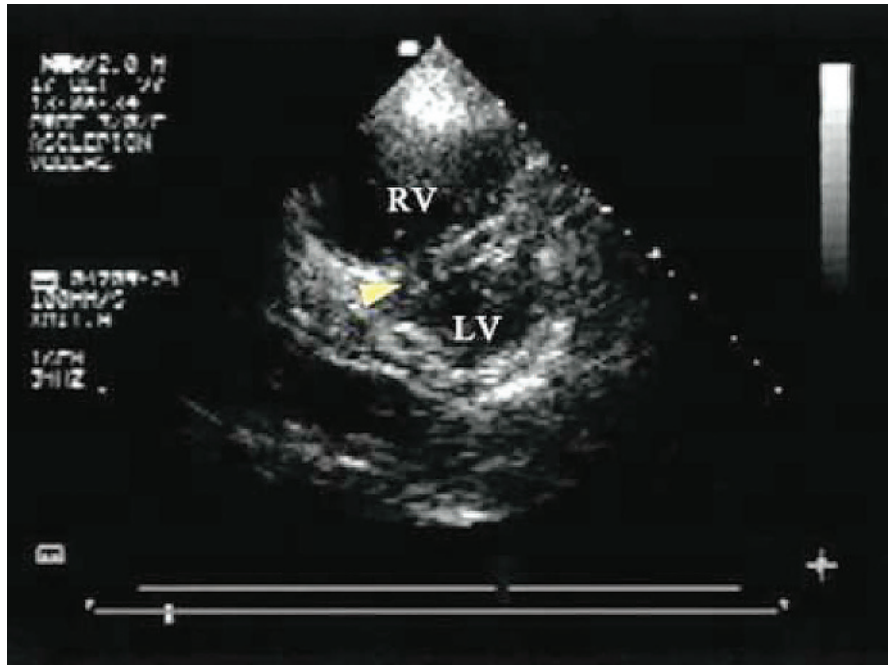
Figure 2. Parasternal short-axis view of the right and left ventricles in a patient with PE showing diastolic flattening of the intraventricular septum as a result of pressure overload. LV, left ventricle; RV, right ventricle.

cardiopulmonary disorders failed to demonstrate correlation between the extent of pulmonary vascular obstruction on V/Q scan and the presence of RV end-systolic dilatation on echocardiography.[20]

Echocardiographic Findings in Acute PE

RV and LV Dysfunction
Although no uniform criteria exist for the diagnosis of RV dysfunction, the qualitative assessment of RV wall motion abnormalities is included in most of the studies. Quantitative values of RV dysfunction in acute PE usually include different parameters of RV dilatation (end-diastolic diameter of > 30 mm in the parasternal view, RV:LV end-diastolic diameter ratio > 0.6 in the parasternal or subcostal views, RV end-diastolic area > 20 cm² in the apical subcostal or the transesophageal [TEE] four-chamber views), loss of inspiratory collapse of the IVC, and the presence of pulmonary hypertension (PH).[21] Other findings in acute PE include flattening and paradoxical motion of the interventricular septum (*D-sign*), PA dilatation (> 12 mm/m²), and diastolic LV impairment.

LV diastolic dysfunction is an indirect index of burden of LV. IVS paradoxical motion reduces LV compliance and increases filling pressures during diastole. The presence of a dominant A wave when sinus rhythm is still maintained indicates a significant contribution of atrial contraction in LV diastolic filling.

Criteria of RV Overload
The diagnosis of RV overload is established when at least one of the following criteria is fulfilled:

