REGULAR ARTICLE

Diagnostic Evaluation of Chronic Thromboembolic Pulmonary Hypertension

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Chronic thromboembolic pulmonary hypertension (CTEPH) is a distinct form of pulmonary hypertension, uniquely characterized by pulmonary artery narrowing and occlusion from clot material. With advances in medical education and therapeutic options, awareness of CTEPH has grown significantly in recent years. The diagnostic evaluation remains complex, warranting an integrated assessment of history, physical exam, echocardiogram, chest imaging including computerized tomography with angiography, ventilation–perfusion scanning, right heart catheterization, catheter-based pulmonary angiography, and assessment for medical and mechanical CTEPH risk factors. The diagnostic evaluation of CTEPH is reviewed here.

INTRODUCTION

While the field of pulmonary hypertension (PH) has evolved dramatically in recent years regarding available medical therapy, much of PH remains a chronic, progressive, and often fatal disease. In the evaluation of the patient with PH, particularly with hemodynamics consistent with precapillary PH (elevated pulmonary vascular resistance [PVR] with normal left heart filling pressures), it is critical to make an accurate diagnosis of chronic thromboembolic PH (CTEPH) as the treatment options are vastly different.[1] CTEPH remains the sole PH diagnosis with the potential for cure, which is achieved on the basis of pulmonary thromboendarterectomy (PTE); alternatively, management may include balloon pulmonary angioplasty (BPA) or medical therapy with riociguat.[2–4]

HISTORY AND PHYSICAL EXAM

The history in CTEPH can range from elusive to quite informative. Up to 50% of patients ultimately diagnosed with CTEPH are not known to have had a prior pulmonary embolism (PE). In patients with an established diagnosis of acute PE followed prospectively, the risk of developing CTEPH is estimated to be approximately 3%–4%.[5] Risk factors for CTEPH are vast and should be elicited in the history. Hematologic abnormalities that portend a hypercoagulable state such as antiphospholipid antibody syndrome, history of splenectomy, red blood cell dyscrasias, history of prior PE, or young age at the time of first PE increase the risk of developing CTEPH. A diagnosis of cancer is a risk factor for CTEPH, both by the associated hypercoagulable state that often coexists with it and from indwelling central venous catheters used for chemotherapy that serve as a nidus for thrombus formation, which can then embolize into the lungs. Similarly, indwelling pacemakers have been associated with small thrombi embolizing and leading to a distal type of CTEPH.[6,7] More recently, pelvic vein obstructions have been described as a risk for developing CTEPH, including uterine fibroids and May-Thurner syndrome. Thus, in women, a history of fibroids, iron deficiency anemia, or menorrhagia can be a clue. May-Thurner syndrome, in which the right common iliac artery overlies and compresses the left common iliac vein, can also lead to stasis and venous thromboembolism (VTE); as such, a history of PE associated with recurrent left lower extremity deep vein thrombosis that by traditional risk factor evaluation is unprovoked can also be a helpful historic clue in the workup of CTEPH.[8,9]

The physical exam in CTEPH typically represents PH and right heart failure, including elevated jugular venous pressure (JVP) with abdominojugular reflux, tricuspid regurgitation markers such as a prominent V wave in the JVP or a holosystolic murmur increasing with inspiration, a loud pulmonic component of the second heart sound (P2), and peripheral edema. Pulmonary bruits may be present from turbulent flow caused by proximal disease, suggesting potentially operable disease. Indwelling venous catheters, ports, or pacemaker devices may reveal the etiology of CTEPH, while also revealing a necessary target for removal to prevent recurrence. Postthrombotic syndrome may be noted in CTEPH, including hyperpigmentation, skin thickening, lower extremity swelling, and varicose veins. If noted in the left lower extremity, May-Thurner syndrome should be considered.[7]