1. Right-sided cardiac thrombus;
2. RV end-diastolic diameter measured in the parasternal long axis view > 30 mm or a RV/LV ratio > 1;
3. Systolic flattening of the IVS;
4. Acceleration time < 90 ms or tricuspid insufficiency pressure gradient > 30 mm Hg in the absence of RV hypertrophy.[22]
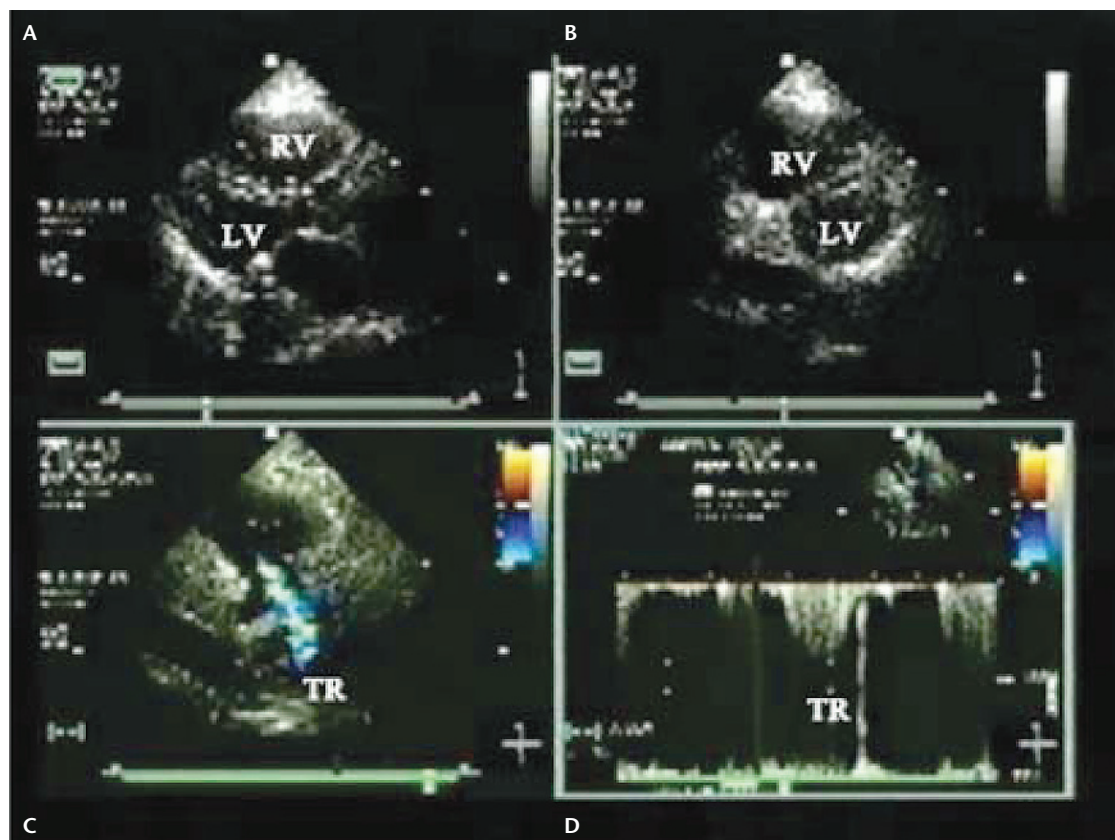
Figure 3. Echocardiography in acute PE. There is dilatation of the right ventricle (A) with diastolic bowing of the intraventricular septum (B), significant tricuspid regurgitation (C), and elevated right ventricular systolic pressure (D). LV: left ventricle; RV, right ventricle; TR, tricuspid regurgitation.

The aforementioned criteria can diagnose PE with 81% sensitivity and 78% specificity. However, patients with previous cardiorespiratory diseases, such as chronic obstructive pulmonary disease (COPD) or primary PH may fulfill the above criteria even in the absence of pulmonary vasculature obstruction. In these patients, specificity and sensitivity for the diagnosis of PE is lower (21% and 80%, respectively).

The McConnell Sign

What is now known as the *McConnell sign* was described by McConnell and colleagues[23] as a distinct pattern of regional RV dysfunction in patients with acute PE presenting as hypokinesia or akinesia of the mid-RV free wall, but with a normal or hyperkinetic RV apex. The finding was shown to have 77% sensitivity and 94% specificity for the diagnosis of acute PE, with a positive predictive value of 71% and a negative predictive value of 96%. RV free wall hypokinesia caused by RV infarction can mimic the McConnell sign; therefore, concomitant echocardiographic signs of RV pressure overload should be present in order to diagnose acute PE.

The McConnell sign represents a useful tool for the differential diagnosis of RV dysfunction. Although no clear interpretation exists, several pathophysiologic mechanisms have been proposed:

1. Tethering of the RV apex to a contracting and often hyperdynamic LV which may account for the preserved contractility of the RV apex.
2. A systolic bulging localized to the mid-RV free wall, which spares the apex and base, as a result of RV shape adjustment induced by the abrupt increase of afterload and the increased regional wall stress. In contrast, RV dysfunction in patients with chronic PH and RV hypertrophy tends to present in a more diffuse pattern, in the absence of tethering of the RV apex and spherical shape changes.
3. Segmental ischemia of the RV free wall secondary to the increased wall stress.

However, recent studies have emphasized the subjectivity of the sign and demonstrated lower sensitivity (< 20%) and higher specificity (> 98%).[13,24] López-Candales and associates[25] assessed RV function by using longitudinal velocity vector imaging and showed that apical RV function is not truly preserved in patients with acute PE and that overall RV strain is reduced. A rare pattern of reversible akinesia of the mid-RV free wall and RV apex with hyperkinesia of the basal segments
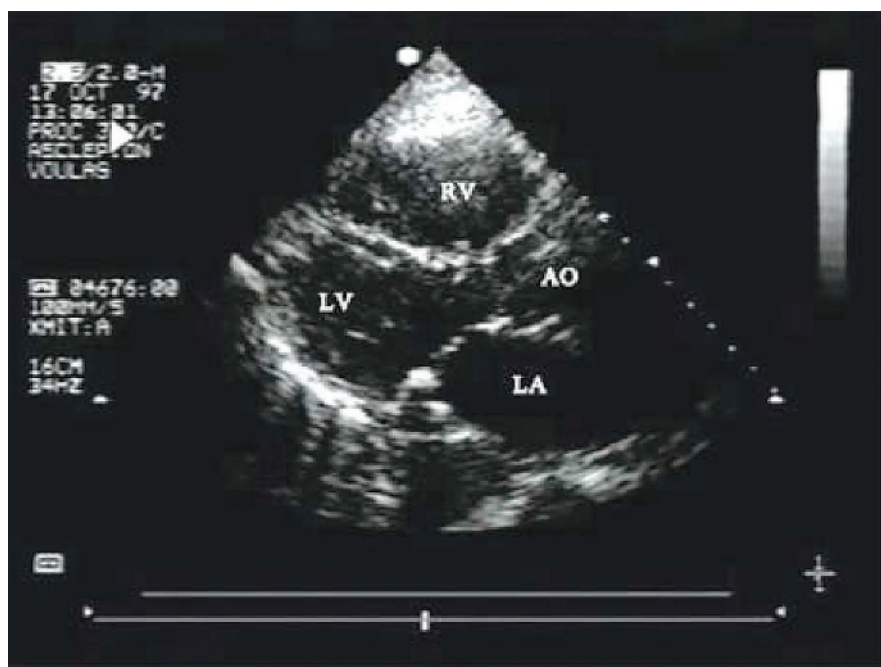
Figure 4. Parasternal long-axis view showing dilatation of the right ventricle secondary to acute pulmonary embolism. Ao, ascending aorta; LA, left atrium; LV, left ventricle; RV, right ventricle.

(reverse McConnell sign) has been described and is considered a result of regional differences in the magnitude of RV ischemia in acute PE.[26]

The 60/60 Sign

The 60/60 sign represents a disturbed RV ejection pattern, defined as an acceleration time value ≤ 60 ms in the presence of tricuspid insufficiency pressure gradient ≤ 60 mm Hg. It has 25% sensitivity and 94% specificity for the diagnosis of acute PE.[13] Specificity can be as high as 100% in patients free of pre-existing cardiopulmonary disease.[22] The short acceleration time and mid-systolic deceleration of flow velocity in the RV outflow tract reflects the premature return of reflected pressure waves through the noncompliant PA. The 60/60 sign has been correlated to lower partial oxygen pressure in the arterial vasculature and diminished respiratory variation of the IVC. Unlike the McConnell sign, with which significant intraobserver variability can exist, the 60/60 sign is not subject to similar restrictions.

The combined specificity and sensitivity of these two echocardiographic signs is 94% and 36%, respectively.[13]

Diagnosis

The initial diagnostic approach to a patient with suspected PE is mainly based on the clinical suspicion and use of established prognostic algorithms, such as the Wells and Geneva scores. Diagnosis is achieved in only 10% of the patients with low clinical suspicion and in 80% of those with high clinical suspicion.[27] Early recognition of high-risk PE is crucial in order to optimize the diagnostic and therapeutic approach. Established risk markers such as the presence of shock or hypotension, myocardial injury, and echocardiographic

features of RV dysfunction should be assessed early in order to risk stratify patients.

In patients with a high clinical probability for PE, CTPA is the imaging study of choice. When CTPA is not readily available, early echocardiographic assessment is recommended.[22] In patients with low or intermediate clinical probability for non–high-risk PE, a negative highly sensitive D-dimer assay will almost always exclude the diagnosis.