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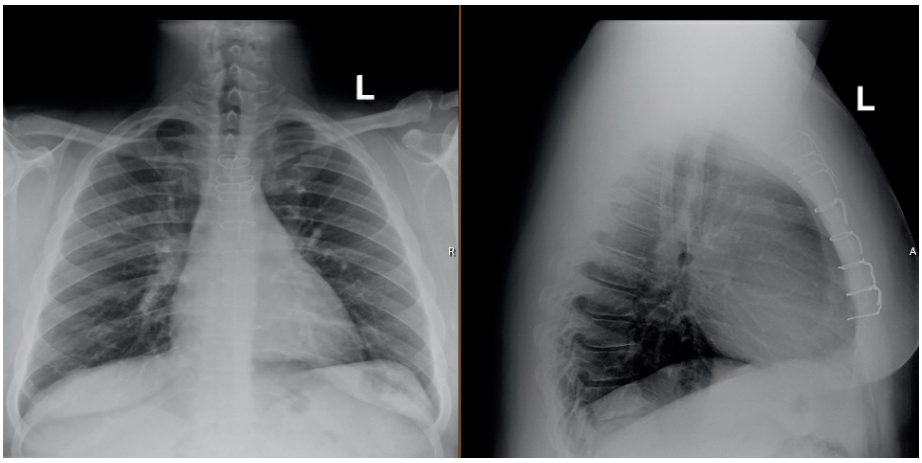

Figure 1: Chest radiograph demonstrating prominent descending right pulmonary artery, right ventricular enlargement with loss of retrosternal space.

CHEST X-RAY

Chest x-ray findings (Figure 1) include a prominent main pulmonary artery (PA) and Palla's sign (enlarged PA along the right atrial border), and often pruning of the distal pulmonary circulation. An enlarged right atrium extends the cardiac silhouette laterally, and a loss of retrosternal space on the lateral film suggests right ventricular (RV) enlargement.[10] Evidence of pulmonary infarct may also be seen as a subpleural wedge or round opacification. This is often referred to as Hampton's hump, described by Hampton and Castleman in 1940.[11]

ELECTROCARDIOGRAM

In chronic thromboembolic disease (CTED) without the presence of PH, the electrocardiogram (ECG) may be normal. When PH is present (CTEPH), there may be significant abnormalities (Figure 2) of the right side of the heart, including right axis deviation, right atrial enlargement, RV hypertrophy (RVH) as indicated by large R waves in V1-V2, and right heart strain evidenced by T-wave inversions in the right-sided precordial (V1-V3) and inferior leads (II, III, avF).[12]

Importantly, the presence or absence of normal sinus rhythm can have very significant implications in patients with CTEPH and right heart failure. Sinus rhythm and the maintenance of atrial-ventricular synchrony is critical to overall right heart function, and loss of this due to atrial tachyarrhythmias such as atrial fibrillation can lead to a loss of up to half of right heart function.[13] Amid the diagnostic workup of CTEPH, if a patient is noted to have significant PH with RV dysfunction, recognition of an atrial tachyarrhythmia should be considered a target for urgent intervention to maintain hemodynamic stability and minimize the clinical syndrome of right heart failure.

ECHOCARDIOGRAM

Like the ECG, the abnormalities seen on transthoracic echocardiography will depend on the degree of elevated PVR impact on the right heart (Figure 3). While acute and chronic PE can cause RV dysfunction and chamber dilatation, the presence of RVH, defined as RV free-wall thickness greater than 5.0 mm, is more indicative of CTEPH.[14]

Multiple findings on echocardiography are well known to predict an elevated PVR, including systolic interventricular septal flattening, a flying W on M mode of the pulmonic valve, and notching with reduced acceleration time (AT) in the pulse wave Doppler profile in the RV outflow tract (RVOT).[15,16] While ventilatory inefficiency contributes significantly to dyspnea in CTEPH, the other major contributor is the degree of RV dysfunction and right heart failure. Tricuspid annular plane systolic excursion, S′ velocity, RV fractional area change (RV FAC), or RV index of myocardial performance are all

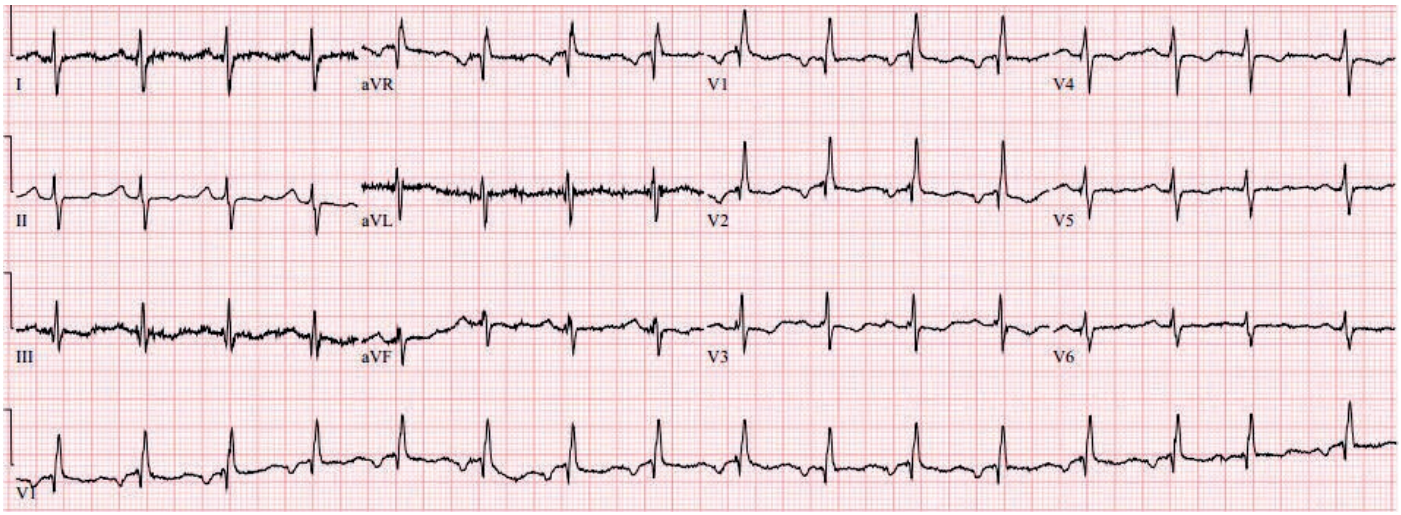

Figure 2: Electrocardiogram demonstrating right ventricular hypertrophy, incomplete right bundle branch block, and right heart strain.