Approximately 50% of the patients with angiographically proven acute PE will have normal echocardiographic findings, whereas 25% of them will demonstrate RV dilatation.[28] Overall, the sensitivity of echocardiography in diagnosing PE is 56% to 70% and its specificity approximately 90%.[28-30] Echocardiography has a prominent role in the initial assessment of patients with acute PE. In hemodynamically unstable PE patients, echocardiography can safely guide prognosis and management. A normal echocardiogram in a patient with shock and clinical suspicion of PE practically

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excludes PE as a cause of hemodynamic collapse. On the other hand, the presence of RV dysfunction in a hemodynamically unstable patient with high clinical suspicion for acute PE is enough to justify immediate thrombolytic therapy without the need for further imaging (eg, CTPA).[22]

In patients without shock or hypotension, a normal echocardiographic study cannot exclude the diagnosis of PE. In this group

of patients, echocardiography is used to risk stratify PE patients to moderate or high risk depending on the presence or absence of RV dysfunction, respectively. RV dysfunction can indirectly indicate a higher risk of latent hemodynamic collapse and a more severely affected pulmonary vasculature.[29] Nevertheless, patients with normal RV function but increased markers of myocardial necrosis (troponin, brain natriuretic peptides) are also considered as moderate risk.[22]

Prognosis

The mortality for patients with PE and concomitant echocardiographic features of RV dysfunction is estimated to be between 4% and 5%, whereas patients with nor-

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mal echocardiographic findings on admission carry an in-hospital mortality of < 1%.[31-33] Patients with moderate or severe RV impairment demonstrate a sixfold increased risk of in-hospital death and a 2.4-fold increase in relative risk during the first year.[12] In a large study of approximately 2500 patients (International Cooperative Pulmonary Embolism Registry), mortality at 90 days after hospital admission was higher in patients with hemodynamic impairment of RV.[10] Congestive heart failure, renal failure, chronic respiratory diseases, age > 70 years, or malignancy were the strongest prognostic factors. Normotensive patients with evidence of RV dysfunction represent almost one-third of the patients with PE. In this subgroup of patients, the negative predictive value of echocardiography for PE-related death is

100%.[29] Furthermore, in a recent large meta-analysis, patients without hemodynamic instability, but with findings of RV impairment, showed increased mortality.[11] Stein and colleagues[33] demonstrated that RV dilatation in patients presenting with hemodynamically stable acute PE was correlated with high in-hospital mortality rates when combined with cardiac enzyme elevation. Jiménez and associates[34] assessed the prognostic ability of three diagnostic tests: troponin I, echocardiography, and lower extremity complete compression ultrasound study (CCUS) in normotensive patients with acute PE. They concluded that the combination of RV dysfunction on echocardiography (defined as end-diastolic diameter > 30 mm, tricuspid systolic velocity > 2.6 m/s, and hypokinesia of the RV free wall) and a positive lower extremity CCUS had the higher prognostic value for PE-related death at 30-day follow-up. The positive predictive value of this two-test strategy was even higher in the high-risk patient subgroup, as defined by the PE severity index.[35]

The assessment of PA pressure showed a significant prognostic value in patients with PE. Systolic PA pressure is usually elevated in patients with acute PE and restored to normal limits within the first 3 weeks.[36] In a prospective study of 78 patients with PE, it was shown that reduction in pulmonary systolic pressure is evident during the first 6 weeks and is associated with gradual improvement of RV systolic function. However, patients with baseline pulmonary systolic

pressure > 50 mm Hg on admission have a threefold increased risk of persistent PH and a lower 5-year survival rate.[12] PA acceleration time correlates inversely to mean RV pressure and is considered to be a sensitive marker of proximal PA thrombosis. Kjaergaard and colleagues[37] studied patients with nonmassive PE and showed that PA acceleration time and LV systolic function are independent predictors of event-free survival.

Patent Foramen Ovale

Patients with a patent foramen ovale (PFO) > 4 mm in diameter have increased risk of embolic events.[38] Transient right to left shunt can occur even in the presence of normal hemodynamic parameters.[39] However, patients with PE and elevated high right-side pressures are at even greater risk of systemic emboli.[40]

In high-risk PE, PFO is found in 35% of the patients and is associated with a 10-fold increase in hospital mortality and increased incidence of embolic stroke and peripheral embolism. Patients with PE and PFO with right to left shunt carry a fivefold greater risk of cardiovascular complications. Detection of a PFO with contrast transthoracic (TTE) or TEE in patients with high-risk PE and increased right atrial pressures has been proposed as an indication for aggressive treatment with thrombolysis or embolectomy, in order to immediately restore patency of the pulmonary vasculature and normalize right-side pressures.[40]

Treatment

The use of thrombolytic therapy appears to yield the greatest benefit in patients with massive PE which is manifested by hypotension or shock and imprinted with signs of RV dysfunction on echocardiography. In addition, echocardiography

is an extremely useful tool for assessing the results of anticoagulation treatment in patients presenting with RV dysfunction or intracavitary thrombi.