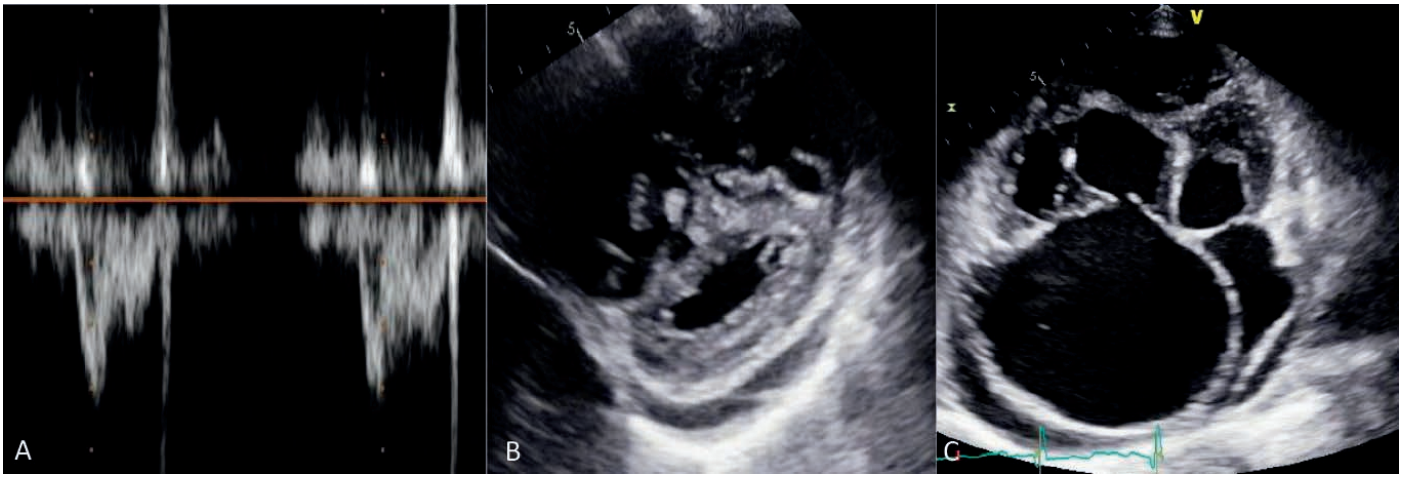

Figure 3: Echocardiography imaging: (**A**) Right ventricular (RV) outflow tract Doppler notch with reduced acceleration time. (**B**) Severe systolic septal flattening. (**C**) Severe right atrial and RV enlargement with RV hypertrophy and pericardial effusion.

methods used on echocardiography to quantify RV function.[17]

After PTE, the abnormal findings on echocardiogram associated with elevated PVR, RV enlargement, and RV dysfunction have been shown to improve. The AT falls; the ratio of RV:LV decreases; RVOT velocity time integral, a representative of stroke volume, increases; and RV FAC increases.[18] Importantly, ongoing RV structure and function abnormalities post-PTE are highly suggestive of residual or recurrent PH and should be monitored carefully after PTE.[19]

VENTILATION-PERFUSION SCAN

The combination of normal ventilation with unmatched perfusion defects, which can occupy an entire lung, lobe, segment, or subsegmental region is very suspicious for CTEPH. In CTEPH, the prevalence of thromboembolic burden tends to favor the lower lobes more so than upper lobes. The sensitivity is >96% for a radioisotopic ventilation–perfusion (VQ) scan in detecting CTEPH.[20] Importantly, a perfusion defect does not distinguish between acute versus chronic disease, nor is it specific to thromboembolic versus other forms of PA obstruction, such as vasculitis, fibrosing mediastinitis, tumor, or sarcoidosis.[7]

Camera positioning may underestimate perfusion defects in planar imaging if there is normal perfusion in overlying lung tissue. Single photon emission computed tomography (SPECT) increases the sensitivity by generating 3-dimensional images (Figure 4).[21] Additionally, partial recanalization of clot can allow for tracer to pass distally, thus underestimating the degree of thromboembolic disease. As such, this may pose a limitation in the accuracy of the VQ scan in delineating the proximal nature of disease, correlating with operability for PTE.[22] This limitation underscores the importance of the use of direct forms of pulmonary vascular imaging such as computed tomography (CT) angiography or magnetic resonance angiography, which are well suited to detect proximal web stenoses that may have been underappreciated by perfusion lung scan.

CT ANGIOGRAPHY

CT of the chest with angiography can provide extensive anatomic information in the evaluation of CTEPH (Figure 5).Like pulmonary arterial hypertension, the cardiac structures are revealing, typically with right atrial and RV enlargement, tricuspid valve annular dilatation, and RVH. In fact, the presence of RVH can be a very telling clue that thromboembolic disease is chronic, rather than acute, which can often be difficult to distinguish, particularly in very proximal disease.[23]

The vascular findings are the hallmark clues in CTEPH, including dilatation of the main pulmonary arteries. Where there is thromboembolic disease, there may be arterial wall thickening with lining thrombus, vessel caliber attenuation with poststenotic dilatation, occlusions, and linear webs representing partially recanalized vessels. This differs from the appearance of acute thromboembolic disease, where clot material is more frequently central in the vessel lumen with bright contrast seen surrounding it, and distal vessel contraction is distinctly absent.[7] Arterial collaterals from systemic to pulmonary circulation can be seen when thromboembolic disease is proximal and occlusive. These collaterals may stem from the aorta, intercostal, internal mammary, or coronary arteries and coexist with enlarged bronchial arteries; rupture may lead to hemoptysis.[24]