Significant improvement of RV systolic function and other parameters of RV dysfunction is usually evident during the first hours after thrombolysis. Greco and associates[41] studied 30 patients with high-risk PE who received thrombolysis with recombinant tissue-type plasminogen activator (rt-PA) under continuous echocardiographic monitoring. Complete dissolution of right heart thromboemboli and significant reduction in RV end-diastolic diameter, RV/LV ratio, and tricuspid regurgitant flow velocity were observed within the first hour of treatment, with concomitant marked clinical improvement. In a smaller study by Nass and colleagues,[42] a significant recovery of RV free wall motion (assessed by the centerline method) and RV end-diastolic and end-systolic diameters was observed following treatment with rt-PA in a heterogenous group of patients with acute PE, although the time of follow-up echocardiography varied significantly. Goldhaber and associates[7] showed improvement of RV wall motion abnormalities and RV diastolic area, as well as improvement in pulmonary perfusion, 24 hours following treatment with rt-PA, compared with treatment with intravenous heparin alone in hemodynamically stable PE patients. Improvement of RV function on 1-month follow-up after anticoagulation treatment has been also demonstrated by reduction of Doppler and Doppler tissue imaging parameters.[43]

TEE
TEE allows direct visualization of thrombi that are often invisible by TTE. Although the main PA, PA bifurcation, and right PA can be easily visualized in the midesophageal views of the ascending aorta, left PA is commonly obscured by the overlapped left main bronchus, whereas peripheral branches are not visible. The sensitivity and specificity of TEE for imaging intracavitary thrombi in patients with acute PE is 80% and 100%, respectively.[44]

There is conflicting evidence regarding the role of TEE in acute hemodynamic collapse due to PE in the perioperative setting or in intensive care unit (ICU) patients. Vieillard-Baron and colleagues[45] reported that overall sensitivity of TEE for the diagnosis of PE in ICU patients was lower compared with CTPA and pulmonary angiography. However, sensitivity was much higher (84%) in patients with proximal PE. Rosenberger and associates[46] showed that TEE sensitivity for intraoperative thrombus visualization at any specific location is only 26% and much lower for thrombi of the left PA (17%). In the same study, TEE evidence of RV dysfunction was observed in 96% of the patients, tricuspid regurgitation in 50%, and leftward interatrial septal bowing in 98%. Although performing a thorough intraoperative study cannot be anticipated due to several technical difficulties, the American Society of Echocardiography and Society of Cardiovascular Anesthesiologists strongly recommend TEE in acute, life-threatening intraoperative hemodynamic collapse.[47]

Right-side Thrombi
Right-side thrombi, contrary to those of the left cavities, may organize topically or represent plasters of peripheral veins when they are initially formed. Right intracavitary thrombi may be seen in various clinical conditions such as right heart failure, RV infarction, patients with indwelling catheters, or pacing electrodes. Thrombi are frequently visualized with TTE or TEE in the inferior vena cava, the right atrium or RV, the PA, and rarely, trapped in a PFO or in the chordae tendinae of the tricuspid valve.[48] Two types of right-cavitary thrombi have been described: type A are sizable and elongated with typical continuous serpentine movement and associated with deep venous thrombosis of the lower extremities. Type B are smaller, less mobile, and usually resemble the thrombi of the left heart. In patients with type A thrombi, PE is diagnosed in 98% of the cases and mortality rates are high. Patients with type B thrombi have a more favorable prognosis and lower incidence of PE (40%).[6] It is estimated that, if left untreated, the mortality of patients with PE and type A thrombi is almost 100%.[49]

In the International Cooperative Pulmonary Embolism Registry, 1113 patients with acute PE underwent imaging with TTE or TEE and thrombus was only visualized in 4% of the cases.[50] The presence of thrombus on echocardiography was associated with RV dysfunction, lower systolic blood pressure on admission, and almost a twofold higher mortality during the first 2 weeks of hospitalization. Although the optimal management of patients with visualized thrombi and PE is controversial, thrombolysis or embolectomy appear more effective than anticoagulation treatment alone.[22]

Novel Echocardiographic Parameters of RV Dysfunction
New echocardiographic parameters of RV dysfunction have been introduced and novel methods of regional and global RV function assessment have been applied following the

recent advances in Doppler and tissue Doppler echocardiography.