Normal perfusion to lung parenchyma, in contrast to hypoperfused dark areas, imparts a mosaic perfusion pattern typical for CTEPH.[10] Also seen on parenchymal lung assessment is evidence of pulmonary infarction, appearing as subpleural or peripheral wedge-shaped hypovascular opacifications with curvilinear, fibrous scarring, loss of lung volume, or at times, thick-walled cavitary type lesions that are conspicuously present distal to an occluded arterial segment. These findings may often lead to misdiagnosis of pneumonia or other chronic processes.[7]

More recent advances in CT have increased diagnostic accuracy in the use of CT for CTEPH. Dual-energy CT scanning acquires information for tissue characterization including parenchymal abnormalities, normal lung tissue, and perfused blood volumes. This can help

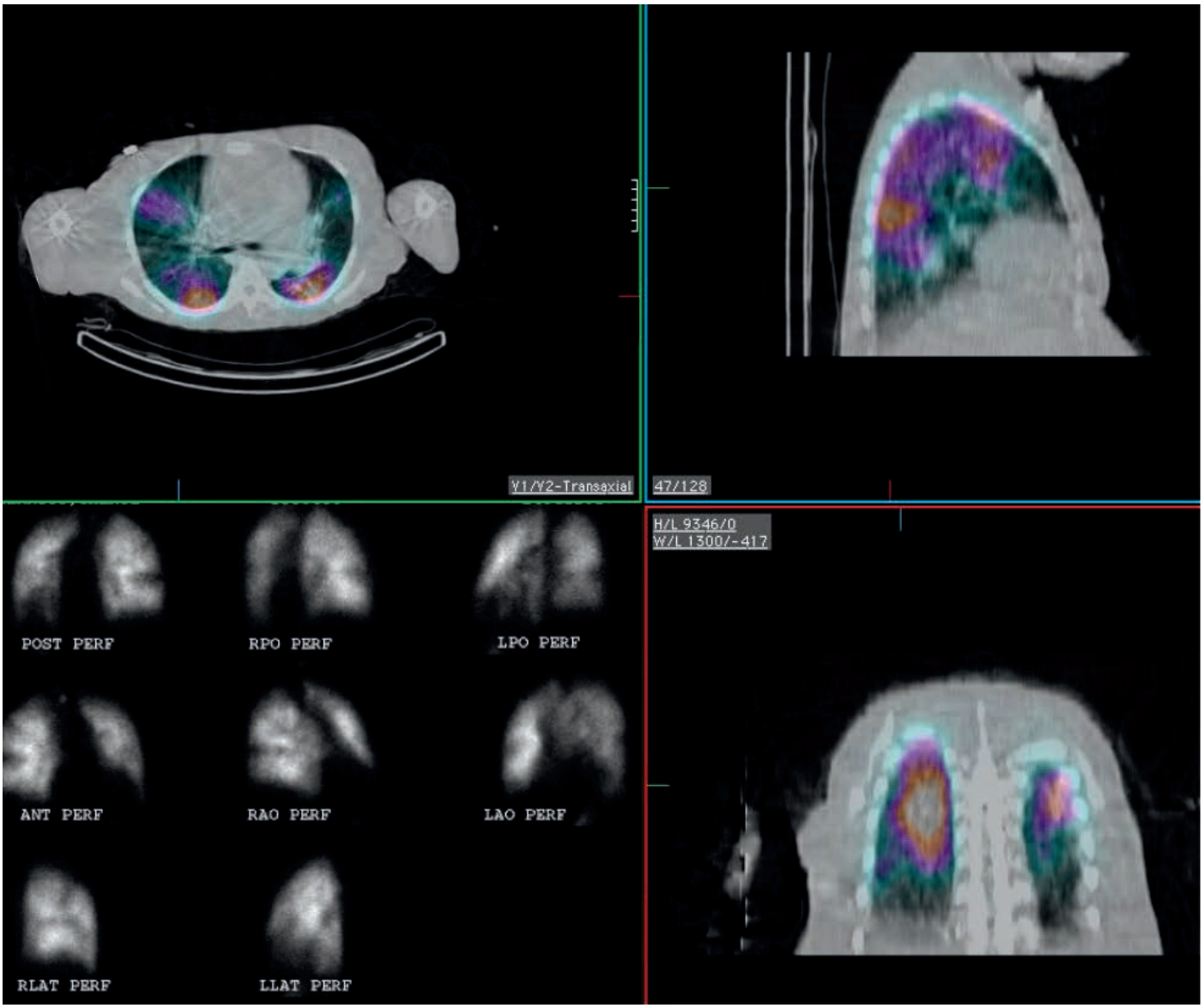

Figure 4: Single photon emission computed tomography (SPECT) and Q scan demonstrating heterogeneous perfusion in chronic thromboembolic pulmonary hypertension.