Tissue Doppler imaging allows the quantitative assessment of RV function by estimation of myocardial velocities. The tricuspid annular plane systolic excursion (TAPSE) and RV-MPI can predict clinical outcomes in patients with chronic heart failure, ischemic cardiomyopathy, PH, and chronic pulmonary disease.[51,52] It has been shown that both TAPSE and RV-MPI are reliable quantitative markers of RV function and correlate well with morbidity and mortality in acute PE.[53] RV-MPI is considered a combinative marker of RV systolic and diastolic function and depends on the length of isovolumic contraction and relaxation and the RV contraction time. Increased RV-MPI in patients with PE has been attributed to the prolongation of RV isovolumic relaxation time and reversibility has been demonstrated following 1-month of anticoagulation treatment.[45] TAPSE is related to the presence and extent of PE and is considered as a marker of persisting RV dysfunction.[18]

kinetics measurement. Strain measurements correlate well with sonomicrometry segment length measurements both in the inflow and outflow tract of the RV. Sugiura and colleagues[57] demonstrated reversible RV regional nonuniformity caused by acute RV pressure overload in PE patients with speckle tracking strain echocardiograph. Similar conclusions were drawn by Takamura and associates,[58] who studied LV function with speckle tracking displacement and strain imaging echocardiography. They demonstrated that acute LV pressure overload was associated with impaired global LV systolic function and significant but reversible LV regional nonuniformities in the three contractile directions. Moreover, cardiac index was independently associated to the radial RV wall motion discoordination.

Noninvasive estimation of PVR by echocardiography was recently reported.[59,60] Kim and colleagues[61] calculated Doppler-derived PVR in PE patients with a standardized formula depending on the tricuspid regurgitant velocity and the time

aggressive management. Moreover, it is extremely useful for assessing anticoagulation or thrombolysis effects on intracavitary thrombi, RV systolic function, and other parameters that are usually affected during an embolic event. Nevertheless, a normal echocardiographic study cannot exclude the diagnosis of PE; therefore, clinical consideration and estimation of other diagnostic modalities, such as CTPA, D-dimer, and CCUS, are equally important. Although new echocardiographic parameters are promising, further studies in larger patient groups are required in order to assess clinical outcomes. ■

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The recent introduction of real-time three-dimensional (3D) echocardiography implied a great progress in the diagnosis of acute PE. 3D echocardiography has been shown to be more accurate in imaging of intracardiac masses and PA thrombus[54,55] and provides additional information on the size, consistency, and mobility of the thrombi.[56]

Speckle tracking displacement and strain echocardiography are promising methods of global and regional myocardial

velocity integral of systolic flow through the RV outflow tract. PVR > 4.5 WU predicted adverse events with 63% sensitivity and 90% specificity, whereas overall survival was strongly correlated to initial PVR values. However, larger studies are required to clarify these findings.

Conclusions

Echocardiography can provide immediate and accurate risk assessment of high-risk patients with acute PE and can safely guide

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MAIN POINTS

- Echocardiography can provide immediate and accurate risk assessment of high-risk patients with acute pulmonary embolism (PE) and can safely guide aggressive management.

- Early recognition of high-risk PE is crucial in order to optimize the diagnostic and therapeutic approach. Established risk markers such as the presence of shock or hypotension, myocardial injury, and echocardiographic features of right ventricular (RV) dysfunction should be assessed early in order to risk stratify patients.

- Echocardiography is extremely useful for assessing anticoagulation or thrombolysis effects on intracavitary thrombi, RV systolic function, and other parameters that are usually affected during an embolic event.

- A normal echocardiographic result cannot exclude the diagnosis of PE; therefore, clinical consideration and estimation of other diagnostic modalities, such as contrast-enhanced computed tomography pulmonary angiogram, D-dimer, and complete compression ultrasound study, are equally important.

- New echocardiographic parameters of RV dysfunction have been introduced and novel methods of regional and global RV function assessment have been applied following the recent advances in Doppler and tissue Doppler echocardiography. Although these parameters are promising, further study is necessary to assess clinical outcomes.

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