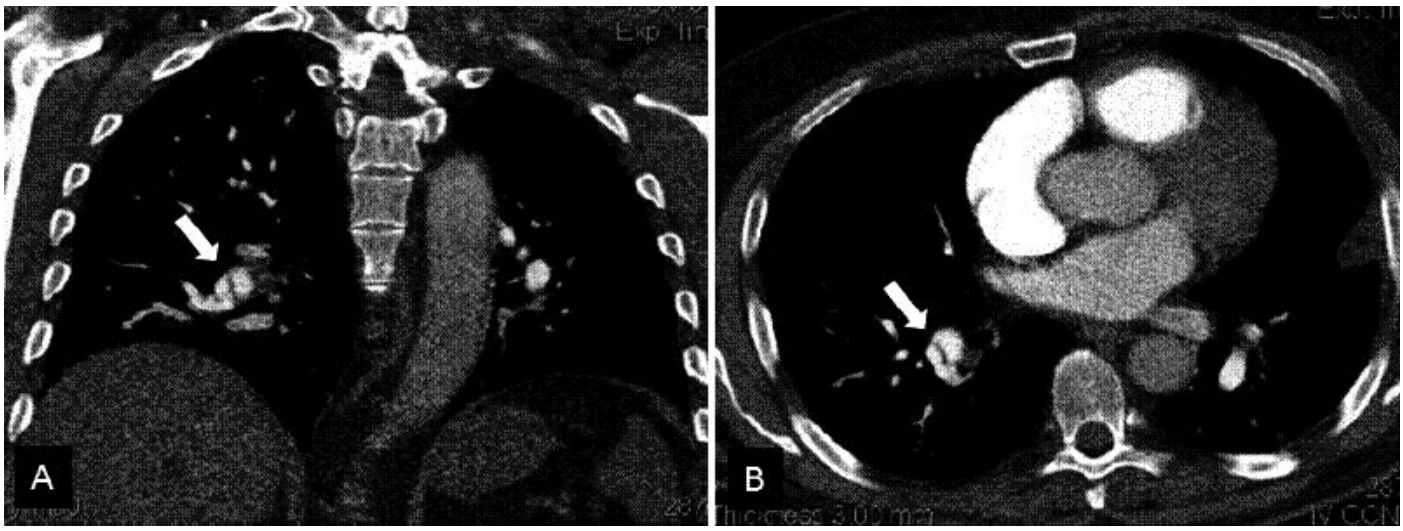

Figure 5: Computed tomography angiography chest with intravascular linear webs characteristic of chronic thromboembolic pulmonary hypertension (arrow). (**A**) Coronal plane. (**B**) Axial plane.

identify wedge-shaped and pleural defects in CTEPH that have been shown to correlate with pulmonary angiography.[25] Lung subtraction iodine mapping with SPECT imaging has been shown to correlate well with VQ scan in identifying regions of vascular malperfusion to the lungs.[26] For further imaging clarity on distal segmental PA branches, 3-dimensional SPECT–CT fusion imaging may have additional value, particularly in the guidance of BPA.[27]

Finally, CT angiography of the chest identifies diagnoses that may have unmatched perfusion defects on VQ scan and similar clinical presentations as CTEPH but for which the treatment is very different. Pulmonary arterial hypertension, when longstanding and associated with systemic-to-pulmonary shunting such as atrial and ventricular septal defects, can lead to markedly enlarged pulmonary arteries with in situ thrombosis that is not flow limiting.[28] Metastatic solid tumors have been known to metastasize to and mimic thromboembolic disease in the pulmonary arteries.[29] Similarly, PA sarcoma can pose significant occlusion, and perfusion defects of proximal pulmonary arteries, often with the conspicuous absence of more distal involvement, are often unilateral and may even involve the pulmonic valve.[30] In the case of PA sarcoma, comparison with a previous CT angiography may reveal an interval increase in size of the intravascular material, providing a clue to tumor growth. Vascular aneurysms with a narrowed main PA, particularly when accompanied by systemic arterial involvement, should raise suspicion for large vessel vasculitis (such as Takayasu or Bechet syndromes).[31] Sarcoidosis or fibrosing mediastinitis may cause significant PA abnormality and occlusion, often associated with marked hilar lymphadenopathy or pulmonary infiltrate in the case of sarcoid, and pulmonary venous stenosis or occlusion in the case of fibrosing mediastinitis.[32]

CARDIOPULMONARY EXERCISE TESTING

Although not warranted in all patients with suspected CTEPH, cardiopulmonary exercise testing (CPET) can be quite informative to further delineate the physiologic contributors to a patient's subjective dyspnea and functional limitation. In an era where our patients are advancing to older ages with many comorbidities, the exact or predominant cause of dyspnea may not be clear. This is particularly the case in the context of other cardiac or pulmonary disease, obesity, deconditioning, and even anemia in patients receiving chronic anticoagulation therapy.

Findings on a CPET that suggest CTEPH are those of cardiac limitation and ventilatory inefficiency. These include a reduced O_2 pulse (representing stroke volume) and systolic blood pressure response to exercise, ventilatory inefficiency with elevated VE/VCO_2, and reduced end-tidal CO_2 ($ETCO_2$). Furthermore, the degree of dead space ventilation in distal CTEPH has been shown to correlate with functional capacity and survival. Particularly in patients with CTED who do not have resting evidence of PH on echocardiography or right heart catheterization but who have significant dyspnea and thrombus burden on chest imaging, CPET findings of elevated VE/VCO_2 and reduced $ETCO_2$ can help secure the link between a patient's dyspnea and CTED.[33–36]

Finally, combined CPET with invasive right heart catheterization can further demonstrate abnormalities in hemodynamics during exertion, such as a fixed or rising PVR, reduced augmentation of stroke volume or cardiac output, and elevated right atrial pressure : pulmonary capillary wedge ratio. This combined assessment can be very helpful in making the decision to proceed with PTE or BPA in a patient who does not have overt PH or right heart failure.[37]

RIGHT HEART CATHETERIZATION AND CATHETER-BASED PULMONARY ANGIOGRAPHY

Right heart catheterization is paramount for hemodynamic assessment and is commonly done in the initial evaluation of a patient with PH, before the diagnosis or recognition of CTEPH. Careful assessment of hemodynamics should be performed, with accurate leveling, calibration, and measurement of pressures at end expiration.[37]

Invasive pulmonary angiography (Figure 6) can characterize the thromboembolic location and burden before consideration for PTE or BPA. Occlusions or pouch defects, narrowed vessels, intravascular webs or bands, poststenotic dilatation, and hypovascularity are all findings of CTEPH.[38]

To optimize diagnostic yield, biplane imaging or sequential imaging with anterior-posterior followed by lateral oblique projections can help reveal filling defects that may have been obscured by overlying vessels. Rather than injecting into the main PA, selective angiography of each lung allows clearer angiographic assessment of distal segmental and subsegmental branches. Finally, digital subtraction angiography limits nonangiographic structures from obscuring the image and allows for less intravenous contrast use.[39]

VENOGRAPHY

As previously discussed, risk factors for CTEPH have historically been well described to include hypercoagulable states related to hematologic abnormalities or other medical comorbidities. Additionally, mechanical pelvic vein obstructions have been recognized as an important association with CTEPH, including large uterine fibroids, May-Thurner syndrome, or other levels of pelvic vein obstruction. As such, as part of the diagnostic evaluation for CTEPH, invasive or noninvasive venography may guide further interventions such as hysterectomy, myomectomy, or iliac vein stenting to reduce the risk of recurrent thromboembolic disease.[8,9,18]

CONCLUSIONS

The diagnostic evaluation for CTEPH remains a multifaceted clinical assessment. History of functional limitation, driven by PH and RV dysfunction and ventilatory inefficiency, accompanies a vast array of potential abnormalities on cardiopulmonary testing. ECG and echocardiogram demonstrate evidence of right heart strain, elevated PVR,

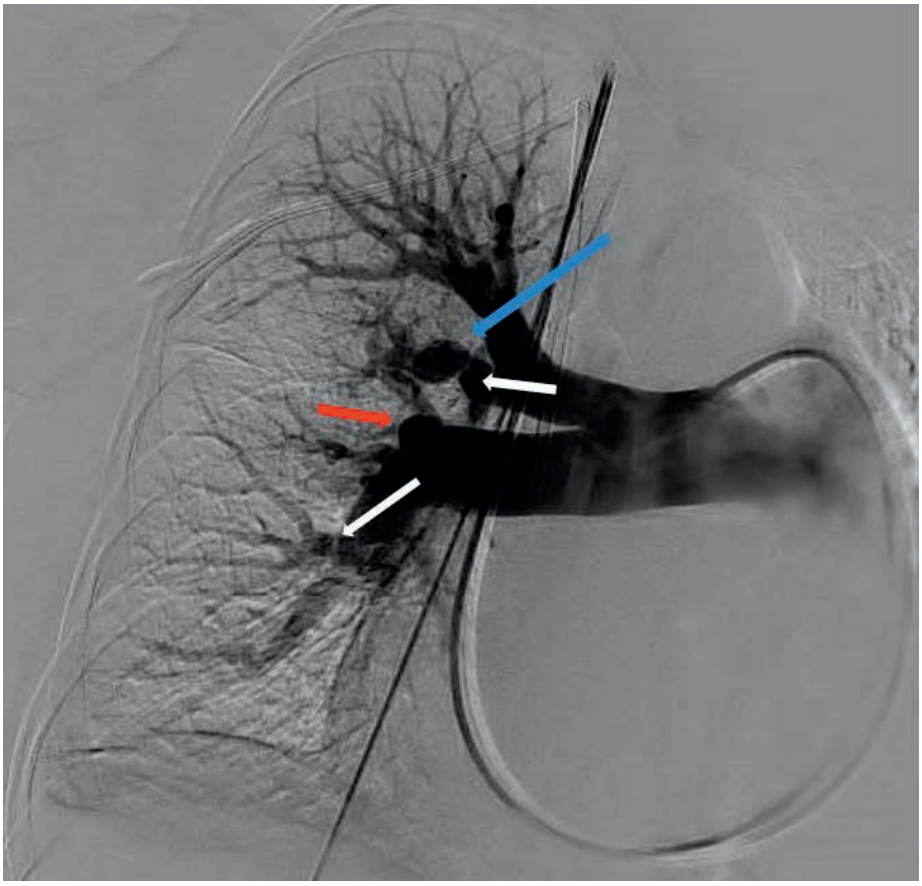

Figure 6: Pulmonary angiography of right lung demonstrating pouch occlusion (red arrow), poststenotic dilatation (blue arrows), and intravascular bands (white arrows).

and RV dysfunction. VQ scan with unmatched perfusion defects has a very high sensitivity for CTEPH. Chest radiography by x-ray and CT angiography reveal enlarged right heart and PA structures. CT may also demonstrate a mosaic perfusion pattern, lung infarct, systemic-to-pulmonary collaterals, and intravascular abnormalities of the PA branches, while providing clues for alternative diagnoses that mimic and often are mistaken for CTEPH. CPET can be performed to characterize findings of ventilatory inefficiency, noninvasively or in conjunction with right heart catheterization at the time of catheter-based pulmonary angiography. Hematologic, medical, and mechanical risk factors for developing CTEPH should be identified for possible intervention to mitigate future recurrent VTE. The clinical assessment remains complex and should ideally be performed by specialized CTEPH centers for accuracy and to guide treatment options.

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